In This Issue:

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Perspectives

Editorials:

Susan K. Schultz
The Neuropsychiatry of Aging

Reviews and Overviews:

Gill Livingston, Kate Johnston, Cornelius Katona, Joni Paton, Constantine G. Lyketsos, and Old Age Task Force of the World Federation of Biological Psychiatry
Systematic Review of Psychological Approaches to the Management of Neuropsychiatric Symptoms of Dementia

Susan A. Ropacki and Dilip V. Jeste
Epidemiology of and Risk Factors for Psychosis of Alzheimer’s Disease: A Review of 55 Studies Published From 1990 to 2003

Introspections:

Richard G. Druss
Egg on Your Face
Clinical Case Conference:

John O. Brooks, III and Jennifer C. Hoblyn
Secondary Mania in Older Adults

Images in Psychiatry:

A. Scott Dowling
George Engel, M.D. (1913–1999)

Presidential Papers: 2005:

Michelle Riba
Presidential Address

Steven S. Sharfstein
Response to the Presidential Address: Advocacy for Our Patients and Our Profession

John F. Greden
Michelle Riba, M.D., M.S., 131st President, 2004–2005

New Research

Articles:

Rebecca L. Gould, Richard G. Brown, Adrian M. Owen, Edward T. Bullmore, Steven C.R. Williams, and Robert J. Howard
Functional Neuroanatomy of Successful Paired Associate Learning in Alzheimer’s Disease

Ulderico Freo, Emiliano Ricciardi, Pietro Pietrini, Mark B. Schapiro, Stanley I. Rapoport, and Maura L. Furey
Pharmacological Modulation of Prefrontal Cortical Activity During a Working Memory Task in Young and Older Humans: A PET Study With Physostigmine

Peter Schönknecht, Johannes Pantel, Andreas Kruse, and Johannes Schröder
Prevalence and Natural Course of Aging-Associated Cognitive Decline in a Population-Based Sample of Young-Old Subjects
Nils Peters, Christian Opherk, Adrian Danek, Clive Ballard, Jürgen Herzog, and Martin Dichgans

The Pattern of Cognitive Performance in CADASIL: A Monogenic Condition Leading to Subcortical Ischemic Vascular Dementia

Sergio E. Starkstein, Ricardo Jorge, Romina Mizrahi, and Robert G. Robinson

The Construct of Minor and Major Depression in Alzheimer’s Disease

Paul S. Appelbaum, Richard J. Bonnie, and Jason H. Karlawish

The Capacity to Vote of Persons With Alzheimer’s Disease


Genotype-Phenotype Studies in Bipolar Disorder Showing Association Between the DAOA/G30 Locus and Persecutory Delusions: A First Step Toward a Molecular Genetic Classification of Psychiatric Phenotypes

Roberto B. Sassi, Jeffrey A. Stanley, David Axelson, Paolo Brambilla, Mark A. Nicoletti, Matcheri S. Keshavan, Renato T. Ramos, Neal Ryan, Boris Birmaher, and Jair C. Soares

Reduced NAA Levels in the Dorsolateral Prefrontal Cortex of Young Bipolar Patients


Risk Factors for Suicide Completion in Major Depression: A Case-Control Study of Impulsive and Aggressive Behaviors in Men

Dean G. Cruess, Steven D. Douglas, John M. Petitto, Thomas Ten Have, David Gettes, Benoit Dubé, Mark Cary, and Dwight L. Evans

Association of Resolution of Major Depression With Increased Natural Killer Cell Activity Among HIV-Seropositive Women

Ivan W. Miller, Gabor I. Keitner, Christine E. Ryan, David A. Solomon, Esteban V. Cardemil, and Christopher G. Beevers

Treatment Matching in the Posthospital Care of Depressed Patients

Christian Otte, Thomas C. Neylan, Sharon S. Pipkin, Warren S. Browner, and Mary A. Whooley

Depressive Symptoms and 24-Hour Urinary Norepinephrine Excretion Levels in Patients With Coronary Disease: Findings From the Heart and Soul Study
Mark Olfson, Amar K. Das, Marc J. Gameroff, Daniel Pilowsky, Adriana Feder, Raz Gross, Rafael Lantigua, Steven Shea, and Myrna M. Weissman

Bipolar Depression in a Low-Income Primary Care Clinic


A 20-Month, Double-Blind, Maintenance Trial of Lithium Versus Divalproex in Rapid-Cycling Bipolar Disorder

D. Jeffrey Newport, Adele C. Viguera, Aquila J. Beach, James C. Ritchie, Lee S. Cohen, and Zachary N. Stowe

Lithium Placental Passage and Obstetrical Outcome: Implications for Clinical Management During Late Pregnancy

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**Brief Reports:**

Kristine Erickson, Wayne C. Drevets, Luke Clark, Dara M. Cannon, Earle E. Bain, Carlos A. Zarate, Jr., Dennis S. Charney, and Barbara J. Sahakian

Mood-Congruent Bias in Affective Go/No-Go Performance of Unmedicated Patients With Major Depressive Disorder

Jeffrey A. Bridge, Rémy P. Barbe, Boris Birmaher, David J. Kolko, and David A. Brent

Emergent Suicidality in a Clinical Psychotherapy Trial for Adolescent Depression

Paul A. Boelen and Jan van den Bout

Complicated Grief, Depression, and Anxiety as Distinct Postloss Syndromes: A Confirmatory Factor Analysis Study

Margaret Stroebe, Wolfgang Stroebe, and Georgios Abakoumkin

The Broken Heart: Suicidal Ideation in Bereavement

Gregg Henriques, Amy Wenzel, Gregory K. Brown, and Aaron T. Beck

Suicide Attempters’ Reaction to Survival as a Risk Factor for Eventual Suicide

Ricardo Segurado, Judith Conroy, Eleanor Meally, Michael Fitzgerald, Michael Gill, and Louise Gallagher

Confirmation of Association Between Autism and the Mitochondrial Aspartate/Glutamate Carrier SLC25A12 Gene on Chromosome 2q31

Jon E. Grant, Laura Levine, Daniel Kim, and Marc N. Potenza

Impulse Control Disorders in Adult Psychiatric Inpatients
Am J Psychiatry 2005 162: 2184-2188.
Communications and Updates

**Letters to the Editor:**

SPIRIDON PAPAPETROPOULOS, STEVE WHEELER, and CARLOS SINGER
*Tardive Dystonia Associated With Ziprasidone*

MICHAEL POYUROVSKY, RONIT WEIZMAN, ABRAHAM WEIZMAN, and LORRIN KORAN
*Memantine for Treatment-Resistant OCD*

BRUNO AOUIZERATE, CORINNE MARTIN-GUEHL, EMMANUEL CUNY, DOMINIQUE GUEHL, HELENE AMIEVA, ABDELHAMID BENAZZOUZ, COLETTE FABRICIOULE, BERNARD BIOULAC, JEAN TIGNOL, and PIERRE BURBAUD
*Deep Brain Stimulation for OCD and Major Depression*

MALEK BAJBOUJ, UNDINE E. LANG, PETER NEU, and ISABELLA HEUSER
*Therapeutic Brain Stimulation and Cortical Excitability in Depressed Patients*

JOHN E. CALAMARI
*Understanding the Heterogeneity of OCD*

DAVID MATAIX-COLS, MARIA CONCEIÇÃO do ROSARIO-CAMPOS, and JAMES F. LECKMAN
*Dr. Mataix-Cols and Colleagues Reply*

PETER A. SHAPIRO
*Heart Transplantation in a Schizophrenia Patient*

DANIEL ANTONIUS
*Insight and Aggression in Schizophrenia*

PETER F. BUCKLEY, DEBBIE HROUDA, LEE FRIEDMAN, STEPHEN G. NOFFSINGER, PHILIP J. RESNICK, and KELLY CAMLIN-SHINGLER
*Dr. Buckley and Colleagues Reply*
STEFAN P. KRUSZEWSKI
Conclusions Inconsistent With Results With Citalopram

ERIC J. LENZE, BENOIT H. MULSANT, M. KATHERINE SHEAR, MARY AMANDA DEW, MARK D. MILLER, BRUCE G. POLLOCK, and CHARLES F. REYNOLDS, III
Dr. Lenze and Colleagues Reply

STEFAN P. KRUSZEWSKI and RICHARD PACZYNISKI
Conclusions Inconsistent With Results With Amphetamines and Divalproex

RUSSELL E. SCHEFFER, ROBERT A. KOWATCH, THOMAS CARMODY, and A. JOHN RUSH
Dr. Scheffer and Colleagues Reply

SHANNON C. MILLER
Psychiatric Effects of Ephedra: Addiction

MICHAEL RACK, JAMES DAVIS, HOWARD P. ROFFWARG, ALLEN RICHERT, and ALP S. BARAN
The Multiple Sleep Latency Test in the Diagnosis of Narcolepsy

LOIS E. KRAHN and HEYDY L. GONZALEZ-ARRIAZA
Drs. Krahn and Gonzalez-Arriaza Reply

ERLEND HEM, TOR HALDORSEN, OLAF GJERLØW AASLAND, REIDAR TYSSEN, PER VAGLUM, and ØIVIND EKEBERG
Suicide Among Physicians

Book Forum:

LAURA A. FLASHMAN
Mechanisms of Memory

MING T. TSUANG
Psychiatric Genetics and Genomics

RICHARD R.J. LEWINE
Unity in Psychology: Possibility or Pipedream?

C. ROBERT SHOWALTER
Law and Mental Health Professionals: Kentucky
WILLIAM H. SLEDGE

Ethics in Electroconvulsive Therapy

JAMES ALLEN WILCOX and DJILLALI BOUDJENAH

Schizophrenia in Late Life: Aging Effects on Symptoms and Course of Illness

FÉLIX-ANTOINE BÉRUBÉ and MARC-ANDRÉ ROY

Dopamine in the Pathophysiology and Treatment of Schizophrenia: New Findings

 Corrections:

Correction

 Official Actions:

Highlights of the 2005 Annual Meeting
How a Cholinergic Boost Affects the Young and Old

Drugs that increase brain levels of the neurotransmitter acetylcholine can enhance cognitive functioning. Cholinergic enhancers are, in fact, the most used pharmacological therapy for patients with Alzheimer’s disease. In young adults asked to remember faces, these drugs increase activity in brain areas specific to visual processing and decrease activity in the prefrontal cortex, where information is maintained and manipulated. The activated brain regions are somewhat different in older adults. Freo et al. (p. 2061) examined whether the brains of young and old adults would respond differently to physostigmine, a cholinergic-enhancing drug, during an exercise involving short-term memory of faces. Without physostigmine, task-related activation occurred in different prefrontal subregions in old and young subjects. Physostigmine reduced activation in these age-specific areas, enhanced activity in visual cortical areas, and improved task performance. Apparently, structural and functional changes during aging can shape the way a drug affects the brain.

Voting Capacity in Alzheimer’s Disease

Many people with diagnosed dementia are still capable of voting. In Doe v. Row, a federal district court ruled that people are incompetent to vote only if they “lack the capacity to understand the nature and effect of voting such that they cannot make an individual choice.” Appelbaum et al. (p. 2094) developed a short test containing three questions assessing the Doe criteria—understanding and choice—and two questions assessing reasoning and appreciation of what voting signifies. The test was administered to 33 people with Alzheimer’s disease. Higher scores on the three Doe questions were associated with better performance on a test of cognitive functioning. Participants with mild dementia had high scores, people with severe dementia had low scores, and people with moderate dementia varied. The reasoning and appreciation questions yielded similar findings but were more demanding than the Doe court’s criteria. The questions based on the Doe standard appear to be an efficient screening tool.

Gene Hunters Target Persecutory Delusions

Both schizophrenia and bipolar disorder show associations with the DA0A/G30 gene locus on chromosome 13. Given the apparent role of DA0A/G30 in the neurochemistry of psychosis, Schulze et al. (p. 2101) postulated that this locus could be associated with psychotic symptoms, rather than the diagnostic categories. Among 300 German patients with bipolar disorder, specific psychotic features were tested individually; persecutory delusions emerged as the only significant discriminatory variable for the risk genotype. This finding was replicated in an independent sample of Polish patients with bipolar disorder, who did not show an overall association with the DA0A/G30 locus but did so when only the cases with a history of persecutory delusions were considered. The consistency of this genetic association illustrates the value of refining patient symptom profiles to produce more phenotypically homogeneous samples.

Early Neuronal Damage in Bipolar Disorder

In many adults with bipolar disorder, the dorsolateral region of the prefrontal cortex has low levels of N-acetylaspartate, which is an indicator of neuronal health. This could be the result of long-term medication, however. Children and adolescents with bipolar disorder have taken less psychoactive medication than adults and provide a glimpse into brain functioning early in the disease. Sass et al. (p. 2109) used magnetic resonance spectroscopy to measure three metabolites in the dorsolateral prefrontal cortex of 14 bipolar subjects ages 10–21 years and 18 healthy subjects. The levels of N-acetylaspartate were lower in the bipolar subjects than in the healthy subjects. This supports the presence of prefrontal neuronal abnormality early in bipolar disorder. It could be due to underdevelopment of neuronal branching and synaptic connections; long-term degeneration seems unlikely in these young patients.

Lithium or Divalproex: Which Sustains Stability Better?

Poor response to lithium is common among patients with bipolar disorder whose episodes alternate rapidly. Divalproex has been effective in short-term maintenance treatment of this condition, and so Calabrese et al. (p. 2152) compared it to lithium in a 20-month maintenance trial. Patients with rapid-cycling bipolar disorder were first stabilized with a combination of lithium and divalproex sodium over 6 months. Then one medication was withdrawn. The relapse rates during the subsequent 20-month trial did not differ significantly between the groups taking divalproex (50%) and lithium (56%), nor did the intervals of stability preceding relapse. Lithium produced higher rates of tremors and polyuria or polydipsia. The overall rates of study discontinuation were 71% and 84% for divalproex and lithium, respectively, which suggest that single-agent therapy for rapid-cycling bipolar disorder is likely to have a poor outcome.
The Neuropsychiatry of Aging

Thou hast nor youth nor age;
But, as it were, an after-dinner's sleep,
Dreaming on both; for all thy blessed youth
Becomes as aged and doth beg the alms
Of palsied eld; and when though art old and rich,
Thou has neither heat, affection, limb nor beauty
To make thy riches pleasant.

—Shakespeare, Measure for Measure

Many questions face our field as we anticipate the impending exponential growth of our elder population. How do we draw distinctions between normal aging and age-related diseases on the moving landscape of physiologic change over time? How do we become experts in the neurobiology of aging to ensure a better quality of life for the oldest old? In a world of tertiary and quaternary care centers, do we risk losing the primary care perspective on the circle of life? Is it possible that some conditions at the end of life reflect developmental stages that cannot respond to interventions any more than an edentulous neonate could respond to dentures? On the more positive side, how can we capitalize on the beneficial attributes of aging, i.e., the wisdom and philosophical perspective that only years of experience can bestow?

Three articles in this issue of the Journal address diverse topics in the trajectory of aging, ranging from the mechanisms of neural activity to the estimation of decisional capacity. In this issue, we find a report on the age-related differences in modulation of prefrontal cortical cerebral blood flow, a report on the functional neuroanatomy of paired associate learning among patients with Alzheimer’s disease, and a report addressing one of the highest levels of cognitive functioning in the real-world setting, i.e., the capacity to vote among persons with Alzheimer’s disease. The scope of these articles reflects the range of topics on aging that will assume great importance in the next several decades.

In the first of these articles, Freo and colleagues used $^{[15}O\text{H}_2\text{O}$ positron emission tomography to assess regional cerebral blood flow (rCBF) during a cholinergic challenge to understand the relative contribution of disrupted cholinergic function to late-life cognitive decline. Regional blood flow during a working memory task in younger and older adults was compared after an intravenous dose of phystostigmine. The phystostigmine was observed to significantly improve working memory performance in both age groups. It was further noted that the prefrontal regions demonstrating increased blood flow during the placebo condition showed significantly lower rCBF during the physostigmine condition in both groups. Notably, there were differences in the younger versus older groups in the location of rCBF changes, i.e., increased rCBF during placebo was observed in the right middle and inferior frontal cortex in the younger subjects but the older individuals demonstrated increased blood flow in the anterior and ventral prefrontal regions. The authors noted that the two groups showed brain regions that were commonly modulated, as well as areas that were differentially affected by cholinergic potentiation. This work raises important questions as to whether recruitment of...
more dispersed areas of the prefrontal cortex with aging may represent an adaptive response compensating for functional losses. Furthermore, this adaptation may then have implications for regions of interest in pharmacological interventions that do not necessarily fall within the anticipated structural regions associated with a given disease. The implications of this work highlight the importance of distinguishing neural adaptations from pathological changes in the pursuit of appropriate interventions that may seek either to support beneficial functional adaptations or reduce any deviations from the optimal function observed in younger adults.

It is precisely this type of research that challenges the field to define “disease” within an aging population. Temple et al. (1) commented that

Disease is a state that places individuals at increased risk of adverse consequences. Treatment is given to those with a disease to prevent or ameliorate adverse consequences. The key element in this definition is risk: deviations from normal that are not associated with risk should not be considered synonymous with disease.

As we look toward advances in genetic research, this distinction becomes ever more complex. For example, the study of polymorphic variations in genes may identify specific genotypes that represent a risk for morbidity but may or may not ultimately lead to the outcome of disease. In the development of interventions that seek to prophylactically treat high-risk conditions based on genetic information, we are now blurring the boundaries of disease and risk factors. When the focus of intervention may be simple age-related functional changes, we are further blurring the distinctions between normal physiological variation and disease.

The article by Gould et al. in this issue addresses the problem of how to estimate differences in functional imaging among persons with Alzheimer’s disease when task performance and effort during a functional imaging procedure may differ markedly from healthy subjects. This study used functional magnetic resonance imaging to assess performance on a visuospatial paired associate learning task after controlling the estimated task difficulty such that patients and comparison subjects performed at the same relative levels of effort. These investigators observed blood-oxygen-level-dependent (BOLD) responses in frontal-parietal and occipital regions during successful associative learning in both groups. With increasing task difficulty, linear increases in occipital-parietal regions were noted during encoding and retrieval, but these did not differ markedly between the patients and the comparison subjects. The authors concluded that similar brain activations occur during successful paired associate learning in patients with Alzheimer’s disease and comparison subjects, providing that the subjects were able to conduct the tasks with approximated levels of task difficulty. This article reveals another example of the complexities associated with estimating compromised neural activity and how task performance and task difficulty may significantly contribute to variance in these estimations. It was observed that lateral and medial parietal regions displayed greater BOLD activation in the patients during encoding and retrieval, which may have reflected additional recruitment of regions that were noted in healthy subjects to be activated during visuospatial paired associate learning. Again, this was thought to reflect a possible adaptive mechanism employed by patients to compensate for disease-related neuropathology. Functional changes that represent adaptation to disease may be difficult to distinguish from direct disease-related pathology. However, this distinction may be critically important as we seek to take future steps in mapping the treatment effects of various interventions.

In a third article on age-related conditions, Appelbaum and colleagues examined arguably the highest level of executive functioning in public life: the act of voting for political leaders and policy. The authors used a competence assessment tool for voting among persons with Alzheimer’s disease based on the elements of understanding the nature of voting, the ability to make a choice, and measures of appreciation and reason-
ing. It was observed that voting capacity performance correlated strongly with Mini-
Mental State Examination scores. Overall, this study found that patients with milder
conditions generally displayed adequate performance on capacity measures, whereas
those with moderate disease were more variable, and persons with severe dementia
generally did not demonstrate an adequate capacity to vote.

Of interest, the competence assessment tool for voting (CAT-V) was derived in part
from the Doe criteria, the result of a federal court decision in Maine—Doe v. Rowe—in
which persons under guardianship due to chronic mental illness contested their auto-
matic exclusion from voting. The court proposed criteria that permitted voting, pro-
vided that the individual did not lack the ability to understand the nature of voting or
lack the ability to make an individual choice. Hence, the result of this decision was to fa-
cilitate voting in a class of citizens who were previously excluded by a provision in
Maine’s constitution. In contrast, as suggested here, the use of tools such as the CAT-V
may effect the opposite result, i.e., they may serve to reduce voting within a group of cit-
izens who are no longer capable. As mentioned by the authors, the increasing number
of elderly persons with dementia, combined with a high rate of voting among older
groups, suggests that “further refinement of approaches to identifying potential voters
with inadequate capacity will become increasingly important to our electoral system.”
Without question, this area begs for much additional research and careful thought, par-
ticularly in view of potential misuse of such tests in populations of any age. In taking the
brave step of raising this issue, the authors opened the door to a host of questions with
significant ethical implications.

Whether the issue is voting, neural activation, or cerebral blood flow, the challenges
ahead lie in separating the aspects of aging that require only simple monitoring from
aspects that require intervention or other decisive actions to protect the patient or soci-
ety. With our increasing awareness of the multiple factors that converge in the develop-
ment of dementia (2), it is clear that the continuum of neurodegeneration will only be-
come more of a continuum as we parse smaller and smaller measures of change.
Progress in mapping brain function combined with an awareness that the experience of
dementia is closely tied to sociocultural influences (3) lends itself to an unlimited num-
ber of important questions and challenges for future research as we try, possibly to no
avail, to discern the lines between aging and age-related disease. Perhaps the best guid-
ance in this endeavor will come from retaining the bigger picture as a backdrop, i.e., the
circle of life.

HERE I am, an old man in a dry month,
Being read to by a boy, waiting for rain.

—T.S. Eliot, “Gerontion”

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808
25:111–124
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Reviews and Overviews

Systematic Review of Psychological Approaches to the Management of Neuropsychiatric Symptoms of Dementia

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Cornelius Katona, M.D., F.R.C.Psych.
Joni Paton, B.Sc.
Constantine G. Lyketsos, M.D., M.H.S.
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Objective: The authors systematically reviewed the literature on psychological approaches to treating the neuropsychiatric symptoms of dementia.

Method: Reports of studies that examined effects of any therapy derived from a psychological approach that satisfied prespecified criteria were reviewed. Data were extracted, the quality of each study was rated, and an overall rating was given to each study by using the Oxford Centre for Evidence-Based Medicine criteria.

Results: A total of 1,632 studies were identified, and 162 satisfied the inclusion criteria for the review. Specific types of psychoeducation for caregivers about managing neuropsychiatric symptoms were effective treatments whose benefits lasted for months, but other caregiver interventions were not. Behavioral management techniques that are centered on individual patients’ behavior or on caregiver behavior had similar benefits, as did cognitive stimulation. Music therapy and Snoezelen, and possibly sensory stimulation, were useful during the treatment session but had no longer-term effects; interventions that changed the visual environment looked promising, but more research is needed.

Conclusions: Only behavior management therapies, specific types of caregiver and residential care staff education, and possibly cognitive stimulation appear to have lasting effectiveness for the management of dementia-associated neuropsychiatric symptoms. Lack of evidence regarding other therapies is not evidence of lack of efficacy. Conclusions are limited because of the paucity of high-quality research (only nine level-1 studies were identified). More high-quality investigation is needed.

Method

Search Strategy

We searched electronic databases through July 2003, reference lists from individual and review articles, and the Cochrane Library and sought expert knowledge of additional studies, even those published after July 2003. We also hand-searched the contents of three journals published during the 10-year period up to July 2003.

We used search terms encompassing individual dementias and interventions. We included studies with quantitative outcome measures that were either direct or proxy measures of neuropsychiatric symptoms (e.g., care costs, quality of life, institutionalization, and decreased medication or restraint). Studies of people without dementia, dementia secondary to head injury, or interventions that either involved medication or were not based on a psychological model (e.g., aromatherapy, homeopathy, occupational therapy, light therapy) were excluded.

Data Extraction Strategy

We used a tool adapted from a review of checklists (11). Ratings of the level of evidence were assigned to studies according to the Oxford Centre for Evidence-Based Medicine guidelines (http://www.cebm.net/levels_of_evidence.asp#levels). Levels of evidence grades ranged from 1 to 5, with lower numbers indicating higher quality. Each type of intervention was then given an overall “grade of recommendation” according to the Oxford Centre for Evidence-Based Medicine criteria. The grades ranged...
Results

We identified 1,632 references; 1,421 were excluded and 162 were included.

Reminiscence Therapy

Reminiscence therapy (Table 1) uses materials such as old newspapers and household items to stimulate memories and enable people to share and value their experiences. We identified five studies of reminiscence therapy interventions (12–16). Three were small randomized, controlled trials. One had 10 participants and reported behavioral improvements when reminiscence therapy was preceded by reality orientation, but not vice versa (13). The improvement was not clearly significant. The other two studies found no benefit of reminiscence therapy (14, 15). Two level-4 studies had small numbers (12, 16). One reported a significant improvement in mood, although the raters were not masked to participants’ treatment group (16).

- We assigned a grade of recommendation of D to reminiscence therapy.

Validation Therapy

Validation therapy (Table 1), rooted within the Rogerian humanistic psychology premise of individual uniqueness, is intended to give an opportunity to resolve unfinished conflicts by encouraging and validating expression of feel-

from A (consistent level of evidence grade of 1) to D (level of evidence grade of 5 or troublingly inconsistent or inconclusive studies at any level).

**TABLE 1. Studies of the Use of Reminiscence Therapy and Validation Therapy in the Management of Neuropsychiatric Symptoms of Dementia**

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomization</th>
<th>Comparison Group</th>
<th>Number of Patients</th>
<th>Number of Comparison Subjects</th>
<th>Therapeutic Regimen</th>
<th>Outcome</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brooker and Duce, 2000 (12)</td>
<td>No</td>
<td>Yes</td>
<td>25</td>
<td>Patients were their own comparison subjects.</td>
<td>Reminiscence therapy, group activities, or unstructured time</td>
<td>Reality orientation therapy or reminiscence therapy</td>
<td>Reminiscence therapy group had improved well-being (time of follow-up not reported).</td>
</tr>
<tr>
<td>Baines et al., 1987 (13)</td>
<td>Yes</td>
<td>Yes</td>
<td>10 (five received reality orientation therapy then reminiscence therapy, five received reminiscence therapy then reality orientation therapy)</td>
<td>5</td>
<td>Reality orientation therapy or reminiscence therapy</td>
<td>Improved behavior at 6-month follow-up in group that received reality orientation therapy then reminiscence therapy, compared to other group (significance not reported)</td>
<td>2b</td>
</tr>
<tr>
<td>Goldwasser et al., 1987 (14)</td>
<td>Yes</td>
<td>Yes</td>
<td>9 (reminiscence therapy), 9 (support)</td>
<td>9</td>
<td>Reminiscence therapy group or supportive group therapy</td>
<td>Reminiscence therapy improved depressed mood but had no effect on behavior at 5 weeks.</td>
<td>2b</td>
</tr>
<tr>
<td>Korb, 1997 (15)</td>
<td>Yes</td>
<td>Yes</td>
<td>10</td>
<td>Patients were their own comparison subjects</td>
<td>Eight sessions of reminiscence therapy or music therapy</td>
<td>Reminiscence therapy had no effect on mood.</td>
<td>2b</td>
</tr>
<tr>
<td>Haight et al., 2003 (16)</td>
<td>No</td>
<td>Yes</td>
<td>11</td>
<td>Reminiscence by life review</td>
<td>Significant improvement in carer-rated mood in intervention group at 2 months</td>
<td>Improvement in irritability scores</td>
<td>4</td>
</tr>
<tr>
<td>Babins, 1988 (17)</td>
<td>No</td>
<td>Yes</td>
<td>5</td>
<td>Not specified</td>
<td>22 validation therapy sessions</td>
<td>Improvement in behavior rating scales</td>
<td>4</td>
</tr>
<tr>
<td>Morton and Bleathman, 1991 (18)</td>
<td>No</td>
<td>Yes</td>
<td>5 single cases</td>
<td>Patients were their own comparison subjects.</td>
<td>20 weeks of validation therapy groups then 10 weeks of group work validation therapy group sessions</td>
<td>No change in depression, psychotropic use, or restraint use in validation therapy group</td>
<td>5</td>
</tr>
<tr>
<td>Toseland et al., 1997 (19)</td>
<td>Yes</td>
<td>Yes</td>
<td>31</td>
<td>57 (28 received social contact, 29 received usual care)</td>
<td>Validation therapy group sessions</td>
<td>No change in depression, psychotropic use, or restraint use in validation therapy group</td>
<td>2b</td>
</tr>
</tbody>
</table>

* Levels of evidence were rated according to Oxford Centre for Evidence-Based Medicine guidelines and ranged from 1 to 5, with lower numbers indicating higher quality. Lowercase letters (“a,” “b,” “c”), used to designate level 1, 2, and 3 studies, indicate finer-quality gradations, with a range from “a” (higher quality) to “c” (lower quality).
ings. We identified three studies of validation therapy. The first, a case series of five individuals, indicated an improvement in irritability after validation therapy (17). The second, which included five patients who served as their own comparison subjects, reported no change in behavior (18). A randomized, controlled trial compared validation therapy and reality orientation therapy in the management of neuropsychiatric symptoms of dementia.

### TABLE 2. Studies of the Use of Reality Orientation Therapy in the Management of Neuropsychiatric Symptoms of Dementia

<table>
<thead>
<tr>
<th>Author</th>
<th>Randomization</th>
<th>Comparison Group</th>
<th>Number of Patients</th>
<th>Number of Comparison Subjects</th>
<th>Therapeutic Regimen</th>
<th>Outcome</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baines et al., 1987 (13)</td>
<td>Yes</td>
<td>Yes</td>
<td>10 (five received</td>
<td>5</td>
<td>Real orientation therapy or reminiscence therapy</td>
<td>Improved behavior at 6-month follow-up in group that received reality orientation therapy, compared to other group (significance not reported)</td>
<td>2b</td>
</tr>
<tr>
<td>Baldelli et al., 1993 (20)</td>
<td>No</td>
<td>Yes</td>
<td>23 (including comparison subjects)</td>
<td>9</td>
<td>Reality orientation therapy group</td>
<td>Decreased depression in reality orientation therapy group</td>
<td>4</td>
</tr>
<tr>
<td>Brook et al., 1975 (21)</td>
<td>No</td>
<td>Yes</td>
<td>9</td>
<td>9</td>
<td>Reality orientation therapy group sessions</td>
<td>Experimental groups showed improvement in scores on a nonstandard social functioning scale.</td>
<td>3b</td>
</tr>
<tr>
<td>Greene et al., 1979 (22)</td>
<td>No</td>
<td>No</td>
<td>3 single cases</td>
<td>0</td>
<td>Reality orientation therapy sessions</td>
<td>Some improvement in behavior (type not specified)</td>
<td>5</td>
</tr>
<tr>
<td>Greene et al., 1983 (23)</td>
<td>No</td>
<td>Yes</td>
<td>20</td>
<td>Patients were their own comparison subjects.</td>
<td>Reality orientation therapy (two 30-minute sessions 2–3 days a week)</td>
<td>Significant improvement in mood of patients at the end of the orientation phase</td>
<td>4</td>
</tr>
<tr>
<td>Hanley et al., 1981 (24)</td>
<td>Yes</td>
<td>Yes</td>
<td>28</td>
<td>29</td>
<td>Classroom reality orientation therapy; ward orientation training</td>
<td>No behavioral change in either group</td>
<td>2b</td>
</tr>
<tr>
<td>Ishizaki et al., 2000 (25)</td>
<td>No</td>
<td>No</td>
<td>6</td>
<td>0</td>
<td>Reality orientation therapy group sessions (3 hours/week for 3 months)</td>
<td>No change in behavior</td>
<td>4</td>
</tr>
<tr>
<td>Johnson et al., 1981 (26)</td>
<td>No</td>
<td>Yes</td>
<td>75</td>
<td>23</td>
<td>Standard classroom reality orientation therapy presented once daily in groups, twice daily in groups, or once daily individually</td>
<td>All groups showed the improvement in nonstandardized scores, relative to untreated comparison group</td>
<td>4</td>
</tr>
<tr>
<td>Metitieri et al., 2001 (27)</td>
<td>No</td>
<td>Yes</td>
<td>46</td>
<td>28</td>
<td>Reality orientation therapy sessions (8–40 weeks)</td>
<td>Reality orientation therapy patients remained at home significantly longer than comparison patients</td>
<td>4</td>
</tr>
<tr>
<td>Reeve and Ivison, 1985 (28)</td>
<td>No</td>
<td>Yes</td>
<td>10</td>
<td>8</td>
<td>Classroom reality orientation therapy, modified informal reality orientation therapy, environmental manipulation</td>
<td>Combined environmental manipulation and informal reality orientation therapy improved behavioral symptoms; effects of combined therapy lasted up to 3 months.</td>
<td>4</td>
</tr>
<tr>
<td>Panella et al., 1984 (29)</td>
<td>No</td>
<td>No</td>
<td>69</td>
<td>0</td>
<td>Reality orientation therapy, validation therapy, family support, recreation therapy</td>
<td>Reduced institutionalization</td>
<td>4</td>
</tr>
</tbody>
</table>

* Levels of evidence were rated according to Oxford Centre for Evidence-Based Medicine guidelines and ranged from 1 to 5, with lower numbers indicating higher quality. Lowercase letters (“a,” “b,” “c”), used to designate level 1, 2, and 3 studies, indicate finer-quality gradations, with a range from “a” (higher quality) to “c” (lower quality).
apy to usual care or a social contact group in 88 patients with dementia (19). Although at 1-year follow-up the nursing staff thought the validation therapy group improved, there was no difference in independent outcome ratings, in nursing time needed, or in use of psychotropic medication and restraint.

- Because of the absence of conclusive evidence, we assigned a grade of recommendation of D to validation therapy.

**Reality Orientation Therapy**

Reality orientation therapy (Table 2) is based on the idea that impairment in orientating information (day, date, weather, time, and use of names) prevents patients with dementia from functioning well and that reminders can improve functioning. Eleven studies assessed reality orientation therapy (13, 20–29). The strongest randomized, controlled trial, which had 57 participants, showed no immediate benefit of reality orientation therapy, compared to active ward orientation (24). In a smaller randomized, controlled trial (N=10), patients who received reality orientation therapy followed by reminiscence therapy had fewer neuropsychiatric symptoms, compared to patients who received the treatments in the reverse order (13). The other smaller nonrandomized, controlled trials mostly found benefits in the reality orientation therapy groups in terms of improved mood, decreased neuropsychiatric symptoms, or delayed institutionalization.

- The grade of recommendation for reality orientation therapy is D.

**Cognitive Stimulation Therapy**

Cognitive stimulation therapy (Table 3), derived from reality orientation therapy, uses information processing rather than factual knowledge to address problems in functioning in patients with dementia. Three of four randomized, controlled trials of cognitive stimulation therapy (31, 32, 34, 35) showed some positive results, although the studies used different follow-up endpoints (immediately after therapy to 9 months after therapy). There were early behavior improvements, relative to waiting list. By 9 months, no significant difference between groups was

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**TABLE 3. Studies of the Use of Cognitive Stimulation and Other Dementia-Specific Therapies in the Management of Neuropsychiatric Symptoms of Dementia**

<table>
<thead>
<tr>
<th>Author</th>
<th>Randomization</th>
<th>Comparison Group</th>
<th>Number of Patients</th>
<th>Number of Comparison Subjects</th>
<th>Therapeutic Regimen</th>
<th>Outcome</th>
<th>Level of Evidencea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitchell and Maercklein, 1996 (30)</td>
<td>Yes</td>
<td>Yes</td>
<td>15</td>
<td>15</td>
<td>Five half-hour sessions with individualized special instruction</td>
<td>No significant deterioration in intervention group</td>
<td>4</td>
</tr>
<tr>
<td>Quayhagen et al., 1995 (31)</td>
<td>Yes</td>
<td>Yes</td>
<td>25</td>
<td>28</td>
<td>12 weekly in-home cognitive stimulation therapy sessions</td>
<td>No significant differences in behavioral symptoms across interventions</td>
<td>2b</td>
</tr>
<tr>
<td>Quayhagen et al., 2000 (32)</td>
<td>Yes</td>
<td>Yes</td>
<td>88 (21) in cognitive stimulation group, 29 in counseling group, 22 in seminar group, 16 in day-care group</td>
<td>15</td>
<td>8-week reality orientation therapy program</td>
<td>No significant differences in behavioral symptoms across interventions</td>
<td>4</td>
</tr>
<tr>
<td>Romero and Wenz, 2001 (33)</td>
<td>No</td>
<td>Yes</td>
<td>43 (number of patients in each group was not specified)</td>
<td>43</td>
<td>3-week inpatient program of self-maintenance therapy</td>
<td>Significant decrease in depression and behavioral symptoms</td>
<td>4</td>
</tr>
<tr>
<td>Spector et al., 2001 (34)</td>
<td>Yes</td>
<td>Yes</td>
<td>17</td>
<td>15</td>
<td>14 cognitive stimulation sessions</td>
<td>Significant decrease in depression</td>
<td>2b</td>
</tr>
<tr>
<td>Spector et al., 2003 (35)</td>
<td>Yes</td>
<td>Yes</td>
<td>115</td>
<td>86</td>
<td>Improvement in quality of life (more improvement in women than in men)</td>
<td></td>
<td>1b</td>
</tr>
</tbody>
</table>

a Levels of evidence were rated according to Oxford Centre for Evidence-Based Medicine guidelines and ranged from 1 to 5, with lower numbers indicating higher quality. Lowercase letters (“a,” “b,” “c”), used to designate level 1, 2, and 3 studies, indicate finer-quality gradations, with a range from “a” (higher quality) to “c” (lower quality).
TABLE 4. Studies of the Use of Non-Dementia-Specific Psychological Therapies in the Management of Neuropsychiatric Symptoms of Dementia

<table>
<thead>
<tr>
<th>Evidence Level and Study</th>
<th>Randomization</th>
<th>Comparison Group</th>
<th>Number of Patients</th>
<th>Number of Comparison Subjects</th>
<th>Therapeutic Regimen</th>
<th>Outcome</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beck et al., 2002 (36)</td>
<td>Yes</td>
<td>Yes</td>
<td>89</td>
<td>54 (30 received placebo, 24 received no intervention)</td>
<td>Behavioral management techniques, including behavioral intervention during activities of daily living or activity or both</td>
<td>No reduction in disruptive behavior.</td>
<td>2b</td>
</tr>
<tr>
<td>Benedict et al., 2000 (37)</td>
<td>Yes</td>
<td>Yes</td>
<td>8</td>
<td>7</td>
<td>Behavioral management techniques/supportive psychotherapy, including education, social skills training, identification of abnormal behavior</td>
<td>Behavioral management techniques reduced social aggression and disinhibition. No effect on depression was found.</td>
<td>2b</td>
</tr>
<tr>
<td>DeYoung et al., 2002 (38)</td>
<td>No</td>
<td>Yes</td>
<td>32</td>
<td>Patients were their own comparison subjects.</td>
<td>Behavior management unit with behavior management program</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Hoeffer et al., 1997 (39)</td>
<td>No</td>
<td>Yes</td>
<td>10</td>
<td>Patients were their own comparison subjects.</td>
<td>Behavioral management techniques, including functional analysis of bathing and person-centered bathing (individualized bathing routines based on the patient’s preferences)</td>
<td>Reduced aggressive, agitated, or disruptive behaviors at 6 months</td>
<td>4</td>
</tr>
<tr>
<td>Mishara, 1978 (40)</td>
<td>No</td>
<td>Yes</td>
<td>40</td>
<td>Patients were their own comparison subjects.</td>
<td>Behavioral management techniques (token economy) (behavior before intervention compared with behavior after intervention)</td>
<td>Intervention reduced bizarre behaviors after 6 months, compared to preintervention period, but was less effective than general milieu treatment. Significant reduction in agitation scores with behavioral management, compared to usual care alone</td>
<td>2b</td>
</tr>
<tr>
<td>Rogers et al., 1999 (41)</td>
<td>No</td>
<td>Yes</td>
<td>84</td>
<td>Patients were their own comparison subjects.</td>
<td>Behavioral management techniques, including usual care, skill elicitation, habit training for activities of daily living tasks (dressing)</td>
<td>Significant reduction in agitation scores with behavioral management, compared to usual care alone</td>
<td>4</td>
</tr>
<tr>
<td>Suhr et al., 1999 (42)</td>
<td>Yes</td>
<td>Yes</td>
<td>17</td>
<td>17</td>
<td>Behavioral management techniques, including progressive muscle relaxation</td>
<td>Significant reduction in behavioral symptoms with behavioral management, compared to usual care</td>
<td>2b</td>
</tr>
<tr>
<td>Teri et al., 1997, 1994 (43, 44)</td>
<td>Yes</td>
<td>Yes</td>
<td>42</td>
<td>30</td>
<td>Behavioral management techniques, including behavior therapy emphasizing pleasant events (manual-guided intervention for patient and care) or behavior therapy emphasizing problem solving (care only)</td>
<td>Significant reduction in depression for both groups immediately after intervention and at 6-month follow-up</td>
<td>1b</td>
</tr>
<tr>
<td>Welden and Yesavage, 1982 (45)</td>
<td>No</td>
<td>Yes</td>
<td>24</td>
<td>24</td>
<td>Behavioral management techniques, including progressive muscle relaxation and imaging</td>
<td>Significant reduction in behavioral symptoms</td>
<td>4</td>
</tr>
</tbody>
</table>

(continued)
TABLE 4. Studies of the Use of Non-Dementia-Specific Psychological Therapies in the Management of Neuropsychiatric Symptoms of Dementia (continued)

<table>
<thead>
<tr>
<th>Evidence Level and Study</th>
<th>Randomization</th>
<th>Comparison Group</th>
<th>Number of Patients</th>
<th>Number of Comparison Subjects</th>
<th>Therapeutic Regimen</th>
<th>Outcome</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alexopoulos, 1994 (46)</td>
<td>No</td>
<td>No</td>
<td>1</td>
<td>Patient was own comparison subject.</td>
<td>Behavioral management techniques, including written cue with spaced retrieval</td>
<td>Sexually disinhibited behavior disappeared</td>
<td>5</td>
</tr>
<tr>
<td>Bakke et al., 1994 (47)</td>
<td>No</td>
<td>Yes</td>
<td>1</td>
<td>Patient was own comparison subject.</td>
<td>Cognitive behavior therapy, including functional analysis of behavior then behavioral reinforcement</td>
<td>Reduced agitation during intervention period</td>
<td>5</td>
</tr>
<tr>
<td>Birchmore and Clague, 1983 (48)</td>
<td>No</td>
<td>Yes</td>
<td>5 single cases</td>
<td>Patients were their own comparison subjects.</td>
<td>Individualized behavioral management programs using fading cues and spaced retrieval</td>
<td>Four of five patients showed “adaptive behavior change.” Effects were not long-lasting. Reduced aggressive behaviors</td>
<td>5</td>
</tr>
<tr>
<td>Bird et al., 1994 (49)</td>
<td>No</td>
<td>Yes</td>
<td>2 single cases</td>
<td>Patients were their own comparison subjects.</td>
<td>Behavioral reinforcement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buchanan and Fisher, 2002 (51)</td>
<td>No</td>
<td>Yes</td>
<td>2 single cases</td>
<td>Patients were their own comparison subjects.</td>
<td>Behavioral management techniques, including functional assessment of disruptive vocalizations followed by noncontingent reinforcement</td>
<td>Significant reduction in disruptive vocalizations</td>
<td>5</td>
</tr>
<tr>
<td>Carpenter et al., 2003 (52)</td>
<td>No</td>
<td>Yes</td>
<td>3</td>
<td>Patients were their own comparison subjects.</td>
<td>Behavioral management techniques, including 16 sessions of restore-empower-mobilize psychotherapy</td>
<td>Depression reduced immediately after intervention but increased at follow-up</td>
<td>5</td>
</tr>
<tr>
<td>Doyle et al., 1997 (53)</td>
<td>No</td>
<td>Yes</td>
<td>7 single cases</td>
<td>Patients were their own comparison subjects.</td>
<td>Behavioral management techniques, including reinforcement of quiet behavior and stimulation</td>
<td>Three of seven patients improved.</td>
<td>5</td>
</tr>
<tr>
<td>Heard and Watson, 1999 (54)</td>
<td>No</td>
<td>Yes</td>
<td>4 single cases</td>
<td>Patients were their own comparison subjects.</td>
<td>Individual behavioral intervention programs</td>
<td>Individualized interventions reduced wandering</td>
<td>5</td>
</tr>
<tr>
<td>Jozsvai et al., 1996 (55)</td>
<td>No</td>
<td>Yes</td>
<td>1</td>
<td>Patient was own comparison subject.</td>
<td>Behavioral management techniques, including a token economy</td>
<td>Intervention reduced but did not extinguish target behaviors</td>
<td>5</td>
</tr>
<tr>
<td>Kipling et al., 1999 (56)</td>
<td>No</td>
<td>Yes</td>
<td>3</td>
<td>Patients were their own comparison subjects.</td>
<td>Group cognitive behavior therapy</td>
<td>Reduced anxiety in all three patients, improved mood in two patients</td>
<td>5</td>
</tr>
<tr>
<td>Koder, 1998 (57)</td>
<td>No</td>
<td>No</td>
<td>2 single cases</td>
<td>Patients were their own comparison subjects.</td>
<td>Anxiety management using cognitive behavior therapy techniques</td>
<td>Mild behavioral change in both patients</td>
<td>5</td>
</tr>
<tr>
<td>Lundervold and Jackson, 1992 (58)</td>
<td>No</td>
<td>No</td>
<td>1</td>
<td>Patient was own comparison subject.</td>
<td>Behavioral management techniques, including applied behavior analysis (conducted by staff)</td>
<td>Patient had lower number of aggressive episodes per month and was free of restraint 99% of time.</td>
<td>5</td>
</tr>
<tr>
<td>Moniz-Cook et al., 2001 (59)</td>
<td>No</td>
<td>No</td>
<td>5 single cases</td>
<td>Patients were their own comparison subjects.</td>
<td>Behavioral management techniques, including individualized functional analysis based on patient’s superstitions</td>
<td>Reduced agitation, aggression, refusal in all cases</td>
<td>5</td>
</tr>
<tr>
<td>Wisner and Green, 1986 (60)</td>
<td>No</td>
<td>Yes</td>
<td>1</td>
<td>Patient was own comparison subject.</td>
<td>Cognitive behavior therapy (time-out, anger management, self-monitoring by patient)</td>
<td>Reduced “outbursts” during intervention</td>
<td>5</td>
</tr>
</tbody>
</table>

*Levels of evidence were rated according to Oxford Centre for Evidence-Based Medicine guidelines and ranged from 1 to 5, with lower numbers indicating higher quality. Lowercase letters (“a,” “b,” “c”), used to designate level 1, 2, and 3 studies, indicate finer-quality gradations, with a range from “a” (higher quality) to “c” (lower quality).
found. One study showed reduced depression, and another showed improvement in quality of life but not in mood (34, 35). The final study did not report whether the differences in behavior were significant (32).

- Given the mostly consistent evidence that cognitive stimulation therapy improves aspects of neuropsychiatric symptoms immediately and for some months afterward, our consensus is that the grade of recommendation is B, although the evidence is not consistent in all respects.

**Other Dementia-Specific Therapies**

We identified two other dementia-specific therapies (30, 33) (Table 3). The first, “individualized special instruction,” consisted of 30 minutes of focused individual attention and participation in an activity appropriate for each individual (30). The participants in the pilot randomized, controlled trial were their own waiting-list comparison subjects. During the intervention period, their behavior did not deteriorate, compared with deteriorating behavior before the intervention period.

The second dementia-specific therapy was “self-maintenance therapy,” which is intended to help the patient maintain a sense of personal identity, continuity, and coherence (33). This intervention incorporates techniques from validation, reminiscence, and psychotherapy. A 3-week admission of patients and caregivers to a specialist unit in which self-maintenance therapy was provided led to a significant decrease in depression and problematic behavior, compared to baseline. This outcome may have been partly attributable to the environment.

- These level-4 studies support a grade of recommendation of C for both interventions.

**Non-Dementia-Specific Therapies**

Twenty-five reports described use of non-dementia-specific psychological therapies for patients with dementia (36–60) (Table 4). Nearly all of the studies examined behavioral management techniques. In one large random-
ized, controlled trial, participants received either manual-guided treatment for the patient and caregiver or a problem-solving treatment for the caregiver only (43). The two interventions were equally successful in improving depressive symptoms immediately and at 6-month follow-up (43, 44). Two other small randomized, controlled trials also had positive results (37, 42). In one of those studies,

<table>
<thead>
<tr>
<th>Author</th>
<th>Randomization</th>
<th>Comparison Group</th>
<th>Number of Patients or Caregivers</th>
<th>Number of Comparison Subjects</th>
<th>Therapeutic Regimen</th>
<th>Outcome</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burgener et al., 1998 (68)</td>
<td>Yes</td>
<td>Yes</td>
<td>35</td>
<td>12</td>
<td>Caregiver education about dementia and how to change interaction with patient</td>
<td>No difference between groups in disruptive behavior at 6 months</td>
<td>2b</td>
</tr>
<tr>
<td>Marriott et al., 2000 (69)</td>
<td>Yes</td>
<td>Yes</td>
<td>14</td>
<td>28</td>
<td>Caregiver training in behavioral management techniques</td>
<td>Significant improvement in behavior in intervention group, relative to the comparison group, immediately after intervention but not at 3 months</td>
<td>2b</td>
</tr>
<tr>
<td>Eloniemi-Sulkava et al., 2001 (70)</td>
<td>Yes</td>
<td>Yes</td>
<td>43</td>
<td>43</td>
<td>Support for patients and caregivers (counseling, advocacy, training)</td>
<td>Reduced institutionalization during first 3 months, with decreasing benefit over time</td>
<td>1b</td>
</tr>
<tr>
<td>Ghatak, 1994 (71)</td>
<td>No</td>
<td>Yes</td>
<td>20</td>
<td>20</td>
<td>Caregiver training in awareness and problem solving</td>
<td>Significant difference between groups in patient behavior was reported (no figures reported)</td>
<td>4</td>
</tr>
<tr>
<td>Haupt et al., 2000 (72)</td>
<td>No</td>
<td>Yes</td>
<td>14</td>
<td>Patients were their own comparison subjects</td>
<td>Manual-guided group intervention with caregivers that included cognitive behavior therapy, modeling, knowledge dissemination, financial and social advice</td>
<td>Significant reduction in patient anxiety and agitation from pre- to postintervention; no change in other neuropsychiatric symptoms</td>
<td>4</td>
</tr>
<tr>
<td>Hebert et al., 2003 (73)</td>
<td>Yes</td>
<td>Yes</td>
<td>79</td>
<td>79</td>
<td>Psychoeducational group program</td>
<td>Frequency of behavior problems was reduced (difference approached significance). Reduction in depression, ideational disturbance, and agitation during family visits, reduced pacing, significant reduction in use of restraint at 6-month follow-up</td>
<td>2b</td>
</tr>
<tr>
<td>McCallion et al., 1999 (74)</td>
<td>Yes</td>
<td>Yes</td>
<td>32</td>
<td>34</td>
<td>Education program, caregiver groups, family conferences, family visit with feedback about interaction</td>
<td>Reduced behavioral problems in family support group after 7 months; no effects on mood</td>
<td>2b</td>
</tr>
<tr>
<td>Droes et al., 2000 (75)</td>
<td>No</td>
<td>Yes</td>
<td>33</td>
<td>23</td>
<td>Integrated family support program</td>
<td>Reduced behavioral problems in patients</td>
<td>4</td>
</tr>
<tr>
<td>Ferris et al., 1987 (76)</td>
<td>No</td>
<td>No</td>
<td>41</td>
<td>0</td>
<td>Family counseling sessions</td>
<td>Reduced behavioral problems in patients</td>
<td>4</td>
</tr>
<tr>
<td>Wells et al., 2000 (77)</td>
<td>Yes</td>
<td>Yes</td>
<td>12</td>
<td>20</td>
<td>Caregiver education in abilities-focused morning care of patient</td>
<td>Reduced agitation in intervention group at 6 months</td>
<td>2b</td>
</tr>
<tr>
<td>Mittelman et al., 1996 (78)</td>
<td>Yes</td>
<td>Yes</td>
<td>103</td>
<td>103</td>
<td>Six sessions of psychoeducation and problem solving plus support groups</td>
<td>Time to nursing home placement was 329 days longer in treatment group than in comparison group.</td>
<td>1b</td>
</tr>
<tr>
<td>Woods et al., 2003 (79)</td>
<td>No</td>
<td>Yes</td>
<td>55</td>
<td>73</td>
<td>Specialist “admiral” nurse service</td>
<td>No differences between groups</td>
<td>2c</td>
</tr>
</tbody>
</table>

* Levels of evidence were rated according to Oxford Centre for Evidence-Based Medicine guidelines and ranged from 1 to 5, with lower numbers indicating higher quality. Lowercase letters (“a,” “b,” “c”), used to designate level 1, 2, and 3 studies, indicate finer-quality gradations, with a range from “a” (higher quality) to “c” (lower quality).
TABLE 7. Studies of the Use of Music Therapy in the Management of Neuropsychiatric Symptoms of Dementia

<table>
<thead>
<tr>
<th>Author</th>
<th>Randomization</th>
<th>Comparison Group</th>
<th>Number of Patients</th>
<th>Number of Comparison Subjects</th>
<th>Therapeutic Regimen</th>
<th>Outcome</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashida, 2000</td>
<td>No</td>
<td>Yes</td>
<td>20</td>
<td>Patients were their own comparison subjects.</td>
<td>Group music therapy sessions</td>
<td>Reduced depressive symptoms during and after therapy, no lasting effect</td>
<td>4</td>
</tr>
<tr>
<td>Brotons and Pickett-Cooper, 1996</td>
<td>No</td>
<td>Yes</td>
<td>20</td>
<td>Patients were their own comparison subjects.</td>
<td>Five music therapy sessions</td>
<td>Reduced agitation during and after music therapy sessions</td>
<td>5</td>
</tr>
<tr>
<td>Casby and Holm, 1994</td>
<td>No</td>
<td>Yes</td>
<td>3</td>
<td>Patients were their own comparison subjects.</td>
<td>Classical or favorite music</td>
<td>Reduced disruptive vocalization in two patients</td>
<td>4</td>
</tr>
<tr>
<td>Clair and Bernstein, 1994</td>
<td>No</td>
<td>Yes</td>
<td>28</td>
<td>Patients were their own comparison subjects.</td>
<td>Comparison of no music, stimulating music, and sedative music during bath time</td>
<td>No significant reduction in agitation</td>
<td>4</td>
</tr>
<tr>
<td>Clark et al., 1998</td>
<td>Yes</td>
<td>Yes</td>
<td>19</td>
<td>Patients were their own comparison subjects.</td>
<td>Quiet music at mealtimes</td>
<td>Reduced agitation during therapy</td>
<td>4</td>
</tr>
<tr>
<td>Denney, 1997</td>
<td>No</td>
<td>Yes</td>
<td>9</td>
<td>Patients were their own comparison subjects.</td>
<td>Either music therapy or reading sessions</td>
<td>Increased sitting time during music, compared with during reading (no statistics provided)</td>
<td>5</td>
</tr>
<tr>
<td>Gardiner et al., 2000</td>
<td>No</td>
<td>Yes</td>
<td>2</td>
<td>Patients were their own comparison subjects.</td>
<td>Music therapy or reading sessions</td>
<td>Reduced disruptive behavior during music sessions</td>
<td>5</td>
</tr>
<tr>
<td>Gaebler and Hemsley, 1991 (88)</td>
<td>No</td>
<td>Yes</td>
<td>6</td>
<td>Patients were their own comparison subjects.</td>
<td>Reminiscence music therapy</td>
<td>Positive outcome for two of six patients</td>
<td>5</td>
</tr>
<tr>
<td>Gerdner, 2000</td>
<td>No</td>
<td>Yes</td>
<td>5</td>
<td>Patients were their own comparison subjects.</td>
<td>Individual music therapy program</td>
<td>Reduced agitation during therapy and in the hour after therapy</td>
<td>5</td>
</tr>
<tr>
<td>Gardiner and Swanson, 1993 (90)</td>
<td>Yes</td>
<td>Yes</td>
<td>39</td>
<td>39</td>
<td>Classical/individualized music therapy for 6 weeks</td>
<td>More reduction in agitation with individualized therapy (30 versus 10 minutes)</td>
<td>2b</td>
</tr>
<tr>
<td>Goddaer and Abraham, 1994 (91)</td>
<td>No</td>
<td>Yes</td>
<td>29</td>
<td>Patients were their own comparison subjects.</td>
<td>Relaxing music followed by no intervention or vice versa</td>
<td>Reduction in agitated behaviors with music, increase in agitated behaviors when music was removed</td>
<td>4</td>
</tr>
<tr>
<td>Groene, 1993</td>
<td>Yes</td>
<td>Yes</td>
<td>30</td>
<td>30</td>
<td>Two reading sessions plus five music sessions or vice versa</td>
<td>Increased time sitting still during mostly music versus mostly reading sessions</td>
<td>2b</td>
</tr>
<tr>
<td>Jennings and Vance, 2002 (93)</td>
<td>No</td>
<td>Yes</td>
<td>17</td>
<td>Patients were their own comparison subjects.</td>
<td>Weekly 30-minute group music session</td>
<td>Reduced agitation after session</td>
<td>4</td>
</tr>
<tr>
<td>Korb, 1997 (15)</td>
<td>Yes</td>
<td>Yes</td>
<td>10</td>
<td>Patients were their own comparison subjects.</td>
<td>30 minutes of music therapy (rhythm or singing) twice a week for 12 weeks or reminiscence therapy</td>
<td>Improved mood immediately after all music sessions, compared to reminiscence sessions</td>
<td>2b</td>
</tr>
<tr>
<td>Lindenmuth et al., 1992 (94)</td>
<td>No</td>
<td>Yes</td>
<td>10</td>
<td>10</td>
<td>Relaxing music played as participants went to sleep</td>
<td>Improved mood and social interaction better in music groups</td>
<td>4</td>
</tr>
<tr>
<td>Lord and Garner, 1993 (95)</td>
<td>Yes</td>
<td>Yes</td>
<td>20 (puzzle); 20 (standard treatment)</td>
<td>Patients were their own comparison subjects.</td>
<td>Big Band music, puzzle-play sessions, standard treatment</td>
<td>Mood and social interaction better in music groups</td>
<td>2b</td>
</tr>
</tbody>
</table>

(continued)
participants had significantly fewer neuropsychiatric symptoms 2 months after being taught progressive muscle relaxation. In the other study, the behavior of patients with the dementia of multiple sclerosis improved with “neuropsychological counseling” (a cognitive behavior intervention). There were two other randomized, controlled trials in which behavioral management techniques were used (36, 40); these techniques were ineffective in one of the studies (36). It used a complex, difficult-to-classify intervention, one after another, both interventions simultaneously and hand massage, both interventions being taught to caregivers with the aim of reducing “bizarre” behavior in patients with severe dementia, compared to a preintervention condition, but less effective than a milieu treatment (40). Several single-case studies are summarized in Table 4.

- The grade of recommendation for standard behavioral management techniques in dementia is B. The findings of the larger randomized, controlled trials were consistent and positive, and the effects lasted for months.

**Psychological Interventions With Caregivers**

Table 5 and Table 6 summarize 19 reports that describe interventions with family caregivers designed to ameliorate neuropsychiatric symptoms or frequency of institutionalization in dementia (61–79). Seven studies involved training the caregiver to use behavioral management techniques (Table 5). A randomized, controlled trial (65) found no difference in agitation or global outcome in a comparison of treatment with behavioral management techniques, haloperidol or trazodone alone, or placebo at 16 weeks. Behavioral management techniques taught to caregivers did not reduce psychotropic drug use or symptom frequency at 1-year follow-up (67). Exercise and behavioral management techniques based on the progressive Lowered Stress Threshold Model were taught to caregivers with the aim of reducing stimulation in response to specific stressors identified by caregivers (63). Both study groups received the intervention, one in the form of written materials, and the other in a training program. A positive effect for care recipients was found in the second group. The evidence that behavioral management techniques with caregivers and exercise training with patients helps depression is strong, but it is unclear which component was the active component.

- Because the findings of other studies are inconsistent, the grade of recommendation for teaching caregivers...
behavioral management techniques to manage psychosocial symptoms is D.

### TABLE 8. Studies of the Use of Sensory Stimulation in the Management of Neuropsychiatric Symptoms of Dementia

<table>
<thead>
<tr>
<th>Author</th>
<th>Randomization</th>
<th>Comparison Group</th>
<th>Number of Patients</th>
<th>Number of Comparison Subjects</th>
<th>Therapeutic Regimen</th>
<th>Outcome</th>
<th>Level of Evidencea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baker et al., 1997 (105)</td>
<td>Yes</td>
<td>Yes</td>
<td>31 in total (one-half of the group were comparison subjects)</td>
<td>31 (one-half of the group were comparison subjects)</td>
<td>Eight one-to-one sessions of Snoezelen or general activity conducted twice weekly</td>
<td>Reduction in socially disturbed behavior in Snoezelen group at home during period of treatment</td>
<td>2b</td>
</tr>
<tr>
<td>Baker et al., 2001 (104)</td>
<td>Yes</td>
<td>Yes</td>
<td>50 in trial, but not clear how many in each group</td>
<td>50 in trial, but not clear how many in each group</td>
<td>Snoezelen or general activity sessions</td>
<td>Improvement in mood and behavior in the Snoezelen group did not last to 1-month follow-up.</td>
<td>1b</td>
</tr>
<tr>
<td>Burgio et al., 1996 (109)</td>
<td>No</td>
<td>Yes</td>
<td>13</td>
<td>Patients were their own comparison subjects.</td>
<td>Exposure to white noise audiotapes during agitation</td>
<td>Significant reduction in agitation during white noise tapes</td>
<td>4</td>
</tr>
<tr>
<td>Hope, 1998 (108)</td>
<td>No</td>
<td>No</td>
<td>29</td>
<td>Exposure to multisensory environment</td>
<td>Positive mood when in multisensory environment (no statistics reported)</td>
<td>No changes</td>
<td>4</td>
</tr>
<tr>
<td>Kempenaar et al., 2001 (110)</td>
<td>Yes</td>
<td>Yes</td>
<td>16</td>
<td>Exposure to white noise audiotapes during agitation</td>
<td>Significant reduction in agitation during white noise tapes</td>
<td>No changes</td>
<td>4</td>
</tr>
<tr>
<td>Kim and Buschmann, 1999 (111)</td>
<td>No</td>
<td>Yes</td>
<td>29</td>
<td>Patients were their own comparison subjects.</td>
<td>Expressive touch for 5.5 minutes/day for 10 days</td>
<td>Improvement in behavior during intervention and for 5 days afterward</td>
<td>4</td>
</tr>
<tr>
<td>Remington, 2002 (98)</td>
<td>Yes</td>
<td>Yes</td>
<td>51</td>
<td>Exposure to white noise audiotapes during agitation</td>
<td>Calming music, hand massage, music followed by massage, or music and massage simultaneously for 10 minutes each</td>
<td>All experimental groups had reduced agitation, relative to the comparison group. Effect lasted for 1 hour.</td>
<td>2b</td>
</tr>
<tr>
<td>Robichaud et al., 1994 (112)</td>
<td>Yes</td>
<td>Yes</td>
<td>84</td>
<td>Three 45-minute sessions of sensory integration for 10 weeks</td>
<td>No significant reduction in disruptive behaviors immediately after treatment and no change in agitated behaviors</td>
<td>2b</td>
<td></td>
</tr>
<tr>
<td>Snyder et al., 1995 (113)</td>
<td>No</td>
<td>Yes</td>
<td>19</td>
<td>Patients were their own comparison subjects.</td>
<td>Hand massage, therapeutic touch, or a comparison condition in a crossover design</td>
<td>No change in agitated behaviors</td>
<td>4</td>
</tr>
<tr>
<td>Spaull and Leach, 1998 (106)</td>
<td>No</td>
<td>Yes</td>
<td>4</td>
<td>Patients were their own comparison subjects.</td>
<td>Snoezelen</td>
<td>Reduction in challenging behaviors after sessions; no difference in well-being scores</td>
<td>5</td>
</tr>
<tr>
<td>Van Diepen et al., 2002 (103)</td>
<td>Yes</td>
<td>Yes</td>
<td>5</td>
<td>Eight one-to-one twice weekly Snoezelen sessions</td>
<td>Agitation scores tended to be lower in the Snoezelen group.</td>
<td>2b</td>
<td></td>
</tr>
<tr>
<td>Young et al., 1988 (114)</td>
<td>Yes</td>
<td>Yes</td>
<td>8</td>
<td>Patients were their own comparison subjects.</td>
<td>White noise played at night</td>
<td>No immediate effect on sleep</td>
<td>2b</td>
</tr>
<tr>
<td>Wareing et al., 1998 (107)</td>
<td>No</td>
<td>Yes</td>
<td>4</td>
<td>Patients were their own comparison subjects.</td>
<td>Three weeks of three weekly Snoezelen sessions</td>
<td>Improved behavioral rating immediately after treatment and for 3 weeks posttreatment</td>
<td>5</td>
</tr>
</tbody>
</table>

(continued)
Table 6 summarizes the results of nine studies (seven randomized, controlled trials) involving psychoeducation to teach caregivers how to change their interactions with patients with dementia. In one large trial, improvement in neuropsychiatric symptoms at 16 weeks was found, but the difference only approached significance (73). In a second trial, primarily powered to improve mental health in caregivers rather than in patients, improvement in neuropsychiatric symptoms occurred immediately after 12 weeks of training in stress management, dementia education, and coping skills but was not maintained at 3-month follow-up (69). A third, smaller trial examining the effects of an intervention with individual families found significant improvements at 6 months in mood and ideational disturbance (74). In a randomized, controlled trial of an educational program for family carers that included supportive counseling, psychoeducation and training in management strategies, and home visits, the rate of institutionalization of patients was decreased (70). The effect continued for 3 months but not 2 years. A fifth randomized, controlled trial involved psychoeducation, instruction to caregivers in how to change their interactions with the patient, or both (68). Patients' behavior improved at 6 months, but the difference only approached significance. The researchers attributed the nonsignificant result to the fact that the trial was a pilot study that had limited power. Another study examined the effects of caregiver psychoeducation in working with nursing home residents to enhance social activities and self-care; the intervention resulted in a decrease in agitation after 6 months (77). Finally, a level-1 study investigated a comprehensive support and counseling intervention for spouse caregivers that included problem solving, management of troublesome behavior, education, and increased practical support, followed by long-term support groups (78). Patients' neuropsychiatric symptoms were not directly measured, but the intervention was found to delay time to institutionalization by nearly a year. The other studies were noncontrolled and showed either improvement that approached significance or significant improvement (71, 72).

- The grade of recommendation for behavioral management techniques in the form of psychoeducation and teaching caregivers how to change their interactions with patients is A, because evidence from level-1, level-2, and level-4 studies consistently supports these interventions, and the effects have been shown to last months.

An uncontrolled study suggested that family counseling is helpful in reducing institutionalization of patients (76). In a nonrandomized, controlled trial, a family support group resulted in a decrease in problem behavior but not in depression (75).

- The grade of recommendation for family counseling is C, because the intervention is supported by two level-4 studies.

A single controlled study compared the effects of “admiral” nurses—specialists in treatment of dementia who worked in the community with persons caring for patients with dementia—to those of usual treatment and showed no effect on institutionalization of patients (79).

- The grade of recommendation for caregiver support by specialist nurses in the community is D.

**Psychosocial Interventions**

**Sensory enhancement**

*Music/music therapy.* Music/music therapy interventions (Table 7) included playing music from specific eras or particular genres, such as Big Band music, as part of activity sessions or at certain times of day, including mealtimes or bath times. Participants also played musical instruments, moved to music, or participated in composition and improvisation sessions. Of 24 music/music therapy interventions (15, 80–102), six were investigated in randomized, controlled trials (15, 84, 89, 92, 95, 98). All were small trials and showed improvements in disruptive behavior. In two, behavior was observed during the music sessions, but there was no evidence that benefit carried over after the sessions (84, 92). In three studies, behavioral change was observed outside of the music/music therapy session. In the first study, patients were significantly less agitated, both during and immediately after music/music therapy in which the music was chosen to fit the individuals' preference (89). The results of the second study were similar (95). In the third
### TABLE 9. Studies of the Use of Simulated Presence Therapy and Therapeutic Activities in the Management of Neuropsychiatric Symptoms of Dementia

<table>
<thead>
<tr>
<th>Author</th>
<th>Randomization</th>
<th>Comparison Group</th>
<th>Number of Patients</th>
<th>Number of Comparison Subjects</th>
<th>Therapeutic Regimen</th>
<th>Outcome</th>
<th>Level of Evidencea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camberg et al., 1999 (117)</td>
<td>Yes</td>
<td>Yes</td>
<td>19</td>
<td>18 (placebo group), 18 (usual care group)</td>
<td>Simulated presence therapy for 17 days</td>
<td>No difference in agitated or withdrawn behaviors</td>
<td>2b</td>
</tr>
<tr>
<td>Miller et al., 2001 (118)</td>
<td>No</td>
<td>Yes</td>
<td>7</td>
<td>Patients were their own comparison subjects.</td>
<td>Modification of simulated presence therapy using audiotapes made by family members</td>
<td>Improved social interaction and attention-awareness during agitation after intervention</td>
<td>4</td>
</tr>
<tr>
<td>Woods and Ashley, 1995 (119)</td>
<td>No</td>
<td>No</td>
<td>27</td>
<td>Patients were their own comparison subjects.</td>
<td>Simulated presence therapy, with audiotapes when patient displayed agitation</td>
<td>Improvements in social isolation and agitation; no improvement in aggression</td>
<td>4</td>
</tr>
<tr>
<td>Woods and Ashley, 1995 (119)</td>
<td>No</td>
<td>Yes</td>
<td>9</td>
<td>Patients were their own comparison subjects.</td>
<td>Simulated presence therapy, with audiotapes played twice daily</td>
<td>Improvement in problem behaviors 91% of the time</td>
<td>4</td>
</tr>
<tr>
<td>Peak and Cheston, 2002 (120)</td>
<td>No</td>
<td>Yes</td>
<td>4 (single cases)</td>
<td>Patients were their own comparison subjects.</td>
<td>Simulated presence therapy, with audiotape played for 10 sessions</td>
<td>Results for four cases were inconsistent.</td>
<td>5</td>
</tr>
<tr>
<td>Hall, 1997 (121)</td>
<td>No</td>
<td>Yes</td>
<td>36</td>
<td>Patients were their own comparison subjects.</td>
<td>Simulated presence using videotape</td>
<td>Significant improvement in positive behaviors during and after video, but no differences in agitated behavior</td>
<td>4</td>
</tr>
<tr>
<td>Buettner and Fitzsimmons, 2002 (122)</td>
<td>Yes</td>
<td>Yes</td>
<td>35 in both groups in total; not clear how many in each group</td>
<td>35 in both groups in total; not clear how many in each group</td>
<td>Small-group discussion, then 15 minutes of biking (total of 1 hour a day, 5 days a week), followed by 10-week maintenance period that included biking twice a week</td>
<td>Significant reduction in depression at 10-week follow-up, no significant effects on agitation</td>
<td>2b</td>
</tr>
<tr>
<td>Fitzsimmons and Buettner, 2002 (123)</td>
<td>Yes</td>
<td>Yes</td>
<td>29</td>
<td>30</td>
<td>Therapeutic recreation activities</td>
<td>Significantly less agitation in activities group</td>
<td>2b</td>
</tr>
<tr>
<td>Ishizaki et al., 2002 (124)</td>
<td>No</td>
<td>Yes</td>
<td>14</td>
<td>11</td>
<td>Activity sessions at day-care center once a week</td>
<td>No change in depression</td>
<td>4</td>
</tr>
<tr>
<td>Kim et al., 2002 (125)</td>
<td>No</td>
<td>No</td>
<td>13</td>
<td>0</td>
<td>Day-care program (individualized and group interventions) for 10 weeks</td>
<td>Increase in agitation over 10-week period</td>
<td>4</td>
</tr>
<tr>
<td>Martichuski et al., 1996 (126)</td>
<td>No</td>
<td>Yes</td>
<td>51</td>
<td>Patients were their own comparison subjects.</td>
<td>Small-group activities led by nurses’ assistants once a week</td>
<td>No behavioral change, but reduction in use of physical restraint and in use of psychotropics in seven of 20 patients</td>
<td>4</td>
</tr>
<tr>
<td>Sival et al., 1997 (127)</td>
<td>No</td>
<td>Yes</td>
<td>3</td>
<td>Patients were their own comparison subjects.</td>
<td>Wide variety of activities</td>
<td>After intervention, one patient was better, one was worse, and one had no change.</td>
<td>5</td>
</tr>
</tbody>
</table>

(continued)
The grade of recommendation for music therapy for immediate amelioration of disruptive behavior is B, because consistent level-2 evidence suggests that music therapy decreases agitation during sessions and immediately after. There is, however, no evidence that music therapy is useful for treatment of neuropsychiatric symptoms in the longer term.

**Snoezelen therapy/multisensory stimulation.** Snoezelen therapy/multisensory stimulation (Table 8), which combines relaxation and exploration of sensory stimuli, such as lights, sounds, and tactile sensations, is based on the idea that neuropsychiatric symptoms may result from periods of sensory deprivation. Interventions occurred in specially designed rooms and lasted 30–60 minutes. Of six trials of Snoezelen therapy/multisensory stimulation, three were randomized, controlled trials. The first was a very small trial with no clear results (103). The other two found that disruptive behavior briefly improved outside the treatment setting but that there was no effect after the treatment had stopped (104, 105). The other reports described studies of individual cases (106, 107) and an uncontrolled trial in which improvements were found but no statistics were provided (108).

The grade of recommendation for Snoezelen for amelioration of disruptive behavior immediately after the intervention is B, on the basis of consistent evidence from level-2 studies. The effects are apparent only for a very short time after the session.

**Other sensory stimulation.** Of seven trials of other forms of sensory stimulation (Table 8), three were randomized, controlled trials. The first trial compared massage with a comparison condition, music, or a combination of massage and music (98). Decreased agitation was observed 1 hour after the intervention. The second trial examined a sensory integration program that emphasized bodily responses, sensory stimulation, and cognitive stimulation; this intervention had no effect on behavior (112). Similarly, a small randomized, controlled trial found that white noise had no effect on sleep disturbance and nocturnal wandering (114). An “expressive physical touch” intervention (5.5 minutes/day of touch) also failed to show beneficial effects (115).

### Table 9. Studies of the Use of Simulated Presence Therapy and Therapeutic Activities in the Management of Neuropsychiatric Symptoms of Dementia (continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Randomization</th>
<th>Comparison Group</th>
<th>Number of Patients</th>
<th>Number of Comparison Subjects</th>
<th>Therapeutic Regimen</th>
<th>Outcome</th>
<th>Level of Evidence&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snyder et al., 2001 (128)</td>
<td>No</td>
<td>Yes</td>
<td>18</td>
<td>Patients were their own comparison subjects.</td>
<td>20 minutes per day on the glider swing</td>
<td>Immediate significant increase in enjoyment; no change in aggression at 5 days</td>
<td>4</td>
</tr>
<tr>
<td>Lawton et al., 1998 (129)</td>
<td>Yes</td>
<td>Yes</td>
<td>49</td>
<td>48</td>
<td>Activity programming, staff training, interdisciplinary care planning, family support</td>
<td>No significant effects on behavior</td>
<td>2b</td>
</tr>
<tr>
<td>Panella et al., 1984 (29)</td>
<td>No</td>
<td>No</td>
<td>69</td>
<td>0</td>
<td>Reality orientation therapy, validation therapy, family support, recreation therapy</td>
<td>Reduced institutionalization</td>
<td>4</td>
</tr>
<tr>
<td>Fitzgerald-Cloutier, 1993 (86)</td>
<td>No</td>
<td>Yes</td>
<td>1</td>
<td>Patient was own comparison subject.</td>
<td>Either music therapy or reading activity sessions</td>
<td>Less time spent in repetitive motor activities</td>
<td>5</td>
</tr>
<tr>
<td>Gardiner et al., 2000 (87)</td>
<td>No</td>
<td>Yes</td>
<td>2</td>
<td>Patients were their own comparison subjects.</td>
<td>Music therapy or reading/book exploration sessions</td>
<td>Both patients improved with reading</td>
<td>5</td>
</tr>
<tr>
<td>Lord and Garner, 1993 (95)</td>
<td>Yes</td>
<td>Yes</td>
<td>20 (puzzle-play)</td>
<td>20</td>
<td>Music therapy, puzzle-play sessions, standard treatment</td>
<td>No effect of puzzle-play on behavior</td>
<td>2b</td>
</tr>
<tr>
<td>Baker et al., 1997 (105)</td>
<td>Yes</td>
<td>Yes</td>
<td>31 in total (one-half were comparison subjects)</td>
<td>31 in total (one-half were comparison subjects)</td>
<td>Snoezelen therapy/multisensory stimulation or general activity sessions</td>
<td>No effect of activity on behavior</td>
<td>2b</td>
</tr>
</tbody>
</table>

<sup>a</sup> Levels of evidence were rated according to Oxford Centre for Evidence-Based Medicine guidelines and ranged from 1 to 5, with lower numbers indicating higher quality. Lowercase letters ("a," "b," "c"), used to designate level 1, 2, and 3 studies, indicate finer-quality gradations, with a range from "a" (higher quality) to "c" (lower quality).
### TABLE 10. Studies of the Use of Other Structured Activity and Alteration of the Visual Environment in the Management of Neuropsychiatric Symptoms of Dementia

<table>
<thead>
<tr>
<th>Author</th>
<th>Randomization</th>
<th>Comparison Group</th>
<th>Number of Patients</th>
<th>Number of Comparison Subjects</th>
<th>Therapeutic Regimen</th>
<th>Outcome</th>
<th>Level of Evidencea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleary et al., 1988 (130)</td>
<td>No</td>
<td>Yes</td>
<td>11</td>
<td>Patients were their own comparison subjects.</td>
<td>Reduced stimulation unit, staff education</td>
<td>No reduction in agitation or change in medication but decreased restraint use</td>
<td>4</td>
</tr>
<tr>
<td>Cott et al., 2002 (131)</td>
<td>Yes</td>
<td>Yes</td>
<td>90</td>
<td>30</td>
<td>Walking/talking program Caregivers trained in Montessori activities</td>
<td>No significant behavioral changes No change in neuropsychiatric symptoms</td>
<td>1b</td>
</tr>
<tr>
<td>Gorrizelle et al., 2003 (132)</td>
<td>No</td>
<td>Yes</td>
<td>10</td>
<td>Patients were their own comparison subjects.</td>
<td>Psychomotor activation program</td>
<td>No overall effect on behavior</td>
<td>4</td>
</tr>
<tr>
<td>Hopman-Rock et al., 1999 (133)</td>
<td>Yes</td>
<td>Yes</td>
<td>72</td>
<td>62</td>
<td>Volunteer-led 90-minute outdoor walking sessions Weekly small-group activities run by nursing assistants</td>
<td>No difference in aggressive incidents</td>
<td>4</td>
</tr>
<tr>
<td>Holmberg, 1997 (134)</td>
<td>No</td>
<td>Yes</td>
<td>11</td>
<td>Patients were their own comparison subjects.</td>
<td>安静/行走活动</td>
<td>No behavioral changes, decrease in physical restraint in all facilities, decrease in use of psychotropics in seven of 20 patients</td>
<td>4</td>
</tr>
<tr>
<td>Martiuchski et al., 1996 (126)</td>
<td>No</td>
<td>Yes</td>
<td>51</td>
<td>Patients were their own comparison subjects.</td>
<td>安静/行走活动</td>
<td>No behavioral changes, decrease in physical restraint in all facilities, decrease in use of psychotropics in seven of 20 patients</td>
<td>4</td>
</tr>
<tr>
<td>Meyer et al., 1992 (135)</td>
<td>No</td>
<td>Yes</td>
<td>11</td>
<td>Patients were their own comparison subjects.</td>
<td>安静/行走活动</td>
<td>Decreased agitation during the week</td>
<td>4</td>
</tr>
<tr>
<td>Namazi et al., 1994 (136)</td>
<td>No</td>
<td>Yes</td>
<td>11</td>
<td>11</td>
<td>Exercise/movement program daily for 40 minutes for 4 weeks</td>
<td>Significant decrease in agitation in exercise group</td>
<td>4</td>
</tr>
<tr>
<td>Okawa et al., 1991 (137)</td>
<td>No</td>
<td>No</td>
<td>24</td>
<td>0</td>
<td>Enforced social activity with nurses (3 hours/day) Montessori activities [group and individual]</td>
<td>Reduced behavioral problems in 30% of sample No differences in depression or agitation No significant decrease in aggression/agitation</td>
<td>5</td>
</tr>
<tr>
<td>Orsulic-Jeras et al., 2000 (138)</td>
<td>Partial</td>
<td>Yes</td>
<td>13</td>
<td>12</td>
<td>Montessori activities [group and individual] Design of internal corridors in nursing home</td>
<td>No behavioral changes, decrease in physical restraint in all facilities, decrease in use of psychotropics in seven of 20 patients</td>
<td>4</td>
</tr>
<tr>
<td>Cohen-Mansfield and Werner, 1998 (139)</td>
<td>No</td>
<td>Yes</td>
<td>27</td>
<td>Patients were their own comparison subjects.</td>
<td>安静/行走活动</td>
<td>Decrease in number of exit attempts</td>
<td>4</td>
</tr>
<tr>
<td>Dickinson et al., 1995 (140)</td>
<td>No</td>
<td>Yes</td>
<td>7</td>
<td>Patients were their own comparison subjects.</td>
<td>安静/行走活动</td>
<td>Signposting alone was not effective; signposting plus training was associated with improvements for all patients. Improvement maintained at 3 months in two of four patients.</td>
<td>5</td>
</tr>
<tr>
<td>Hanley, 1981 (141)</td>
<td>No</td>
<td>Yes</td>
<td>6</td>
<td>Patients were their own comparison subjects.</td>
<td>安静/行走活动</td>
<td>Signposting alone was not effective; signposting plus training was associated with improvements for all patients. Improvement maintained at 3 months in two of four patients.</td>
<td>5</td>
</tr>
<tr>
<td>Hewawasam, 1996 (142)</td>
<td>No</td>
<td>Yes</td>
<td>10</td>
<td>Patients were their own comparison subjects.</td>
<td>安静/行走活动</td>
<td>Horizontal grid pattern was effective in reducing exiting behavior in all patients. Problem behaviors were reduced in all patients during intervention period.</td>
<td>4</td>
</tr>
<tr>
<td>Hussain, 1988 (143)</td>
<td>No</td>
<td>Yes</td>
<td>5</td>
<td>Patients were their own comparison subjects.</td>
<td>安静/行走活动</td>
<td>Horizontal grid pattern was effective in reducing exiting behavior in all patients. Problem behaviors were reduced in all patients during intervention period.</td>
<td>5</td>
</tr>
</tbody>
</table>

(continued)
gentle massage and 3 minutes/day of intermittent touching with some talking) over a 10-day period decreased disturbed behavior from baseline immediately and for 5 days after the intervention (111). White noise tapes led to immediate decrease in agitation (109). A controlled trial of stimulation with "natural elements" while bathing (sounds of birds, brooks, and small animals were played and large bright pictures were displayed) found that agitation decreased significantly only during bathing (115). The other study of single cases found no difference in agitation before and after therapeutic touch or massage (113). In the final two studies, the effects of several forms of sensory stimulation involving touch, smell, and taste were examined. A small randomized, controlled trial reported no change associated with the intervention (110), and the other study found that the intervention was helpful (116).

- The grade of recommendation for short-term benefits of sensory stimulation is C, but there is no evidence for sustained usefulness.

**Simulated presence therapy.** Six studies investigated the effects of simulated presence therapy, in which positive autobiographical memories are presented to the patient in the form of a telephone conversation usually involving a continuous-play audiotape made by a family member or surrogate (Table 9). One randomized, controlled trial found no change in agitated or withdrawn behaviors (117). Staff observations suggested reduced agitation in patients who received the intervention, compared to a placebo group but not compared to patients receiving usual care (117). A small study found improved social interaction and attention (118). Simulated presence therapy used to address agitation led to significant decreases in agitation and improved social interaction but no change in aggressive behaviors (119). When simulated presence therapy was used regularly, problem behaviors were reduced by 91% (119). Finally, in a series of single case studies, Peak and Cheston (120) reported mixed results, with increased ill-being in one participant and reduced anxiety and increased social interaction in other participants. Use of video to provide simulated presence was not associated with significant changes in agitated behavior (121).

- The grade of recommendation for simulated presence therapy is D.

**Structured activity**

**Therapeutic activity programs.** There were five randomized, controlled trials of therapeutic activities (Table 9). In a small-scale randomized, controlled trial, therapeutic activities at home were associated with significant decreases in agitation (123). Another study found that small group discussion and being carried on a bicycle pedaled by volunteers alleviated patients’ depression but

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**TABLE 10. Studies of the Use of Other Structured Activity and Alteration of the Visual Environment in the Management of Neuropsychiatric Symptoms of Dementia (continued)**

<table>
<thead>
<tr>
<th>Author</th>
<th>Randomization</th>
<th>Comparison Group</th>
<th>Number of Patients</th>
<th>Number of Comparison Subjects</th>
<th>Therapeutic Regimen</th>
<th>Outcome</th>
<th>Level of Evidencea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hussain and Brown, 1987 (144)</td>
<td>No</td>
<td>Yes</td>
<td>8</td>
<td>Patients were their own comparison subjects</td>
<td>Two-dimensional grid pattern by door of ward</td>
<td>Ambulation was reduced in seven of eight patients with grids; pattern of eight horizontal lines was most effective.</td>
<td>4</td>
</tr>
<tr>
<td>Kincaid and Peacock, 2003 (145)</td>
<td>No</td>
<td>Yes</td>
<td>12</td>
<td>Patients were their own comparison subjects</td>
<td>Mural painted over doors of ward</td>
<td>Significantly fewer door testings with mural</td>
<td>4</td>
</tr>
<tr>
<td>Kittur and Ruskin, 2001 (146)</td>
<td>No</td>
<td>Yes</td>
<td>2</td>
<td>Patients were their own comparison subjects</td>
<td>Removing mirrors</td>
<td>Reduced agitation for 1 week in one patient</td>
<td>5</td>
</tr>
<tr>
<td>Mayer and Darby, 1991 (147)</td>
<td>No</td>
<td>Yes</td>
<td>9</td>
<td>Patients were their own comparison subjects</td>
<td>Full-length mirror placed in front of door</td>
<td>Significant reduction in door contacts</td>
<td>4</td>
</tr>
<tr>
<td>Namazi et al., 1989 (148)</td>
<td>No</td>
<td>Yes</td>
<td>9</td>
<td>Patients were their own comparison subjects</td>
<td>Nine types of visual barriers (grids, door knob cover, barriers)</td>
<td>Cloth covering door/door handle was most effective in reducing exiting behavior.</td>
<td>4</td>
</tr>
<tr>
<td>Williams et al., 1987 (149)</td>
<td>No</td>
<td>Yes</td>
<td>5</td>
<td>Environmental changes in ward (e.g., signposting and informal reality orientation therapy with staff)</td>
<td></td>
<td>Significant improvement in behavior in patients on intervention ward, relative to comparison group</td>
<td>4</td>
</tr>
<tr>
<td>Chafetz, 1990 (150)</td>
<td>No</td>
<td>Yes</td>
<td>30</td>
<td>Grid marking on floor by exit</td>
<td>No reduction in exiting behavior</td>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>

* Levels of evidence were rated according to Oxford Centre for Evidence-Based Medicine guidelines and ranged from 1 to 5, with lower numbers indicating higher quality. Lowercase letters (“a,” “b,” “c”), used to designate level 1, 2, and 3 studies, indicate finer-quality gradations, with a range from “a” (higher quality) to “c” (lower quality).
not agitation at 10 weeks (122). The third found no effects of puzzle play on social interaction and mood (95). Similarly, a comparison of games and puzzle play with Snoezelen and another study comparing structured activity with a control condition found no improvements in mood and behavior (104, 129).

The other studies of therapeutic activities were non-randomized, controlled trials. Ishizaki et al. (124) found

<table>
<thead>
<tr>
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<th>Number of Comparison Subjects</th>
<th>Therapeutic Regimen</th>
<th>Outcome</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annerstedt, 1997 (151)</td>
<td>No</td>
<td>Yes</td>
<td>28</td>
<td>29</td>
<td>Designed environment (group living)</td>
<td>At 1 year, reduced aggression, anxiety, and depression; lower costs; and reduced use of neuroleptics for group living patients; no difference at 3 years</td>
<td>4</td>
</tr>
<tr>
<td>Annerstedt, 1993 (152)</td>
<td>No</td>
<td>Yes</td>
<td>28</td>
<td>28</td>
<td>Designed environment (group living)</td>
<td>Reduced institutionalization and slight reduction in anxiety and depression in group living patients; increase in aggression in group living patients, but increase was less than in the comparison group</td>
<td>4</td>
</tr>
<tr>
<td>Bianchetti et al., 1997 (153)</td>
<td>No</td>
<td>No</td>
<td>17</td>
<td>0</td>
<td>Designed environment</td>
<td>Significant reduction in behavioral problems, use of psychotropics, and use of physical restraints at 6 months</td>
<td>4</td>
</tr>
<tr>
<td>Namazi and Johnson, 1992 (154)</td>
<td>No</td>
<td>No</td>
<td>32</td>
<td>0</td>
<td>Doors unlocked for 3-hour periods</td>
<td>Reduction in negative and aggressive behaviors and in wandering when door unlocked</td>
<td>4</td>
</tr>
<tr>
<td>Wells and Jorm, 1987 (155)</td>
<td>Yes</td>
<td>Yes</td>
<td>12</td>
<td>10</td>
<td>Specialized design</td>
<td>No differences in problem behaviors</td>
<td>2b</td>
</tr>
<tr>
<td>Wimo et al., 1995 (156)</td>
<td>No</td>
<td>Yes</td>
<td>46</td>
<td>62</td>
<td>Group living</td>
<td>Significant increase in behavioral disturbances in group living patients versus comparison subjects at 6 and 9 months; aggression significantly increased in group living patients after 6 and 12 months</td>
<td>4</td>
</tr>
<tr>
<td>Benson et al., 1987 (157)</td>
<td>No</td>
<td>Yes</td>
<td>32</td>
<td>Patients were their own comparison subjects</td>
<td>Specialized care plans for each patient, education for nurses, family support and education</td>
<td>Emotional status significantly increased at 12 months; increased quality of life</td>
<td>4</td>
</tr>
<tr>
<td>Brane et al., 1989 (158)</td>
<td>No</td>
<td>Yes</td>
<td>17</td>
<td>19</td>
<td>Staff training in integrity in promoting care</td>
<td>Improvement in anxiety and depressed mood in treatment group</td>
<td>4</td>
</tr>
<tr>
<td>Cohen-Mansfield et al., 1997 (159)</td>
<td>No</td>
<td>No</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Training program for 103 nursing staff members</td>
<td>No change in patients’ agitation or mood; significant increase in restraint at follow-up</td>
<td>4</td>
</tr>
</tbody>
</table>

(continued)
no beneficial effects of weekly therapeutic activities on depression. In another study, a combination of group and individualized activity sessions in day care significantly increased agitation over 10 weeks (125). A controlled, nonrandomized clinical trial of weekly activity groups led by nursing assistants found no behavioral changes (126). There was, however, less use of physical restraint generally, and psychotropic medication use was reduced in seven of 20 participants. A specialist day-care program providing structured daily activities for patients with dementia was associated with decreased institutionalization and was more cost-effective than nursing home care (29). Patients who were rocked on a swing did not show a decrease in aggression (128). Three case studies of diverse group activities (games, music, exercise, socializing) found equivocal effects on behavior (127). In two studies that used reading sessions as an intervention, some improvement was seen in wandering (86) and disruptive behaviors were decreased in both patients in the study both during and 1 week after the reading intervention (87).

- Not all therapeutic activity programs used the same interventions, but overall, the study findings are inconsistent and inconclusive. The grade of recommendation is D.

**Montessori activities.** Montessori activities use rehabilitation principles and make extensive use of external cues and progression in activities from simple to complex (Table 10). Three nonrandomized, controlled trials utilized Montessori-based activities and found no change in depression and agitation (132, 135, 138).

- The grade of recommendation for Montessori activities is D.

**Exercise.** Three studies examined the use of exercise/movement/walking as an intervention for neuropsychiatric symptoms (Table 10). A well-conducted randomized, controlled trial found no effects on behavior in a “walk-talk” program in which one caregiver walked with two residents or walked and talked with two residents (131). A randomized, controlled trial of a psychomotor activation program found no behavioral effect (133). The other two studies were nonrandomized, controlled trials. One study, in which 11 patients were their own comparison subjects, found a significant reduction in aggressive behaviors on days when a walking group was held (134). The other study, a small matched, con-

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**TABLE 11. Studies of the Use of Other Environmental Manipulation and Staff Education in the Management of Neuropsychiatric Symptoms of Dementia (continued)**

<table>
<thead>
<tr>
<th>Author</th>
<th>Randomization</th>
<th>Comparison Group</th>
<th>Number of Patients</th>
<th>Number of Comparison Subjects</th>
<th>Therapeutic Regimen</th>
<th>Outcome</th>
<th>Level of Evidencea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edberg and Hallberg, 2001 (160)</td>
<td>No</td>
<td>Yes</td>
<td>11</td>
<td>11</td>
<td>Staff training, individualized care plans, clinical supervision</td>
<td>No difference between groups</td>
<td>4</td>
</tr>
<tr>
<td>Hagen and Sayers, 1995 (161)</td>
<td>No</td>
<td>Yes</td>
<td>171 caregivers</td>
<td>Not stated</td>
<td>Staff education for 171 staff members</td>
<td>Significant reduction in aggression directed toward staff 2 weeks after program</td>
<td>4</td>
</tr>
<tr>
<td>Matthews et al., 1996 (162)</td>
<td>No</td>
<td>Yes</td>
<td>33</td>
<td>Patients were their own comparison subjects.</td>
<td>Staff educated to provide client-centered care to address agitation and sleep problems</td>
<td>Significant reduction in verbal agitation 6–8 weeks postintervention, increase in other agitated behaviors, no change in sleep</td>
<td>4</td>
</tr>
<tr>
<td>McCallion et al., 1999 (163)</td>
<td>Yes</td>
<td>Yes</td>
<td>49 nursing assistants</td>
<td>56 nursing assistants</td>
<td>Manual-guided course for nursing assistants</td>
<td>Significant reduction in disturbances and aggression at 3 months and in depression at 6 months; no change in use of restraint</td>
<td>1b</td>
</tr>
<tr>
<td>Schrijnemaekers et al., 2002 (164)</td>
<td>Yes</td>
<td>Yes</td>
<td>77</td>
<td>74</td>
<td>Training in emotion-focused care</td>
<td>No difference between groups at 3, 6, and 12 months</td>
<td>2b</td>
</tr>
<tr>
<td>Testad et al., 2005 (165)</td>
<td>Yes</td>
<td>Yes</td>
<td>140</td>
<td>140</td>
<td>Staff education program</td>
<td>Reduced use of restraint in the treatment group; no change in agitation score postintervention</td>
<td>2b</td>
</tr>
</tbody>
</table>

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a Levels of evidence were rated according to Oxford Centre for Evidence-Based Medicine guidelines and ranged from 1 to 5, with lower numbers indicating higher quality. Lowercase letters (“a,” “b,” “c”), used to designate level 1, 2, and 3 studies, indicate finer-quality gradations, with a range from “a” (higher quality) to “c” (lower quality).
trolled trial of exercise groups, found no significant reduction in agitated behaviors (136).

- The grade of recommendation for exercise is D.

Social interaction. A small report of single cases studies showed decreased neuropsychiatric symptoms in one-third of patients who had enforced social interaction with nurses for 3 hours/day for 1–2 months (137).

- The grade of recommendation for enforced social interaction is D.

Decreased sensory stimulation. Two small studies investigated decreased sensory stimulation (Table 10). A “quiet

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TABLE 12. Studies of the Use of Special Care Units Combined With Staff Education in the Management of Neuropsychiatric Symptoms of Dementia

<table>
<thead>
<tr>
<th>Author</th>
<th>Randomization</th>
<th>Comparison Group</th>
<th>Number of Patients</th>
<th>Number of Comparison Subjects</th>
<th>Therapeutic Regimen</th>
<th>Outcome</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annerstedt et al., 1996 (166)</td>
<td>No</td>
<td>Yes</td>
<td>28</td>
<td>31</td>
<td>Designed environment and staff training</td>
<td>Improvement in emotional functioning at 6 months, no difference at 12 months; increased use of medication in comparison group; group living less costly</td>
<td>3</td>
</tr>
<tr>
<td>Bellelli et al., 1998 (167)</td>
<td>No</td>
<td>No</td>
<td>55</td>
<td>0</td>
<td>Designed environment, staff training, activity provision</td>
<td>Reduction in behavioral disturbances (measured with neuropsychiatric inventory), especially agitation and aberrant motor behavior; in special care dementia units at 6-month follow-up; reduced neuroleptic medication use</td>
<td>4</td>
</tr>
<tr>
<td>Chafetz, 1991 (168)</td>
<td>No</td>
<td>Yes</td>
<td>12</td>
<td>8</td>
<td>Special care dementia units with designed environment, staff training, family involvement</td>
<td>No difference in problem behavior at 15-month follow-up</td>
<td>4</td>
</tr>
<tr>
<td>Frisoni et al., 1998 (169)</td>
<td>No</td>
<td>Yes</td>
<td>31</td>
<td>35</td>
<td>Special care dementia units with designed environment, staff training, family involvement</td>
<td>Reduction in neuropsychiatric symptoms in both groups after 3 months; reduction in depression and improvement in psychotic symptoms in special care dementia units, no change in use of physical restraints in special care dementia units, increase in use of physical restraints in comparison group</td>
<td>3</td>
</tr>
<tr>
<td>Kovach and Stearns, 1994 (170)</td>
<td>No</td>
<td>Yes</td>
<td>26</td>
<td>Not specified</td>
<td>Specialist dementia care unit, staff training</td>
<td>Significant reduction in behavioral problems was found at time 2 (not clear when); biggest reduction was in activity disturbance and aggression</td>
<td>4</td>
</tr>
<tr>
<td>Morgan and Stewart, 1998 (171)</td>
<td>No</td>
<td>Yes</td>
<td>52</td>
<td>11</td>
<td>Low-density special care dementia units</td>
<td>Reduction in disruptive behavior in low-density group at 1 year</td>
<td>3</td>
</tr>
<tr>
<td>Warren et al., 2001 (172)</td>
<td>No</td>
<td>Yes</td>
<td>44</td>
<td>36</td>
<td>Admission to special care dementia units</td>
<td>Behavioral and depression scores did not significantly change for special care dementia units residents at 18 months. No significant differences in neuropsychiatric symptoms between special care dementia units and standard care at 6 months</td>
<td>3</td>
</tr>
<tr>
<td>Webber et al., 1995 (173)</td>
<td>No</td>
<td>Yes</td>
<td>22</td>
<td>Not specified</td>
<td>Specialized unit design, staffing, and activity programming</td>
<td>No significant differences in neuropsychiatric symptoms between special care dementia units and standard care at 6 months</td>
<td>4</td>
</tr>
</tbody>
</table>

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a Levels of evidence were rated according to Oxford Centre for Evidence-Based Medicine guidelines and ranged from 1 to 5, with lower numbers indicating higher quality.
week” intervention (turning off the television, lowering voices, and reducing fast movement by staff at a day center) led to an immediate significant reduction in agitation as measured by a nonstandardized scale, compared to the period before the intervention (135). In another study, patients on a specially designed reduced stimulation unit—without television, radio, telephones; with scheduled rest periods and limited access to visitors—had no reduction in neuropsychiatric symptoms as measured by a standardized scale, compared with the period before the intervention, but use of restraint decreased (130).

- The grade of recommendation for decreased sensory stimulation is D.

**Environmental manipulation.** Visually complex environments. Eight studies (no randomized, controlled trials) investigated the effects of changing the visual environment (Table 10). The presence of two-dimensional grids on the floor near doors did not reduce exiting behaviors (150). However, two studies in which a horizontal grid pattern was used reported significant decreases in patients’ attempts to open doors and in patients’ ambulation (142, 144). Similar results were found in a study of the effects of murals on the walls above doorways (145). Blinds and cloth barriers placed over doors/door handles and signs installed to provide a focus of patients’ attention were also effective in reducing time spent attempting to exit the ward (140, 143, 148). Enhancement of the visual environment in a selected area of a residential home was associated with a decrease in agitated behaviors, although the finding was not statistically significant (139).

- Consistent evidence from level-4 studies for changing the environment to obscure the exit indicates a grade of recommendation of C.

**Mirrors.** Two small nonrandomized, controlled trials investigated the effects of mirrors in the patient’s environment (Table 10). In a study with a single case design, one of two patients was less agitated after removal of mirrors from the ward environment (146). Placing a full-length mirror over a doorway led to a significant decrease in exiting during the intervention for nine patients (147).

- The grade of recommendation for use of mirrors is D.

**Signposting.** Three nonrandomized, controlled trials investigated the effects of signposting on neuropsychiatric symptoms (Table 10). Two single case studies found that signposting alone was ineffective, but signposting in combination with reality orientation therapy led to improvements in ward orientation in two of four and five of five patients, respectively (141, 149). In the third study, signposts were placed alongside prompts that served to draw attention to the signs; this arrangement led to a reduction in neuropsychiatric symptoms in all five study participants (143).

- The grade of recommendation for signposting is D.

**Other environmental manipulations.** **Group living.** Group living is the name given to specially designed nursing homes that encourage a homelike atmosphere (Table 11). In a randomized, controlled trial, no change in neuropsychiatric symptoms was found in those in a group living setting, compared to community-dwelling waiting-list comparisons (155). Two other randomized, controlled trials showed decreased aggression, anxiety, and depression and less use of neuroleptic medication for 1 year in residents in group living settings (151, 152). No differences between group living and comparison subjects were observed 3 years later. Both studies were limited, because residents were selected for admission and were ineligible if they had frontal lobe symptoms, severe dementia, or a severe physical morbidity. A smaller uncontrolled trial of group living reported beneficial effects on neuropsychiatric symptoms at 6 months and reduced use of physical restraints (153). However, in another study, neuropsychiatric symptoms significantly increased in group living subjects, relative to comparison subjects, at 6 months and 1 year (156). In summary, group living may have beneficial or deleterious effects—or no effect—on neuropsychiatric symptoms.

- The grade of recommendation for group living is D.

**Unlocking doors.** One small uncontrolled study examined the effect of unlocking ward doors for 3-hour periods (154) (Table 11). Patients showed fewer neuropsychiatric symptoms and decreased wandering when the door was open (154).

- The grade of recommendation for unlocking doors is D.

**Staff education in managing behavioral problems.** Nine studies investigated the effects of staff education in treatment of neuropsychiatric symptoms. Three of the studies were randomized, controlled trials (163–165) (Table 11). A randomized, controlled trial of communication skills training for nursing and auxiliary staff showed significant reductions in patients’ aggression at 3 months and in patients’ depression at 6 months (163). Education of staff to implement an emotion-focused care program (validation, reminiscence, sensory stimulation) did not result in any change in neuropsychiatric symptoms (164). Staff education programs focused on knowledge of dementia and potential management strategies reduced use of physical restraint use (165) and, in a nonrandomized, controlled trial, decreased aggressive behavior toward staff (161). Specialized care programs for individuals in a residential home plus staff education improved emotional status and quality of life for residents 12 months later (157). A similar approach in a controlled trial with only 11 people in each arm led to nonsignificant differences favoring the intervention group (160). The result of a client-centered approach to agitation and sleep disturbance for 33 residents of a nursing home was equivocal. Verbal aggression decreased significantly, but the (less frequent) episodes of
nonverbal agitation increased (162). Training staff in integrity-promoting care (staff gave more time, made the environment more homelike, encouraged patients to do more and to wear their own clothes) improved patients’ anxiety and depressed mood in a small controlled trial (158). In a large uncontrolled trial, training for nursing staff in using unstandardized observational outcomes led to an increase in restraint use but had no effect on agitated behavior (159).

- The grade of recommendation for specific staff education programs in managing neuropsychiatric symptoms is B, on the basis of consistent evidence from level-1 and level-2 studies, as well as supportive evidence from level-4 studies.

Environmental interventions combined with staff education. Eight nonrandomized, controlled trials investigated the effects of environmental interventions such as special care units designed for patients with dementia and staffed by specially trained workers who received ongoing training (Table 12). In a controlled trial, admission to a “low-density” special care dementia unit, which had fewer residents and larger living areas than standard units, was associated with a decrease in disruptive behavior (171). Similarly, in a controlled trial, a combination of group living and staff training was found to improve patients’ emotional and physical outcomes and was less costly than standard care (166, 167). In other studies, special care dementia units were associated with a reduction in neuropsychiatric symptoms, especially agitation and depression, and with a reduction in use of neuroleptic medication (167, 169). Aggression and activity disturbances were reduced in a small controlled trial of a special care dementia unit care (170). However, three other studies found no effect (168, 172, 173).

- The grade of recommendation for special care units combined with staff education is D.

Discussion

We found numerous studies reporting psychological approaches to neuropsychiatric symptoms. We have tried to summarize and classify these studies using evidence-based guidelines in order to help clinicians understand which interventions are efficacious and over what time period. We also tried to distinguish interventions that are ineffective from interventions for which too little evidence is available to judge their effectiveness. Because some interventions are made up of several elements, we could have classified them in different ways. We tried to use the best fit and, by describing the interventions, to make our judgments transparent. Some therapies may require a huge amount of work for very little benefit, and we did not measure this aspect. In addition, some therapies may provide pleasure (either for the patients with dementia or for staff members) and thus may be worthwhile even if the intervention does not alter the patients’ neuropsychiatric symptoms. We did not attempt to judge these differential effects. Similarly, we did not study cognition as an endpoint, although some therapies are intended to have an effect on cognition.

Effective Psychological Therapies

Behavioral management techniques centered on individual patients’ behavior are generally successful for reduction of neuropsychiatric symptoms, and the effects of these interventions last for months, despite qualitative disparity. Psychoeducation intended to change caregivers’ behavior is effective, especially if it is provided in individual rather than group settings, and improvements in neuropsychiatric symptoms associated with these interventions are sustained for months. We therefore recommend these types of interventions.

Music therapy and Snoezelen, and possibly some types of sensory stimulation, are useful treatments for neuropsychiatric symptoms during the session but have no longer-term effects. The cost or complexity of Snoezelen for such small benefit may be a barrier to its use.

Specific types of staff education lead to reductions in behavioral symptoms and use of restraints and to improved affective states. Staff education is, however, heterogeneous, although instruction for staff in communication skills and enhancement of staff members’ knowledge about dementia may improve many outcomes related to neuropsychiatric symptoms. Teaching staff to use dementia-specific psychological therapies for which there is limited evidence of efficacy may not improve these outcomes.

What Interventions Need More Evidence?

Little evidence is available on the effectiveness of reminiscence therapy, but more positive evidence exists for cognitive stimulation therapy. Training for caregivers in behavioral management techniques had inconsistent outcomes but merits further study. The evidence for therapeutic activities is very mixed, and the study findings for these interventions are contradictory and inconclusive. Specialized dementia units were not consistently beneficial, but changing the environment visually and unlocking doors successfully reduced wandering in institutions. These promising interventions merit more study. There is no convincing evidence that simulated presence interventions or reduced stimulation units are efficacious for neuropsychiatric symptoms.

Which Interventions Were Ineffective?

Reality orientation therapy, validation therapy, “admiral” nurses, and Montessori activities had no effect on neuropsychiatric symptoms. In addition, convincing evidence suggests that simple repetitive exercise does not work for neuropsychiatric symptoms.
Conclusions

Overall our conclusions are limited because of the paucity of high-quality research. We found only nine studies with level-1 evidence. However, lack of evidence of efficacy does not mean lack of efficacy. Because the system of rating research assigns the highest ratings to randomized, controlled trials, most published studies of psychological interventions will not be rated as having the highest quality. The literature on behavioral interventions places greater weight on experimental single case studies, particularly in describing individualized interventions. The purpose of publication, however, is to provide evidence that can be generalized for future use. We have, therefore, used the Oxford Centre for Evidence-Based Medicine's system for assessing evidence. We encourage the use of standardized interventions (which can be individualized within a context of adherence to basic principles) in future research so that interventions found to be effective can be used in other populations.

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Epidemiology of and Risk Factors for Psychosis of Alzheimer’s Disease: A Review of 55 Studies Published From 1990 to 2003

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Objective: The authors reviewed studies published between 1990 and 2003 that reported the prevalence, incidence, and persistence of, as well as the risk factors associated with, psychosis of Alzheimer’s disease.

Method: PubMed and PsycINFO databases were searched by using the terms “psychosis and Alzheimer disease” and “psychosis and dementia.” Empirical investigations presenting quantitative data on the epidemiology of and/or risk factors for psychotic symptoms in Alzheimer’s disease were included in the review. A total of 55 studies, including a total of 9,749 subjects, met the inclusion criteria.

Results: Psychosis was reported in 41% of patients with Alzheimer’s disease, including delusions in 36% and hallucinations in 18%. The incidence of psychosis increased progressively over the first 3 years of observation, after which the incidence seemed to plateau. Psychotic symptoms tended to last for several months but became less prominent after 1 year. African American or black ethnicity and more severe cognitive impairment were associated with a higher rate of psychosis. Psychosis was also associated with more rapid cognitive decline. Some studies found a significant association between psychosis and age, age at onset of Alzheimer’s disease, and illness duration. Gender, education, and family history of dementia or psychiatric illness showed weak or inconsistent relationships with psychosis.

Conclusions: Psychotic symptoms are common and persistent in patients with Alzheimer’s disease. Improved methods have advanced the understanding of psychosis in Alzheimer’s disease, although continued research, particularly longitudinal studies, may unveil biological and clinical associations that will inform treatments for these problematic psychological disturbances.

From the time of Alzheimer’s first description of psychotic symptoms in a patient with Alzheimer’s disease in 1907, psychosis has been recognized as a major clinical syndrome in this illness. The consequences of psychotic symptoms in Alzheimer’s disease may be painful and costly for the affected individuals, those who care for them, and society at large. Psychotic symptoms have been linked to greater caregiver distress (1–3) and have been found to be a significant predictor of functional decline and institutionalization (4–7). Compared to patients with Alzheimer’s disease without psychosis, those with Alzheimer’s disease and psychotic symptoms are also more likely to have worse general health (8) as well as a greater incidence of other psychiatric and behavioral disturbances (9–11). Psychotic patients tend to have more frequent and problematic behaviors, including agitation (12–14), episodes of verbal and physical aggression (10, 15–18), and anxiety (11).

Reviews completed before the early 1990s found that psychotic symptoms were common in dementia, including Alzheimer’s disease (19–23). In their review of 21 studies, for example, Wragg and Jeste (23) found that approximately one-third of all patients with Alzheimer’s disease had delusions at some point during their illness, 28% had hallucinations, and nearly 35% had other psychotic symptoms that were difficult to categorize. Overall, however, the reviewed studies were compromised by sampling deficiencies and methodological problems. Wragg and Jeste’s review included studies with as few as nine subjects. Moreover, only five of the 21 studies had a sample size larger than 100 subjects. Other methodological problems included the use of unreliable or nonvalidated diagnostic criteria for Alzheimer’s disease. Consequently, samples included individuals with various types of dementias, and thus generalizability was limited, and findings as they related to Alzheimer’s disease specifically were obscured. Imprecise operational definitions of psychosis (24) and utilization of assessment methods with questionable reliability and validity also undermined these investigations. Moreover, all of the studies published before 1990 were cross-sectional or descriptive and thus did not provide data on the incidence or course (e.g., persistence) of symptoms.

Since the early 1990s, research on psychosis of Alzheimer’s disease has advanced considerably. There have been improvements in the development of diagnostic criteria...
for Alzheimer’s disease and for psychosis of Alzheimer’s disease (25) and the development of more reliable measures of psychotic symptoms, including the Behavioral Pathology in Alzheimer’s Disease Rating Scale (26) and the Neuropsychiatric Inventory (27). Larger sample sizes have become available because of increased awareness of the disease and the establishment of Alzheimer’s disease centers. Longitudinal data from these centers have become available, and more investigators have undertaken prospective studies on this topic.

We reviewed studies published from 1990 through 2003 that investigated psychosis of Alzheimer’s disease with the aim of providing a systematic overview of the current state of knowledge in this area. In so doing, we employed more stringent inclusion criteria than were applied in reviews conducted before the early 1990s. In this article, we summarize findings on the epidemiology of psychotic symptoms in Alzheimer’s disease. Delusions and hallucinations are also reviewed separately, and we include findings on other uncategorized psychotic symptoms. In addition, we examine the literature on potential risk factors for psychosis of Alzheimer’s disease. Implications of the findings for clinical practice and for future research are discussed.

Method

Computerized searches using PubMed and PsycINFO databases were performed for English-language articles published between 1990 and the end of 2003 with the keywords “psychosis and Alzheimer disease” and “psychosis and dementia.” Additional articles were identified by using the “related articles” function in PubMed and by cross-referencing identified articles. Only empirical investigations reporting data on psychotic symptoms in patients with Alzheimer’s disease were selected. If a given study included subjects with dementias other than Alzheimer’s disease (e.g., vascular dementia or mixed dementia), sufficient data on the Alzheimer’s disease group itself (e.g., number of subjects and a prevalence rate of psychotic symptoms) must have been provided. In addition, the study design, study setting, some descriptions of the method of diagnosing Alzheimer’s disease (e.g., National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association criteria), and description of how psychotic symptoms were measured or defined must have been clearly stated. Target symptoms that could not be well categorized as delusions or hallucinations were considered “other psychotic symptoms.” Using these methods, we identified 55 articles for review.

Results

Sample Size and Subject Characteristics

The mean sample size in the 55 studies reviewed (Table 1) was 177 subjects (median=135; range 27 to 1,155). These findings represent an increase in sample sizes from those in the studies of psychosis in Alzheimer’s disease prior to 1990 that were included in a previous review (23). In that review, the largest sample size among 21 studies was merely 175 subjects, and the median sample size was 33. In the current review, the mean age of subjects with Alzheimer’s disease was 75.5 years (median=74.0, range=69–85), and the mean level of education was 10.7 years (median=12.0, range=6–13). Inclusion of education data was not possible for some studies because of the use of alternative scales of measurement (e.g., less than high school versus high school). Nearly two-thirds of the total subject sample were women (mean=64.2%), although considerable variability in gender distribution was noted across studies, with the proportion of women ranging from 28.8% to 83.4%. In general, subjects included in the studies tended to have mild or moderate cognitive impairment, as reflected by a mean Mini-Mental State Examination (MMSE) score of 15.5 (median=16.3; range 5–21), although there was considerable variability in this regard across studies as well. Relatively few studies provided data on age at onset or the mean duration of illness. These variables may be considered unreliable estimates because they are based on a patient’s or informant’s retrospective memory and/or perceptions.

Study Design and Setting

Although a majority of the reports (63.6%) were cross-sectional (8, 10, 12, 17, 29–60), 34.5% of the studies provided longitudinal data (9, 13, 16, 63–78). The primary settings for 72.7% of the studies were outpatient clinics, Alzheimer’s disease clinical centers, or Alzheimer’s disease research centers (8, 10, 12, 13, 16, 17, 29–32, 34–39, 43, 44, 48–50, 52, 53, 55, 57–74); relatively few studies included samples of inpatients (33, 41, 45–47, 56, 75) or a combination of inpatients and outpatients (9, 42). Even fewer re-
ports (51, 54) included community-based samples, which are often more difficult to obtain. The setting was not clear in one investigation (76).

**Diagnosis and Measurement**

The National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria (77) were used most commonly for diagnosis of Alzheimer's disease (8, 10, 12, 16, 31–34, 36, 40–44, 48, 50–55, 57, 61–63, 65, 66, 71–75). Both those criteria and the DSM criteria were used together in several studies (9, 13, 17, 29, 30, 35, 37, 45–47, 50, 59, 63, 64, 67, 69). Autopsy results, specifically those that utilized criteria of the Consortium to Establish a Registry for Alzheimer's Disease (78), were used infrequently.

Numerous measures or tools were used alone or in combination to assess psychotic symptoms. Informal or semistructured interviews of patients and/or their caregivers (such as the National Institute of Mental Health Diagnostic Interview Schedule [79], the Structured Clinical Interview for DSM-IV Axis I Disorders [80], and the Initial Evaluation Form [81]) were utilized most frequently (15 studies), with an additional six studies incorporating other measures in addition to interviews. The Behavioral Pathology in Alzheimer's Disease Rating Scale and the Neuropsychiatric Inventory, or both, were also used frequently.

**Results**

**Epidemiology**

**Prevalence.** The median prevalence of psychotic symptoms (delusions or hallucinations) in patients with Alzheimer's disease was 41.1% (range=12.2%–74.1%). The median prevalence of delusions was 36% (range=9.3%–63%). Delusions of theft were the most common type of delusions reported (50.9% of studies). Hallucinations occurred less frequently, with a median prevalence of 18% (range=4%–41%). Visual hallucinations were more prevalent than auditory hallucinations (median=18.7% and 9.2%, respectively). Between 7.8% and 20.8% of subjects (median=13%) experienced both hallucinations and delusions. Psychotic symptoms not categorized as delusions or hallucinations were reported by 3.6% to 38.9% of patients with Alzheimer's disease (median=25.6%). Most often, this category comprised misidentifications (frequently considered to be a type of delusion, although it may be a separate phenomenon). Prevalence data are summarized in Table 1.

Prevalence is affected by several factors, including the study setting and study design. A higher prevalence of psychotic symptoms tended to occur in inpatient settings (e.g., acute care hospitals, nursing homes, neurobehavioral units) (31.2% to 74.1%) (33, 40, 41, 45–47, 56, 75), whereas lower rates (12.2% to 65.2%) were noted in patients referred to outpatient memory or research clinics (8, 10, 12, 13, 16, 17, 29–32, 34–38, 43, 44, 48–50, 52, 53, 55, 57–61, 63–70, 72–74). Two studies included a community sample (51, 54), and one reported that 26.9% of the subjects experienced psychosis (51). Delusions among inpatients were present in 44.4% to 62.9% and hallucinations were present in 5.7% to 34%. In outpatient samples, 9.3% to 63% of subjects experienced delusions, and 3.8% to 41% had hallucinations. In the two studies of community-dwelling subjects, 21.8% and 22.7% had delusions, and 12.8% and 13.1% had hallucinations.

**Incidence.** The incidence of psychosis of Alzheimer's disease refers to the percentage of individuals with Alzheimer's disease who are initially not psychotic and who develop one or more psychotic symptoms by a specified end-point. No studies before 1990 reported data on incidence. In studies conducted since 1990, however, seven studies (13, 61, 63, 64, 66, 69, 73) reported data on incidence over observation periods ranging from 1 to 5 years. Paulsen et al. (69) reported a 1-year incidence of 20%. Levy and colleagues (13) reported a comparable incidence of 25% after 1 year. Over a 2-year period, Paulsen and colleagues (69) reported an incidence of 36.1%, and in the study by Caligiuri et al. (63) of neuromotor abnormalities and risk for psychosis, 32.5% of subjects developed psychotic symptoms over the course of 2 years. The latter rates are likely comparable because the samples from the two studies overlapped to some extent, given that subjects in both studies were drawn from the same group of individuals enrolled in longitudinal studies at the Alzheimer's Disease Research Center in San Diego. Delusions and hallucinations both seem to develop more readily within a 1-year to 2-year span, although these data are limited by the small number of studies addressing delusions and hallucinations specifically over more than two assessment points (60, 65). Incidence seemed to plateau after 3 years, as there was little difference between 3-year (49.5%) and 4-year (51.3%) cumulative rates for psychosis in the study by Paulsen et al. (69). In the study by Chen and colleagues (64), 29.7% of the subjects developed psychosis over an average of 5 years of follow-up. However, the authors pointed out that subjects were not evaluated the same number of times or at the same time points. The 14.9% incidence reported by Sweet and associates (73) was difficult to compare to the findings of other studies because the length of follow-up was not specified.

**Persistence.** Persistence of psychosis of Alzheimer's disease refers to whether an individual experiences a symptom at two or more consecutive evaluations. Again, comparison of rates across studies is limited because variable follow-up periods were used by different researchers. In one study, subjects were evaluated every 3 months over 1 year, and 57% had psychotic symptoms on at least two occasions (13). In another study, a similarly high persistence of psychosis was found for individuals evaluated at baseline and 1 year later: 44% for delusions, 26% for visual hallucinations, and 45% for auditory hallucinations (61). Psychotic symptoms rarely seemed to persist after several
months, however. Haupt et al. (66) reported that after 2 years, psychotic symptoms did not persist in any of 21 subjects who had delusions or in any of 11 subjects who had hallucinations at baseline. The results may have been affected by the small number of patients manifesting psychotic symptoms. Furthermore, the authors assessed symptoms at 1 and 2 years but reported persistence on the basis of the presence of a symptom at both time points. A low persistence rate over a 2-year period was also found by Devanand and colleagues (9), who reported that delusions persisted in only 12.8% of 180 subjects and hallucinations in only 5.6%. Rosen et al. (70) and Zubenko et al. (76) considered a symptom to be persistent if it was present on any two consecutive annual evaluations conducted over the course of the study (on average, 2 and 5 years, respectively). Using this definition, these authors reported that 86.7% and 84.6%, respectively, of the same subject sample had persistent psychotic symptoms.

**Risk Factors**

Seven studies examined the relationship between African American or black ethnicity and psychosis. Five found a positive association (8, 16, 31, 36, 52), and two found no relationship (9, 32). Bassiony and colleagues (31) reported that African Americans were significantly more likely to have hallucinations than Caucasians; the investigators did not report on other psychotic symptoms. Lopez et al. (52) reported that African Americans in the moderate to severe stages of Alzheimer's disease had significantly more psychotic symptoms than Caucasians in the same stages; the relationship between ethnicity and psychotic symptoms was not significant in mild stages, however. No studies reported associations with any other ethnic groups. Associations between risk factors and psychosis are summarized in Table 2.

Severity of cognitive impairment (assessed with the MMSE or a similar global cognitive measure) showed a significant positive association with the presence of psychosis in individuals with Alzheimer's disease in 20 studies (8, 9, 12, 13, 31, 32, 34, 36, 37, 40, 44, 45, 48, 52, 57, 65, 67–69, 74) and no association in 10 studies (10, 33, 39, 42, 47, 50, 51, 58, 62, 70). Overall, the prevalence of psychosis in general increased as cognitive impairment became more severe. Delusions tended to initially become more prevalent as cognitive functioning worsened but then decreased again as cognitive impairment became more severe in later stages of the illness. Hallucinations, like general psychotic symptoms, also increased in prevalence as cognitive impairment became more severe. When subjects were categorized as mildly, moderately, or severely cognitively impaired on the basis of MMSE scores (28), a similar pattern was observed. The median prevalence of psychosis was 25.5% (range=3.1%–50%) in mildly impaired individuals (MMSE scores 21–25), 37% (range=18.8%–56%) in those with moderate cognitive impairment (MMSE scores 20–11), and 49% (range=21.9%–79%) in severely impaired sub-

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Projects (MMSE score 10 or below). Delusions were reported in a median of 23.5% (range=11%–50%) of mildly impaired individuals, 46% (range=13%–67%) of those with moderate cognitive impairment, and 33.3% (range=23%–57%) of severely impaired subjects. The median prevalence of hallucinations among those with mild cognitive impairment was 11.4% (range=9%–33%) and increased to 19% in those with moderate cognitive impairment (range=13%–48%) and to 28% (range=16%–44%) in severely impaired patients with Alzheimer's disease. Other psychotic symptoms occurred in 5.9% and 16.7% of mildly impaired subjects (as reported in two studies), in 43.5% of moderately impaired individuals, and in 41.7% of those with severe cognitive impairment (one study). Overall, a statistical examination of the mean prevalence figures for psychotic symptoms and cognitive severity level revealed a significant difference only between the mean prevalence of hallucinations in mildly and moderately impaired individuals, with hallucinations being more prevalent in the moderately impaired than in the mildly impaired subjects. There were no other significant differences in mean prevalence of symptoms at any other levels of cognitive impairment.

Education, gender, and family history of dementia or psychiatric disorder were weakly associated with increased risk for psychosis in the majority of reviewed studies. A majority of studies (76.5%) found that education level was not correlated with the presence of psychotic symptoms (10, 16, 31, 36, 37, 44, 45, 47, 48, 50, 51, 56, 69). In contrast, education level was positively associated with delusions in one study (33) and negatively associated with psychosis in three (8, 32, 52). Gender was not associated with psychosis in 17 studies presenting these data (9, 10, 16, 31, 32, 36, 37, 44, 47, 48, 50, 55, 56, 68–70, 76), but it was associated with psychosis in seven. Of those seven, four found that women were at greater risk for psychotic symptoms (45, 51, 63, 65) and three found that men had a higher risk for psychosis (39, 42, 62). Of seven studies that investigated the association of family history of dementia and/or other psychiatric disorders and psychosis in Alzheimer's disease (8, 10, 12, 31, 37, 48, 56), none found a positive relationship. However,
lack of knowledge and diagnostic inaccuracy in diagnosis among family members could have obscured such an association.

The relationships between psychosis and patients’ age, age at onset of Alzheimer’s disease, and duration of Alzheimer’s disease were generally equivocal. Older age was correlated with psychotic symptoms (delusions, hallucinations, or both) in 12 of 25 studies (8, 13, 17, 32, 36, 37, 40, 45, 47, 50, 55, 56) and was not associated with psychosis in the remaining 13 investigations (9, 10, 31, 42, 43, 48, 57, 59, 62, 69, 70, 75, 76). In 12 studies reporting on the relationship between age at onset of Alzheimer’s disease and psychotic symptoms, seven studies found no relationship (12, 16, 42, 47, 51, 68, 76), four found that the later the age at onset of Alzheimer’s disease, the more likely the individual was to experience psychosis (40, 45, 56, 75), and only one found that an earlier age at onset was associated with psychosis (62). Nine of 17 studies found no relationship between duration of Alzheimer’s disease and the occurrence of psychotic symptoms (36, 47, 51, 55, 56, 58, 68, 71, 76). The other eight studies, however, found that a longer duration of Alzheimer’s disease was correlated with the occurrence of psychosis (12, 17, 31, 32, 34, 37, 39, 45).

Other Associations

Psychotic symptoms were significantly associated with more rapid cognitive decline over time in all nine studies that examined this relationship (13, 37, 40, 58, 62, 69–71, 74), supporting the notion that psychosis may denote a subset of patients with Alzheimer’s disease with a more aggressive course of the disease (see references 13, 69, 70). It is interesting to note that only two of these studies examined the relationship between the rate of cognitive decline and hallucinations or delusions separately, and each found that hallucinations, but not delusions, were significantly associated with more rapid cognitive decline (62, 74).

Discussion

Our review of 55 studies of psychosis in possible or probable Alzheimer’s disease revealed that a sizable proportion (median 41%) of individuals with the disease experience psychotic symptoms at some time during the course of their illness. Delusions occurred more frequently (median=36%) than hallucinations (median=18%). Other psychotic symptoms not categorized as delusions or hallucinations occurred in 25% of individuals. The incidence of psychotic symptoms seemed to increase with increasing follow-up intervals over the first 3 years. Psychotic symptoms tended to be reported in a majority of patients at least over a period of several months but often were not observed beyond 1 or 2 years. African American or black ethnicity and greater degree of cognitive impairment were strongly associated with a higher rate of psychosis. Psychosis was also associated with a faster rate of cognitive decline. Age, age at onset of Alzheimer’s disease, and duration of Alzheimer’s disease were associated with psychosis in approximately one-half of studies. Education, gender, and family history of dementia or psychiatric illness showed a weak or inconsistent relationship with psychosis in patients with Alzheimer’s disease.

The prevalence rate of psychosis in patients with Alzheimer’s disease found in our review was 41%. The median rate for delusions was 36%, which is comparable to the median rate of 33.5% reported in one of the only review studies of psychosis in Alzheimer’s disease published before the early 1990s (23). The rate of hallucinations found in the present review (18%) represents a decrease from the 28% reported by Wragg and Jeste (23). The fact that prevalence remains high in light of pharmacologic treatment may reflect increased awareness that these disturbances are consequences of Alzheimer’s disease, improved detection, or the use of better criteria and rating scales that allow for psychotic symptoms to be diagnosed with greater accuracy. As an increasing number of patients with Alzheimer’s disease are treated with cholinesterase inhibitors over the coming years, we might expect that the prevalence and incidence of psychosis would decrease, although findings for the efficacy of these drugs in reducing psychotic symptoms specifically have been mixed (see references 13, 82, 83).

The fact that psychosis is persistent over a short interval of a few months may reflect the reasonable amount of time it takes to begin typical treatment for psychosis and to observe amelioration of symptoms. To assess the true persistence of symptoms, subjects would have to be enrolled in a placebo-controlled study in which some psychotic patients did not receive the typical treatment for symptoms. In the studies that were reviewed, it was more the exception than the rule that subjects would be excluded if they were taking an antipsychotic drug or cholinesterase inhibitor or that a drug washout period would be invoked. Furthermore, there were no means of determining whether the patients who were taking these drugs were being treated optimally, and the extent to which psychotic symptoms persist despite antipsychotic treatment is not known. Therefore, persistence values may reflect the experience of psychosis given current treatments rather than the true persistent nature of psychotic symptoms.

Few equivocal associations with psychosis emerged from the reviewed studies. The association between African American or black ethnicity and psychosis is intriguing, although it is also limited by the fact that only Caucasian samples are available for comparison. Issues of acculturation and genetic influences are yet to be adequately examined, highlighting an area in need of exploration. Cognitive impairment and the rate of cognitive decline were also found to be strongly associated with psychotic symptoms.

The findings of the present review suggest that psychosis represents a developmental feature marking the progression of Alzheimer’s disease or that it represents a distinct disease subtype marked by psychotic symptoms and a particularly rapid disease course. The fact that delusions,
specifically, seemed most prevalent in patients with moderate cognitive impairment supports the hypothesis that a certain amount of neuronal integrity must be present for delusions to occur (see references 48, 84). Conclusions are limited, however, by a general failure to include severely cognitively impaired subjects in these studies. In addition, the association between psychosis and cognitive impairment and between psychosis and rate of cognitive decline may be influenced by medications, including antipsychotics and cholinesterase inhibitors, the former of which is recommended as a first-line treatment for dementia patients and cholinesterase inhibitors, the former of which is recommended as a first-line treatment for dementia patients (85). Yet, a majority of the studies reviewed did not account for the potential effects of medication on cognition and simply reported that these effects were a possible limitation to their findings. A number of studies altogether failed to report what, if any, medications the subjects were taking. The importance of considering medication effects is illustrated in studies of antipsychotic use and cognition. The use of two atypical antipsychotics (clozapine and risperidone) in cognitively impaired patients was reviewed by Jeste et al. (86) and Gladso et al. (87). Jeste and colleagues found that the effects of clozapine on cognition were somewhat conflicting, which they posited was due, at least in part, to the strong anticholinergic activity of clozapine, which is likely to confound or diminish any enhancement of cognitive functioning. Berman and colleagues (88, 89) reported significant increases in MMSE scores in patients with schizophrenia or mild dementia treated with risperidone. Moreover, cholinesterase inhibitors have been shown to improve cognitive symptoms or temporarily reduce the rate of cognitive decline (90). Certainly, future studies should examine the potential influence of medication use, not only to examine any potential effects, positive or negative, on cognitive functioning but also to elucidate underlying biological mechanisms of psychosis in dementia. Furthermore, difficulties in diagnosing patients with Lewy body dementia may have led to their inadvertent inclusion in studies of patients with Alzheimer’s disease, thereby affecting the association between some psychotic symptoms and rate of cognitive decline, given that psychotic symptoms, and hallucinations in particular, may occur in nearly one-half of those with Lewy body dementia (30, 91).

For many variables that were found not to be associated with psychosis, including age, age at onset, and duration of illness, small standard deviations likely affected the detection of associations. In the case of age and age at onset, few individuals who were younger than age 55 years or who had an early age at onset (age 55 years or younger) were included in these studies. Similarly, the range and standard deviation for illness duration were restricted (range=2.8–7.7 years, SD=1.33 years), thus limiting the potential to detect a positive association. In addition, many authors noted that age at onset of Alzheimer’s disease was inherently difficult to determine, because it was often an estimate that relied on the failing memory of those with Alzheimer’s disease or the recall and dating by others of behaviors that occurred several years earlier.

The results of this review are also limited by problems in assessing psychosis. Despite more regular use of accepted diagnostic criteria, some researchers continue to use diagnostic criteria that are nonspecific to Alzheimer’s disease (e.g., DSM-III or DSM-IV criteria). Even when accepted criteria are utilized, inconsistencies in interpreting those criteria are evident. Presumably, the rates reported herein may underestimate the prevalence of delusions and hallucinations specifically, as evidenced by the fact that from 3.6% to 38.9% of psychotic symptoms remained uncategorized and were labeled “other psychotic symptoms.” Conversely, as suggested by Devanand and colleagues (24), the lack of clarity may result in an overestimation of prevalence rates for symptoms such as delusions, as some symptoms are classified as delusions when they would otherwise be better classified as other psychiatric symptoms or as behavioral problems of Alzheimer’s disease. Clarity regarding the definition of psychosis and the categorization of symptoms such as misidentifications will be necessary to produce data that can be better compared across studies.

Overall, the present review reflects improvements in sampling, study design, diagnosis, and assessment, compared to reviews conducted before the early 1990s. Subject samples were larger, providing a more accurate picture of the nature and frequency of psychosis. More studies were prospective in nature and thus used methods designed to answer a directed research question. Longitudinal data were more readily available, providing information on incidence that had not previously been reported and other insights into how psychotic symptoms affect the course of Alzheimer’s disease over time. More reliable assessment tools have also come into use over the past decade with the advent of measurements such as the Neuropsychiatric Inventory and Behavioral Pathology in Alzheimer’s Disease Rating Scale and the use of structured clinical interviews, as opposed to the previously employed methods of chart review and behavioral observation. However, future studies should continue to address the remaining shortcomings of the past 15 years. Research should use longitudinal designs to advance our understanding of the incidence and persistence of psychosis. Future studies should also develop or utilize appropriate diagnostic criteria and rating scales for psychosis in the Alzheimer’s disease population. By taking into account medication use (such as antipsychotics and anticholinergics) among subjects included in these studies, we may also learn about the relative benefits of various pharmacological agents in treating psychosis as well as the mechanisms underlying the occurrence of psychotic symptoms in Alzheimer’s disease and other illnesses.
Conclusions

Research since the early 1990s shows that psychotic symptoms affect a sizable proportion of individuals with Alzheimer’s disease. The incidence of psychosis in any sample of patients typically continues to climb during the first 3 years of observation and may persist for several months, pointing to the necessity for early detection and treatment. With recognition of how prominent and devastating psychotic symptoms may be, it becomes increasingly clear that research should continue to focus on the epidemiology of and risk factors for psychosis of Alzheimer’s disease. As Alzheimer’s disease affects a growing number of individuals over time, so too will psychosis as a syndrome. Systematic delineation of the epidemiology of and risk factors for psychosis in Alzheimer’s disease may clarify the biological underpinnings of these symptoms and direct indications for early interventions, facilitate patient management, reduce caregiver burden, improve patients’ quality of life, and open the door to discovering the nature of psychosis in other diseases.

References


PSYCHOSIS OF ALZHEIMER’S DISEASE


Egg on Your Face

Rand van Sant (all names have been disguised) was always late for our psychotherapy sessions. By exactly 5 minutes. I decided not to ask him about it; he was late for everything and had a lifetime of excuses ready for any inquiry.

Rand was Vice President in charge of municipal bonds for Van Sant Trust, a small but prestigious investment house catering to individuals and institutions with at least $10 million to invest. Randy's father, Peter van Sant, was the firm's founder and president. Randy was single, 25, and had just graduated from an Ivy League business school. Since graduation he had been living with his parents in a prosperous community a little over an hour up the Hudson River from New York City.

Rand told me that he and his father had a daily ritual. His father would take the 7:03 train, get off at Grand Central Station, walk the seven blocks to their office, and be waiting for his son at 9:00 a.m. sharp. Randy, choosing not to accompany his father, would drive alone in his black Porsche (a graduation gift from his mother) to New York City. With the vagaries of traffic and/or garage attendants, he would arrive at Van Sant Trust between 9:05 and 9:15. Each morning his father would angrily ask, “How come you're late?” Randy would reply with a terse “traffic” or “the weather.”

Evening dinner was a nightmare. It was officially called to order at 7:00 p.m. Randy would dawdle and arrive at the dinner table 5 to 10 minutes late. After an angry glare from his father, the dinner would be conducted in Dutch, his parents' native language, or in silence.

After about 6 weeks of psychotherapy Randy must have miscalculated because one day he arrived a minute early! Finally for the first time I addressed the issue. “How come you're on time?” I asked. Randy laughed at this irony and a therapeutic alliance had now been formed. He was rarely late after that.

Randy told me his father was controlling to the point of suffocation. He was impossible to please: Randy's high grades should have been higher; his time in the mile race should have been faster. His father never hesitated to cut Randy down and humiliate him, not only in private but in front of others. Randy's mother was rarely sober after 5:00 p.m. and was quite peripheral to this ongoing battle. Randy was their only child.

Randy was dating a young woman when he began his twice-a-week psychotherapy with me. As he began to feel better about himself, he worked up the courage to propose to Sara Griswold. He was crazy about her.

They were married in a ceremony befitting her own wealthy background, and they moved into a nice home 20 minutes across the Hudson River from New York City. Randy felt liberated living in his own home with his own wife, and within a year, with his own son Thomas.

In contrast to his father, Randy was a full-time parent from the start, participating in pregnancy and labor classes—quite unusual for the 1970s. He stayed home a week during the childbirth period, and, when he resumed psychotherapy, proudly brought in a picture of little Tommy van Sant taken moments after birth.

He told me that in 3 weeks there would be a “showing” of the baby to his parents, to Sara's parents, and to Sara's brother and sister who would be flying in from Palm Springs.

The morning after the “showing,” Randy came into my office. As soon as he arrived, he said, "Boy am I embarrassed! Do I have egg on my face!"

“Randy and I had spent more time on anger toward his father (or rather the lack thereof) than on any other topic.”
“Tell me about it,” I said.

“Well, Dr. Druss, Tommy was upstairs finishing his nap. Sara and I were shoveling drinks into my folks and the Griswolds. I dressed Tommy and brought him downstairs. First I handed him to Mrs. Griswold, who made a big fuss, rocking Tommy and kissing him. Then I handed him to Mr. Griswold, who laughed and said ‘great kid’ as he handed him back to me. Then to Rod Griswold, who lifted Tommy up over his head. Then to Amy, who hugged him lovingly before she handed Tommy back. Then, next in the semi-circle, I gave him to mom, who smiled broadly and gave him back to me. Then, as I approached my father, I shouted out, ‘Baby tired,’ and ran Tommy up the stairs back to his crib. As you can imagine, my father looked hurt and bewildered, but I couldn’t control myself.”

Randy and I had spent more time on anger toward his father (or rather the lack thereof) than on any other topic. Initially he denied having any anger at all, justifying his father’s behavior toward him as a “generation gap” or cultural differences because his father was first-generation Dutch.

But soon Randy admitted being “irritated” or “annoyed” at his father. When he actually did admit that he was angry it was without emotion (and he may even have been trying to please me). The day when they first had Sara’s family over, his father had squashed Randy extra vigorously. I remember asking Randy, “Why do I feel more angry than you do when you tell me this?”

This intervention of mine was no more helpful than any of the others I had tried previously. The only kind of intervention that convinced Randy about his true feelings was his own cruel behavior toward his father at the showing, in front of the whole family, when he got egg on his face.

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Clinical Case Conference

Secondary Mania in Older Adults

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Although mania is commonly associated with bipolar disorder, it can have many etiologies (1). Thus, "primary mania" results from bipolar disorder, whereas "secondary mania" results from pharmacological, metabolic, or neurologic causes (1, 2). Older adults are at risk for secondary mania because of increased medical comorbidities and neurological changes. In one retrospective study of 50 patients with mania who were older than 65 years, it was the first manic episode for 28% of the patients and 71% had a comorbid neurological disorder (3).

The etiology of mania is important because although acute symptomatic treatment of both primary and secondary mania may be similar, appropriate treatment of secondary mania includes addressing the cause (1). We present here two case histories of secondary mania in older adults, discuss their presentations and differential diagnosis in turn, and discuss treatment.

Case 1

Past History

Ms. A, a 67-year-old married African American woman with no previous psychiatric history, was seen for an acute manic episode with psychotic symptoms. She had been in her usual state of health until 3 days before admission, when she developed an abnormally elated mood accompanied by delusions and racing thoughts.

The patient’s medical history was remarkable for a history of well-controlled hypertension, a resection of a left parieto-occipital meningioma, and a three-vessel coronary bypass graft for angina 4 years earlier. She reported two episodes of transient slurred speech, one just before the meningioma resection and the other 4 months before she was seen for the manic episode. Her usual medications included extended-release nifedipine (60 mg/day), ticlopidine (250 mg t.i.d.), and benazepril (20 mg/day).

Present Illness

Approximately 3 weeks before her hospital admission, Ms. A reported that she had contracted an upper respiratory tract infection with a cough and had begun treatment with intermittent doses of pseudoephedrine, 60 mg, plus hydrocodone, 5 mg. Her infectious symptoms were not improving, so clarithromycin was added. After 7 days of clarithromycin therapy, Ms. A awoke from her bed earlier than usual and announced to her daughter, “I feel free! I feel alive!” These statements were accompanied by an elated mood and an unprecedented interest in the Bible. The family reported this was a marked change, as Ms. A was typically rather quiet and reserved.

Over the next 2 days, Ms. A became increasingly hyperverbal and would quote scripture while she ran through the house with her hands up in the air. She began frantically writing a lengthy and disorganized missive to God in which she apologized for past sins and transgressions. Her manic symptoms persisted and escalated to include emotional effusiveness, overfamiliarity, sleeplessness, and the development of delusions and auditory hallucinations. She asserted that she was receiving messages from Bob Hope through the television, appeared suspicious of family members when they expressed concern, and was unwilling to undergo an outpatient magnetic resonance imaging (MRI) scan because she thought she was under arrest. She described hearing voices of individuals from previous “waking” dreams. There was no history of confusion, disorientation, stereotyped motor activity, or changes in level of consciousness.

Ms. A was first admitted to the neurology service for evaluation and management, and she was subsequently transferred to the inpatient psychiatry service. There were no remarkable physical or neurological findings. During the mental status examination Ms. A was noted to be an attentive, cooperative woman who appeared her stated age and had a lively, engaging demeanor and normal motor activity. Her speech was mildly pressured and tangential, requiring redirection to guide her back to the question. She described herself as “better than ever—excellent,” and her affect was congruent with her mood. She described ideas of reference in that characters on television shows were making special references to her recent religious enlightenment. She denied further auditory hallucinations. Notably, her cognitive abilities were not impaired, and she scored 28 out of 30 on the Mini-Mental State Examination (MMSE) (4), although she exhibited some errors on confrontation naming, e.g., “tie” for a “tassel.”

Ms. A’s serum chemistry, cerebrospinal fluid and cultures, urinalysis, blood cultures, and chest X-ray were unremarkable. The hematology profile was notable for a mild normocytic anemia with a hematocrit of 33.0 ml/dl. Her erythrocyte sedimentation rate was slightly elevated at 48 mm/hour. Her level of thyroid-stimulating hormone was low at 0.23 μU/ml (normal=0.39–4.45) with a normal free T₄ level. A brain computed tomography (CT) scan showed evidence only of her past meningioma resection. A brain MRI revealed encephalomalacia related to the previous surgery as well as abnormal hyperintensities in the brain stem, periventricular matter, and deep white matter. These hyperintensities most likely repre-
sented chronic ischemic changes. An electroencephalogram (EEG) showed slow sharp waves in the area of the surgical resection but no epileptiform activity or other abnormal patterns.

Low-dose haloperidol was administered from the beginning of Ms. A’s stay in the psychiatry unit and was tapered off by the time of discharge. Throughout her hospital stay, her manic and psychotic symptoms gradually dissipated. At the time of discharge, Ms. A was taking clonazepam, 0.5 mg b.i.d., which was tapered and discontinued after discharge. Her family members reported that her disposition at the time of discharge was somewhat brighter than her baseline but not remarkably so.

Discussion

Although bipolar disorder can have a late onset in persons over the age of 50 without a previous psychiatric history or a family history of bipolar disorder (5–8), new-onset mania in older adults is most commonly secondary (1, 2). Mania in older adults tends to be more debilitating than in younger adults, as evidenced by the lower scores on the Global Assessment Scale scores of older manic patients (9). In addition, patients whose first manic episode is after the age of 58 exhibit increased cognitive impairment, which is partially reversible (9, 10). Thus, it is important to rule out delirium and dementia. Mania is typically characterized by an abnormally elevated or irritable mood lasting at least 1 week. It may be accompanied by one or more of the following: grandiosity, decreased need for sleep, increased talkativeness, flight of ideas, distractibility, increased goal-directed activity, psychomotor agitation, and excess involvement in potentially harmful activities, all of which lead to a marked decrease in the level of functioning. These features distinguish themselves from delirium, in which the cardinal feature is a waxing and waning alteration in consciousness accompanied by a change in cognition (e.g., disorientation or memory or language disturbances). The symptoms of delirium may be accompanied by changes in affect, such as anxiety and fear. Differentiation between the two is accomplished by longitudinal observation as well as monitoring for affective changes. This patient had manic symptoms without any waxing or waning of consciousness or other evidence of delirium, which suggests a diagnosis of mania.

The cognitive dysfunction that often accompanies mania in older adults (11) may suggest a diagnosis of dementia. However, there are differences in the presentations and premorbid histories of dementia and mania. Agitation and psychosis in dementia are typically phenomena that occur later in the course of illness, rather than in the initial presentation (12, 13). Agitation without psychosis occurs in dementia and may be manifest as “sundowning,” which is commonly defined as increased agitation and restlessness beginning in the late afternoon and extending to early evening (14).

Most important, dementia would likely be preceded by changes in cognitive abilities in the absence of affective symptoms. The cognitive changes of dementia usually occur over years, in contrast to those of mania, which are abrupt and accompanied by affective symptoms. After a period of agitation, the cognitive abilities of the demented patient may improve slightly but will still be markedly impaired, given the likely advanced stage of dementia. The nondemented manic patient would tend to recover mostly from the cognitive impairment (15). Comprehensive neuropsychological testing of Ms. A was not performed because of her relatively normal score on the MMSE. It is interesting that Ms. A did not exhibit the pronounced cognitive deficits described by Young (11). Had she exhibited such deficits, dementia would have been ruled out on the basis of her premorbid history.

Because Ms. A had a history of a meningeoma resection, it is possible that her mania was related to seizure activity. Mania may occur in epileptic patients during interictal periods and can last up to 8 weeks (16). This finding highlights the fact that mania in epilepsy need not be associated with the disturbances of a seizure but perhaps the brain insult itself. For Ms. A, seizure would be a reasonable avenue to pursue because there were several factors that could have given rise to epileptic foci. Her meningioma resection could provide such a focus, although its occipital location makes it unlikely that a related seizure would give rise to her behavioral changes. Epileptic foci can originate from stroke—a very real possibility in this older patient with a history of vascular disease, cardiac bypass surgery, and two possible transient ischemic attacks. Neuroimaging studies, however, did not reveal any evidence of stroke, nor did the EEG reveal any epileptiform activity.

Although Ms. A and her family reported no history of falls, she was taking nifedipine, ticlopidine, and benazepril. All of these agents are capable of causing hypotensive episodes. If Ms. A had an episode of orthostasis, she may have fallen and sustained a head injury. Indeed, in a 1-year follow-up study of 66 subjects with closed-head injuries, 9% experienced manic episodes, and many of them had basal temporal lesions (17). Damage to the hypothalamus has been associated with lasting, rapidly fluctuating moods (18). Mania after head injury has mostly been described in case reports after closed-head injuries and postsurgical intervention for subdural hematomas. In one case series, the average onset of mania after head injury was 2.8 years, with a range of 0–12 years, and irritable euphoria and aggressive behaviors were common symptoms (19). Some researchers have found a preponderance of right-sided lesions following mania related to head injury (20), but there have been isolated case reports of mania following left hemispheric lesions (21). The CT showed no evidence of contusion or skull fracture for Ms. A.

It was important to rule out endocrine disorders in this older female patient, as endocrine abnormalities, such as thyroid disorders, should be considered in older patients with acute mental status changes. Classically, hypothyroidism is associated with mental slowing and depression, but it can lead to florid psychosis (22), as can hyperthyroidism (23, 24). It is interesting that the degree of hypothyroidism appears to be unrelated to the degree of psychiatric symptoms in patients who are psychotic because of hypothyroidism (25).
Antibiotics can cause mania in older adults, which raised the possibility that clarithromycin was the source of Ms. A’s mania. For this reason, her clarithromycin was stopped at admission. There are several reports of secondary mania apparently induced by clarithromycin (26–30). This could be a side effect of this class of medications (albeit an infrequent one), as other macrolides have been reported to be associated with mania (27). Older adults may be more vulnerable to such effects not only because they are more likely to receive antibiotics but also because slower P450 microenzyme metabolism could result in higher plasma levels of the drug. For example, older adults metabolize clarithromycin more slowly than do younger adults (31, 32). The mechanism behind antibiotic-induced mania is unclear but could be related to γ-aminobutyric acid (GABA) antagonism. There is evidence that ciprofloxacin is a GABA antagonist (33). Clarithromycin may have led to CNS disinhibition brought about by GABA antagonism, but we know of no documentation of GABA antagonism by clarithromycin.

The short-term treatment of Ms. A required only low-dose haloperidol and clonazepam. As her symptoms subsided, both of these medications were tapered and discontinued. Because the presumptive etiological agent, clarithromycin, was removed, Ms. A did not require continuing therapy with a mood stabilizer.

Case 2

Past History

Mr. B, a 60-year-old man with no past psychiatric history, was involuntarily admitted after being seen in a clinic with insomnia, increased energy level, pressured speech, tangential thinking, and grandiose delusions. He had been married and divorced twice, with no children, and was living alone in his own home. He was employed as a freelance sports journalist. Although he claimed to have unusually close relationships with several women, there was no evidence to support this claim; he did not meet criteria for a diagnosis of erotomania. On a recent business trip he spent several hundred dollars on clothing to “catch the ladies’ eyes” and had his eyebrow and tongue pierced as he thought this would make him more attractive.

Mr. B had been diagnosed with hypertension but was untreated. He acknowledged episodes of depression in the past, but none had required hospitalization. He denied abuse of alcohol or illicit substances in the past, and the only remarkable aspect of his family psychiatric history was that his brother was diagnosed with panic disorder.

Present Illness

Mr. B was admitted to the inpatient psychiatry service, where he continued to display manic symptoms for approximately 4 days while his medication doses were being titrated, all the while requesting a “decongestant for the brain.” His speech was pressured with some clanging, and his affect was superficial, dysphoric, and tearful at times. Mr. B felt he possessed special powers; he claimed that he was a “sounder,” which he described as a person who can see into the future, and that he had the ability to “run the United Nations.” He stated that his powers “make quantum leaps look like picnics.” His rapid thought processes led him to feel that the rest of the world was slow, to the point that he felt telephones dialed too slowly. At times Mr. B experienced auditory hallucinations of music and television commercials.

The results of serum chemistries, a complete blood count, liver function tests, and thyroid function tests were all within normal limits. The results of a fluorescent treponema antibody absorption test and a urine drug screen were negative.

During a workup for his manic episode, a CT scan revealed a right-sided heterogenous, partially cystic, and calcified mass in the medial aspect of the right temporal lobe. Differential diagnosis included a giant aneurysm dermoid/epidermoid lesion, a glioma, and a nerve sheath tumor, such as a meningioma or an atypical schwannoma. An MRI with gadolinium performed 2 days later revealed a well-circumscribed extra-axial mass 3.4 cm (anterior-posterior) by 3.0 cm (transverse) by 3.0 cm (cranio-caudal), which extended into the right foramen ovale, medial to the right temporal lobe (Figure 1). The neurosurgery service was consulted and opted to debulk the tumor in approximately 2 months.

Mr. B’s drug doses were titrated to 20 mg/day of olanzapine and 1500 mg b.i.d. of divalproex sodium. By the ninth day of his hospitalization he insisted on being discharged to his own home with outpatient follow-up. His mental status examination was markedly improved with euthymic mood, no abnormal movements, and logical...
and goal-directed thought processes, without psychosis or thoughts of harming himself or others.

Follow-Up

Mr. B underwent a right pterional craniotomy, and the mass was resected. The psychiatry consultation service followed him closely during his hospital stay. Postoperatively his recovery was complicated by pneumonia and some dysphagia. He was treated with several antibiotics and transferred to the rehabilitation medicine service, where his mental status continued to improve.

Discussion

Older patients with new-onset mania include individuals who have a history of depression as well as those without any past psychiatric history (34). It was possible that Mr. B’s clinical picture was one of first-episode mania in bipolar disorder. However, as in case 1, it was important to rule out other contributing factors.

For a 60-year-old man with impulsive behaviors (piercing his eyebrow and tongue), one should consider the possibility of substance abuse even though the patient may deny it, as this patient did. Although substance abuse is often associated with younger adults, it must be ruled out in older adults with mania (5). Although we know of no specific data regarding the incidence of substance-induced manic syndromes among older adults, older adults are likely more sensitive to the effects of illicit substances, such as amphetamines, methamphetamine, and cocaine. We did not find any evidence of substance abuse in this patient.

Although Mr. B had a history of depressed mood, he was not taking an antidepressant. If he had been, it would have been important to bear in mind that several psychotropic medications can cause mania. Indeed, some researchers have found that older adults are more likely to have initial manic episodes from antidepressant therapy than are younger adults (35). Tricyclic antidepressants have long been recognized as a risk factor for secondary mania (36). The mechanism underlying this association is unknown but could be related to noradrenergic activity. Venlafaxine, which is a norepinephrine reuptake inhibitor at higher doses (37), has been associated with mania (38). However, some selective serotonin reuptake inhibitors, such as paroxetine (39) and fluoxetine (40), have been associated with manic episodes in younger adults yet have relatively little norepinephrine reuptake inhibition (37). Thus, mania may be induced by receptor activity that is not related to antidepressant action.

Paradoxically, several atypical antipsychotics (olanzapine, risperidone, quetiapine, and ziprasidone), which are approved for treatment of bipolar disorder and/or mania, have been associated with mania (41). In a critical review of 33 reported cases, Rachid et al. (41) concluded that there was “strong evidence” to support a causal link. They discussed the hypothesis that secondary mania induced by atypical antipsychotics may reflect potent blockade of serotonin 5-HT2A but not dopamine D2 receptors. This pattern of receptor activity could presumably lead to frontal disinhibition.

In a review of 50 consecutive psychiatric admissions for mania of people over the age of 65, Tohen et al. (3) found that 12 of 14 cases of first-episode mania were related to a neurological disorder or infection, most commonly stroke. Fujikawa et al. (44) also suggested that most cases of secondary mania in older adults result from stroke. However, the incidence of poststroke mania is low and has been estimated at 1% of all strokes (43). We considered the possibility that Mr. B had had a stroke in light of his untreated hypertension, although in the absence of any focal deficits this would be unlikely. Indeed, there was no evidence of stroke on the CT or MRI.

In the course of the neurological workup for Mr. B, the right-sided mass was discovered. Older adults with new-onset mania are more than twice as likely to have an underlying neurological disorder as are older bipolar patients who have had many manic episodes (3, 44). Although mania is not a common presentation of cerebral tumors, of six patients who developed mania either before or after the removal of a tumor, five had tumors that were frontal or temporal in location and often in the right hemisphere (45). This patient’s right-sided tumor is in keeping with these observations.

As Mendez (46) discussed, a variety of brain lesions have been reported as correlates of mania. Bilateral orbitofrontal and right temporal-parietal (47, 48), right basal and medial temporal lobe (49), basal ganglia (50), thalamic (51), and right frontotemporal (52) lesions have all been associated with mania. A young patient with bilateral dorsomedial thalamic lesions exhibited a secondary mania, and a single photon emission computed tomography (SPECT) study revealed hypoperfusion of the bilateral prefrontal regions (53). Subcortical arteriosclerotic encephalopathy (Binswanger’s disease) led to first-episode mania in a 65-year-old man (54). Subcortical hyperintensities have been reported in geriatric patients with mania (11). Jorge et al. (17) found that temporal basal polar lesions were a commonality underlying secondary mania after traumatic brain injury. Jorge et al. reported that this association was significant even after they accounted for lesions in other areas of the brain.

The exact mechanism by which brain insult leads to mania is unclear, although there is evidence of associations between right-sided lesions and mania (46, 55). Fenn and George (56) reported an instance in which a left-sided temporal infarct preceded the first episode of mania in a 78-year-old man. Several researchers have argued that right orbitofrontal damage is the sine qua non of secondary mania (45, 48, 57). Case reports of mania associated with other lesions are consistent with the argument for right orbitofrontal damage, in that there could be disruption of the pathways between limbic or prefrontal areas and other deeper structures, such as the basal ganglia, thalamus, and hypothalamus (50, 58).
Treatment Considerations

The symptomatic treatment of secondary mania in older adults is relatively similar to the treatment of primary mania, but proper treatment demands a determination of the etiology of secondary mania. Here we shall discuss treatment options for behavioral management of acute mania in older adults. Regardless of the agent used, secondary mania typically does not require prophylaxis, as does primary mania.

For acute agitation associated with secondary mania, benzodiazepines and antipsychotics are reasonable choices. Benzodiazepines may be used in the treatment of acute agitation associated with secondary mania, but one must use them cautiously in older adults. Aging tends to slow the oxidative metabolic pathways in the liver, so benzodiazepines that are metabolized through conjugated processes, which are not impaired, are preferred. Thus, a shorter-acting benzodiazepine that is metabolized conjugatively, such as lorazepam, would be a suitable choice.

Atypical antipsychotics lessen many of the complications of typical antipsychotics, but they can cause sedation. Although the Food and Drug Administration (FDA) does not differentiate between primary and secondary mania, it seems reasonable to use atypical antipsychotics while bearing in mind the recent FDA warning regarding death and atypical antipsychotics in older adults. The consensus guidelines on the use of antipsychotics for older adults suggest that a preferred treatment of mania is an atypical antipsychotic and a mood stabilizer (52). Further, the consensus guidelines indicate that the preferred medications could be chosen from risperidone, quetiapine, and olanzapine and, in some instances, aripiprazole as well (52). The major factors influencing selection are the presence of complicating medical conditions, such as constipation, diabetes, etc.

Mood stabilizers, such as divalproex sodium or lithium, are viable treatment options but tend to have more side effects for older adults. Unfortunately, both medications can cause sedation and nausea. Lithium can be especially problematic in older patients because they are more likely to take nonsteroidal antiinflammatory drugs as well, which would reduce the renal clearance of lithium. Moreover, lithium can lead to hypothyroidism. Older adults are often more sensitive to side effects of medications than are younger adults, so doses should be lowered accordingly. Mania associated with structural central nervous system disease may respond better to valproate or carbamazepine (59). To our knowledge, the newer anticonvulsant agents topiramate and lamotrigine have not been studied in this particular patient population (59), and lamotrigine is less desirable because of its protracted titration period. Overall, unless the patient has hepatic failure, divalproex is a reasonable choice for treatment when a mood stabilizer is needed.

Conclusions

Secondary mania in older adults is a serious medical condition that requires a comprehensive differential diagnosis. Older adults are more susceptible to disorders that can lead to secondary mania, so a thorough past psychiatric history is essential. Late-onset bipolar disorder is possible, but it is not the most likely etiology in older adults (3). New-onset mania in older adults calls for neuroimaging studies to rule out tumor and stroke as causes. Pharmacological treatment of the acute condition is largely the same as for primary mania but with doses lower than those for younger adults because of older adults’ slower metabolism and sensitivity to side effects (9). Because secondary mania generally does not require prophylactic treatment, it is questionable whether treatment with divalproex, lithium, or carbamazepine is necessary. Fortunately, the majority of deficits that accompany secondary mania in older adults resolve if the etiology is determined and treated.
54. Hain C, Peter K: [Initial manifestation of a manic syndrome in advanced age in subcortical arteriosclerotic encephalopathy (Binswanger disease)]. Psychiatr Prax 1999; 26:305–307 (German)
George Engel, M.D. (1913–1999)

George Engel’s basic convictions are best known from his "biopsychosocial model," a general theory of illness and healing (1–3). When these ideas were forming in the early 1950s, he had already made a name for himself in neurology and medicine through his studies of fainting, delirium, and ulcerative colitis and was beginning the studies that would document the correlation of loss with the onset of a variety of diseases.

George Engel’s own story, his biopsychosocial profile, highlights the influence of his family—especially his uncle and distinguished biomedical stalwart, Emanuel Libman, and his identical twin, Frank, also a physician, whose death in 1963 imposed a deeply personal sense of loss and self-awareness (4). Dr. Engel’s profile would reflect the physiological orientation of his basic training and early research with Soma Weiss, Ralph Gerard, and, in Leningrad, Alexander Gurwitsch.

Dr. Weiss was his postgraduate mentor at Peter Bent Brigham in 1941. He introduced him to John Romano, M.D., a young psychiatrist; they worked jointly on studies of delirium. He joined with Romano, first tentatively and then wholeheartedly, at Harvard, then in Cincinnati, and finally in Rochester.

An early effect of the Romano-Engel combination was a revolution in medical education at Rochester, bringing together the usual medical-psychiatric distinctions, to the mutual advantage of all (5).

Psychoanalysis and Dr. Engel’s studies with Theresa Benedek played a part in his broadened syncretic view, providing a concept of symbolic use of the body for the expression of fantasy, conflict, or affect. Unlike Franz Alexander, he appreciated that autonomic functioning could serve as an avenue of symbolic expression, an awareness that led to his own and his colleagues’ studies of disease onset and exacerbation.

The Monica case study is probably best remembered by the generations of physicians influenced by George Engel (6, 7). Who can forget the movies of Monica, an infant with esophageal atresia who was fed by gastrostomy, Franz Reichsman (the “friendly doctor”), and George Engel (the “somber stranger”)? We recall her wriggling excitement, beaming smile, and the gastric juice gushing from her gastrostomy tube when Franz approached and her sudden, dramatic quietude, bodily withdrawal, and dry gastric mucosa when George appeared. It was and is a classic case study, followed from 1953 when Monica was 1 year old until Dr. Engel’s death 46 years later. By then Monica was a grandmother, and the family epic—or portions of it—was forever captured on film. From this study came the familiar phrases “conservation-withdrawal,” "giving up—given up,” and “hellessness/hopelessness affect” (8).

In the 1980s and early 1990s, biopsychosocial medicine became the watchword of progressive unification of the medical and behavioral sciences, including psychiatry, in a search for etiological and preventive factors in human health and disease (9). Today that goal has been replaced by neuroscience and a return to descriptive psychiatry.

In his later years, George Engel never lost his good humor, his bite, or his generosity (10). He loved and was deeply loved by the students and physicians who worked and learned with him. He would appreciate the fact that some of us have taken on a bit of his flintiness, attempt his wry humor, and retain his determination to see our patients as “united, biopsychosocial persons” rather than as “biomedical persons” divorced from their psychological and social dimensions.

References

A. SCOTT DOWLING, M.D.

Address correspondence and reprint requests to Dr. Dowling, 22300 S. Woodland Rd., Beachwood, OH 44122-3067; asdowling@msn.com (e-mail). The photograph was provided courtesy of the University of Rochester.
First, let me thank Dr. John Greden for that very kind introduction and, more importantly, for his friendship and strong support of me and my work for so many years.

I owe very special thanks and appreciation to my husband, Dr. Arthur Riba; our daughters Alissa and Erica; family and friends; and my colleagues at the University of Michigan, especially Linda Gacioch.

I am indebted to APA Medical Director Dr. Jay Scully; President-Elect Dr. Steven Sharfstein, who will make a wonderful APA President; Assembly Speaker Dr. James Nininger; and the entire Board of Trustees and Assembly.

It has been a true team effort.

I want to also acknowledge and thank my patients—so incredibly flexible and encouraging. A week ago, I made a home visit to one of my patients who is in hospice care. I didn’t think she was keeping track of my comings and goings, given her declining medical condition, and we had never previously talked about APA. When I was leaving her home, she told me that she was glad that her psychiatrist was the APA President…but glad that I wouldn’t be traveling so much.

It was a reminder that ultimately what we do is about how to best serve our patients. Toward that goal, in the past year, I’m pleased to report that we’ve made great progress in many areas, but I would like to share with you five specific initiatives that will improve how we care for our patients: mental health on college campuses, education in psychiatry, government relations, psychosomatic medicine, and communications.

Let me summarize:

In terms of mental health on college campuses, we realized that there was an important task before us—to better serve the needs of our students with quality and competent mental health services. In fact, the need for mental health services on college and university campuses is increasing because 1) more students enter college already taking psychiatric medications, 2) most colleges report increases in medications being prescribed at their mental health services, 3) most colleges report seeing increases in students with severe psychopathology and comorbidity, and 4) suicide is the second leading cause of death in college students.

I gained greater insight into the issues faced by students during our annual Depression on College Campuses conference at the University of Michigan. We heard from students from around the country. They talked about their difficulties with a range of psychiatric problems, including eating disorders, alcohol, suicide, and depression.

The students told us how hard it was to see a qualified mental health professional and to receive continuity of care. The increased pressures of examinations, being away from home, sleep deprivation, loneliness, availability of drugs and alcohol, loss of privacy, large lecture halls, and lack of structure make for obvious problems.

During my presidency, we decided to begin confronting these issues. We established the APA Presidential Task Force on Mental Health on College Campuses. It is co-chaired by Drs. David Fassler and Rachel Glick. The task force is working on an initiative to increase awareness of the challenges and risks faced during the college years and where students can turn for help and assistance.

It’s some relief to know that we have a number of allies to help address the problem: public policy and coalitions can complement and support our clinical work.

An encouraging development was President Bush’s recent signing of the Garrett Lee Smith Memorial Act. I had the opportunity to be at the White House last fall when this key measure became law. But I also heard firsthand about the tragic incident that prompted the federal government’s new suicide prevention effort: the September 2003 suicide of Senator Gordon Smith’s 21-year-old son.

Indeed, suicide is a very real problem that can touch anyone. I’m thankful that APA is strongly positioned to continue leading on this front. We sincerely appreciate the Smith family’s willingness to turn this tragedy into a positive action for our nation.

So mental health on college campuses has been our first major focus.

The second area of attention has been psychiatric education.

This includes recognizing our teachers, determining what medical students should be learning, and finding ways to encourage and fund research training in medical student and residency education to ensure more attractiveness to the career choice of becoming a physician scientist.

Last month, APA brought together some of our leading educators for a presidential summit to frame the issues for medical student education in psychiatry. The summit provided a forum to develop strategic, new undergraduate medical education curricula in psychiatry. These will incorporate the latest advances in psychiatry content and teaching methods. My appreciation to Dr. Deborah Hales, Director of the APA Division of Education, and to the Association of Directors of Medical Student Education in Psychiatry for its support of this successful summit.

Earlier today, APA’s Council on Medical Education and Lifelong Learning, chaired by Dr. Richard Balon, presented...
the Board of Directors of the American Psychiatric Institute has the full support of APA leadership. Please join me in ex-
in patient-oriented psychiatric research.

to increasing the number of residents who choose careers from assuring research literacy at one end of the spectrum Jay Scully, for placing the full support and resources of APA rector of the APA Division of Research and APIRE; and Dr. Darrel Regier, Di-

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denistry: to develop proposals for implementing recom-

dentations contained in the highly regarded Institute of Medicine report Research Training in Psychiatry Resi-
dency: Strategies for Reform (1). The recommendations en-

compass a variety of goals tailored to residency training in our age of evidence-based medicine. These goals range from assuring research literacy at one end of the spectrum to increasing the number of residents who choose careers in patient-oriented psychiatric research.

Clearly, this is a comprehensive, long-term endeavor. It has the full support of APA leadership. Please join me in ex-

ressing appreciation to Dr. Herbert Pardes, President of the Board of Directors of the American Psychiatric Institute for Research and Education (APIRE); Dr. Darrel Regier, Di-

rector of the APA Division of Research and APIRE; and Dr. Jay Scully, for placing the full support and resources of APA behind this critical initiative for the field of psychiatry. We are also making progress in training patient-oriented psychiatrist-investigators, in adult and child psychiatry. Just over 1 year ago, the Director of the National Institute of Mental Health (NIMH), Dr. Thomas Insel, convened the National Psychiatry Training Council. This is a group of 15 psychiatrists representing the full complement of academic organizations necessary for training and cre-

dentialing future psychiatric practitioners and research-

ers. I am most honored to have the opportunity to serve on this council, chaired by Dr. John Greer and Dr. James Leckman.

The council was formed with an explicit mandate from NIMH: to develop proposals for implementing recom-

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We look forward to working in collaboration with NIMH, the National Institute on Drug Abuse, the National Institute on Alcohol Abuse and Alcoholism, and other in-
stitutes to train more residents choosing a career in pa-


tient-oriented psychiatric research.

So education has been our second important focus. The third area of concentration during my tenure as President has been advocacy.

This includes scope of practice, specifically psychologist prescribing. Over the past year, many of our members and professional staff have continued to actively engage in ad-

vocating for our profession. They have worked diligently to educate and lobby for important issues that impact on patient care.

Let me highlight some of these wonderful advocates and their work. When the 2005 Hawaii psychologist prescribing legislation appeared likely to pass, given the strong push by two Senate committees, Dr. Jeffrey Akaka and his team didn’t give up their fight to defeat this bill. The bill did fail during a full Senate floor vote. How was it defeated? With the strong and enduring leadership of Dr. Akaka, who labeled the bill as “crash course prescribing.” And he led members of the Hawaii Psychiatric Medical Association, the local chapter of the National Alliance for the Mentally Ill, and the University of Hawaii Department of Psychiatry attend-
ings and residents to educate the legislature through phone calls, testimony, and face-to-face visits in their offices on numerous occasions. More than a dozen members of this psychiatry delegation submitted testimony in writing and in person.

I’d like to highlight several other outstanding examples of advocacy.

Dr. Joan Anzia, President of the Illinois Psychiatric Soci-

ety, led a group of 12 attending psychiatrists and residents from Chicago to Springfield, where she testified before a state senate committee on psychologist prescribing legis-

lation. The committee members were very impressed by the testimony. Thanks to Dr. Anzia and her colleagues, the bill was defeated.

Dr. George Greer has worked tirelessly as the Legislative Representative of the Psychiatric Medical Association of New Mexico. Along with many colleagues, Dr. Greer led an effort to defeat outrageous formulary expansion legisla-

tion. Dr. Greer’s relentless efforts to defeat the bill some-
times called for trekking through rain and snow—make that blizzards. The hard work of Dr. Greer and his col-

leagues ultimately paid off with a legislative victory.

Barbara Gard is the longtime Executive Director of the California Psychiatric Association. She is an example of APA’s invaluable resources to other district branch and state association executives. She has generously shared with them her time, legislative experience, and resource materials. Most recently, she served as a member of my Presidential Task Force on Psychologist Prescribing.

Working in full partnership with our district branches and state associations, APA’s Department of Government Relations, under the direction of Nick Meyers and Gene Cassel, and our Council on Advocacy and Public Policy, chaired by Dr. Jeremy Lazarus, continue to provide key support in struggles with efforts by psychologists to secure prescribing privileges. To underscore our continuing com-

mitment to this issue, I appointed a task force, chaired by APA past President Dr. Allan Tasman. The task force re-

ceived more than 500 e-mails and other helpful comments. The task force report was received by the Board of Trustees in March. As a result, we continue to strengthen our com-
prehensive national strategy to better equip our district branches to fight this threat to patient care and safety.

APA’s core values include advocacy for patients and patient-focused treatment decisions. Typical of this is the work of APA Trustee-at-Large Dr. David Fassler, who is a child psychiatrist. David is a true advocate for quality patient care. Over the past year, he has provided enormous leadership and insight on issues ranging from the Task Force for the FDA Black Box Warnings to the recent Supreme Court juvenile death penalty case.

When the Food and Drug Administration (FDA) began scrutinizing selective serotonin reuptake inhibitor (SSRI) antidepressants last year, Dr. Fassler ably represented APA at the hearings and in the media. But it’s just as accurate to say he ably represented children with depression and their parents. Before the FDA’s black box warning, Dr. Fassler voiced deep concerns over whether kids in need of medication would continue to have appropriate access to it. The FDA proceeded and, indeed, prescriptions declined. Dr. Fassler responded by working with colleagues and more than a dozen allied organizations to create an information web site. It has helped hundreds of thousands of parents and physicians make informed treatment decisions.

Please join me in applauding the tremendous work of all our members who advocate for our profession and quality patient care.

The fourth area of focus is nurturing our new field of psychosomatic medicine, which is why we chose this theme for our annual meeting. As the largest gathering in the world of the psychiatric profession, our meeting offers the optimal platform for thoughtful discussion and discoveries in clinical research and education in psychosomatic medicine. I hope you will attend as many of the numerous sessions as possible to learn more about this exciting area.

Our new APA Council on Psychosomatic Medicine, chaired by Dr. Phil Muskin, was created a year ago to address issues critical to psychiatry at its interface with the rest of medicine. These concerns include clinical care, reimbursement, education of psychiatrists and nonpsychiatrists, and research.

The council is exploring the issues of access and reimbursement for psychiatric care in the medical setting, as well as barriers to care, and is developing a research agenda.

Our fifth area of focus has been the all-important job of getting our messages across to the public.

At our April 12 Academic Consortium, Representative Patrick Kennedy noted the impact of federally funded research on mental illness. As he put it, “Today, thanks to that research, patients who would otherwise be consigned to a lifetime of inpatient treatment are fully functioning in their communities and at home with their loved ones.”

Representative Kennedy said this is one of our brightest success stories. Yet, he said, stigma of mental health issues still remains in the general population and particularly in minority communities. Their members are undertreated and underrepresented in clinical research.

So while APA’s Capitol Hill visits are one way to bring the good news of our success stories to Congress, we also need to energize the public and reach out to minority and underserved groups.

This year we have strengthened our efforts to reach out to the public. We have changed APA’s message to one of hope and determination: “Healthy Minds, Healthy Lives.”

We need to get across the difference between what physicians do and what nonphysicians do—to focus on the greatest benefit we, as psychiatrists, can offer patients. This new public information campaign is designed to achieve this goal. At the same time, it puts a fresh, new face on patient care, APA, and our profession; it addresses stigma associated with mental illness; and it highlights the importance of seeking treatment from psychiatric physicians.

This awareness campaign is a step forward in strengthening APA as the leading voice on mental health. And it’s a step forward in promoting our members as the leading providers of psychiatric care. Let us thank the APA communications team, led by Lydia Sermons-Ward, and the Division of Advocacy in helping us reach the public with these important messages.

APA has made great strides in diversifying its staff and programs to better connect with people from many walks of life. Our understanding of and ability to treat multiethnic and multicultural populations is an important part of our efforts in advocating for the scientific basis of psychiatry.

Our work with the World Psychiatric Association and its leaders, under the direction of Dr. Ahmed Okasha, has helped us better understand and appreciate psychiatric issues across the globe.

And thanks to the work of Dr. Annelle Primm, Director of APA Office of Minority and National Affairs, we are expanding our reach into, and improving understanding of the needs of, minority communities. APA is developing programs and events that focus on the interests and recruitment of minority psychiatrists, as well as the elimination of mental health disparities in underserved ethnic and racial groups.

All the colleagues I have mentioned today, and so many more, have helped us achieve progress this year on 1) mental health on college campuses, 2) education in psychiatry, 3) government relations, 4) psychosomatic medicine, and 5) communications.

Finally, I want to share with you what a deep honor and privilege it has been to serve you as your President. We, as psychiatrists, are fortunate to be leaders in many efforts to intervene in support of our fellow citizens and their well-being. Our clinical work, research, teaching, advocacy, and our efforts across specialties are interrelated—each part is vital to safeguarding mental health, always putting patients first.
We owe our patients a debt of gratitude. They are our highest priority, and it is a privilege to be their physicians.

In addition, we owe our colleagues in medicine and mental health many thanks. Our colleagues challenge us and support us. Through allied organizations and advocacy groups, we are able to collaborate to achieve the best results for our patients and their families.

Most important—I want to express to you my admiration and sincere appreciation. This is your association and your profession. I am grateful to all of you for your confidence in me to lead the American Psychiatric Association. Your support, your ideas, your energy—these are the elements that have made for a spectacular year as your President, and I thank you.

Presented at the 158th Annual Meeting of the American Psychiatric Association, Atlanta, May 21–26, 2005. Dr. Riba, 131st President of the American Psychiatric Association, is Associate Chair for Integrated Medicine and Psychiatry Services and Clinical Professor, Department of Psychiatry, University of Michigan, and Director of the Psycho-Oncology Program, University of Michigan Comprehensive Cancer Center. Address correspondence and reprint requests to Dr. Riba, Rm. F6236, MCHC, Box 0295, Department of Psychiatry, University of Michigan, 1500 East Medical Center Dr., Ann Arbor, MI 48109-0295; mriba@umich.edu (e-mail).

Reference
Response to the Presidential Address: Advocacy for Our Patients and Our Profession

Steven S. Sharfstein, M.D.

Thank you. It is with great pleasure that I assume the Presidency of the American Psychiatric Association, following in the footsteps of the outstanding leadership provided by Dr. Michelle Riba. Dr. Riba has brought psychiatry and medicine closer together through her active involvement in the subspecialty of psychosomatics, has highlighted the importance of college mental health and suicide on campuses, and during difficult times, has led the Association with sensitivity, courage, and good humor.

For me, the path to the Presidency of APA has been a long and winding professional journey, a real mental health marathon.

From my residency days in Boston and my work as a community psychiatrist...to Washington, D.C., where I led the federal Community Mental Health Centers Program and helped Rosalynn Carter in her fight to expand access to care.

Then on to the National Institutes of Health, where, as Director of Behavioral Medicine, I puzzled over the psychiatric manifestations of a new immune system disorder called AIDS. From there to the staff of the American Psychiatric Association, where, as Deputy Medical Director, I gained a true appreciation of our complicated and challenging profession.

For the last 19 years, I have run a nonprofit psychiatric hospital system in Maryland, in an era of transformation for the psychiatric hospital. On my watch, our average length of stay dropped from 80 days to 10 days. We survived by expanding our services into community-based settings, special schools for youth, general hospitals, housing, and rehab. And now we are the largest psychiatric care system in Maryland, treating almost 40,000 individuals a year in 33 locations throughout the state.

During this entire time, I have continued to treat patients, publish papers on the economics of psychiatry, and escalate my involvement in APA. This involvement culminated in five campaigns for national office, including a very memorable one 10 years ago, which I lost to my friend Harold Eist.

After this election, I considered restarting my psychoanalysis. But instead, I hit the campaign trail again. Maybe that was a mistake, and I should have returned to the couch.

During these last several campaigns, I spoke with hundreds of psychiatrists about the issues you face and the challenges you have to meet.

Many of you assailed the abuses of managed care. Others expressed concern about the threat of prescribing by psychologists. Some criticized the excessive influence of pharmaceutical companies, others bemoaned the stigma that pervades not only the mentally ill but also the profession that treats them.

I have tried to keep all of these challenges in mind as I have prepared to assume the Presidency of APA. As today has approached, I have asked myself what I can give back to a profession that has given so much to me.

And I have concluded that I gain nothing by mincing words.

Today, I have a simple and candid message. All of the various issues that you and I have discussed over the years are important and deserve APA’s effort and attention.

But none can be solved without addressing a more fundamental problem—a crisis of credibility for American medicine and American psychiatry.

If we step back and survey the health care system, it is not difficult to see what is wrong.

One problem is access. Millions of Americans need care and cannot get it. There are 45 million Americans without health insurance. There are another 20 to 30 million whose coverage for treatment for mental illness is so minimal that they are essentially uninsured.

A second problem is cost. Twenty years ago, health care represented about 10% of the gross domestic product. Today, it is nearly 15% and growing. By 2014 it is estimated to approach 20%, with $3.6 trillion being spent on health care.

The third problem is quality. How well we care for patients is rarely measured and even more rarely reimbursed.

Problems with access, cost, and quality—these are the three sides of an iron triangle that undermines care, satisfaction, and medical progress.

In the face of these challenges, the question everyone asks is, “What should be done?” Yet this may be the wrong question to start with. There is a blizzard of policy proposals that sit unadopted, because nobody has the moral authority to pull together a winning political coalition.

So I would like to draw your attention to a more fundamental question: Who can be trusted to lead?

In one corner, we hear the voice of consumers arguing that the patient and family know best.

In another corner, there are the insurers and employers who tell us to follow the Golden Rule. He who has the gold makes the rules.

In a third corner, large pharmaceutical companies claim that the key to the future is research innovation, and the
key to innovation is adequate investment—which requires them to charge high prices.

And then there is our profession.

Unlike consumers, we understand the basics of illness and how to treat it. Unlike insurers, our duty and our Hippocratic Oath are to the patient and not the payer. Unlike drug companies, we recognize that innovative pharmacotherapies are just a small part of the successful management of illness.

Only the psychiatric profession can provide access to care, manage the costs, and ensure quality.

Only doctors are willing to justify the care we provide, respond to the needs of our community, and fight for those who are disenfranchised.

Only doctors have the moral and intellectual authority to break this iron triangle.

Yet, we are failing to lead.

In my view, the problem is not that we don't have the right ideas or solutions. The American Psychiatric Association supports access to universal health care and fights for the patients. Let me quote from our vision statement:

Every American with significant psychiatric symptoms should have access to an expert evaluation leading to accurate and comprehensive diagnosis, which results in an individualized treatment plan that is delivered at the right time and place, in the right amount, and with appropriate support such as adequate housing, rehabilitation, and case management when needed. Care should be based on continuous healing relationships and engagement with whole persons rather than a narrow, symptom-based, symptom-focused perspective. Timely access to care and continuity to care remain today the cornerstones for quality.

The problem is not our policy positions. It is that our profession lacks credibility and leverage.

When we speak, too few listen.

And to a large extent, we have only ourselves to blame.

Let me explain.

We do not ensure quality in our own ranks. Our system of self-discipline is erratic, inconsistent, and also not in the public interest. We allow an unacceptable rate of medical errors in our practice, even as we campaign for tort reform.

We have let the biopsychosocial model become the bio-bio model.

As a profession we have neglected the uninsured, the poor, the needy, and the seriously and persistently mentally ill.

We allow gross disparities in health care for racial and ethnic minorities even as we ask for better reimbursement.

We have addressed the challenge of managed care erratically. Many of us opt out of managed care altogether. Others acquiesce to unreasonable limits on the quality and quantity of care.

We have allowed ourselves to be corrupted in this marketplace with lucrative consulting to industry, speaker panels, boards of directors, and visits from industry representatives bearing gifts.

We compromise the core value of confidentiality in an effort to guarantee payment and stay on managed care panels.

We are seen, above all, as an interest group, a trade association, and too often we have behaved like one.

So, in my view, the central issue facing American psychiatry is our credibility. The health care system is in crisis and there is a leadership void. But the days of ringing a bell and expecting to be in charge because we've gone to medical school are over.

We must earn back our moral authority.

We must regain the public's trust.

Let me suggest three steps to this goal:

First, we must recommit ourselves to advocating for our patients. Individuals with mental illness are stigmatized, mistreated, and ignored. We must strongly advocate for better care in battles with insurers and discussions with policy makers. The unconscionable cuts in federal Medicaid passed recently by Congress will hurt our patients first and foremost. Medicaid is the safety net program for the seriously and persistently mentally ill. They will be neglected during this period of fiscal retrenchment unless funding is restored.

Our advocacy must extend beyond the doctor-patient relationship to broader issues of the public health. Thousands of youth are incarcerated unnecessarily each night because community mental health services are not available. This must be psychiatry's concern.

Adults with mental illness are shot and killed by police who have little or no training to deal with them. This, too, must be psychiatry's concern.

We will not always agree with the consumer movement. But we can do much more to show that our disagreements are born of our judgment, not our self-interest. We must make creative alliances with such groups as the Alliance for the Mentally Ill and the Mental Health Association in pursuing our objectives. The advocacy of Nada Stotland, APA Trustee, with the Mental Health Association is one example of psychiatric advocacy at its best.

Our second step toward credibility is to create and enforce ethical standards to make the rest of our nation take note.

While there are many ethical areas for improvement, let me briefly mention the topical issue of the relationship between psychiatrists and the pharmaceutical companies. It is my view that these relationships have been rife with the appearance of conflict of interest and, frankly, with conflict of interest itself.

These topics are becoming better known to the public. We must stay ahead of the curve, evaluate arrangements, provide guidance, and set standards. We must strengthen the integrity of our continuing medical education. Ultimately, we must recognize that pharmaceutical compa-
nies, as profit-seeking companies, make offers that can and must be refused.

Our third step is to defend our core professional values, including confidentiality, academic inquiry, and scientific integrity.

It is not proper in an age of terrorism to insist upon total confidentiality of our records. But it is appalling that the government, through the Patriot Act, has the right not only to see our records but also to forbid us from telling our patients of this breech. Speaking up for confidentiality, even if we have a lone voice, is absolutely essential to our credibility and our professionalism.

Another core value is academic inquiry. As a scientific profession, we need data. It is unacceptable for any drug company to withhold clinically important information from us and our patients. Thanks in large part to the efforts of Dr. David Fassler, another wonderful advocate for American psychiatry, APA has made great progress in access to data. We continue to fight for legislation establishing a registry for all clinical trials.

And then there is the core value of scientific integrity. On the fringes of the political spectrum are individuals who want to shut down mental health as a field, maybe because it involves medications, or it involves vulnerable groups in our society, or they believe there is no such thing as mental illness.

Sometimes these fringe individuals and organizations are surprisingly close to the political centers of power. For example, a member of Congress, Representative Ron Paul, is crusading against psychiatric care for children. He claims that psychiatric diagnosis is inherently subjective, that psychiatric treatments frequently ruin the developing brains of children, and that mental health screening in schools has—and I quote—“no place in a free and decent society.”

Let me send a message today to Representative Ron Paul, a physician. As President of the American Psychiatric Association, I support a “free and decent society.” A society where all youth and their families can obtain care for devastating mental illnesses. A society where parents have the freedom to seek such care without the stigma that you spread with your ignorant attacks.

Threats to scientific integrity are also coming from government agencies that our profession has long respected. Just a few months ago, officials at the Substance Abuse and Mental Health Services Administration demanded that researchers presenting a study about the suicidality of gay, lesbian, bisexual, and transgender individuals not use the words “gay,” “lesbian,” “bisexual,” and “transgender.”

Now, some might say that we need to overlook such incidents and defer to those in power to avoid losing some of the little perks that an Administration can offer. This type of thinking is penny wise and pound foolish. If we abandon our core principles, then we lose our moral and professional authority—which is the light we must use to lead.

Telling researchers to delete the words “gay,” “lesbian,” “bisexual,” and “transgender” was a profound insult, not only to all of us who support the rights of gays and lesbians, but to science itself. When asked by the Washington Post to respond to scientists’ concerns, the Administration’s spokesperson took offense at protests from—and I quote—“these people.”

We need to send a memo. TO: Anyone who will try to interfere with scientific progress on mental health and psychiatry FROM: The American Psychiatric Association MESSAGE: We are “these people.”

During my Presidential term, I will work on psychologists’ prescribing, malpractice, parity, and other issues. Above all, I will work tirelessly to enhance the credibility of our profession.

If you are already shaking your head, let me console you with a little cognitive behavior therapy. Just keep reminding yourself that my term, as any Presidential term, is only a year. No one person can do too much damage.

But if you share my concern about our profession and its future, I urge you to become more involved in APA. Urge your colleagues to join APA and give back. Become active at the local and national levels, and advocate.

This is a message that I know would have pleased my good friend, Jay Cutler, who served as the chief lobbyist and advocate for the American Psychiatric Association for over 25 years. Jay died just a few weeks ago. When I visited him in the hospital, on the day before he died, he apologized to me. He said he was sorry because he knew that he would not make it to Atlanta to hear this speech. That’s the kind of person Jay was. My commitment to advocacy is inspired by Jay’s example.

In Jay’s honor, let us set a goal of transforming psychiatry, setting examples for American medicine, and ultimately remaking our flawed health care system.

This is not just a goal worthy of our profession. It is the only goal worthy of our profession. Let us all “give back through advocacy.” Thank you very much.

Presented at the 158th Annual Meeting of the American Psychiatric Association, Atlanta, May 21–26, 2005. Dr. Sharfstein, 132nd President of the American Psychiatric Association, is President and Chief Executive Officer of Sheppard Pratt Health System, Baltimore, and Clinical Professor and Vice Chair of the Department of Psychiatry, University of Maryland School of Medicine, Baltimore. Address correspondence and reprint requests to Dr. Sharfstein, Sheppard-Pratt Health System, 6501 North Charles St., Towson, MD 21204-6819; ssharfstein@sheppardpratt.org (e-mail).
Michelle Riba, M.D., M.S., 131st President, 2004–2005

John F. Greden, M.D.

I have the distinct honor of introducing Dr. Michelle Riba, President of our esteemed American Psychiatric Association.

I will begin her introduction with a story. I first met Michelle in 1993 when we recruited her for a position at the University of Michigan. As the interview closed, I looked at her and asked, “How long do you suppose it will take before you become President of the American Psychiatric Association?” Despite preconceived stereotypes among some in our society about psychiatrists, I had no crystal ball. Michelle simply radiated leadership 12 years ago even as she does now. A few selected examples illustrate her wide-ranging skill sets.

First, Michelle is a world leader in education. Teaching appears to be in her genes. Indeed, before becoming a psychiatrist, she taught high school chemistry and biology. At the University of Michigan Department of Psychiatry, she served first as our Director of Residency Education and later as Associate Chair for Education and Academic Affairs. She has received APA’s Nancy Roeske award for excellence in medical student education twice and served as President of both the American Association of Directors of Psychiatric Residency Training and the Association for Academic Psychiatry. When the Institute of Medicine compiled a team to help remedy the severe shortage of academic psychiatry clinical investigators, Michelle was appropriately asked to be a member of that elite group. As APA President, she has played a key role in the National Psychiatry Training Council, which the National Institute of Mental Health established to implement the Institute of Medicine guidelines. I have the privilege to co-chair that group, a collection of ALL key players in the field, and as a side commentary, it is my hope that all members of our profession will recognize and support this vitally important effort to create a new generation of academic psychiatrists.

In clinical domains, Michelle excels in consultation-liaison psychiatry. Some teach and talk collaboration; Michelle exemplifies it. At Michigan, she led the development of the PsychOncology Program and serves as its Director. The Ford Motor Company awarded her the “Partners in Health Award”—the Cancer Center’s highest annual honor—for this program.

I recently asked Dr. Riba to assume a new position as Associate Chair for Integrated and Collaborative Services in our department. This new position requires her to lead, develop, organize, integrate, and manage new opportunities for clinical, educational, and research collaborations among our Department of Psychiatry and the Depression Center, on the one hand, and other Centers of Excellence within our health system, on the other. Without such bridge building, it is my belief that psychiatry will not succeed in forging and solidifying the partnerships that enable our most promising tremendous scientific advances to be translated into the mainstream clinical delivery in our nation’s complex health system.

Academically, Dr. Riba is a prolific, practical, and powerful voice. She has over 100 peer-reviewed articles, chapters, and abstracts and has edited or co-edited more than 25 books. She is an administrative legend. She prioritizes, organizes, and accomplishes, quietly juggling multiple projects without ever appearing to be multitasking, and is not afraid to dream. She also is not afraid to take positions that firmly defend values of importance to our patients and families and that emphasize the role of psychiatrists in their care. For example, she recently launched a task force on college mental health, emphasizing the essential participation of psychiatrists in the delivery of care for our student populations.

Finally, Michelle is a wonderfully balanced individual: a dedicated daughter, a remarkable spouse to Artie, and a devoted Mom for Elisa and Erica. In essence, she does it all. The American Psychiatric Association has been privileged to be led by this President, Dr. Michelle Riba.

Dr. Greden is Rachel Upjohn Professor of Psychiatry and Clinical Neurosciences and Chair, Department of Psychiatry; Executive Director, University of Michigan Comprehensive Depression Center; and Research Professor, Molecular and Behavioral Neuroscience Institute, University of Michigan. Address correspondence and reprint requests to Dr. Greden, Department of Psychiatry, University of Michigan, MCHC Box 0295, 1500 East Medical Center Dr., Ann Arbor, MI 48109-0704; gredenj@umich.edu (e-mail).
Objective: The purpose of the study was to develop a strategy for functional imaging of neurodegenerative disorders that overcomes confounds associated with differential performance between patient and comparison groups.

Method: Functional magnetic resonance imaging was used to examine responses to increasing difficulty of visuospatial paired associate learning in 12 patients with mild probable Alzheimer's disease and 12 age-matched healthy comparison subjects. Performance was matched across groups by only examining successful encoding and retrieval attempts. Adjustment for task difficulty was made on an individual basis so that the patients with Alzheimer’s disease and the comparison subjects performed at the same relative levels of difficulty.

Results: A network of lateral and medial frontoparietal and occipital regions was engaged in all subjects during successful associative learning. As task difficulty increased, blood-oxygen-level-dependent responses increased linearly in occipito-parietal regions during encoding and retrieval. Differential activations in patients with Alzheimer’s disease and comparison subjects were small and were found only when an uncorrected statistical threshold was used.

Conclusions: By controlling for confounds of varying task difficulty and subsequent performance, remarkably similar brain activations were identified during successful paired associate learning in patients with Alzheimer’s disease and in healthy comparison subjects. The study methods provide a useful model for further applications of functional imaging involving cognitive activation paradigms in the study of neuropsychiatric disorders.

A major limitation of functional activation imaging studies in Alzheimer’s disease has been failure to control for differences in levels of task performance and effort across groups of patients and healthy subjects. Little consideration is typically given to such potential confounds, with differences in brain activity between patient and comparison groups often being interpreted as a reflection of intrinsic cognitive deficits. However, there is no reason to assume that the same cognitive processes are in operation when a task is performed at an 80% success level, compared to a 20% success level. Accordingly, brain activity under two such conditions may reflect fundamentally different cognitive operations.

Unfortunately, to date, most functional imaging studies of Alzheimer’s disease have failed to control for the effects of performance and task difficulty. For example, increased hippocampal activation was found in comparison subjects, relative to patients with Alzheimer’s disease, during encoding of color pictures (1). Subsequent mean correct picture recognition scores, however, were 63% in the comparison subjects and only 13% in the patients with Alzheimer’s disease. A similar study found greater medial temporal lobe activity during encoding of photographs in comparison subjects than in patients with Alzheimer’s disease, accompanied by significantly better performance in comparison subjects on measures of free recall (6.1 of 12 versus 1.75 of 12) and recognition (96.1% versus 85.7%) (2). During a task involving novel versus familiar face-name encoding, patients with Alzheimer’s disease were found to additionally activate the left precuneus, fusiform gyrus, posterior cingulate, and dorsolateral prefrontal cortex and bilateral middle temporal gyrus, while the comparison subjects showed greater activation within the right hippocampal formation (3). However, the comparison subjects were found to correctly recognize and name more faces than the patients with Alzheimer’s disease (face recognition: 78% versus 60%; name recall: 40% versus 12%). Finally, different networks of brain activity underlying semantic and episodic memory have been identified in patients with Alzheimer’s disease, relative to comparison subjects (4). However, patients with Alzheimer’s disease performed less well than the comparison subjects on the semantic and episodic tasks, with approximately one-fourth of the patients scoring below the score expected by chance. In all of these studies, variations in performance between the patient and comparison groups mean that observed functional differences could just as likely represent the effects of patients’ working harder at the tasks (because of greater subjective task difficulty) or performing less well than healthy comparison subjects.
One strategy to overcome nonequivalent task-related difficulty and performance involves manipulation of task difficulty such that performance is matched at an individual level. Although some studies have attempted to examine or control for performance differences between younger and older adults (5–7), this adjustment has rarely been attempted in Alzheimer’s disease imaging studies. In a study in which this adjustment was made by manipulating task difficulty so that both patients and comparison subjects achieved 75% accuracy, different brain networks were found to be active during serial verbal recognition learning in patients with Alzheimer’s disease, relative to the comparison subjects (8). Manipulation of task difficulty across groups in order to control for performance by using a task more sensitive to Alzheimer’s disease has yet to be tried, however.

In the current study, a visuospatial paired associate learning task was used, because this type of learning is known to be impaired early in the course of Alzheimer’s disease (9), and was combined with the experimental control of performance success and relative task difficulty across groups. We predicted that the patients with Alzheimer’s disease and comparison subjects would display similar functional responses during encoding and retrieval of object-location pairs if task performance were matched across groups. We further predicted that brain regions demonstrating linear and nonlinear relationships between task difficulty and the blood-oxygen-level-dependent (BOLD) response would be located in similar areas to those identified in our previous visuospatial paired associate learning study (10).

**Method**

**Subjects**

Twelve patients who met the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association criteria (11) for mild probable Alzheimer’s disease and 12 age-matched healthy comparison subjects were recruited. Seven patients were receiving treatment with cholinesterase inhibitors. Subjects were screened for concomitant serious medical diagnoses and previous psychiatric history and were assessed with a comprehensive battery of neuropsychological tests, including the Mini-Mental State Examination, Geriatric Depression Scale (12), Dementia Rating Scale-2 (13), logical memory test from the Wechsler Memory Scale (14), and National Adult Reading Test (15) (Table 1). All subjects provided written informed consent before participating in the study. The study had been approved by the Research Ethics Committee of the South London and Maudsley Trust.

**Materials and Procedure**

During the visuospatial paired associate learning task, subjects were required to remember the locations of objects that appeared on a computer screen (Figure 1). An object appeared in a white box for 5 seconds and was replaced after 500 msec by another object in a different location until all of the objects in that problem were presented (encoding phase). During encoding subjects heard the instruction “remember.” After 6 seconds, a previously presented object appeared in one of the boxes with the question “Was this here?” (retrieval phase). Subjects were required to make a recognition decision (yes/no) by pressing one of two response
FIGURE 1. Visuospatial Paired Associate Learning Task Presented to Patients With Alzheimer’s Disease (N=12) and Healthy Comparison Subjects (N=12));

Subjects were required to remember objects and the locations in which they appeared. Task difficulty was varied by increasing the number of objects and locations presented in each problem. The example problem shown has three objects and six locations.

keys. If the subject made no response, then the object remained on the screen for 5 seconds. If a response was made, the object disappeared and all locations remained blank until 5 seconds had passed. After 500 msec another object was presented, and the process continued until all objects presented during encoding had been tested. At the end of each retrieval phase, there was a baseline rest period (8 seconds if unsuccessful, 11 seconds if successful or if five failed attempts had been made) before the next encoding phase. After an incorrect attempt, the same object-location pairings were repeated in a different order in the next attempt at the problem. This procedure continued until there was correct identification of all object-locations, or until five successive attempts had been failed, after which subjects were presented with new object-location pairings.

Before scanning, all subjects received off-line testing to identify individual levels of increasing difficulty that could be successfully performed in the scanner. Difficulty was manipulated by varying the number of objects and locations in each problem (Table 2). Problems were pseudorandomly presented at each difficulty level so that no more than two problems at the same level appeared consecutively. The comparison subjects completed three practice sessions, which took place 3–4 days before the first scan, 1 hour before the first scan, and 1 hour before the second scan. The patients with Alzheimer’s disease completed five practice sessions at 6–7 days, 3–4 days, and 1 hour before the first scan and at 3–4 days and 1 hour before the second scan. After scanning, the subjects rated the subjective difficulty at each level of the task.

Image Acquisition

Data were acquired on the 1.5-T General Electric Neuro-optimized Signa LX Horizon system (General Electric, Milwaukee) at the Maudsley Hospital. In each functional series, 150 T2*-weighted images depicting BOLD contrast were acquired by using an interleaved echo planar sequence at 16 axial slices (TR=2000 msec, TE=5.8 msec, TR=17.1 msec, flip angle=20°, matrix=256×256, thickness=1.5 mm). An 8 mm full width at half maximum Gaussian kernel (18) was used to remove low-frequency noise. Successful encoding and retrieval performance was assessed by using Mann-Whitney U tests.

Data Analyses

Two-way mixed analyses of variance with task difficulty as a within-subjects factor and group as a between-subjects factor were used to assess behavioral data. Mean response times to incorrect trials at each subject’s hardest level of difficulty were submitted to an independent samples t test. Neuropsychological test performance was assessed by using Mann-Whitney U tests.

By using statistical parametric mapping (16), functional data were slice-timing corrected, realigned to the first echo-planar imaging volume and unwarped to correct for motion-related variance, coregistered to the high resolution T1-weighted image, normalized by using affine transformations into standard space (17) based on the Montreal Neurological Institute reference brain, and spatially smoothed with an 8 mm full width at half maximum Gaussian kernel (18). Data were then parametrically analyzed to identify regions displaying differential responses to increasing task difficulty. Within the general linear model, task difficulty was regressed onto the BOLD response to the onset of stimuli, and data were modeled with an epoch design convolved with a canonical hemodynamic response function. Encoding epochs were calculated from the first object’s presentation onset to the last object’s offset, and retrieval epochs were calculated from the first object’s presentation onset to the last object’s response time onset (or presentation offset if no response was made). Epochs corresponding to two, three, four, and five objects lasted 11, 16.5, 22, and 27.5 seconds, respectively. A 128-second high-pass filter was used to remove low-frequency noise. Successful encoding and retrieval epochs were modeled as separate covariates of interest,
Behavioral Data

Behavioral data are presented in Table 1, Table 2, and Table 3. Subjective task difficulty ratings were collected only from comparison subjects because the patients with Alzheimer’s disease did not provide reliable reports. For the mean number of attempts per problem, all main effects and interaction terms were significant (task difficulty: F=20.08, df=3, 66, p<0.0005; group: F=11.12, df=1, 22, p<0.005; interaction: F=3.88, df=3, 66, p<0.05). Post hoc Tukey’s pairwise comparisons revealed that the patients with Alzheimer’s disease made a greater mean number of attempts per problem at the hardest level of difficulty. For the mean number of successful problems, the main effect of task difficulty was significant (task difficulty: F=3.11, df=3, 66, p<0.0005), whereby ratings were collected only from comparison subjects because the patients with Alzheimer’s disease did not provide reliable reports. Results

and unsuccessful epochs and the 6-second interval between encoding and retrieval phases were covariates of no interest.

Load-independent and load-dependent relationships between task difficulty and BOLD responses were assessed by using polynomial regression in which zero-order (boxcar), first-order (linear), and second-order (nonlinear quadratic) terms were compared to a resting baseline. Using this method, we were able to identify both increases in activation and deactivation with increasing task difficulty. Contrast images generated from parameter estimates were entered into one- and two-sample t tests (accounting for subject-to-subject response variability at the random-effects level) to form statistical parametric maps of the z statistic. Voxel-level contrasts were thresholded at p<0.05 (false discovery rate corrected for multiple comparisons), unless stated otherwise, and activations were reported only if the clusters consisted of at least five contiguous voxels. Statistical parametric map coordinates were converted from Montreal Neurological Institute coordinates to standard space to better localize activations by using the Talairach and Tournoux atlas (19).

Encoding and retrieval epochs associated with success, compared to failure, were also assessed. Data were examined as for the parametric analyses with the following exceptions. Only epochs relating to the hardest level of difficulty were assessed to ensure approximately equal success versus failure epochs (in which there were 1 plus incorrect retrieval decisions). This procedure resulted in exclusion of data from two patients and two comparison subjects because of insufficient data associated with failure. All other epochs at easier levels of task difficulty and the encoding/retrieval interval were modeled as covariates of no interest. Contrast images of the difference between correct and incorrect epochs were generated for each subject. The statistical parametric map of this contrast was then masked with a statistical parametric map of the contrast (corresponding to correct plus incorrect attempts > rest) to separate differential activations from suppressions with respect to baseline.

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(2972.8 msec, SD=278.5) and the comparison subjects (2859.9 msec, SD=374.0) (t=0.65, df=12, p=0.53).

**Functional Data**

**Within-group analyses.** Characterization of the relationship between task difficulty and the BOLD response using a zero-order function revealed similar patterns of activation underlying successful visuospatial paired associate learning in all subjects (Figure 2, Table 4). During encoding, significant activations that were independent of task difficulty were observed bilaterally in the superior parietal lobule (Brodmann's area 7, which extended to the occipital gyrus, inferior parietal lobule, and precuneus) and in the middle frontal gyrus (Brodmann's area 46/9, Brodmann's area 46, extending to the anterior cingulate and inferior frontal gyrus). During retrieval, significant activation changes were located in the right precuneus (Brodmann's area 7, including the superior parietal lobule), left medial frontal gyrus (Brodmann's area 6), and bilaterally in the middle frontal gyrus (Brodmann's area 9,
encoding, which approached significance (p=0.06, corrected); cluster size >4 for all activations.

Cluster included the right inferior parietal lobule (Brodmann’s area 19). 

Cluster included the right inferior frontal gyrus (Brodmann’s area 46). 

Cluster included the left anterior cingulate (Brodmann’s area 32). 

Cluster included the left inferior and middle frontal gyri (Brodmann’s areas 45, 6). 

Cluster included the right inferior parietal lobule (Brodmann’s area 40). 

Cluster included the right middle frontal gyrus (Brodmann’s area 46). 

Cluster included the left superior parietal lobule (Brodmann’s area 7). 

Cluster included the left superior occipital gyrus (Brodmann’s area 19) and the left inferior parietal lobule (Brodmann’s area 40).

Cluster included the right middle frontal gyrus (Brodmann’s area 19). 

Cluster included the right precuneus (Brodmann’s area 7). 

Cluster included the right middle frontal gyrus (Brodmann’s area 19, Brodmann’s area 18), and positive linear increases in deactivation with increasing task difficulty during encoding and retrieval (Figure 3). The main effect of task difficulty was significant (F=2.77, df=3, 66, p<0.05), and the main effect of group and the interaction of task difficulty and group were not significant (group: F=1.84, df=1, 22, p=0.19; interaction: F=0.14, df=3, 66, p=0.93). Furthermore, a comparison of the regression lines for the patient and comparison group revealed a nonsignificant difference between groups in the slope of change in BOLD response with increasing task difficulty (mean difference between slopes=0.00001, SD=0.00003) (t=0.16, df=92, p=0.87).

Between-group analyses. All differences in activation between the patients with Alzheimer’s disease and the comparison subjects during visuospatial paired associate learning failed to survive correction for multiple comparisons. It has been argued that correction for multiple comparisons should not be used “when asserting that a response is truly absent at a given location” (20, p. S85). Therefore, in order to avoid the possibility of making a type II statistical error, differences were assessed by using a threshold of p<0.001 (uncorrected for multiple comparisons). Even with this liberal threshold, very few significant differences in brain activation between the patients and
comparison subjects were found (Figure 5, Table 5). Differences in the response to correct, compared to incorrect stimuli between the patients and the comparison subjects also failed to survive correction for multiple comparisons, with only a few differences being significant at an uncorrected threshold of $p < 0.001$ (Table 6).

At $p < 0.001$ (uncorrected), zero-order activations that were greater in the patients, relative to the comparison subjects, were located in the left middle frontal gyrus (Brodmann’s area 9) and the left medial frontal gyrus (Brodmann’s area 6) during encoding and in the left lenticular nucleus during retrieval. Linear signal intensity changes during encoding were observed in the left lateral cerebral sulcus, left inferior parietal lobule (Brodmann’s area 40), and right supramarginal gyrus (Brodmann’s area 40). During retrieval, linear responses were observed in the right superior/medial frontal gyrus (Brodmann’s area 8) and right superior/inferior parietal lobule (Brodmann’s area 7/40). Finally, brain regions demonstrating greater nonlinear responses in the patients than in the comparison subjects were located in the right middle frontal gyrus (Brodmann’s area 10) during encoding and in the right middle temporal gyrus (Brodmann’s area 21) and left precuneus (Brodmann’s area 7) during retrieval.

Differences in activation that were independent of task difficulty and that were greater in the comparison subjects than in the patients were located in the right cerebellum during encoding and in the right superior temporal gyrus/lateral cerebral sulcus (Brodmann’s area 22) during retrieval. Linear task difficulty-dependent activations were found in the precentral gyrus bilaterally (Brodmann’s area 4) during encoding, and no significant activations were observed during retrieval. Finally, nonlinear responses that were greater in the comparison subjects than in the patients were located in the left posterior cingulate gyrus.

- **Zero-Order**:
  - **Encoding**:
  - **Retrieval**:

- **First-Order**:
  - **Encoding**:
  - **Retrieval**:

- **Second-Order**:
  - **Encoding**:
  - **Retrieval**:

Legend:
- Red circles: Alzheimer’s disease patients (N=12)
- Blue circles: Age-matched comparison subjects (N=12)
GOULD, BROWN, OWEN, ET AL.

In this study, both similarities and differences in brain activations underlying paired associate learning were examined in patients with Alzheimer's disease and comparison subjects, after adjustment for differences in performance and task difficulty. Independent of the level of difficulty, the majority of subjects in both groups activated a network of brain regions, including the anterior cingulate, lateral, and medial occipitoparietal and frontal cortices, during successful encoding and retrieval. Activations and deactivations in lateral and medial occipitoparietal areas were found to be better characterized by positive linear response functions, especially during retrieval rather than encoding. Greater linear responses during retrieval than encoding most likely reflect fewer cognitive demands during encoding, especially when multiple exposures to stimuli may have reduced the need for information to be encoded. The interactions of group and task difficulty revealed some small but significant differences in activation (albeit at an uncorrected threshold) in cerebellar, temporal, precentral, and posterior cingulate regions (comparison subjects > patients) and in frontalparietal regions (patients > comparison subjects).

Cognitive Function of Brain Regions Associated With Paired Associate Learning

Lateral parietal activations reported during episodic tasks are thought to reflect recognition processes (21) and retrieval processing of spatial information (22). Medial parietal activity has been proposed to underlie imagery (23) and retrieval success (24), and activity in the occipital cortex has been related to perceptual and recognition processes (25). Of the activations within the frontal regions, those in the anterior prefrontal cortex have been attributed to retrieval mode (26) and to postretrieval monitoring (27), while dorsolateral prefrontal cortex activations have been related to monitoring and verification processes and semantic production operations during episodic retrieval (28). Dorsolateral prefrontal cortex activity has also been associated with increasing task difficulty rather than mnemonic processes (29). Other studies have demonstrated increases in anterior cingulate activation during cognitively demanding tasks (30), and such activation has been attributed to inhibition of inappropriate responses (31) and initiation or willed control of behavior (32). Cerebellar activity has been commonly reported in studies of episodic retrieval and has been related to retrieval effort and mode (33) and self-initiation of retrieval processes (34). Finally, frontoparietal activity observed in the current study may also reflect practice-related effects.

TABLE 5. Regions Displaying Zero-Order, Linear, and Nonlinear Differential Activations During Encoding and Retrieval in a Visuospatial Paired Associate Learning Task in Patients With Alzheimer's Disease (N=12) and Healthy Comparison Subjects (N=12)

<table>
<thead>
<tr>
<th>Comparison and Region</th>
<th>Hemisphere</th>
<th>Brodmann’s Area</th>
<th>Talairach Coordinates</th>
<th>z Score</th>
<th>p &lt; 0.001, uncorrected, cluster size &gt;4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients &gt; comparison subjects Encoding &gt; baseline Zero-order responses</td>
<td>Left</td>
<td>9</td>
<td>–36</td>
<td>27</td>
<td>37</td>
</tr>
<tr>
<td>Middle frontal gyrus</td>
<td>Left</td>
<td>6</td>
<td>–16</td>
<td>5</td>
<td>55</td>
</tr>
<tr>
<td>Linear responses</td>
<td>Lateral cerebral sulcus</td>
<td>Left</td>
<td>–38</td>
<td>–34</td>
<td>20</td>
</tr>
<tr>
<td>Inferior parietal lobule</td>
<td>Left</td>
<td>40</td>
<td>–54</td>
<td>–51</td>
<td>23</td>
</tr>
<tr>
<td>Supramarginal gyrus</td>
<td>Right</td>
<td>40</td>
<td>46</td>
<td>–55</td>
<td>32</td>
</tr>
<tr>
<td>Nonlinear responses: middle frontal gyrus</td>
<td>Right</td>
<td>10</td>
<td>28</td>
<td>51</td>
<td>18</td>
</tr>
<tr>
<td>Retrieval &gt; baseline Zero-order responses: lentiform nucleus</td>
<td>Left</td>
<td>8</td>
<td>12</td>
<td>41</td>
<td>38</td>
</tr>
<tr>
<td>Linear responses</td>
<td>Superior/inferior parietal lobule</td>
<td>Right</td>
<td>7/40</td>
<td>42</td>
<td>–50</td>
</tr>
<tr>
<td>Nonlinear responses</td>
<td>Middle temporal gyrus</td>
<td>Right</td>
<td>21</td>
<td>44</td>
<td>–45</td>
</tr>
<tr>
<td>Precuneus</td>
<td>Left</td>
<td>7</td>
<td>–18</td>
<td>–66</td>
<td>36</td>
</tr>
<tr>
<td>Comparison subjects &gt; patients Encoding &gt; baseline Zero-order responses</td>
<td>Cerebellum</td>
<td>Right</td>
<td>4</td>
<td>–49</td>
<td>–6</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>Right</td>
<td>4</td>
<td>–51</td>
<td>–19</td>
<td>3.27</td>
</tr>
<tr>
<td>Linear responses</td>
<td>Precentral gyrus</td>
<td>Left</td>
<td>4</td>
<td>–46</td>
<td>–3</td>
</tr>
<tr>
<td>Precentral gyrus</td>
<td>Right</td>
<td>4</td>
<td>53</td>
<td>4</td>
<td>44</td>
</tr>
<tr>
<td>Nonlinear responses: posterior cingulate gyrus</td>
<td>Left</td>
<td>31</td>
<td>–4</td>
<td>–40</td>
<td>37</td>
</tr>
<tr>
<td>Retrieval &gt; baseline Zero-order responses: superior temporal gyrus/lateral cerebral sulcus</td>
<td>Right</td>
<td>22</td>
<td>48</td>
<td>–11</td>
<td>8</td>
</tr>
<tr>
<td>Nonlinear responses: middle temporal gyrus</td>
<td>Left</td>
<td>21</td>
<td>–57</td>
<td>–10</td>
<td>–1</td>
</tr>
</tbody>
</table>

Table 5. All activations were significant at a threshold of p < 0.001, uncorrected, cluster size >4.

(Brodman's area 31) during encoding and in the left middle temporal gyrus (Brodman's area 21) during retrieval.

Discussion

In this study, both similarities and differences in brain activations underlying paired associate learning were examined in patients with Alzheimer's disease and comparison subjects, after adjustment for differences in performance and task difficulty. Independent of the level of difficulty, the majority of subjects in both groups activated a network of brain regions, including the anterior cingulate, lateral, and medial occipitoparietal and frontal cortices, during successful encoding and retrieval. Activations and deactivations in lateral and medial occipitoparietal areas were found to be better characterized by positive linear response functions, especially during retrieval rather than encoding. Greater linear responses during retrieval than encoding most likely reflect fewer cognitive demands during encoding, especially when multiple exposures to stimuli may have reduced the need for information to be encoded. The interactions of group and task difficulty revealed some small but significant differences in activation (albeit at an uncorrected threshold) in cerebellar, temporal, precentral, and posterior cingulate regions (comparison subjects > patients) and in frontoparietal regions (patients > comparison subjects).
This interpretation is supported by a recent functional magnetic resonance imaging (fMRI) study in which activation in the lateral prefrontal, superior, and inferior parietal cortices increased after extensive training of visuospatial working memory over a 5-week period (35).

### Between-Group Differences in Activation

Differences in activation between the patients with Alzheimer's disease and the comparison subjects were found to result from activation in one group and deactivation in the other. Such differential patterns of activity may reflect the use of different mnemonic strategies across the two groups or may reflect functional compensation for neuropathological changes associated with Alzheimer's disease. However, they may also reflect differences in effort between the patients and the comparison subjects at the hardest level of difficulty. Although we took as many steps as possible to control for relative difficulty of the task across four levels of difficulty included in the design, the behavioral data indicated that, on average, the patients needed an extra 0.71 attempt to successfully complete problems at the hardest level of difficulty. Given this difference, the findings of increased activation in the comparison subjects and decreased activation in the patients may have resulted from increasing item familiarity in the patient group (because of the additional attempts), while findings of activation in the patients and activation and deactivation in the comparison subjects may reflect increased effort at the hardest level of task difficulty in the patients with Alzheimer's disease. This interpretation, however, is not supported by our observation that areas of increased activation in the patients and in the comparison subjects match neither brain regions previously identified as being involved in effort nor item familiarity. Instead, the greater signal changes in the lateral and medial parietal regions in the patients, relative to the comparison subjects, during encoding and retrieval appear to reflect additional activity within regions found to be active in comparison subjects during visuospatial paired associate learning. Thus, these small increases in activity in the patients with Alzheimer's disease may reflect compensatory reallocation of neural resources to compensate for Alzheimer's disease-related neuropathology. It has previously been argued that increases in activity in the right middle frontal gyrus, right precentral gyrus, and left cerebellum during overt rehearsal of word lists are associated with engagement of the articulatory loop within the white matter (36). Therefore, differential activations observed in the comparison group may be attributable to strategic effects such as greater engagement of subvocalization during encoding.

### Alzheimer's Disease Treatment Effects

In the current study seven patients were receiving acetylcholinesterase inhibitor treatment for cognitive impairment. Little is known about the effect of such treatment on the BOLD response in patients with Alzheimer's disease, although findings of positron emission tomography and fMRI studies of cholinergic enhancement in healthy adults who performed explicit memory tasks suggest that cholinergic stimulation enhances activation in extrastriate regions (37), while cholinergic blockade decreases activation in these regions (38). The effect of cholinergic stimulation or blockade is less consistent in the frontal cortices, with frontal decreases in activation being reported with cholinergic stimulation and blockade during performance of explicit memory tasks (37, 38). Some evidence suggests that a single dose of rivastigmine increased activation in the fusiform gyrus bilaterally during face encoding, in the left superior frontal gyrus during a 1-back working memory task, and in the right inferior and superior frontal gyri during a 2-back working memory task in patients with Alzheimer's disease (39). Decreases in activation were found in the right middle and superior frontal gyri in the 2-back working memory task alone. Therefore, it is possible that increased activation in frontal-occipital regions in patients receiving acetylcholinesterase treatment in the current study may have reduced any possible activation differences in these regions between the patients and comparison subjects. However, a report of decreases in right frontal activation with increasing memory load under rivastigmine administration (39) suggests that any possible differences in activation within this region between the patients and comparison subjects should have been enhanced. Therefore, the minimal...
activation differences between the patients and the comparison subjects in the current study are most likely attributable to our attempts to make adjustments for performance and relative task difficulty rather than to the effect of treatment.

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GOULD, BROWN, OWEN, ET AL.
Pharmacological Modulation of Prefrontal Cortical Activity During a Working Memory Task in Young and Older Humans: A PET Study With Physostigmine

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Objective: Age-associated cholinergic dysfunction may contribute to the cognitive decline observed during aging, including a decline in working memory. The current study was designed to determine how healthy aging influences the neural response to working memory before and during pharmacological potentiation of the cholinergic system.

Method: In 13 young and 13 older healthy volunteers, regional cerebral blood flow (rCBF) was measured by using [15O]H2O and positron emission tomography across 10 scans that alternated between a working-memory-for-faces task and rest. In all subjects, the first two scans were obtained during intravenous saline infusion. Seven young and eight older subjects then received intravenous infusion of physostigmine, a cholinesterase inhibitor, and the remaining six young and five older subjects continued to receive saline.

Results: In the placebo condition, task-specific rCBF increases in prefrontal regions were observed in the right middle and inferior frontal cortices in young subjects and in more anterior and ventral prefrontal regions in older individuals. Physostigmine during the working memory task significantly improved performance in both age groups. The right prefrontal regions that were selectively recruited in each age group during the placebo condition showed significantly lower rCBF during physostigmine administration.

Conclusions: Cholinergic enhancement does not affect structurally defined cortical regions but rather modulates neural activity in functionally defined regions, that is, in task-related prefrontal cortical areas that are selectively and distinctively recruited in young and older subjects.

Working memory refers to a cognitive process that temporarily maintains an active representation of information for further processing or recall (1, 2). Visual working memory utilizes a widely distributed neural system that includes occipital and temporal visual processing areas and critically relies on regions in the prefrontal cortex for maintaining and manipulating information (3–6).

Given the pivotal role of the cholinergic system in modulating memory and attention (7), in previous studies we examined the effects of pharmacological potentiation of cholinergic activity on behavioral and neural responses during a task that tested visual working memory for faces in young healthy adults. We showed that cholinergic enhancement decreased task-related neural activity in the right prefrontal cortex (8). Moreover, cholinergic enhancement modulated much of the working memory system, including the anterior cingulate, hippocampus, and visual processing areas in occipitotemporal cortex, in a way that correlated with improvement in task performance (9). A subsequent study demonstrated that cholinergic enhancement selectively increased the processing of task-relevant information in visual cortex (10). Together, these findings suggest that the reduction of activity in the prefrontal cortex may be due to an indirect effect, as the enhanced processing in visual regions resulted in an improved representation of the visual percept that in turn facilitated working memory and thus diminished the need to recruit prefrontal cortical areas.

Aging is associated with anatomical, chemical, and functional changes in the brain (11–13). Among the most prominent changes are alterations in the cholinergic system, including decreases in the number of cholinergic neurons in the basal forebrain and in the number of cholinergic receptors and afferent projections to cortex (14–18). Although their significance has been questioned by some researchers (19, 20), these changes may contribute to age-associated deficits observed in working memory, attention, and other cognitive tasks (7, 11, 14, 15, 21–23). Indeed, the pharmacological potentiation of cholinergic neurotransmission improves performance on working memory tasks in elderly subjects (21, 24). Furthermore, chronic treatment with drugs that enhance the cholinergic system is used to ameliorate cognitive dysfunction (25, 26). Despite the well-documented clinical effects of cholinergic enhancement in elderly subjects, the underlying neural mechanisms remain to be elucidated.
Functional brain imaging studies have shown that different patterns of neural responses are elicited by the same visual working memory task in young and older individuals (27–29). These differences include reduced neural activity in the dorsolateral prefrontal cortex, a critical working memory region (28, 29), accompanied by increased activity in other prefrontal cortical areas (30) in older individuals, compared to younger individuals. These observations suggest that the aging brain undergoes a functional reorganization in an attempt to compensate for age-associated regional dysfunction (13, 22, 28, 30–33).

The present study was designed to determine how healthy aging influences neural responses to cholinergic potentiation during working memory. Given that enhancement of cholinergic activity causes a reduced involvement of the right prefrontal cortex in young subjects and that different prefrontal cortical areas are recruited during working memory in elderly subjects, we predicted that the pharmacological potentiation of cholinergic transmission would modulate selectively those prefrontal cortical regions differentially recruited in the two age groups. This prediction assumes that the reduction in right prefrontal cortical activity reflects a reduction in the need to recruit prefrontal areas, perhaps because of improved processing in visual cortical regions.

**Method**

**Subjects**

Thirteen young (six male, seven female; mean age=27 years, SD=6) and 13 older (eight male, five female; mean age=65, SD=11) healthy volunteers were included in the study. All were right-handed and normotensive and had no abnormalities on clinical examinations and on laboratory tests (including routine blood and urine tests, EKG, EEG, brain magnetic resonance imaging scan, and chest X-ray) and no history of any relevant medical, neurological, or psychiatric disorder. All were free of medication, including over-the-counter medications, for 4 weeks before the study (34). Written informed consent was obtained from all subjects before their participation in the study. The study was approved by the National Institutes of Health (NIH) Intramural Review Board (NIH protocol 93-AG-193).

**Positron Emission Tomography Scan and Working Memory Task**

Absolute regional cerebral blood flow (rCBF) was measured by using $[^{15}O]H_2O$ and a Scanditronix PC2048–15B positron emission tomography (PET) scanner (Uppsala, Sweden) (full width at half maximum: 6.5 mm) at the PET Department of the Clinical Center at NIH in Bethesda, Maryland. Ten 4-minute scans were acquired; they alternated between a resting condition and a visual working memory (face recognition) task. Saline solution was infused during the first scan pair for both age groups; subsequently, the placebo group in each age group continued to receive saline infusion, while the drug group in each age group received intravenous physostigmine infusion for the duration of the session. During the match-to-sample working memory task, faces were presented in three squares of equal size, one centered above two positioned side by side.
squares of equal size, one centered above two that were positioned side by side. Each item began with a 4-second presentation of a novel face in the upper square, followed by a 6-second delay, and then by two test faces presented for 4 seconds in each of the lower two squares. Subjects were instructed to indicate which test face matched the face presented at the beginning of each trial by pressing a button in the corresponding hand. All subjects were unaware of whether they would receive placebo or drug. For all subjects, the first scan pair (including one rest and one task scan) was obtained during an intravenous infusion of saline (placebo condition). Subsequently, seven young subjects and eight older subjects received an intravenous loading dose of physostigmine before the third scan at a rate of 1.95 mg/hour for 10 minutes, followed by a maintenance solution that continued to completion of the study at the rate of 0.816 mg/hour for a total dose of 1 mg/hour of physostigmine (drug condition) (36). Before the infusion of physostigmine, 0.2 mg of glycopyrrolate, a peripheral cholinergic antagonist, was administered intravenously to reduce the potential for side effects (37). The remaining six young subjects and five older subjects continued to receive an infusion of saline (placebo groups). Heart rate and blood pressure were monitored continuously throughout each study (8).

**Performance Data Analysis**

Accuracy and reaction time data were analyzed in a repeated-measures two-way analysis of variance (ANOVA) (repeated reaction time/accuracy by age group by infusion condition)). T tests were used to evaluate age-group differences at baseline. Drug effects on reaction time were assessed by using one-tailed tests on the basis of previously reported findings (8–10).

**PET-rCBF Data Analysis**

Using SPM 99 (Wellcome Department of Cognitive Neurology, Institute of Neurology, University College, London) (www.fil.ion.ucl.ac.uk/spm), PET data were registered to correct for between-scan movements; spatially normalized to the orientation, size, and shape specified in the brain atlas of Talairach and Tournoux (38); and smoothed using a 12×12×12 mm Gaussian filter.

The first scan pair (scans 1 and 2) was used to assess differences between the placebo and drug groups within each age group before drug administration, both at rest and during the working memory task. Values for rCBF at rest during the drug and placebo conditions were compared to determine any potential effect of physostigmine on rCBF at rest (8). Furthermore, to control for potential effects of multiple task repetition, the same analyses were performed within the two placebo groups that received saline throughout the examination (8).

**Brain Response to Working Memory Task Before and During Physostigmine Administration**

Brain regions showing rCBF increases during the task (scans 4, 6, 8, and 10), relative to rest (scans 3, 5, 7, and 9), were identified through pairwise t test comparisons separately in the young and old age groups. Brain regions with a significant (individual voxel level of $p<0.05$) rCBF change during the task, compared to rest, were identified across groups, and these regions were used to restrict the search volumes in all subsequent analyses for age group and/or drug interaction effects.

By contrasting task scans with rest scans within each drug group, brain regions that showed rCBF increases or decreases with the working memory task during drug administration were determined in the young subjects and the older subjects.

Statistical significance was assumed at an individual voxel level of $p<0.01$ and required cluster-level significance of $p<0.05$ uncorrected. Results that approached significance are reported only when individual voxels were significant at a $p<0.01$ level, but the correction for spatial extent was $p<0.10$.

Although these statistical thresholds may appear relatively less stringent, all the experiments were based on specific hypotheses from previous studies (8–10), and therefore a whole-brain correction would have been excessively conservative.

Task-by-drug interactions were identified within each age group by contrasting regions with increased or decreased rCBF during the task in the placebo and drug groups. Drug effects within each age group also were determined by contrasting task activations during drug administration (scans 3–10) with rCBF measures acquired during the first scan pair (during placebo infusion). In these contrasts, t tests were used to confirm differences in drug effects between the placebo and drug groups.

**Effects of Age**

**Interaction of age group and task during placebo and physostigmine administration.** Interactions of age group and task during placebo and physostigmine administration were identified by contrasting the regions showing significant rCBF changes during the task between the young and old age groups. For all two-way ANOVA interactions, statistical significance was assumed at an individual voxel level of $p<0.05$ and required 100 contiguous significant voxels.

**Interaction of age group, task, and drug.** Task-by-drug-by-age interactions were identified by contrasting regions with rCBF changes during the task between the placebo and drug groups and between the young and old age groups. For all three-way ANOVA interactions, statistical significance was assumed at an individual voxel level of $p<0.05$ and required 50 contiguous significant voxels.

**Task-associated rCBF decreases during placebo and physostigmine administration.** Brain regions showing rCBF decreases during the task (scans 4, 6, 8, and 10), relative to rest (scans 3, 5, 7, and 9), were identified through t test analyses separately in young and old age groups.

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**FIGURE 2. Effects of Physostigmine on Change in Reaction Time on a Visual Working Memory Task in Healthy Younger Subjects (N=13) and Healthy Older Subjects (N=13)**

![Graph showing changes in reaction time](http://ajp.psychiatryonline.org)
Results

Behavioral Results

Performance accuracy did not differ between young and older subjects in the placebo condition (young subjects: mean=97.2%, SD=4.5%; older subjects: mean=97.9%, SD=3.0%), and physostigmine administration had no significant effect on performance accuracy (young subjects: mean=97.4%, SD=1.6%; older subjects: mean=94.3%, SD=4.6%). During placebo infusion, reaction times in young subjects were significantly faster than in older subjects (young subjects: mean=393 ms, SD=113 ms; older subjects: mean=423 ms, SD=128 ms, p<0.05). Physostigmine administration had no significant effect on reaction times (young subjects: mean=388 ms, SD=110 ms; older subjects: mean=425 ms, SD=136 ms).

TABLE 1. Cortical Regions With Significant Regional Cerebral Blood Flow (rCBF) Increases or Decreases During a Working Memory Task Before and During Physostigmine Infusion in Younger and Older Healthy Subjects

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(continued)
Regional Cerebral Blood Flow

Significant increases and decreases in rCBF during the working memory task during placebo and physostigmine infusion in young and older subjects are summarized in Table 1. Task-associated rCBF increases were superimposed on the right hemisphere of a brain template and on four coronal sections selected to illustrate the findings in the prefrontal cortex for young and older groups (Figure 3).

No difference was observed in the drug groups in resting state rCBF (for main effects of group [drug versus placebo] and time [pre- versus postinfusion] and for their interaction). No significant change in rCBF was observed in the placebo group with comparable within- and between-group subtractions.

Brain response to working memory task before and during physostigmine administration.

Young subjects. During placebo infusion, task-specific rCBF increases were observed in the right dorsolateral prefrontal cortex, with loci in the middle frontal gyrus and inferior frontal gyrus/insula, and in the occipital and temporal visual extrastriate regions (Table 1, Figure 3, and Figure 4). During physostigmine infusion, rCBF increases were observed in several loci in the right prefrontal cortex, including the middle frontal gyrus, in the inferior frontal gyrus/insula, and in the occipital and temporal visual extrastriate regions (Table 1, and Figure 4). Significant lower task-specific rCBF during physostigmine infusion, compared to placebo infusion, was present in the right prefrontal cortex, with loci in dorsal middle frontal gyrus and inferior frontal gyrus/insula, as well as in the occipital and temporal visual regions (Table 1, and Figure 3).

Older subjects. During placebo infusion, task-specific rCBF increases were seen in the right dorsolateral prefrontal cortex, including the right middle frontal gyrus and inferior frontal gyrus/insula, and in the occipital and temporal visual extrastriate regions, similar to the pattern shown by the young group (Table 1, Figure 3, and Figure 4). How-

TABLE 1. Cortical Regions With Significant Regional Cerebral Blood Flow (rCBF) Increases or Decreases During a Working Memory Task Before and During Physostigmine Infusion in Younger and Older Healthy Subjects (continued)

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a Statistical significance was assumed at an individual voxel level of p<0.01 and a cluster level of p<0.05, uncorrected (two-tailed).

b Analyses of interaction effects (drug or age-group interactions) were restricted to brain regions identified as having significant changes in rCBF in the within-age-group analyses. For all two-way interactions, significance was assumed at an individual voxel level of p<0.05 and required 100 contiguous significant voxels. For all three-way interactions, statistical significance was assumed at an individual voxel level of p<0.05 and required 50 contiguous significant voxels. Interactions where older subjects showed significantly larger effects than young subjects are shown in boldface type.

c Talairach and Tournoux brain atlas coordinates (38): x=distance in millimeters to the right (+) or the left (–) side of the mid line, y=distance anterior (+) or posterior (–) to the anterior commissure, z=distance superior (+) or inferior (–) to a horizontal plane through the anterior and posterior commissures.

d Result approached significance; statistical significance was achieved at the individual voxel level (p<0.01), but the significance with correction for spatial extent was p<0.10.
FIGURE 3. Significant Increases in Regional Cerebral Blood Flow (rCBF) During a Working Memory Task With Placebo and Physostigmine Infusion in Healthy Younger Subjects (N=13) and Healthy Older Subjects (N=13)\textsuperscript{a}

\textsuperscript{a} Results are projected onto the right hemisphere of a brain template, which indicates the locations for the four coronal sections located at 10, 22, 35, and 45 mm anterior to the anterior commissure. Increases for which the z score exceeded a threshold of 2.35 (p=0.01, two-tailed, before correction for multiple comparisons on the basis of spatial extent) are shown.
ever, the older subjects also had rCBF increases that were not present in the young group; these increases were located in more anterior and ventral loci of middle and inferior frontal gyri (Table 1). In addition, an increase that approached significance was found in the inferior frontal gyrus in the left hemisphere ($p=0.051$, cluster level). During physostigmine administration, rCBF increases were observed in the occipital and temporal visual extrastriate regions (Table 1 and Figure 3). No region in the right prefrontal cortex showed significant task-related rCBF reductions during the working memory task in the presence of physostigmine, relative to placebo. The graphs show that younger individuals had a significant reduction in the magnitude of the response to the task in the presence of physostigmine, relative to placebo, in middle frontal gyrus (Talairach coordinates: $x=22$, $y=34$, $z=33$); older subjects showed reductions in response magnitude in the presence of physostigmine, relative to placebo, in more ventral and anterior aspects of middle frontal gyrus (Talairach coordinates: $x=33$, $y=41$, $z=12$).

Within-group comparisons. Within the young and older groups that received physostigmine, rCBF during the working memory task was compared between the scans during drug infusion (scans 3 to 10) and the scans during placebo infusion (scans 1 and 2). These comparisons confirmed the differences found in the right prefrontal cortex and in the ventral temporal cortex in the between-group (drug versus placebo) analyses (data not shown).

**Effects of Age**

**Interaction of age group and task during placebo and physostigmine administration.** During placebo infusion, larger increases in rCBF in response to the working memory task were observed in the insular cortex and in the ventral temporal cortex in the young subjects, compared to the older subjects. Conversely, the older subjects had significantly larger task-specific rCBF increases in the right ventral and left inferior frontal gyri and in the ventral occipital cortex.

During physostigmine administration, young subjects, compared to older subjects, showed greater activation during the working memory task in the right inferior frontal cortex and in the right ventral temporal cortex (Table 1). Older subjects showed greater activation in the left inferior frontal cortex and in the right occipital and left ventral temporal cortices, compared to the younger group.

Significantly larger rCBF increases during task and physostigmine administration, relative to placebo administration, were observed only in older subjects in the bilateral medial occipital cortex (Talairach coordinates: $x=-3$, $y=-81$, $z=-19$ [$z=5.26$, $p<0.01$]; $x=8$, $y=-96$, $z=-2$ [$z=3.92$, $p<0.01$]).
**Interaction of age group, task, and drug.** When the effects of physostigmine administration on the brain response to working memory were compared directly between young and older subjects, physostigmine significantly decreased task-related activations in the right inferior and middle frontal gyri and in the right anterior ventral temporal cortex to a greater extent in the older subjects than in the younger subjects. In addition, physostigmine reduced the magnitude of task-related response in the ventral occipital and temporal regions and in the right posterior ventral temporal cortices significantly less in the older subjects than in the younger subjects (Table 1).

**Task-associated rCBF decreases during placebo and physostigmine administration.** During placebo administration, rCBF decreases during the working memory task, compared to rest, were observed in some frontal and temporal cortical regions and limbic structures, as detailed in Table 1. Physostigmine administration did not change significantly the pattern of task-related rCBF reductions observed before drug administration, with the exception of a greater reduction in the left insula in young subjects and in the medial frontal gyrus in older subjects (data not shown).

**Discussion**

Cholinergic potentiation induced by acute intravenous administration of the anticholinesterase physostigmine modulated neural activity throughout the distributed visual working memory system, including both the prefrontal cortex and the visual processing areas, and improved task performance similarly in young and older healthy individuals. In the two age groups, some brain regions were commonly modulated and some areas were differentially affected by cholinergic potentiation. Specifically, in the presence of similar behavioral improvement, cholinergic enhancement modulated selectively the prefrontal cortical regions that were recruited differentially by young and older individuals during a working memory task before drug administration.

During placebo administration, young subjects activated more dorsal regions of the right prefrontal cortex, and older subjects recruited more anterior and ventral regions and areas in the left prefrontal cortex. This pattern, including the involvement of the ventrolateral and left prefrontal cortices, is consistent with previous findings and further supports the hypothesis that the recruitment of additional prefrontal cortical areas during working memory and other cognitive tasks in elderly subjects may reflect a functional reorganization to compensate for age-associated changes in neural function (13, 22, 28, 30, 33).

During the working memory task, in the presence of the drug, compared with placebo, the younger subjects showed reduced activation in the dorsal middle frontal and inferior frontal gyri, and the older subjects had reduced activation in the right prefrontal cortex, with loci that were more anterior and more ventral than in the young subjects.

Previously, we demonstrated that cholinergic potentiation with physostigmine improved working memory efficiency and reduced task-related neural activity in the right prefrontal cortex and that the degree of improvement correlated with the magnitude of reduction in prefrontal cortical activity (8). Physostigmine also modulated neural processing in a manner that correlated with behavioral improvement in multiple task-related cortical areas, including visual cortical regions (9, 10). Overall, these results suggest that cholinergic potentiation enhances memory performance by augmenting attention in perceptual representation of the visual cortex, thereby improving information processing efficiency and reducing the need for prefrontal cortical participation (10). Consistent with and further supporting this hypothesis (8–10), in the current study cholinergic enhancement modulated neural activity in visual cortical areas and reduced prefrontal cortical involvement in both young and older individuals.

Other studies that used different cognitive tasks have demonstrated that the functional recruitment of the right prefrontal cortex is proportional to the effort required to perform the task (35, 39, 40). For instance, recognition of progressively degraded faces was associated with a parallel rCBF increase in the right prefrontal cortex in young healthy subjects (35). The physostigmine-associated decrease in the neural response in the right prefrontal cortex may be secondary to a reduction in the effort needed to perform the working memory task, consistent with the observed improvement in task performance. The relation between cholinergic function, prefrontal cortical activity, and cognitive effort might be further investigated by varying the difficulty of the working memory task, such as by modifying visuoperceptual integrity (35) or modulating the length of the working memory retention interval (39, 41).

The cholinergic system undergoes structural and functional changes associated with cognitive impairment in elderly persons (21, 25, 42) and more severe changes in patients with Alzheimer’s disease. Indeed, cholinergic enhancement strategies remain a primary approach for treating cognitive dysfunction in Alzheimer’s disease. Our results suggest that, despite age-associated changes in the cholinergic system, the mechanism by which cholinergic enhancement modulates working memory is similar in younger and older individuals. However, our results also suggest the critical finding that the effects of cholinergic enhancement on prefrontal cortical activity are not specific for structurally defined cortical regions but rather that they affect functionally defined regions, that is, the task-related prefrontal cortical areas that are selectively recruited by younger and older subjects.

To our knowledge, this study provides the first demonstration of a selective age-dependent effect of cholinergic modulation on prefrontal cortical neural activity during working memory.
The results of this study may have important general implications, as they suggest that structural and functional brain changes that take place during the physiological aging process shape the way a given pharmacological agent interacts with distinct brain structures. As these modifications are far more remarkable in patients affected by neurodegenerative disorders such as Alzheimer’s disease, these results may also provide some novel ground for developing and evaluating new therapeutic agents for these patients.

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References


Prevalence and Natural Course of Aging-Associated Cognitive Decline in a Population-Based Sample of Young-Old Subjects

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Objective: "Mild cognitive impairment" refers to cognitive deficits in older age that exceed age-related cognitive decline but do not fulfill criteria for dementia. Affected subjects are assumed to be at higher risk for the development of dementia, such as Alzheimer’s disease. However, little is known about the group of young-old subjects with respect to the prevalence and natural course of cognitive decline.

Method: Within the population-based Interdisciplinary Longitudinal Study on Adult Development and Aging, neuropsychological functioning was assessed in 500 community-dwelling young-old subjects of two German urban regions who were born during 1930–1932. The participants were carefully screened for physical and mental health and reexamined 4 years later. The concept of "aging-associated cognitive decline" was applied.

Results: At baseline, 13.4% of the subjects fulfilled criteria for aging-associated cognitive decline. Four years later, the prevalence rates rose to 23.6%; 52.3% of the subjects initially classified as having aging-associated cognitive decline retained the diagnosis at follow-up. Although subjects with aging-associated cognitive decline showed a reduced performance in all neuropsychological domains addressed, a significant decline was confined to delayed verbal memory test performance during the 4-year follow-up period in relation to comparison subjects. Aging-associated cognitive decline did not predict conversion to dementia during the follow-up interval.

Conclusions: In young-old community-dwelling individuals, aging-associated cognitive decline is a frequent condition with a high temporal stability. During a 4-year follow-up, subjects with aging-associated cognitive decline deteriorated specifically in measures of episodic memory, underscoring the value of the respective deficits in characterizing “mild cognitive impairment.”

Mild cognitive impairment refers to cognitive deficits that exceed age-related cognitive decline but do not fulfill criteria for dementia. Clinical and epidemiological evidence have indicated that patients with Alzheimer’s disease undergo a long-standing preclinical phase in which cognitive deficits remain subtle over a long-standing phase before the threshold of dementia is reached (1). Because it has been postulated that elderly subjects with mild cognitive impairment are at an increased risk of developing dementia, a reliable identification of those preclinical stages is important for successful preventive strategies and early therapeutic interventions.

Studies have reported age-dependent prevalence rates of mild cognitive impairment in the elderly population (2, 3). When we take into account that older age is the most important risk factor for Alzheimer’s disease and mild cognitive impairment precedes Alzheimer’s disease in a considerable proportion of affected individuals, it is conceivable that not only the prevalence rates of mild cognitive impairment but also the conversion rates to Alzheimer’s disease differ with respect to selective age ranges within the elderly population (e.g., the young-old, the old-old, and the oldest-old) (4). To date, studies investigating the prevalence and course of mild cognitive impairment have mainly focused on subjects in their 70s and older.

Furthermore, the majority of studies did not address mild cognitive impairment because of significant somatic comorbidity. This is of particular importance since diabetes mellitus, heart disease, and hypertension were recently found to be more prevalent among subjects with mild cognitive impairment than otherwise healthy participants in a longitudinal study (5). This effect could clearly be addressed more thoroughly by the prospective investigation of young-old subjects, in whom these conditions are less frequent.

To date, various research diagnostic criteria as well as clinical manuals have been proposed to further define mild cognitive impairment (2, 6, 7). Those include age-associated memory impairment (8) and its modifications: age-consistent memory impairment (9) and late-life forgetfulness (9), the amnestic variant of mild cognitive impairment introduced by Petersen and colleagues (mild
cognitive impairment, amnestic) (10), and the ICD-10 criteria of “mild cognitive disorder.” To meet some of the limitations affecting earlier attempts to define mild cognitive impairment, a working party of the International Psychogeriatric Association introduced the concept of “aging-associated cognitive decline” (11). In contrast to most previous concepts, aging-associated cognitive decline not only uses age- and educational-adjusted normal levels to define a cognitive deficit but also considers decline in a broader potential range of cognitive domains, namely, memory and learning, attention and concentration, thinking, language, and visuospatial functioning. This agrees with the hypothesis that not only mnestic but also language deficits, such as verbal fluency impairment, might indicate further cognitive decline (12).

The use of normal values adjusted for educational levels constitutes another advantage of the aging-associated cognitive decline concept because higher education might be associated with increased cognitive reserve capacity, leading to delayed onset of cognitive decline. Thus, it has been postulated that aging-associated cognitive decline has an improved potential to identify individuals who experience cognitive decline that falls short of dementia (11).

Until now, three longitudinal population-based studies have been performed to establish the prevalence rates of aging-associated cognitive decline in the elderly population and to assess its predictive validity (13–15). Notably, all three studies found similar prevalence rates for aging-associated cognitive decline in the investigated populations (20%–27%). Furthermore, aging-associated cognitive decline proved to be superior to other concepts of mild cognitive impairment with respect to temporal stability and the prediction of dementia, yielding conversion rates of 28%–47% within a 2–3-year period. Although these results indeed support the notion that aging-associated cognitive decline is of high use for the identification of preclinical stages of Alzheimer’s disease, they are not necessarily generalizable to the elderly population as a whole. Because previous studies mainly focused on the group of old-old individuals, little is known about the prevalence and conversion rates of aging-associated cognitive decline for individuals in their 60s. However, the latter age group does not only constitute a major proportion of the individuals asking for advice in outpatient memory clinics but might also represent a promising target population for early preventive interventions. This holds particularly true considering that most of these young-old individuals are still living independently in the community.

Accordingly, the aims of the present study were twofold: 1) to establish prevalence rates for mild cognitive impairment according to criteria for aging-associated cognitive decline within a population-based sample of young-old individuals and 2) to investigate the longitudinal course of this condition, particularly with respect to its temporal stability, neuropsychological test performance, and conversion to dementia.

Method

Subjects and Psychometric Instruments

The subjects were participants in the Interdisciplinary Longitudinal Study on Adult Development and Aging who were born between 1930 and 1932. The Interdisciplinary Longitudinal Study on Adult Development and Aging is a prospective study on adult development in Germany that is based on two birth cohorts born during 1930–1932 and 1950–1952 (16). The subjects were randomly identified and recruited according to community registers. These registers are regularly updated for changes of address and marital status. Because it is compulsory for each resident in Germany ages 16 and older to be registered, this recruitment procedure yielded an almost representative sample for the respective communities.

All 500 participants of the elderly birth cohort who were living in the urban regions of Leipzig (Saxony) and Heidelberg/Mannheim (Palatine) were included in the present study. The study was approved by the ethical committee of the University of Heidelberg. After complete description of the study to the subjects, written informed consent was obtained.

The participants were carefully screened for physical and mental health by extensive interviews, physical examinations, and laboratory tests. In addition, potential psychiatric disorders were assessed by using the German version of the Structured Clinical Interview for the DSM-III-R (17).

Most of the neuropsychological instruments applied for the assessment of cognitive performance were subtests of the Nürnberger-Alters-Inventar (18) and the Leistungsprüfystem (19), both of which are well established and commonly used test batteries in Germany. In particular, the following instruments were used for the investigation of the respective cognitive domains:

1. Memory and learning—immediate word list recall and delayed word list recognition (Nürnberg-Alters-Inventar)
2. Attention and concentration—Aufmerksamkeits-Belastungs-Test (20)
3. Abstract thinking—similarities subtest (Hamburg-Wechsler-Intelligenztest für Erwachsene) (21)
4. Language—subtest of verbal fluency (Leistungsprüfystem)
5. Visuospatial functioning—subtest of visual imagination (Räumliche Vorstellung Leistungsprüfystem)

Subjective cognitive complaints were assessed by interviewing and applying the appropriate items of the Nürnberg Selbstein-schätzungliste (22). The Nürnberg Selbstein-schätzungliste is a self-assessment questionnaire on general functioning in the elderly and contains four items with a direct relation to cognitive functioning. Subjective complaints were explored on a “yes or no” basis. In addition, the Self-Rating Depression Scale (23) was applied.

To date, the first two waves of the Interdisciplinary Longitudinal Study on Adult Development and Aging are complete and served as the database for the present study. Examinations took place between December 1993 and January 1995 (time 1) and between December 1997 and January 2000 (time 2). The mean age of the subjects was 62.4 years (SD=2.4) at baseline (time 1) and 66.7 years (SD=1.1) at the 4-year follow-up (time 2). The sample had a balanced gender distribution (249 women and 251 men).

Definition of Diagnostic Categories

Aging-associated cognitive decline was diagnosed according to the criteria of the International Psychogeriatric Association working party (11). Those include 1) subjective impairment: a report by the individual (or a reliable informant) that cognitive function has declined and 2) objective impairment: difficulties in any of the following cognitive domains, as indicated by a neuropsychological test performance of at least one standard deviation below
normal age and educational levels: memory and learning, attention and concentration, abstract thinking (problem solving, abstraction), language, and visuospatial functioning. Age-adjusted normal values were available for all psychometric instruments administered, but normal values adjusted for educational level were missing for the tests addressing verbal fluency and visuospatial functioning. In these instances, the results of the entire age cohort were differentiated according to high (secondary school) and low (primary school) educational levels. In the latter instances, the test results of the entire age cohort (1930–1932) were differentiated according to high (secondary school) and low (primary school) educational levels, and each of the resulting distributions was used as a reference. The same differentiation was applied for the remaining tests on the basis of the normal levels reported in the literature.

Exclusion criteria were that none of the abnormalities listed was of a sufficient degree for a diagnosis of dementia or could be attributed to a clinically significant psychiatric disorder (in particular, depression, substance abuse, or psychosis). Furthermore, there should have been no objective evidence from physical and neurological examinations or laboratory tests and no history of cerebral disease, damage, or dysfunction or of a systemic physical disorder that is known to cause cognitive dysfunction.

As pointed out in the International Psychogeriatric Association consensus paper (11), the differential diagnosis between aging-associated cognitive decline, dementia, and ICD-10 “mild cognitive disorder” should be considered the most important. In our investigation, dementia was defined in line with DSM-IV criteria. In short, this includes the development of multiple cognitive deficits that are severe enough to cause significant impairment in social or occupational functioning. The diagnosis of mild cognitive disorder was assigned if a mild cognitive deficit according to the two criteria for aging-associated cognitive decline was present, but a history and/or an objective examination revealed evidence for a cerebral and/or systemic disorder that was sufficient to cause cerebral dysfunction (exclusion criterion for aging-associated cognitive decline).

Data Analysis

Complete data sets were available for 485 of the 500 investigated subjects. For each time point of the investigation, prevalence rates for aging-associated cognitive decline, mild cognitive disorder, and dementia were determined according to the criteria just described. Furthermore, conversion rates from one to another diagnostic category were calculated. Repeated-measures analysis of variance (ANOVA) was used to analyze the time course of cognitive deficits across diagnostic groups with respect to different cognitive domains.

Results

At time 1, subjective complaints about cognitive decline were found in 226 subjects (46.6%), and 200 subjects (41.2%) scored below one standard deviation of age- and education-adjusted normal values on at least one of the cognitive tests applied. Ninety-two subjects (19.0%) of the total sample suffered from medical and/or neuropsychiatric conditions with a potential causative relation to cognitive decline. When diagnostic criteria were applied to these findings, 65 subjects (13.4%) fulfilled the criteria for aging-associated cognitive decline. Additionally, 28 subjects (5.8%) had evidence of subjective and objective cognitive impairment but simultaneously met the exclusion criteria of aging-associated cognitive decline. Those were classified as suffering from mild cognitive disorder. None of the investigated participants was diagnosed as suffering from dementia according to the DSM-IV criteria; data sets from 15 subjects had to be excluded owing to missing values.

At time 2, after a follow-up period of 4 years, 449 subjects, or 89.8% of the original sample, could be reexamined. Twenty subjects had died. Other reasons for dropout (N=31) were severe physical handicaps that would make the investigation too troublesome, lost of interest/motivation, having moved to other places in the country, or no reason given for refusal. Dropout rates were highest in the subjects with aging-associated cognitive decline, followed by those fulfilling ICD-10 criteria for mild cognitive disorder, and then comparison subjects (15.4%, 14.3%, and 7.6%, respectively); however, these differences did not reach statistical significance ($\chi^2=3.2$, df=2, n.s.). Among the subjects who were reexamined at time 2, the prevalence rate of aging-associated cognitive decline increased to 23.6% (N=106). An additional 7.8% of the subjects (N=35) fulfilled the ICD-10 criteria for mild cognitive disorder. None of the reexamined subjects had developed dementia during the 4-year follow-up.

Of the subjects diagnosed with aging-associated cognitive decline at time 1, 34 (52.3%) retained the diagnosis at time 2 (see Figure 1). Two subjects (3.1%) no longer com-
The arrows signify the status of 106 subjects with aging-associated cognitive decline at time 1 and 4-year follow-up (time 2). A The arrows signify the status of 106 subjects with aging-associated cognitive decline at time 1, although 20 of them had already complained about cognitive decline at the time of the first examination. Another 35 incidence patients with aging-associated cognitive decline had previously been impaired on cognitive testing but did not fulfill the subjective criteria at time 1.

At time 1, the majority of subjects with aging-associated cognitive decline demonstrated cognitive deficits on one or two (N=28, 82.3%) neuropsychological tests, whereas deficits in three or four (N=6, 17.7%) domains were less frequent. At time 2, the proportion of subjects with aging-associated cognitive decline who were impaired on one or two (N=22, 64.7%) tests had lower ratings, whereas more subjects showed deficits in three or more domains (N=12, 35.3%) (χ²=2.7, df=1, p=0.09).

The prevalence of isolated mnestic deficits according to “mild cognitive impairment, amnestic” (10) was rather low. The respective criteria were applied for 4.1% of the subjects at time 1 and 4.2% at time 2, respectively. A total of 27.8% (N=5) of the subjects who fulfilled the criteria for “mild cognitive impairment, amnestic” at time 1 could be reclassified accordingly at time 2.

In a further step, the development of performance across different cognitive domains during the follow-up period was compared between subjects who retained the diagnosis of aging-associated cognitive decline from time 1 to time 2 (N=34) and comparison subjects who were cognitively unimpaired both at time 1 and time 2 (N=39) (Table 1). According to the ANOVAs calculated, the subjects with aging-associated cognitive decline were significantly impaired on all cognitive tests applied in relation to the comparison subjects (word list immediate recall—diagnosis main effect: F=39.2, df=1, 71, p<0.0005; time main effect: F=0.3 df=1, 71, p=0.60; word list delayed recognition—diagnosis main effect: F=16.8, df=1, 71, p<0.0005; time main effect: F=0.5, df=1, 71, p=0.50; Aufmerksamkeits-Belastungs-Test [attention and concentration]—diagnosis main effect: F=16.1, df=1, 69, p<0.0005; time main effect: F=0.2, df=1, 69, p=0.60; Hamburg-Wechsler-Intelligenztest für Erwachsene similarities subtest [abstract thinking]—diagnosis main effect: F=24.8, df=1, 71, p<0.0005; time main effect: F=4.6, df=1, 71, p<0.05; verbal fluency—diagnosis main effect: F=36.8, df=1, 71, p<0.0005; time main effect: F=3.5, df=1, 71, p=0.06; and visual imagination—diagnosis main effect: F=19.8, df=1, 71, p<0.0005; time main effect: F=14.2, df=1, 71, p<0.0005).

Additionally, the subjects with aging-associated cognitive decline showed a significant decline in performance on the delayed word recognition task in relation to the comparison subjects during the follow-up, as demonstrated by a significant diagnosis-by-time interaction (word list delayed recognition—diagnosis-by-time interaction: F=4.3, df=1, 71, p<0.05). The respective interaction for verbal fluency also reached the significance level (verbal fluency—diagnosis-by-time interaction: F=4.4, df=1, 71, p<0.05). However, this effect resulted from an increased performance in the comparison subjects, whereas...
the subjects with aging-associated cognitive decline showed rather stable values. None of the other interactions for the remaining neuropsychological test scores addressing immediate recall, attention and concentration, abstract thinking, and visuospatial functioning reached significance (0.1< F<2.9, df=1, 71).

In relation to the comparison subjects, the subjects with aging-associated cognitive decline demonstrated significantly (diagnosis main effect: F=24.4, df=1, 71, p<0.005) more mild depressive symptoms at time 1 (Self-Rating Depression Scale score—subjects with aging-associated cognitive decline: mean=37.7, SD=7.8; comparison subjects: mean=30.3, SD=5.6) and time 2 (Self-Rating Depression Scale score—subjects with aging-associated cognitive decline: mean=38.0, SD=7.5; comparison subjects: mean=30.4, SD=5.7). Similar results were obtained when all subjects diagnosed with aging-associated cognitive decline at time 2 (N=106) were compared with all cognitively unimpaired comparison subjects at time 2 (N=245).

Discussion

According to our findings, aging-associated cognitive decline represents a frequent condition affecting 13.4% of the 60–64-year-old population. In addition, the prevalence of aging-associated cognitive decline showed an age-related increase that rose to 23.6% within a 4-year follow-up period. The established prevalence rates are in line with the results from previous population-based studies that applied the criteria for aging-associated cognitive decline (13–15). However, although previous investigations mainly focused on subjects in their 70s and 80s, our study for the first time, to our knowledge, indicates that aging-associated cognitive decline is also common in the population of young-old. Because all subjects underwent a thorough physical examination, the prevalence rates of aging-associated cognitive decline in the present study may not be attributed to the early effects of severe systemic or neurological disorders.

Furthermore, the diagnosis of aging-associated cognitive decline was characterized by a relatively high temporal stability. This finding emphasizes the existence of a distinct diagnostic entity, such as mild cognitive impairment, that has been challenged (24, 25). It has been argued that mild cognitive impairments might considerably fluctuate over time and would not be suitable to define a circumscribed diagnostic category. Indeed, several population-based studies revealed that, in particular, the amnestic form of mild cognitive impairment (mild cognitive impairment, amnestic) (10) was rather unstable over time, in that only about 7% of the affected subjects were still classified under this category after 2 to 3 years, whereas more than 40% reverted to normal (14, 25). This is in contrast to our finding that 52.3% of the subjects with a baseline diagnosis of aging-associated cognitive decline retained the diagnosis at follow-up. Furthermore, 6.2% had persisting deficits in cognitive tests, although they had to be excluded from the group with aging-associated cognitive decline for other reasons (lack of subjective complaints, severe medical conditions). Only 23.1% of the original subjects with aging-associated cognitive decline improved with respect to cognitive testing. A single person (1.5%) reverted to normal, insofar as he was neither subjectively nor objectively impaired at follow-up. Similar data were reported by Ritchie et al. (14), who found that 50%–60% of the subjects classified as having aging-associated cognitive decline retained this diagnosis when they were reexamined after 1 year. Taken together, these findings indicate that in contrast to other concepts of mild cognitive impairment, aging-associated cognitive decline defines a distinct syndrome that is reproducible over time in a considerable proportion of elderly subjects.

In relation to the comparison subjects, a significantly larger percentage of subjects with aging-associated cogni-

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**TABLE 1. Neuropsychological Test Performance of 34 Young-Old Subjects With Aging-Associated Cognitive Decline and 39 Comparison Subjects**

<table>
<thead>
<tr>
<th>Cognitive Domain and Neuropsychological Test</th>
<th>Score at Time 1</th>
<th>Score at Time 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subjects With Aging-Associated Cognitive Decline</td>
<td>Comparison Subjects</td>
</tr>
<tr>
<td>Episodic memory: Nürnberger Selbstschätzungsliste</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Word list immediate recall</td>
<td>4.4</td>
<td>1.3</td>
</tr>
<tr>
<td>Word list delayed recognition</td>
<td>5.2</td>
<td>2.5</td>
</tr>
<tr>
<td>Attention and concentration: Aufmerksamkeits-Belastungs-Test</td>
<td>334.8</td>
<td>84.4</td>
</tr>
<tr>
<td>Abstract thinking: Hamburg-Wechsler-Intelligenztest für Erwachse</td>
<td>21.7</td>
<td>7.2</td>
</tr>
<tr>
<td>Language: verbal fluency (Leistungsprüfsystem)</td>
<td>24.8</td>
<td>7.0</td>
</tr>
<tr>
<td>Visuospatial functioning: visual imagination (Leistungsprüfsystem)</td>
<td>18.5</td>
<td>7.4</td>
</tr>
</tbody>
</table>

*Significant difference between diagnoses (16.1<F<36.8, df=1, 71, p<0.05).*

**Abstract thinking:**

**Language:** verbal fluency (Leistungsprüfsystem)

**Visuospatial functioning:** visual imagination (Leistungsprüfsystem)

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tive decline suffered from mild depressive symptoms. Because patients with manifest depression were excluded from the group with aging-associated cognitive decline, cognitive impairment due to affective disorders did not contribute to this finding. Otherwise, in patients with manifest dementia, depressive symptoms and apathy often overlap, making it difficult to differentiate depressive disorder comorbidity in dementia. Thus, mild depressive symptoms in aging-associated cognitive decline might represent an epiphenomenon of increasing cognitive decline.

In our population of the young-old, aging-associated cognitive decline did not predict conversion to dementia within a 4-year follow-up period. Ritchie et al. (14) and Busse et al. (15) determined conversion rates of 28% and 47% within a comparable time interval, respectively. However, the investigated population in these studies was considerably older. Dropout rates were highest in subjects with aging-associated cognitive decline, followed by those fulfilling ICD-10 criteria for mild cognitive disorder, and then comparison subjects, and it is likely that at least some of the subjects with aging-associated cognitive decline might have converted into dementia. However, we could not definitely prove this assumption. Nevertheless, other factors must be considered to explain this discrepancy. In particular, length of the follow-up interval has to be weighed against the age of the subjects. Previous studies on cognitive deficits in preclinical Alzheimer’s disease have revealed some empirical evidence that deficits across multiple cognitive domains are apparent not only years but even decades before the diagnosis of dementia can be made (26) and that the magnitude of those preclinical cognitive deficits appears to be relatively stable until a few years before the clinical diagnosis is made (1). Consequently, the likelihood of observing accelerated changes in cognitive performance among incident Alzheimer’s disease increases as time before the eventual diagnosis decreases. When we take into account that the incidence and prevalence of dementia are relatively low during the seventh decade of life but increase exponentially from the age of 70, the divergent results with respect to conversion rates might mainly be explained by age differences between the studied populations. Accordingly, our results suggest that age and length of follow-up interval are of crucial relevance when the predictive validity of different concepts of mild cognitive impairment is assessed.

Nonetheless, longitudinal analysis of our data indicates that the respective neuropsychological deficits follow a progressive course. At time 2, the subjects with aging-associated cognitive decline were impaired on more neuropsychological tests than at time 1. This observation is in line with the assumption that the putative pathological process involved a broader range of cognitive domains during the follow-up period. In relation to comparison subjects, the subjects with aging-associated cognitive decline deteriorated significantly during follow-up in the test on delayed word recognition. In contrast, performance on immediate recall remained rather stable in the subjects with aging-associated cognitive decline or improved slightly in the comparison subjects. Obviously, the slight performance gains observed in the comparison group in this cognitive domain, as well as with respect to delayed recognition and verbal fluency, may refer to an increased awareness of the participants of the study toward their neuropsychological performance. Moreover, the double dissociation found between immediate and delayed verbal memory argues against an effect of other conditions, such as depressive syndromes, that should affect both recall conditions simultaneously.

Several previous studies have addressed the question of whether deficits in specific cognitive domains predict the development of Alzheimer’s disease (26–31). They all agreed that, in particular, deficits with respect to episodic memory tasks but also, to a lesser degree, other cognitive dysfunctions are associated with an increased risk of further cognitive decline. Notably, Palmer et al. (30) also found that specific tests of word recall and verbal fluency had positive predictive value for dementia. These findings are paralleled by the results of recent neuroimaging studies. Pantel et al. (32) demonstrated (in a subsample of the subjects with aging-associated cognitive decline investigated here) atrophic changes of medial temporal lobe structures that are specifically involved in episodic memory function. Similar findings were obtained in a variety of previous neuroimaging studies in patients with manifest Alzheimer’s disease (for a review, see references 33 and 34).

In conclusion, we show that aging-associated cognitive decline is a frequent condition in community-dwelling young-old subjects. The prevalence of aging-associated cognitive decline increased with age, and the diagnosis of aging-associated cognitive decline was characterized by a rather high temporal stability. However, in this particular sample of young-old subjects, aging-associated cognitive decline did not predict dementia during a 4-year follow-up period. The subjects with aging-associated cognitive decline were characterized by a selective further decline of episodic memory that occurred independently from physical comorbidity.
References


The Pattern of Cognitive Performance in CADASIL: A Monogenic Condition Leading to Subcortical Ischemic Vascular Dementia

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Christian Opherk, M.D.
Adrian Danek, M.D.
Clive Ballard, M.D.
Jürgen Herzog, M.D.
Martin Dichgans, M.D.

Objective: Subcortical ischemic vascular lesions, which are closely related to small vessel disease, are a common substrate of cognitive impairment and dementia. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a monogenic variant of small vessel disease resulting from mutations in NOTCH3. Mutation carriers almost invariably develop cognitive deficits and eventually dementia. The current study describes the profile of cognitive abnormalities in CADASIL subjects.

Method: A cross-sectional study of 65 mutation carriers (mean age=47.3 years, SD=10.5) and 30 matched comparison subjects (mean age=47.2 years, SD=14.0) was conducted. Participants underwent a series of assessments that included ratings of global cognition, the cognitive portion of the Vascular Dementia Assessment Scale, and specific tests of executive function and attention with measures of processing speed and error monitoring.

Results: CADASIL subjects had pronounced impairments of the timed measures (Stroop II and III, Trail Making Test, symbol digit, digit cancellation). Measures of error monitoring (Stroop III, Trail Making Test, symbol digit, maze task) were also significantly affected but to a lesser extent. Prominent deficits further included verbal fluency and ideational praxis. Recall, orientation, and receptive language skills were largely preserved. Subgroup analyses indicated a similar profile in subjects with early and advanced impairment of global cognitive performance.

Conclusions: The findings highlight processing speed as the most substantial area of cognitive impairment in CADASIL subjects, with less pronounced yet significant deficits in other aspects of executive performance and attention. This profile of cognitive impairment is present at an early stage and enables the construction of targeted test batteries for clinical trials. It is hypothesized that the profile of dysfunction described here represents the core of the cognitive syndrome associated with small vessel disease and subcortical ischemic vascular lesions.

Vascular dementia is the second most frequent cause of dementia following Alzheimer's disease (1). Moreover, concurrent vascular pathology is present in 40% or more of Alzheimer's disease patients (2, 3), having an impact upon the clinical features (4) and the threshold of Alzheimer's disease pathology required for dementia to occur (5). Cerebrovascular disease hence plays an important role in the majority of people with dementia. Yet, there are a number of mechanisms that may contribute individually or in combination to cognitive impairment in patients with cerebrovascular disease. They include large infarcts, multiple infarcts, strategic infarcts, and incomplete ischemic lesions of subcortical white matter (3, 6–8).

In comparison with Alzheimer's disease patients, those with a diagnosis of vascular dementia display a relative preservation of episodic memory but greater impairments of verbal fluency and frontal executive functioning (9–11). However, the pathological heterogeneity of vascular dementia causes considerable difficulty in defining the clinical syndrome and associated neuropsychological impairments and how these relate to the specific key types of vascular lesion (7). Despite these difficulties, concepts pertaining to distinct subtypes of vascular dementia have been developed. The best established of these is subcortical ischemic vascular dementia, which describes vascular dementia related to small vessel disease that combines the overlapping clinical syndromes of “Binswanger's disease” and “lacunar state” (6, 12).

Subcortical ischemic vascular dementia is hypothesized to be caused by a loss of subcortical neurons or disconnection of cortical neurons from subcortical structures. The neuropsychological profile is described as characteristic of a dysexecutive syndrome (difficulties in goal formulation, initiation, planning, organizing, sequencing, set-shifting, and abstracting), with slowed cognitive and motor processing speed as well as more general attentional impairments (3, 6, 12). It has further been proposed that memory deficits with impaired recall but relatively intact recognition are part of the syndrome.
This profile has emerged mainly from studies that have combined neuropsychological and neuroimaging data (13–17). In fact, many of these observations suggest that subcortical ischemic vascular dementia is a distinct clinical and neuropathological syndrome (3, 6, 12). This is difficult to substantiate, however, since the majority of patients with dementia are in older age groups and at high risk of concurrent pathologies (3, 6, 12).

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a monogenic variant of small vessel disease caused by mutations in the NOTCH3 gene (18). Patients develop early and recurrent strokes as well as cognitive deficits that eventually lead to dementia (19, 20). Advanced cases are clinically indistinguishable from sporadic “Binswanger’s disease” (21). Similarly, histopathology shows a combination of small subcortical infarcts and incomplete ischemic lesions of the white matter and subcortical gray matter. CADASIL is hence an archetype of “pure” subcortical ischemic vascular dementia. Patients have a clearly defined vasculopathy, the diagnosis can be established with high accuracy in vivo (100% specificity), and, because of the younger age of these patients, concurrent pathology that could have an impact on cognition is unusual. In addition, mutational screening enables the reliable identification of presymptomatic or early symptomatic cases. Therefore, CADASIL provides a unique opportunity to address many of the issues related to subcortical ischemic vascular lesions and the concept of subcortical ischemic vascular dementia in rather the same way as studies of familial Alzheimer’s disease have provided valuable information about Alzheimer’s disease (22, 23).

There are few specific studies that have reported neuropsychological findings in CADASIL subjects. In a series of eight mutation carriers without dementia, deficits were identified on the Wisconsin Card Sorting Test and Trail Making Test in the majority of individuals (24). Other small preliminary case reports have also suggested a prominent disturbance of frontal-executive performance (25). A recent more systematic study compared cognitive performance in 34 CADASIL patients (13 prestroke and 13 poststroke patients and eight with dementia) and 15 comparison subjects (26). Deficits in short-term memory (digits forward and working memory (digits backward, Rey-Osterrieth memory test) were evident in the CADASIL patients who had not experienced a stroke. Among patients who had experienced a stroke, impairments in cognitive processing speed and set shifting (Trail Making Test part B) were identified. Recall, however, was still preserved even in the group with dementia. Given the prominence of slowed cognitive processing in patients with sporadic subcortical ischemic vascular dementia (27, 28), it is slightly surprising that slowed processing speed was not an earlier feature in patients with CADASIL (26).

The aims of the present study were twofold. First, we wanted to describe the profile of cognitive abnormalities in CADASIL subjects. Second, we wanted to test the hypothesis that cognitive impairment related to small vessel disease is characterized by a particular cognitive profile with executive and attentional dysfunction including slowed processing speed. To address these issues, we prospectively studied a large number of unselected mutation carriers and matched comparison subjects using a predefined protocol and comprehensive neuropsychological test battery. To provide additional information about the cognitive profile in early and advanced cases, we also undertook analyses of subsets of subjects grouped by global cognitive performance.

**Method**

**Subjects**

Sixty-five CADASIL subjects from 51 unrelated families were included in the study, with a diagnosis of CADASIL established by mutational screening of the NOTCH3 gene (29, 30). All patients were able to perform the testing procedure (no exclusions due to aphasia, motor deficits affecting the dominant hand, or severe dementia). None of the patients had experienced a stroke within the preceding 3 months, and there were no cases of alcoholism, drug abuse, or organic brain disease other than CADASIL. None of the patients was receiving cholinergic therapies. All CADASIL subjects underwent brain magnetic resonance imaging, which showed CADASIL-typical microangiopathic changes in the absence of territorial infarctions or other structural brain lesions. The comparison group consisted of 30 healthy subjects (mostly spouses of CADASIL patients) who were matched in terms of age, gender, and educational level. Informed consent was obtained from all participants (or caregivers in the case of dementia) after the procedures of the study had been fully explained. The study was approved by the local ethics committee.

**Data Acquisition**

Subjects were prospectively enrolled at a single institution (Department of Neurology, Klinikum Grosshadern, Ludwig-Maximilians-University, Munich) between March 2002 and August 2003.
All CADASIL subjects were examined by a trained neurologist. They all received a complete physical and neurological examination that included assessment with the NIH stroke scale (31). Their dominant hand was established, and particular attention was paid to symptoms affecting their dominant upper extremity. Disability was rated with the modified Rankin scale (32) and the Barthel Index (33).

Neuropsychological testing was performed by a trained psychometrist in a quiet, well-illuminated room. All participants underwent detailed neuropsychological testing with the following battery of psychometric tests adapted for use with native German speakers:

1. Global measures of cognitive function: Mini-Mental State Examination (MMSE) (34), Mattis Dementia Rating Scale (35), and the cognitive subscale of the Alzheimer’s Disease Assessment Scale (part of the Vascular Dementia Assessment Scale [36]).

2. Standardized assessment of vascular dementia: the cognitive portion of the Vascular Dementia Assessment Scale (36), which includes the following items/tests: word recall, commands, constructional praxis (figures), delayed word recall, naming (figures and fingers), ideational praxis, orientation, word recognition, symbol digit modalities, digits backward, maze task, digit cancellation task, verbal fluency, remembering test instructions, spoken language ability, word finding difficulty, comprehension, and concentration/distractibility.

3. Specific “frontal” tests with an emphasis on executive function including error monitoring and processing speed: Stroop test (37) and Trail Making Test parts A and B (38).

**Data Analysis**

To obtain an overview on the pattern of performance across cognitive processes and to address the issue of selectivity of deficits, we generated z scores using the mean values and standard deviations of the healthy group. The use of z scores enables direct comparison of performance in different cognitive domains.

To evaluate the pattern of cognitive performance in CADASIL subjects with mild to moderate impairment in global cognitive performance relative to those with severe impairment, subjects were divided into two groups according to their Mattis Dementia Rating Scale score using the widely accepted cutoff values (<122 and ≥123).

The Mattis Dementia Rating Scale score was used exclusively for classifying patients, i.e., it was not part of the data analyzed.

Group comparisons between CADASIL subjects and healthy subjects were undertaken using the Mann-Whitney U test. To account for multiple testing a p value <0.005 was considered significant. Statistical analysis was completed by using SPSS software version 12.01 for Windows.

**TABLE 2. Cognitive Test Results in CADASIL Subjects and Healthy Comparison Subjects**

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Processing speed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroop (time)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>9.6</td>
<td>2.6</td>
<td>8.4</td>
</tr>
<tr>
<td>II</td>
<td>13.7</td>
<td>3.8</td>
<td>11.1</td>
</tr>
<tr>
<td>III</td>
<td>35.6</td>
<td>17.6</td>
<td>23.6</td>
</tr>
<tr>
<td>Trail Making Test (time)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Part A</td>
<td>52.4</td>
<td>42.9</td>
<td>29.3</td>
</tr>
<tr>
<td>Part B</td>
<td>120.9</td>
<td>73.0</td>
<td>74.0</td>
</tr>
<tr>
<td>Symbol digit modalities</td>
<td>32.7</td>
<td>14.9</td>
<td>47.2</td>
</tr>
<tr>
<td>Digit cancellation</td>
<td>23.3</td>
<td>7.2</td>
<td>30.0</td>
</tr>
<tr>
<td>Maze task (time to completion)</td>
<td>6.1</td>
<td>5.0</td>
<td>4.4</td>
</tr>
<tr>
<td>Planning/error monitoring</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroop (errors)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0.03</td>
<td>0.17</td>
<td>0.0</td>
</tr>
<tr>
<td>II</td>
<td>0.37</td>
<td>0.76</td>
<td>0.13</td>
</tr>
<tr>
<td>III</td>
<td>1.7</td>
<td>2.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Trail Making Test (errors)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Part A</td>
<td>0.34</td>
<td>0.59</td>
<td>0.07</td>
</tr>
<tr>
<td>Part B</td>
<td>1.7</td>
<td>2.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Digit backward</td>
<td>5.6</td>
<td>1.8</td>
<td>6.1</td>
</tr>
<tr>
<td>Maze task (errors)</td>
<td>0.17</td>
<td>0.42</td>
<td>0.0</td>
</tr>
<tr>
<td>Recall memory</td>
<td></td>
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<tr>
<td>Delayed word recall</td>
<td>6.2</td>
<td>2.2</td>
<td>5.6</td>
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<tr>
<td>Remembering test instructions</td>
<td>0.06</td>
<td>0.30</td>
<td>0.0</td>
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<tr>
<td>Word recall</td>
<td>5.0</td>
<td>1.9</td>
<td>4.3</td>
</tr>
<tr>
<td>Vascular Dementia Assessment Scale, cognitive portion items</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Commands</td>
<td>0.26</td>
<td>0.48</td>
<td>0.17</td>
</tr>
<tr>
<td>Constructional praxis</td>
<td>0.32</td>
<td>0.62</td>
<td>0.17</td>
</tr>
<tr>
<td>Naming objects/fingers</td>
<td>0.60</td>
<td>1.0</td>
<td>0.17</td>
</tr>
<tr>
<td>Ideational praxis</td>
<td>0.22</td>
<td>0.41</td>
<td>0.0</td>
</tr>
<tr>
<td>Orientation</td>
<td>0.25</td>
<td>0.56</td>
<td>0.13</td>
</tr>
<tr>
<td>Word recognition</td>
<td>3.3</td>
<td>2.5</td>
<td>2.0</td>
</tr>
<tr>
<td>Symbol digit modalities (incorrect)</td>
<td>1.0</td>
<td>1.8</td>
<td>0.30</td>
</tr>
<tr>
<td>Digit cancellation (incorrect)</td>
<td>0.17</td>
<td>0.90</td>
<td>0.03</td>
</tr>
<tr>
<td>Digit cancellation (times reminded of task)</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>18.6</td>
<td>6.4</td>
<td>24.0</td>
</tr>
</tbody>
</table>

a Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.
b Significant following correction for multiple testing (p<0.005).
c Not completed by six CADASIL patients and one comparison subject. Incomplete items were not included in the analysis.


Results

Demographic Characteristics

Demographic characteristics of the 65 CADASIL subjects and 30 healthy comparison individuals are illustrated in Table 1. There was no significant difference between the two groups with respect to age, sex distribution, and years of education. At the time of investigation 56 (86%) of the CADASIL subjects had become symptomatic, and nine (14%) were asymptomatic. Forty-four (68%) individuals had experienced a transient ischemic attack or stroke. Manifestations further included migraine with aura (39%), psychiatric disturbance (mostly mild depression) (42%), and epileptic seizures (one patient). Global cognitive performance, as assessed by the MMSE and Mattis Dementia Rating Scale, was significantly more impaired in CADASIL subjects than comparison subjects (both p < 0.005). Nine (14%) of the 65 CADASIL subjects had a Mattis Dementia Rating Scale score below the traditional cutoff value (≤122).

Cognitive Performance Profile

The cognitive evaluations of the CADASIL and comparison subjects are shown in Table 2. CADASIL subjects were significantly more impaired than healthy subjects for all of the following items: the timed measures of the Stroop II, Stroop III, Trail Making Test parts A and B; the error measure of the Trail Making Test B; the correct responses on the symbol digit and digit cancellation task, and the verbal fluency task (all p < 0.005).

The differential magnitude of impairment in different aspects of cognition is profiled in Figure 1, which displays the mean z scores achieved by CADASIL subjects relative to comparison subjects. Apart from the pronounced areas of deficit emphasized in Table 2, impairments were also evident on ideational praxis, with some but less marked impairments of other aspects of performance. Memory (delayed recall, remembering test instructions) was relatively preserved. Orientation and receptive language skills (commands) were also largely unaffected. The same pattern was obtained if all subjects with neurological symptoms affecting their dominant arm were excluded (data not shown).

Subgroup Analyses

To explore the pattern of cognitive abnormalities in different disease stages, we looked at the effect of global cognitive performance as assessed by the Mattis Dementia Rating Scale on the different cognitive domains. Figure 2 shows the z scores for CADASIL subjects with no or mild impairment of global cognitive performance (Mattis De-
mentia Rating Scale score ≥123, mean age=46.5 years, SD=10.6) and those with advanced deficits (Mattis Dementia Rating Scale score ≤122, mean age=52.8 years, SD=8.4). As shown in the figure, the profile of deficits was very similar in both groups. Also, all variables significantly different between the overall group of CADASIL subjects and healthy subjects (Stroop II [time], Stroop III [time], Trail Making Test A [time], Trail Making Test B [time], Trail Making Test B [errors], symbol digit [correct], digit cancellation [correct], and verbal fluency task) remained significant in CADASIL subjects with early cognitive impairment (Mattis Dementia Rating Scale ≥123) (Figure 2 and Table 3).

Discussion

In the largest study so far to examine cognitive function in CADASIL patients, significantly greater impairments were evident for the time and error measures of the Stroop and Trail Making Test tasks and other tasks of processing speed relative to age-matched comparison subjects. Thus, deficits of executive function and cognitive processing speed are emphasized as the characteristic cognitive hallmarks of the condition. We also observed significant decrements in ideational praxis, probably because of executive processes needed to plan and engage in abstract tasks (39). Of importance is that this profile of deficits was evident even in patients with mild overall impairment. There was no significant difference from comparison subjects in performance on delayed recall tasks or orientation. The findings suggest that there is a clear and specific pattern of neuropsychological deficits in CADASIL patients that is distinct from that seen in other conditions with impairment of higher cortical functions, such as Alzheimer’s disease. In fact, our data suggest a double dissociation regarding processing speed and recall in CADASIL and Alzheimer’s disease, the latter of which is characterized by early deficits in recall but relatively preserved processing speed. These results suggest that sensitive tests of processing speed and error monitoring are likely to be particularly useful for the identification of early cognitive deficits and for monitoring change.

In the current study, timed tasks from the Stroop and Trail Making assessments were sensitive discriminators between CADASIL patients and comparison subjects and were internally consistent with other speed tasks such as the symbol digit and digit cancellation tasks (40, 41), even in subjects with early cognitive impairment. There was also a consistent pattern of impairment in tasks of planning and error monitoring. This characteristic pattern of cognitive deficits is broadly similar to that reported in the
only previous published study with a substantial cohort (26). For example, both studies are consistent with regard to the Trail Making Test B error score and relative preservation of recall. However, there are several important differences. In the Amberla et al. study (26), which included 34 CADASIL subjects and 15 comparison subjects, no significant differences were found in the timed component of the Trail Making Test part A, and differences in the timed component of the Trail Making Test part B were observed only for the poststroke patients. The studies are also discrepant with regard to the presence of deficits in verbal fluency and constructional praxis. These discrepancies may be explained in part by different methods of assessment. For example, the present study used a category fluency test, whereas Amberla et al. used a letter fluency task; previous studies support greater impairments of category fluency than letter fluency in vascular dementia (42).

CADASIL is an archetype of pure small vessel disease and hence pure subcortical ischemic vascular dementia. The profile of cognitive impairment identified in this study allows us to make some inferences about the core of the cognitive syndrome attributable to subcortical ischemic lesions. This is important because there is considerable heterogeneity of vascular pathology in dementia patients and frequent overlap with neurodegenerative changes, making it difficult to clarify the neuropathological substrates of specific aspects of cognitive dysfunction (43). The observed pattern may be explained in large part by the disruption of specific prefrontal-subcortical circuits by ischemic lesions (44–48). These circuits involve multiple transmitter systems, offering potential therapeutic opportunities. Thus, for example, there is evidence for a localized cholinergic deficit related to the disruption of

### TABLE 3. Cognitive Test Results in CADASILSubjects Who Had Mild to Moderate Impairment and Healthy Comparison Subjects

<table>
<thead>
<tr>
<th>Cognitive Domain and Measure</th>
<th>CADASIL Subjects (N=56)</th>
<th>Healthy Subjects (N=30)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean SD</td>
<td>Mean SD</td>
<td></td>
</tr>
<tr>
<td>Processing speed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroop (time)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>9.1 2.4</td>
<td>8.4 1.8</td>
<td>0.28</td>
</tr>
<tr>
<td>II</td>
<td>13.2 3.4</td>
<td>11.1 2.3</td>
<td>&lt;0.001c</td>
</tr>
<tr>
<td>III</td>
<td>31.3 12.7</td>
<td>23.6 9.5</td>
<td>0.003c</td>
</tr>
<tr>
<td>Trail Making Test (time)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>41.8 21.9</td>
<td>29.3 10.8</td>
<td>0.004c</td>
</tr>
<tr>
<td>B</td>
<td>105.2 58.9</td>
<td>74.0 28.2</td>
<td>0.008</td>
</tr>
<tr>
<td>Symbol digit modalities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit backward</td>
<td>24.8 6.5</td>
<td>30.0 6.1</td>
<td>&lt;0.001c</td>
</tr>
<tr>
<td>Maze task (time to completion)</td>
<td>5.2 3.1</td>
<td>4.4 2.2</td>
<td>0.23</td>
</tr>
<tr>
<td>Planning/error monitoring</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Stroop (errors)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0.02 0.13</td>
<td>0.0 0.0</td>
<td>0.46</td>
</tr>
<tr>
<td>II</td>
<td>0.27 0.59</td>
<td>0.13 0.35</td>
<td>0.33</td>
</tr>
<tr>
<td>III</td>
<td>1.3 2.3</td>
<td>0.6 1.4</td>
<td>0.13</td>
</tr>
<tr>
<td>Trail Making Test (errors)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>0.23 0.50</td>
<td>0.07 0.26</td>
<td>0.12</td>
</tr>
<tr>
<td>B</td>
<td>1.4 2.1</td>
<td>0.4 1.1</td>
<td>0.008</td>
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<td>Digit backward</td>
<td>5.9 1.6</td>
<td>6.1 1.6</td>
<td>0.045</td>
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<td>Maze task (errors)</td>
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<td>0.0 0.0</td>
<td>0.003c</td>
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<tr>
<td>Recall memory</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Delayed word recall</td>
<td>5.9 2.1</td>
<td>5.6 1.7</td>
<td>0.59</td>
</tr>
<tr>
<td>Remembering test instructions</td>
<td>0.07 0.32</td>
<td>0.0 0.0</td>
<td>0.20</td>
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<tr>
<td>Word recall</td>
<td>4.7 1.7</td>
<td>4.3 1.4</td>
<td>0.22</td>
</tr>
<tr>
<td>Vascular Dementia Assessment Scale, cognitive portion items</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Commands</td>
<td>0.18 0.39</td>
<td>0.17 0.46</td>
<td>0.64</td>
</tr>
<tr>
<td>Constructional praxis</td>
<td>0.23 0.47</td>
<td>0.17 0.46</td>
<td>0.35</td>
</tr>
<tr>
<td>Naming objects/fingers</td>
<td>0.41 0.78</td>
<td>0.17 0.46</td>
<td>0.14</td>
</tr>
<tr>
<td>Ideational praxis</td>
<td>0.14 0.35</td>
<td>0.0 0.0</td>
<td>0.03</td>
</tr>
<tr>
<td>Orientation</td>
<td>0.13 0.38</td>
<td>0.13 0.35</td>
<td>0.74</td>
</tr>
<tr>
<td>Word recognition</td>
<td>3.0 2.4</td>
<td>2.0 1.8</td>
<td>0.07</td>
</tr>
<tr>
<td>Symbol digit modalities (incorrect)</td>
<td>1.0 1.9</td>
<td>0.30 0.79</td>
<td>0.03</td>
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<tr>
<td>Digit cancellation (incorrect)</td>
<td>0.05 0.23</td>
<td>0.03 0.18</td>
<td>0.67</td>
</tr>
<tr>
<td>Digit cancellation (times reminded of task)</td>
<td>0.0 0.0</td>
<td>0.0 0.0</td>
<td>1.00</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>20.2 5.3</td>
<td>24.0 4.9</td>
<td>0.003c</td>
</tr>
</tbody>
</table>

a Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.
b Mild to moderate impairment defined as a mean Mattis Dementia Rating Scale score ≥123.
c Significant following correction for multiple testing (p<0.005).
specific white matter tracts in CADASIL (49). Such findings may be important for generating treatment approaches to CADASIL and a broader population of patients with subcortical ischemic vascular dementia.

The current study has several methodological strengths. First, neuropsychological evaluations were undertaken on a large cohort of patients with genetically proven CADASIL who were compared to a matched group. Second, we carefully controlled for a possible confounding effect of motor deficits affecting the dominant hand. Third, the battery of cognitive tests covered specific domains hypothesized to be impaired in subcortical ischemic vascular dementia and included instruments that are widely used in dementia studies. Thus, we consider it unlikely that the selection of tests biased the apparent profile of cognitive impairments. These methodological aspects, together with the internal consistency of the data, strongly indicate that the findings are robust.

In summary, the current study highlights a specific profile of neuropsychological deficits evident in CADASIL. This profile enables the construction of targeted cognitive test batteries relevant to clinical trials. Our data further provide information about the spectrum of cognitive deficits attributable to small vessel disease and subcortical ischemic lesions. Studies focusing on more targeted tests of executive function and memory may further enhance our understanding of subcortical ischemic vascular dementia.

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The Construct of Minor and Major Depression in Alzheimer’s Disease

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Ricardo Jorge, M.D.
Romina Mizrahi, M.D.
Robert G. Robinson, M.D.

**Objective:** This study examined the frequency of major and minor depression in Alzheimer’s disease and determined whether these types of depression have a different functional and psychopathological impact and whether there is a change in the prevalence of major and minor depression throughout the stages of Alzheimer’s disease.

**Method:** A consecutive series of 670 patients with probable Alzheimer’s disease were assessed with the Structured Clinical Interview for DSM-IV; specific instruments to rate the presence and severity of depression, anxiety, apathy, irritability, delusions, pathological affective crying, performance of activities of daily living, and social functioning; and a standardized neuropsychological evaluation. Diagnoses of major and minor depression were generated from DSM-IV criteria.

**Results:** Twenty-six percent of the patients had major depression, 26% had minor depression, and 48% were not depressed. Major depression was significantly associated with sad mood in all three stages of the illness, although this association dropped significantly for minor depression in severe Alzheimer’s disease. Both major and minor depression were significantly associated with more severe psychopathology, functional impairments, and social dysfunction. Depressive symptoms that most strongly discriminated between Alzheimer’s disease patients with and without sad mood were guilty ideation, suicidal ideation, loss of energy, insomnia, weight loss, psychomotor retardation/agitation, poor concentration, and loss of interest.

**Conclusions:** Our study demonstrates that DSM-IV criteria for major and minor depression identify clinically relevant syndromes of depression in Alzheimer’s disease, mild levels of depression can produce significant functional impairment, and the severity of psychopathological and neurological impairments increases with increasing severity of depression.

Although depressive mood is a frequent complaint of patients with Alzheimer’s disease, the diagnosis of depressive disorders in dementia is still a complex issue. Early studies diagnosed depression among patients with Alzheimer’s disease using arbitrary cutoff scores on depression rating scales (1). To avoid rating symptoms of dementia as secondary to depression, some studies excluded so-called physical and autonomic symptoms of depression from the rating scales (2, 3). Other studies replaced physical with psychological symptoms of depression or accepted both physical and psychological symptoms of depression, regardless of their potential association with the underlying dementia (4).

In one study, we used the Structured Clinical Interview for DSM-IV (SCID) (5) to diagnose depression in a consecutive series of patients with Alzheimer’s disease and examined the validity of DSM-IV criteria for major depression for this condition (6). The main finding was that patients with sad mood (present most of the day, nearly every day, over 2 weeks) scored significantly higher on each of the DSM-IV criteria for major depression, except loss of appetite, than Alzheimer’s disease patients without sad mood (6). Only 4% of 92 Alzheimer’s disease patients with sad mood failed to meet the DSM-IV criteria for either major or minor depression.

A workshop organized by the National Institute of Mental Health (NIMH) proposed standardized diagnostic criteria for depression in Alzheimer’s disease (4, 7). These criteria are similar to the DSM-IV criteria for a major depressive episode, but loss of interest was revised to indicate loss of pleasure in response to social contact, and specific criteria for irritability and social isolation were included. A significant departure from the criteria for a major depressive episode is that the NIMH criteria for depression in Alzheimer’s disease require at least three symptoms for diagnosis, compared to five or more symptoms for the diagnosis of a major depressive episode. One potential limitation is that requiring only three criteria for a diagnosis of depression in Alzheimer’s disease could greatly increase the risk of overdiagnosing depression among these patients. This is most likely to happen in the late stages of dementia, when severe cognitive and motor deficits may reduce the specificity of depressive symptoms. To our knowledge, the threshold at which depres-
sion should be diagnosed, as well as whether minor and major depression are valid constructs in Alzheimer’s disease, has not been empirically examined.

The present study included a consecutive series of 670 patients with probable Alzheimer’s disease and mild, moderate, or severe dementia who were assessed with a comprehensive psychiatric evaluation. The main aims of the study were to examine the frequency of major and minor depression in Alzheimer’s disease, to determine whether these types of depression have a different functional and psychopathological impact, and to examine whether there is a change in the prevalence of major and minor depression throughout the worsening stages of Alzheimer’s disease.

Method

The Alzheimer’s disease group included a consecutive series of outpatients visiting the dementia clinic of a tertiary care center in Buenos Aires between January 1996 and October 2002 for evaluation and treatment of progressive cognitive decline. The inclusion criteria were the following:

1. Meeting criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association for probable Alzheimer’s disease (8)
2. No history of closed head injuries with loss of consciousness, strokes, or other neurological disorder with involvement of the CNS
3. Normal results on laboratory tests (to rule out other etiologies of dementia)
4. No focal lesions on a magnetic resonance imaging (MRI) scan
5. A Hachinski Ischemic (9) score <4

The institutional human subjects committee approved the study. After the methods of the study had been fully explained, written informed consent was obtained from the patients and their respective caregivers.

Psychiatric Examination

A psychiatrist who was blind to the neurological and neuropsychological findings assessed the patients with the following instruments:

1. The SCID (5) is a semistructured diagnostic interview for making major axis I DSM-III-R diagnoses. The psychiatrist administered the SCID to the patient and at least one first-degree relative. Sad mood was rated according to the DSM-III-R definition (i.e., sad mood present most of the day, nearly every day, over 2 weeks). Based on the SCID responses, a DSM-III-R axis I diagnosis of major depressive episode or a DSM-III-R research diagnosis of minor depression disorder was made. The reliability of the SCID was assessed as part of a previous study (6). Test-retest reliability was examined in 14 patients (four with major depression, three with minor depression, and seven without depression). The patients and their respective first-degree relatives were assessed in two separate interviews no more than 2 weeks apart. There was perfect (100%) agreement of depression diagnosis and depression type for both assessments. Interrater reliability was examined in 15 patients and their respective first-degree relatives by two raters (who were blind to each other's ratings) in a single interview for each subject. There was perfect agreement (100%) for major depression (N=5) and 93% agreement for minor depression (one patient was diagnosed with minor depression by the senior interviewer and as not depressed by the second interviewer).
2. The Mini-Mental State Examination (MMSE) (10) is an 11-item examination found to be valid and reliable in assessing a limited range of cognitive functions in a global manner.
3. The Clinical Dementia Rating (11) is a global device for rating dementia stages.
4. The Hamilton Depression Rating Scale (12) is a 17-item interviewer-rated scale that measures psychological and autonomic symptoms of depression.
5. The Hamilton Anxiety Rating Scale (13) is an 11-item interviewer-rated scale that measures the severity of generalized or persistent anxiety.
6. The Apathy Scale (14) includes 14 items that are scored by the patient’s relative or caregiver. Apathy was diagnosed with the diagnostic scheme detailed in a previous publication (15). We have demonstrated the reliability and validity of the Apathy Scale in Alzheimer’s disease (14).
7. The Irritability Scale (14) is a 14-item scale that is rated by the patient’s relative or caregiver. Following our previous findings, the patients with an Irritability Scale score above 20 points were considered irritable (14). We have demonstrated the validity and reliability of this scale in Alzheimer’s disease (14).
8. The Dementia Psychosis Scale (16) is an 18-item caregiver-rated scale that quantifies the severity and types of delusions in Alzheimer’s disease patients at the time of their psychiatric evaluation. We have demonstrated the validity and reliability of this scale in Alzheimer’s disease (16).
9. The Social Ties Checklist (17) is a 10-item scale that measures the quantity and quality of social supports
10. The Pathological Laughing and Crying Scale (18) is an interviewer-rated scale that quantifies aspects of pathological affect, including the duration of the episodes, their relation to external events, the degree of voluntary control, the inappropriateness in relation to emotions, and the degree of resultant distress. We have demonstrated the validity and reliability of this scale in Alzheimer’s disease (18).
11. The Functioning Independence Measure (19) is an 18-item ordinal scale that assesses self-care, sphincter control, mobility, locomotion, communication, and social cognition. Higher scores indicate fewer impairments in activities of daily living.

The patients with Alzheimer’s disease were first interviewed with the full psychiatric assessment, except for the SCID. Simultaneously, caregivers, who were blind to the results of these interviews, rated the patients’ behaviors with the same instruments. Finally, the psychiatrist administered the SCID to each patient with both the patient and the caregiver present. Signs and symptoms of depression were scored with the inclusive method without the need to interpret whether a clinical feature was attributable to the neurodegenerative process.

Neurological Examination

The patients had full neurological examinations and were assessed with the Unified Parkinson’s Disease Rating Scale (20) by a neurologist who was blind to their psychiatric ratings.

Neuropsychological Examination

The cognitive evaluation was carried out by a neuropsychologist who was blind to the other clinical findings and consisted of the following tests:

1. The Boston Naming Test (21) examines the ability to name pictured objects.
TABLE 1. Demographic and Clinical Characteristics of Patients With Alzheimer’s Disease and Major, Minor, or No Depression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients With No Depression (N=316)</th>
<th>Patients With Minor Depression (N=177)</th>
<th>Patients With Major Depression (N=177)</th>
<th>Analysis</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>N  %</td>
<td>N  %</td>
<td>N  %</td>
<td>χ²</td>
</tr>
<tr>
<td>Female gender</td>
<td>194  61</td>
<td>115  65</td>
<td>105  59</td>
<td>13.4</td>
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<td>Clinical Dementia Rating</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>185  48</td>
<td>99  26</td>
<td>98  26</td>
<td>0.0001</td>
</tr>
<tr>
<td>2</td>
<td>109  50</td>
<td>46  21</td>
<td>62  29</td>
<td>0.0001</td>
</tr>
<tr>
<td>3</td>
<td>22  31</td>
<td>32  45</td>
<td>17  24</td>
<td>0.0001</td>
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<tr>
<td>Family history of affective disorders</td>
<td>18  6</td>
<td>21  12</td>
<td>17  10</td>
<td>n.s.</td>
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<td>Antidepressant therapy</td>
<td>18  6</td>
<td>20  11</td>
<td>27  15</td>
<td>n.s.</td>
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<td>Neuroleptic therapy</td>
<td>16  8</td>
<td>21  12</td>
<td>27  15</td>
<td>n.s.</td>
</tr>
<tr>
<td>Anxiolytic therapy</td>
<td>54  17</td>
<td>33  19</td>
<td>51  29</td>
<td>n.s.</td>
</tr>
<tr>
<td>Personal history of affective disorders</td>
<td>35  11</td>
<td>17  10</td>
<td>19  11</td>
<td>n.s.</td>
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<tr>
<td>Age (years)</td>
<td>72.3  7.6</td>
<td>72.8  7.2</td>
<td>72.0  8.4</td>
<td>n.s.</td>
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<tr>
<td>Education (years)</td>
<td>11.5  5.9</td>
<td>11.7  7.7</td>
<td>11.4  9.3</td>
<td>n.s.</td>
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<td>Mini-Mental State Examination score</td>
<td>19.6  6.1</td>
<td>18.4  6.9</td>
<td>19.2  5.9</td>
<td>n.s.</td>
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<td>Dementia Psychosis Scale score</td>
<td>1.93  2.9</td>
<td>2.71  3.0</td>
<td>3.56  3.7</td>
<td>12.2</td>
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<tr>
<td>Hamilton Depression Rating Scale score</td>
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<td>12.3  4.6</td>
<td>19.0  6.8</td>
<td>300.6</td>
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<td>Hamilton Anxiety Rating Scale score</td>
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<td>8.75  6.4</td>
<td>12.8  8.3</td>
<td>58.2</td>
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<td>Functioning Independence Measure score</td>
<td>68.6  20.2</td>
<td>63.7  20.6</td>
<td>62.5  19.6</td>
<td>5.56</td>
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<td>Social Ties Checklist score</td>
<td>5.32  1.9</td>
<td>6.0  1.9</td>
<td>6.31  2.0</td>
<td>13.8</td>
</tr>
<tr>
<td>Apathy Scale score</td>
<td>18.9  9.4</td>
<td>22.7  8.3</td>
<td>25.7  8.0</td>
<td>30.7</td>
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<tr>
<td>Pathological Laughing and Crying Scale crying subscale score</td>
<td>2.43  4.2</td>
<td>5.56  5.2</td>
<td>5.52  5.0</td>
<td>26.2</td>
</tr>
<tr>
<td>Irritability Scale score</td>
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<td>15.7  9.5</td>
<td>16.9  9.2</td>
<td>11.9</td>
</tr>
<tr>
<td>Unified Parkinson’s Disease Rating Scale score</td>
<td>9.39  9.4</td>
<td>17.3  15.6</td>
<td>21.4  16.7</td>
<td>36.8</td>
</tr>
<tr>
<td>Buschke Selective Reminding Test score</td>
<td>20.1  17.4</td>
<td>20.1  16.4</td>
<td>17.7  17.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>Boston Naming Test score</td>
<td>14.3  4.1</td>
<td>13.8  4.1</td>
<td>14.6  3.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>Controlled Oral Word Association Test score</td>
<td>29.4  10.6</td>
<td>29.2  10.2</td>
<td>26.8  9.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Digits forward score</td>
<td>5.0  1.0</td>
<td>4.8  1.3</td>
<td>4.8  1.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Digits backward score</td>
<td>3.2  1.0</td>
<td>3.1  1.1</td>
<td>3.1  1.0</td>
<td>n.s.</td>
</tr>
<tr>
<td>Block Design test score</td>
<td>3.7  2.3</td>
<td>3.2  2.5</td>
<td>2.9  2.5</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

2. The Controlled Oral Word Association Test (22) examines access to semantic information with time constraints.
3. The Buschke Selective Reminding Test (23) measures verbal learning and memory during a multiple-trial list-learning task (long-term retrieval was used as the outcome measure).
4. The Digit Span Test (24) examines auditory attention and includes two parts. In the first part (digits forward), the patient is asked to repeat a string of numbers exactly as it is given, whereas in the second (digits backward), the patient must repeat the digit string in reverse order.
5. The Block Design Test (24) examines constructional praxis.

**Statistical Analysis**

Statistical analysis was carried out by using means, standard deviations, and analysis of covariance (ANCOVA) with post hoc planned comparisons (Tukey’s test for unequal samples). Frequency distributions were calculated with chi-square tests and Fisher’s exact test. All p values are two-tailed.

**Results**

One hundred seventy-seven of the 670 Alzheimer’s disease patients (26%) had major depression, 177 patients (26%) had minor depression, and 316 patients (48%) were not depressed. There were no significant between-group differences in their main demographic characteristics (Table 1).

**Depression and Severity of Alzheimer’s Disease**

A hypothesis of unequal frequency of depression based on the stages of Alzheimer’s disease was statistically substantiated ($\chi^2=16.7, \text{df}=4, p<0.01$). Although the frequency of minor depression increased from 21% (46 of 217 patients) in the moderate stage of Alzheimer’s disease to 45% (32 of 71 patients) in the severe stage of Alzheimer’s disease, euthymia declined from 50% (109 of 217 patients) in the moderate stage of Alzheimer’s disease to 31% (22 of 71 patients) in the severe stage of Alzheimer’s disease ($\chi^2=14.9, \text{df}=1, p<0.0001$). Ninety-one percent of the patients (89 of 98) with major depression had a depressed mood in the mild stage of Alzheimer’s disease, 90% (56 of 62 patients) in the moderate stage of Alzheimer’s disease, and 94% (16 of 17 patients) in the severe stage of Alzheimer’s disease, indicating that the SCID was applied appropriately in all stages of the illness. Seventy-five percent of the patients (74 of 99) with minor depression and mild Alzheimer’s disease had sad mood (as ascertained by a score of 3 points on the respective SCID item) compared to 76% (35 of 46 patients) in the moderate stage of Alzheimer’s disease and 44% (14 of 32 patients) in the severe stage of Alzheimer’s disease ($\chi^2=14.9, \text{df}=4, p<0.005$). This finding suggests that the patients’ perception of mood may be altered unless the depression itself is severe. The frequency
of patients with three symptoms of depression (according to the NIMH criteria for depression in Alzheimer’s disease) but without sad mood was 22% (22 of 100 patients) in mild Alzheimer’s disease, 23% (six of 26 patients) in moderate Alzheimer’s disease, and 41% (13 of 32 patients) in severe Alzheimer’s disease.

We also examined the association of sad mood with the different DSM-IV criteria for major depression and with the presence of apathy and irritability. Based on the responses to the SCID item rating sad mood, the patients were divided into those without sad mood (i.e., a score of 1 [absent]) (N=262) and those with sad mood (i.e., a score of 3 [threshold]) (N=316). (Patients with a score of 2 [i.e., subthreshold] were not included in this analysis.) (Figure 1). We calculated a ratio for each DSM-IV criterion of major depression and for the constructs of apathy and irritability using the following formula: percentage positive for patients with sad mood minus percentage positive for patients without sad mood over the sum of both. This ratio was highest (i.e., most strongly associated with sad mood) for guilty ideation (84%), followed by suicidal ideation (80%), loss of energy (68%), insomnia (59%), weight loss (59%), psychomotor retardation/agitation (58%), poor concentration (58%), loss of interest (55%), apathy (24%), and irritability (17%).

**Comorbidity of Depression in Alzheimer’s Disease**

The frequency of delusions was lowest in Alzheimer’s disease patients without depression and highest in patients with major depression (Table 1). A similar distribution (i.e., major depression > minor depression > no depression) was found for scores of depression, anxiety, apathy, pathological affective crying, and parkinsonism. The patients with either major or minor depression scored significantly worse than the nondepressed group on the Functioning Independence Measure and the Social Ties Checklist, but there were no significant differences between major depressed patients and minor depressed patients on these variables.

To determine whether the differences observed between the patients with minor depression or no depression resulted from the higher frequency of severe dementia in the group with minor depression, we restricted the analysis to patients with mild or moderate Alzheimer’s disease. The patients with minor depression still had significantly worse scores than the nondepressed patients on ratings of depression (Hamilton depression scale score: mean=12.2, SD=4.7, versus mean=5.4, SD=4.1, respectively) (t=13.2, df=437, p<0.0001), anxiety (Hamilton anxiety scale score: mean=8.3, SD=6.3, versus mean=5.7, SD=5.5) (t=3.13, df=400, p<0.0001), apathy (Apathy Scale score: mean=21.4, SD=8.0, versus mean=18.5, SD=9.1) (t=3.13, df=400, p<0.0001), pathological affective crying (Pathological Laughing and Crying Scale score: mean=4.9, SD=5.0, versus mean=2.2, SD=4.1) (t=5.00, df=336, p<0.0001), and parkinsonism (Unified Parkinson’s Disease Rating Scale score: mean=14.9, SD=13.6, versus mean=8.9, SD=9.0) (t=4.79, df=332, p<0.0001). No significant differences were found on the remaining clinical variables.

**Neuropsychological Findings**

To avoid floor effects, the statistical analysis included only patients with either mild or moderate Alzheimer’s disease.
Eighty-four patients had one or more missing values and had to be excluded from the statistical analysis. A two-way ANCOVA (three groups [major, minor, and no depression] on scores from six cognitive tests, with MMSE scores as a covariate) showed a significant overall effect (Rao's $R^2=2.04$, df=12, 888, $p<0.05$). On post hoc comparisons, the patients with major depression had significantly lower scores than the patients with no depression on the Block Design Test ($t=3.45$, df=380, $p<0.001$), but there were no significant between-group differences on the remaining neuropsychological variables (Table 1).

**Discussion**

We examined the frequency and clinical correlates of major and minor depression in the different stages of Alzheimer's disease, and there were several important findings. First, the patients meeting the DSM-IV criteria for either minor or major depression had more severe social dysfunction and greater impairment in activities of daily living than the nondepressed Alzheimer's disease patients. Second, the patients with major depression had more severe anxiety, apathy, delusions, and parkinsonism than the patients with minor depression, suggesting that the severity of psychopathological and neurological impairments in Alzheimer's disease increases with increasing severity of depression. On the other hand, the patients with major depression or minor depression had similar deficits in activities of daily living and social functioning, suggesting that even mild levels of depression are significantly associated with increased functional impairment in Alzheimer's disease. Finally, the syndrome of minor depression was associated with less mood change in severe compared to mild or moderate stages of Alzheimer's disease, suggesting that the symptoms of depression may change with increasing severity of Alzheimer's disease.

Before further comments, several limitations of our study should be pointed out. First, 14% of the patients with mild or moderate Alzheimer's disease had to be excluded from the neuropsychological evaluation owing to missing data. However, the proportions of patients with major, minor, or no depression after a full neuropsychological evaluation (26%, 24%, and 50%, respectively) were similar to the proportions of depression in our full study group (27%, 27%, and 46%, respectively). Although all 670 patients were assessed with the SCID, the Hamilton depression scale, and the MMSE, incomplete evaluations resulted from missing data on the remaining instruments, which ranged from 8% for the Hamilton anxiety scale to 26% for the Unified Parkinson's Disease Rating Scale. However, the proportion of depressed patients who were assessed with the various instruments was similar to the proportion of depressed patients in the full group. Second, our study group consisted of patients attending a dementia clinic at a tertiary care center, which may have biased our findings toward more severe cases. In spite of these limitations, this is, to our knowledge, among the few studies of mood disorders in Alzheimer's disease to include a large group of consecutive patients and to use structured psychiatric interviews and standardized diagnostic criteria. Third, we have no pathological confirmation of our clinical diagnosis of probable Alzheimer's disease. However, the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association have been demonstrated to have high sensitivity and specificity for the diagnosis of probable Alzheimer's disease. Moreover, all of our patients were assessed with either computerized tomography or MRI, and those with one or more stroke lesions were excluded from the study. Finally, the possibility of pseudodementia in some of our Alzheimer's disease patients with depression needs to be discussed. In a longitudinal study that used the same diagnostic methods (25), the authors found that Alzheimer's disease patients with depression at baseline who were no longer depressed at a follow-up evaluation 18 months later (N=20) had a similar rate of cognitive decline as Alzheimer's disease patients with depression at baseline who were still depressed at follow-up (N=13). These findings argue against the possibility of pseudodementia in the present study.

One of the main findings of the study was that both minor and major depression had a significant psychopathological and functional impact on Alzheimer's disease: both groups showed significantly more severe apathy, delusions, anxiety, pathological affective crying, irritability, deficits in activities of daily living, impairments in social functioning, and parkinsonism than Alzheimer's disease patients without depression. These findings were not explained by differences in age, education, overall cognitive status, or severity of dementia. Major (but not minor) depressed Alzheimer's disease patients had significantly more severe cognitive deficits than nondepressed Alzheimer's disease patients, but this finding was of marginal significance. Whether depression produced significant functional impairment, or vice versa, or whether a common factor may increase the likelihood of both depression and functional impairment should be investigated in longitudinal studies.

Forssell and co-workers (25) suggested that depression may become more frequent as Alzheimer's disease progresses from mild to moderate dementia and becomes less common in severe dementia. However, in the first study to address minor depression in Alzheimer's disease in a systematic way, Lyketsos and co-workers (26) found no significant differences in the frequencies of major and minor depression among the stages of mild, moderate, and severe Alzheimer's disease. In a recent study, Lopez and co-workers (27) found that major depression was less frequent in Alzheimer's disease patients with severe cognitive deficits than in those with mild/moderate cognitive deficits. Our study demonstrated a similar frequency of major depression in the different stages of Alzheimer's dis-
ease, and important methodological differences may explain this discrepancy. We classified patients into mild, moderate, or severe Alzheimer’s disease categories using the Clinical Dementia Rating, whereas Lopez and co-workers (27) graded the severity of cognitive deficits according to the MMSE. Their finding of a lower frequency of major depression in late Alzheimer’s disease conflicts with their findings of a similar frequency of depressed mood, suicidal ideation, low self-esteem, guilt, episodes of crying, and hopelessness between Alzheimer’s disease patients with mild and moderate/severe Alzheimer’s disease. They also found that sleep problems, anhedonia, and loss of energy were more frequent in patients with moderate/severe Alzheimer’s disease than in those with mild Alzheimer’s disease.

We followed the DSM-IV provision that depressed mood should be present most of the day, nearly every day, whereas the NIMH criteria do not require the presence of symptoms nearly every day (it is not clear whether this temporal qualification pertains to the symptom of depressed mood only or should also apply to the other symptoms of depression) (4). The rationale for this change is not clear, and loosening the temporal requirement may substantially decrease the reliability and specificity of the criteria. When patients were diagnosed with the NIMH criteria (i.e., depressed mood or loss of positive affect and at least three additional symptoms of depression), 41% of depressed patients in the stage of severe Alzheimer’s disease had no sad mood, suggesting that the NIMH criteria may have low specificity for depression in the late stages of dementia.

The question also arises as to whether a dimensional or a categorical strategy to diagnose depression should be used in Alzheimer’s disease. Studies of depression in the elderly have demonstrated that subsyndromal depressions might have an adverse functional impact that is sometimes undistinguishable from the negative effects of major depression (28). Our findings of more severe functional deficits in major depression compared to minor depression and in minor depression compared to no depression seems to fit a dimensional approach. The use of a dimensional strategy, such as establishing a cutoff score on a well-validated scale like the Hamilton depression scale, might detect subthreshold depression that may potentially benefit from early antidepressant treatment. We addressed this question by dividing our group of nondepressed patients into those who had a Hamilton depression scale score of 10 or more (N=41) and those who had Hamilton depression scale score of 9 or less (N=275). The patients with higher Hamilton depression scale scores had evidence of more severe delusional symptoms (Dementia Psychosis Scale—subthreshold depression score: mean=3.4, SD=3.7, versus euthymia score: mean=1.6, SD=3.7, respectively) (t=3.48, df=257, p=0.001), apathy (Apathy Scale score: mean=22.7, SD=8.2, versus mean=18.3, SD=9.4) (t=2.16, df=285, p=0.01), irritability (Irritability Scale score: mean=19.4, SD=8.1, versus mean=11.8, SD=8.3) (t=5.23, df=279, p<0.0001), and pathological affective crying (Pathological Laughing and Crying Scale score: mean=3.7, SD=4.0, versus mean=2.2, SD=4.0) (t=1.98, df=248, p=0.05). However, there were no significant differences between the two groups in activities of daily living or psychosocial adjustment, casting doubt about what is the functional impact of subthreshold depression defined with this dimensional approach.

Another relevant finding was that loss of interest was significantly more frequent among patients with either minor depression or major depression than in nondepressed patients, in contradiction to the NIMH consensus suggestion that loss of interest may not be specific for depression in Alzheimer’s disease. We did not assess decreased positive affect, which replaces the criterion of loss of interest in the NIMH criteria. However, the concept of “positive affect” may be difficult to assess in clinical practice unless clear guidelines are provided, and loss of positive affect could be confused with the blunted affect of apathy or with the loss of facial emotional expression typical of Alzheimer’s disease patients with parkinsonism. In addition, the NIMH criteria do not provide a clear definition of irritability, and this criterion may have low reliability. In a recent study that included 65 patients with Alzheimer’s disease who remitted from a depressive episode during a 3-month follow-up period (29), we found a significant improvement in all symptoms included in the DSM-IV clinical criteria for a major depressive episode. On the other hand, no improvement was found on scores for irritability, suggesting that depression and irritability are comorbid disorders in Alzheimer’s disease. Moreover, in a study that assessed 103 patients with Alzheimer’s disease using the Irritability Scale (14), we found no significant differences in the frequencies of major and minor depression between Alzheimer’s disease patients with and without irritability. In the present study, the patients with major depression or minor depression had significantly higher scores for irritability than nondepressed patients, but the association between irritability and sad mood was of marginal significance.

Finally, we found that patients with either major depression or minor depression had significantly higher scores on the Pathological Laughing and Crying Scale subscale for crying than nondepressed patients, demonstrating that affective lability is significantly associated with depression in Alzheimer’s disease. The NIMH criteria explicitly exclude affective lability, suggesting that this symptom would be better classified as “affective dysregulation because of dementia.” This suggestion is based on a study that found that the Consortium to Establish a Registry for Alzheimer’s Disease Behavior Rating Scale for Dementia item rating “sudden changes in emotion” loaded on a factor of irritability/aggression but not on a factor of depressive features (30, 31). In a study that used a structured psychiatric interview and a valid instrument to rate the frequency and severity of affective lability in Alzheimer’s disease (18), we
found that 25% of the sample had affective lability with crying episodes, and 81% of this group had either major or dysthymic depression compared to 30% for Alzheimer’s disease patients without affective lability. Important methodological differences may explain our discrepancies with the findings from the Consortium to Establish a Registry for Alzheimer’s Disease. Its assessment of affective lability was based on responses to the item rating “sudden changes in emotion,” and its validity to rate affective lability has not been demonstrated (30, 31). Our findings suggest that affective lability is not only a frequent symptom in Alzheimer’s disease but may be a useful clinical marker of depression.

In conclusion, our study demonstrates that the DSM-IV criteria for major depression and minor depression identify clinically relevant syndromes of depression in Alzheimer’s disease. Future studies should demonstrate the long-term stability and predictive validity of major depression and minor depression in Alzheimer’s disease, as well as further explore the relationship of subsyndromal depression and functional impairment.

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References


The Capacity to Vote of Persons With Alzheimer’s Disease

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Objective: The right to vote can be abrogated when persons become incompetent to cast a ballot. This applies particularly to people with Alzheimer’s disease, who at some point will lose capacity. A 2001 federal court decision offered the first clear criteria (“Doe voting capacity standard”) for determining voting competence, focused on understanding the nature and effect of voting and on the ability to choose. This article explores how persons with Alzheimer’s disease perform on these criteria.

Method: The Doe standard was operationalized in a brief questionnaire, along with measures of appreciation and reasoning about voting choices. Performance was assessed in 33 patients attending an Alzheimer’s disease clinic and was related to dementia severity and demographic characteristics.

Results: The interview questions were scored with high reliability. Performance on the Doe questions, along with appreciation and reasoning, correlated strongly with Mini-Mental State Examination (MMSE) scores. Patients with very mild to mild Alzheimer’s disease generally retained adequate ability to vote, and most persons with severe Alzheimer’s disease did not. Performance was highly variable among persons with moderate Alzheimer’s disease. The desire to vote was a poor predictor of voting capacity.

Conclusions: The capacity to vote, as embodied in the Doe voting capacity standard, can be measured simply and reliably. Structured assessment is particularly likely to be useful for people with moderate Alzheimer’s disease, whose performance cannot be predicted from MMSE scores alone. This approach can ensure retention of voting rights by capable persons and exclusion of clearly impaired persons from the voting booth.

Voting is a quintessential right of citizens in democratic societies. Although universal suffrage is now taken for granted in the United States, it has been less than a century since women were accorded the right to vote and barely more than a generation since that right was made meaningful for African Americans (1). But some persons are still often denied the right to vote, including convicted felons and persons thought to be incompetent to cast a ballot (2). For the latter group, the justification for exclusion is usually the state’s interest in protecting the integrity of the vote. How one might identify persons who lack the capacity to vote is the focus of this study.

In the United States, state laws generally govern election procedures. Most states have prescribed criteria by which people might be deemed incompetent to vote. Unfortunately, these criteria often focus on membership in a class (e.g., all persons under guardianship) rather than on an assessment of a person’s functional abilities (3, 4). The states’ failure to require an individualized determination of capacity to vote has been challenged on the grounds that it deprives competent would-be voters of their constitutional right to vote (5). A 2001 federal district court decision in Maine, Doe v. Rowe, for the first time laid out the criteria that should be applied in individualized assessments of capacity to vote (6).

The lawsuit in Doe was brought by three people with mental illness who objected to a provision in Maine’s constitution excluding all persons under guardianship for reasons of mental illness from casting ballots. Maine voters had twice rejected referenda that would have repealed the provision. But the federal district court ruled that the automatic exclusion of this class of persons violated their rights to procedural due process and equal protection and the guarantees against discrimination of the Americans With Disabilities Act. In striking down the offending provision of the Maine constitution, the court adopted a test proposed by the parties in the case: persons are considered incompetent to vote only if they “lack the capacity to understand the nature and effect of voting such that they cannot make an individual choice.” Although the case dealt with persons with mental illness, the criteria apply to all persons whose competence to vote may be in question. (We refer to these criteria hereafter as the “Doe voting capacity standard.”)

The move to individualized, functional determinations of the specific capacity to vote parallels similar trends with regard to assessments of the capacity to consent to treatment or research, complete an advance directive, manage finances, and make other important decisions (7). In all these areas, efforts have been made to operationalize the...
relevant legal criteria in assessment instruments that can be applied in a reliable fashion. With regard to voting, such a process not only will help to limit the number of persons excluded from voting by the courts but will also permit election officials and caregivers to decide when a person has become incapable of voting. This is of particular importance for the growing number of persons with Alzheimer’s disease and other progressive cognitive disorders, many of whom now vote (8, 9), since such a transition is almost inevitable in those disorders and many of them eventually reside in long-term care facilities, where federal regulations stipulate that the facility must respect the residents’ civil rights, including the right to vote (10). Facility staff, however, are at present without practical guidance as to how to distinguish between residents who are capable and incapable of voting.

In this article, we report the results of a study that explored consequences of applying the criteria identified in the Doe case to persons with very mild to severe Alzheimer’s disease. We focus on the relationships of the Doe voting capacity standard and other measures of capacity to the severity of dementia. Our a priori hypotheses were that voting capacity would correlate inversely with dementia severity and that the criteria cited by the Doe court decision would prove less restrictive than alternative approaches.

**Method**

**Subjects**

Eligible subjects were community-dwelling persons (N=33) with very mild to severe Alzheimer’s disease (possible or probable) who attended an annual assessment as part of the longitudinal cohort followed at the Memory Disorders Clinic at the University of Pennsylvania. The diagnosis of Alzheimer’s disease was based on the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (11), and dementia severity was defined by using standard cut points on the Mini-Mental State Examination (MMSE): very mild, >23; mild, 20 to 23; moderate, 12 to 19; and severe, <12 (12). Most subjects were white (85%); 12% were African American, and 3% were Asian. No subjects refused to participate, although four subjects who originally agreed did not complete the interview because of scheduling issues.

**Development of Assessment Tool and Scoring Criteria**

The instrument used to assess the capacity to vote, the Competence Assessment Tool for Voting (CAT-V), is based on the structure and scoring criteria of other capacity assessment instruments (13, 14). It assesses a person’s performance on all four standard decision-making abilities: understanding, appreciation, reasoning, and choice (15). Although only understanding and choice were required by the Doe court, we added appreciation and reasoning questions for comparative purposes.

We designed the CAT-V understanding and choice questions on the basis of the standard for voting capacity described in the Doe case (6). As noted, that case held that a person has the capacity to vote if he or she understands the nature and effect of voting and has the capacity to make a choice. The CAT-V operationalizes these criteria into three questions based on the Doe standard (“Doe standard questions”), which are distinct from the remaining CAT-V questions.

Following an introduction that asks the subject to imagine that it is the day for election of the governor of the state, an interviewer inquires about the person’s understanding of the nature of voting and then asks a question to assess understanding of the effect of voting. Next the interviewer reads aloud a description of two candidates for governor, gives this written description to the person, and then asks the person to choose one of the candidates.

The CAT-V also includes three questions that go beyond the Doe voting capacity standard to assess the abilities to reason about the electoral choice by comparing the candidates and identifying the ways in which choosing one over the other could affect the subject’s own life. Subjects are queried about their appreciation of the significance of voting by being asked to explain why they would or would not want to vote in the next election for governor of their state.

For each CAT-V item, we developed scoring criteria using a 2, 1, or 0 scale where a score of 2 described adequate performance on the measure, 1 described marginal performance, and 0 described clearly inadequate performance. Drafts of the instrument and its scoring criteria were tested on a convenience sample of approximately 10 cognitively normal people (co-workers) and five persons with Alzheimer’s disease. A final version was then administered to consecutive persons with Alzheimer’s disease attending the Memory Disorders Clinic, with recruitment adjusted to approximate equal numbers across the severities of dementia. The instrument and its scoring criteria are shown in Appendix 1.

**Data Gathering**

Each subject participated in a face-to-face interview with an investigator (J.H.K.). The interview was digitally recorded to allow two raters (P.S.A. and R.J.B.) to score the interviews independently. The raters (although not the interviewer) were blind to the subject’s MMSE score, age, and education. Periodically, the investigators reviewed their scoring to adjudicate cases of disagreement so as to arrive at a set of final scores that were used in the data analyses. The participants’ demographic data and MMSE scores were taken from the Memory Disorders Clinic database.

**Data Analyses**

We used a quadratically weighted kappa to assess the interrater reliability of the CAT-V scoring criteria prior to agreement on a consensus score. For each participant, we created a Doe score (range=0–6) by summing the scores on the two measures of understanding (range=0–4) and the measure of choice (range=0–2), created a reasoning score (range=0–4) by summing the subject’s scores on the two measures of reasoning, and assigned an appreciation score on the basis of the single item (range=0–2). Appropriate summary statistics and cross tabulations are used to display the nature of the participants’ performance. We used Fisher’s exact test to examine associations between CAT-V measures, and the Spearman correlation coefficient or the Kruskal-Wallis test was used to examine the associations of CAT-V performance with MMSE scores and the participants’ demographic characteristics.

**Human Subjects Protections**

Each participant was recruited by an initial contact with the person who accompanied the participant on visits to serve as a knowledgeable informant and decision maker for the person with Alzheimer’s disease, typically a spouse or adult child, referred to as the “caregiver.” If this person agreed to an interview, the person with Alzheimer’s disease provided either verbal informed consent or assent (in which case the caregiver provided verbal informed consent), after disclosure of the nature of the study. This project was approved by the University of Pennsylvania institutional review board. The subjects were assured that the...
Performance on CAT-V Subscales

Cross-tabular comparisons of scores on the ability to understand the nature of voting to scores on the reasoning and appreciation measures showed that the subjects performed better on the ability to understand the nature of voting than on the abilities to reason about (Fisher’s exact test, p=0.001) and to appreciate the effect of (Fisher’s exact test, p=0.0001) voting. Similar results were found when we compared the scores on the ability to understand the effect of voting and scores on the abilities to reason (Fisher’s exact test, p=0.0001) and appreciate the significance of voting (Fisher’s exact test, p=0.0001).

Table 2 shows cross-tabulations relating the subjects’ scores on the Doe standard questions to their scores on the measures of reasoning and appreciation and their desire to vote. The table suggests that persons whose score on the Doe questions was a 6, the maximum score, were more likely to have the maximum scores on reasoning and appreciation.

Every participant who scored 5 or 6 on the Doe questions indicated a desire to vote, but so did eight participants who scored less than 5, including four who scored 2 and two who scored 0. Looked at another way, eight of the 14 subjects who scored 4 or less (including two of the three with scores of 0) expressed a desire to vote.

Relationships Between CAT-V Performance and Dementia Severity

Figure 1 shows that higher scores on the Doe questions were associated with better performance on the MMSE ($r_2=0.75$, df=32, $p<0.0001$). Inspection of the graph shows that all persons with severe dementia (MMSE score <12) scored a 2 or lower on the Doe standard questions and that all persons with very mild and most with mild dementia scored a 6. In contrast, persons with moderate-stage dementia showed substantial variability in their scores on the Doe questions, ranging from 2 to 6.
Figure 2 and Figure 3 show associations between higher MMSE scores and better performance on the measures of reasoning (r_s=0.70, df=32, p<0.0001) and appreciation (Kruskal-Wallis test: χ²=11.8, df=2, p=0.003). All subjects who scored the maximum of 4 on reasoning had an MMSE score of 15 or greater, and all who scored the maximum of 2 on appreciation had an MMSE score of 11 or greater. However, for both of these CAT-V measures, the figures show that some subjects whose MMSE scores were in the mild to moderate range had CAT-V scores less than either 4 on reasoning or 2 on appreciation.

The mean MMSE score of persons who did not want to vote was 13.0 (SD=7.2, range=2–20), and among those who wanted to vote it was 17.3 (SD=6.6, range=5–28). No relationship was found between the desire to vote and performance on the MMSE (rank-sum test: z=-1.3, p=0.20).

Discussion

Using a set of commonsense criteria for the capacity to vote that were elaborated by a federal court, this study demonstrates a strong correlation between dementia severity and the capacity to vote. The data exploring the relationship between the responses to the questions intended to operationalize the Doe voting capacity standard (understanding and choice) and the participants’ MMSE scores suggest that most (but not all) persons with very mild to mild dementia of the Alzheimer’s type retain adequate ability to vote and that most persons with severe dementia do not. The variability in scores on the Doe standard questions among persons with moderate dementia suggests the need for individualized assessments for these potential voters. In contrast to most types of capacity assessment, performance was independent of age and education, although the range of educational levels was compressed.

The Doe voting capacity standard, which emphasizes understanding of the nature and effect of voting and the ability to make a choice, reflects the tendency of American law to place few barriers in the way of citizens who desire to vote. For example, neither the ability to read nor knowledge of English is required of voters and probing a potential voter’s reasoning ability, understanding of the context in which the election is held, or understanding of the merits of any given ballot question would open the door to arbitrary (and possibly discriminatory) judgments reminiscent of the literacy tests used in the South to disenfranchise black voters until the middle of the 20th century (1).

To allow a comparison of the Doe standard of competence with alternative approaches to determining decisional capacity, however, we also included in this study questions intended to address participants’ abilities to reason about and appreciate the significance of voting. Relationships between reasoning and appreciation scores and the MMSE score suggest that many persons with very mild to mild Alzheimer’s disease retain the abilities to reason and appreciate in the voting context. As expected, however, the data also confirm that a standard for voting capacity that measures the ability to reason or appreciate the significance of voting would likely disenfranchise some persons who retain the abilities to understand the nature and effect of voting and to make an electoral choice.

<table>
<thead>
<tr>
<th>Score on Questions Assessing Reasoning, Appreciation, and Desire to Vote</th>
<th>Score on Three Doe Questions Assessing Understanding and Choice</th>
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<tr>
<td>Reasoning (two questions)</td>
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a Established by the 2001 federal district court case Doe v. Rowe in Maine.
b Significant difference between groups (Fisher’s exact test, p=0.04).
c Significant difference between groups (Fisher’s exact test, p=0.0001).
d N=31 for this analysis. Two patients did not answer yes or no to the question “Would you want to vote in the next election for governor of your state? If yes, why? If no, why not?”

Figure 1. Relation of Mini-Mental State Examination Scores to Scores on Questions Derived From the Doe Voting Capacity Standarda for 33 People With Alzheimer’s Disease

a Established by the 2001 federal district court case Doe v. Rowe in Maine.
Because of concerns that the use of any test of voting capacity creates a risk of misuse and selective exclusion of persons who are in fact competent to vote, it is sometimes suggested that any person who expresses a desire to vote should be allowed to do so. It was clear from our data, however, that not all persons who say they want to vote understand the nature and effect of voting. Indeed, the majority of persons who scored 5 or below on the questions derived from the Doe voting capacity standard, including several who scored 0, expressed a desire to vote in the next election for governor of their state. In the absence of an objective criterion for judging capacity to vote, it seems likely that voters who do not understand what voting is may still cast ballots, potentially compromising the integrity of the electoral process.

The instrument we used to operationalize the Doe criteria was easy and efficient to administer. Only 3–4 minutes were required to ask the questions related to the Doe voting capacity standard. This suggests that those questions from the CAT-V or a similar interview could be used efficiently to screen persons whose voting capacity is in question. Since the appreciation and reasoning questions do not reflect judicially approved criteria, we do not recommend their use for this purpose. Given that the Doe questions are drawn directly from the court’s criteria, they appear to have face validity, and the correlation with severity of dementia suggests validity for the construct as well. Whether other courts and legislatures embrace the Doe court’s criteria (the decision was not appealed) remains to be seen.

On the basis of this relatively small study group, we are inclined to think that responses on the two understanding items can be objectively scored as adequate or inadequate, without any intermediate score. Further thought may need to be given to whether the item assessing the ability to choose (which functions clearly as a binary variable) is needed in the interview. Including this item would increase the time needed to administer the interview, and it could be argued that a person who is unable to make a choice will not be able to cast an effective ballot in any event. On the other hand, identifying such potential voters in advance may save the time and difficulties associated with getting them to the polls or attempting to assist them in completing absentee ballots. If the choice item is retained, the scoring should acknowledge that being undecided is a choice too.

Using a structured interview, such as the CAT-V, offers advantages over unstructured or clinical assessments. It focuses an assessor on the specific abilities needed for the capacity to vote and also may provide a basis for educating the person being evaluated so that he or she might acquire sufficient understanding to achieve capacity. What an instrument cannot do is determine which scores represent adequate capacity. The extremes of performance are not controversial: a 0 clearly indicates lack of ability and a 6 (or 4, depending on whether the ability to choose is necessary) on the Doe questions indicates adequate capacity. But intermediate scores require a judgment to be made, the basis of which at this point is not clear. Data on the performance of nondemented subjects may be helpful in identifying appropriate cutoffs.

These preliminary data also suggest that persons with severe Alzheimer’s disease as measured by the MMSE are likely not competent to vote and that persons with very mild to mild Alzheimer’s disease are likely competent to do so (although the latter may benefit from memory aids when casting their ballots). For persons with moderate Alzheimer’s
APPENDIX 1. Competency Assessment Tool for Voting (CAT-V)

[Note the potential modifications to the instrument suggested in the text.]

<table>
<thead>
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<th>Understanding</th>
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<tbody>
<tr>
<td>“Imagine that two candidates are running for Governor of [fill in name: your state], and that today is Election Day in [fill in name: your state].”</td>
</tr>
<tr>
<td>Understands the Nature of Voting</td>
</tr>
<tr>
<td>“What will the people of [fill in name: your state] do today to pick the next Governor?”</td>
</tr>
<tr>
<td>Note to interviewer: If subject describes how he/she or people in general would choose between the two choices for governor (i.e., watch TV ads, listen to their campaign issues, etc.), ask:</td>
</tr>
<tr>
<td>“Well that’s how you might decide who you think should be governor. But how would you actually indicate your choice?”</td>
</tr>
<tr>
<td>[Score of 2: Ambiguous or partially correct response, e.g., “They will go to the polls and vote.” “Each person will cast his/her vote for one or the other.” Score of 1: Incorrect or irrelevant response, e.g., “There’s nothing you can do; the TV guy decides.”]</td>
</tr>
<tr>
<td>Understands the Effect of Voting</td>
</tr>
<tr>
<td>“When the election for governor is over, how will it be decided who the winner is?”</td>
</tr>
<tr>
<td>[Score of 2: Completely correct response, e.g., “The votes will be counted and the person with more votes will be the winner.” Score of 1: Ambiguous or partially correct response, e.g., “By the numbers.” Score of 0: Incorrect or irrelevant response, e.g., “It all depends on which sign they were born under.”]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Hand subject a card with the information in the following paragraph in large print; allow subject to retain and consult this card for the remainder of the interview:]</td>
</tr>
<tr>
<td>“Let me ask you to imagine the following about the two candidates who are running. Candidate A thinks the state should be doing more to provide health insurance to people who don’t have it, and should be spending more money on schools. He is willing to raise taxes to get the money to do these things. Candidate B says the government should not provide health insurance but should make it easier for employers to offer it. He believes that the schools have enough money already but need tighter controls to make sure they use it properly. He is against raising taxes.”</td>
</tr>
<tr>
<td>Note to interviewer: If subject can not choose a candidate or is vacillating, ask:</td>
</tr>
<tr>
<td>“Based on what I just told you, which candidate do you think you are more likely to vote for: A or B?”</td>
</tr>
<tr>
<td>[Score of 2: Clearly indicates choice. Score of 1: Choice is ambiguous or vacillating, e.g., “I think I might go for the guy who doesn’t like taxes, but I’m not sure because schools are important too.” Score of 0: No choice is stated, e.g., “I don’t know. I can never make up my mind.”]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reasoning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparative Reasoning</td>
</tr>
<tr>
<td>If subject identifies a choice, ask:</td>
</tr>
<tr>
<td>“How is voting for [subject’s choice] better than voting for [name of other candidate]?”</td>
</tr>
<tr>
<td>[Score of 2: Identifies at least one comparative attribute in relation to the views of the two candidates, e.g., “Someone who really cares about health care would be a better governor.” Score of 1: Ambiguous response, e.g., “Health care.” Score of 0: Fails to mention a comparative attribute of the respective candidates, e.g., “I just think he’s good” or “I can’t see any difference”]</td>
</tr>
</tbody>
</table>

Note to interviewer: If subject describes how he/she or people in general would choose between the two choices for governor (i.e., watch TV ads, listen to their campaign issues, etc.), ask:

“Let me ask you to imagine the following about the two candidates who are running. Candidate A thinks the state should be doing more to provide health insurance to people who don’t have it, and should be spending more money on schools. He is willing to raise taxes to get the money to do these things. Candidate B says the government should not provide health insurance but should make it easier for employers to offer it. He believes that the schools have enough money already but need tighter controls to make sure they use it properly. He is against raising taxes.”

“Based on what I just told you, which candidate do you think you are more likely to vote for: A or B?”

“Imagine that two candidates are running for Governor of [fill in name: your state], and that today is Election Day in [fill in name: your state].”

“What will the people of [fill in name: your state] do today to pick the next Governor?”

“What’s how you might decide who you think should be governor. But how would you actually indicate your choice?”

“When the election for governor is over, how will it be decided who the winner is?”

“Let me ask you to imagine the following about the two candidates who are running. Candidate A thinks the state should be doing more to provide health insurance to people who don’t have it, and should be spending more money on schools. He is willing to raise taxes to get the money to do these things. Candidate B says the government should not provide health insurance but should make it easier for employers to offer it. He believes that the schools have enough money already but need tighter controls to make sure they use it properly. He is against raising taxes.”

“Based on what I just told you, which candidate do you think you are more likely to vote for: A or B?”

“How is voting for [subject’s choice] better than voting for [name of other candidate]?”

“Imagine that two candidates are running for Governor of [fill in name: your state], and that today is Election Day in [fill in name: your state].”

“What will the people of [fill in name: your state] do today to pick the next Governor?”

“What’s how you might decide who you think should be governor. But how would you actually indicate your choice?”

“When the election for governor is over, how will it be decided who the winner is?”

“What’s how you might decide who you think should be governor. But how would you actually indicate your choice?”
APPENDIX 1. Competency Assessment Tool for Voting (CAT-V) (continued)

<table>
<thead>
<tr>
<th>Generating Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>“If [subject’s choice or Candidate A if subject had no choice] were elected governor in your state, how could that affect your life?”</td>
</tr>
<tr>
<td>Note to interviewer: Probe for a reason if subject says it will not affect them.</td>
</tr>
<tr>
<td>[Score of 2: Identifies a consequence for his or her life, e.g., “I’d have more money to spend” or “I’d have better access to health care”; if sees no personal consequences, subject gives a coherent reason (“I’ll be moving to another state soon.” “I’ll be dead in a year anyway.”) Score of 1: Gives a vague consequence for his or her life, e.g., “Health.” Score of 0: Does not give a consequence for his or her life or a reason for saying that there are no personally relevant consequences.]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Appreciation</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Would you want to vote in the next election for governor of your state? If yes, why? If no, why not?”</td>
</tr>
</tbody>
</table>
| [Score of 2: Response based on reason that reflects reality of voting situation. E.g., if yes: “My doing that makes it more likely that the candidate I like will win.” If no, “I don’t care who wins”; “My one vote is unlikely to make much of a difference.” Score of 1: Ambiguous response that partially reflects reality of voting situation. E.g., if yes: “It helps to run the country.” If no, “They might not let me.” Score of 0: Responses that fail to reflect subject’s choice or Candidate A if subject had no choice.]

References

Genotype-Phenotype Studies in Bipolar Disorder Showing Association Between the DAOA/G30 Locus and Persecutory Delusions: A First Step Toward a Molecular Genetic Classification of Psychiatric Phenotypes

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Piotr M. Czerski, Ph.D.
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Layla Kassem, Psy.D.
Monika Deschner, M.Psych.
Magdalena Gross, M.Psych.
Monja Tullius, M.D.
Vivien Heidmann, M.Psych.
Svetlana Kovalenko, M.D.
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Tim Becker, Ph.D.
Anna Leszczynska-Rodziewicz, M.D.
Joanna Hauser, M.D.
Thomas Illig, Ph.D.
Norman Klopp, Ph.D.
Stefan Wellek, Ph.D.
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Fritz A. Henn, M.D., Ph.D.
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Marcella Rietschel, M.D.

Objective: The authors previously reported an association between the D-amino acid oxidase activator (DAOA)/G30 locus and both schizophrenia and bipolar affective disorder. Given the presumed role of DAOA/G30 in the neurochemistry of psychosis and its localization in a schizophrenia and bipolar affective disorder linkage region (13q34), it was hypothesized that the bipolar affective disorder finding would be mainly due to an association with psychotic features.

Method: The marker/haplotype associations obtained in a subset of 173 bipolar affective disorder patients with psychotic features were similar to those in the overall patient group, suggesting that stratification on the basis of psychotic features in general might be too crude a procedure. The authors therefore tested whether confining caseness to specific psychotic features would improve detection of genotype-phenotype correlations.

Results: In a logistic regression, “persecutory delusions” were found to be the only significant explanatory variable for the DAOA/G30 risk genotype among 21 OPCRIT symptoms of psychosis. The authors therefore tested for association between DAOA/G30 and bipolar affective disorder in the 90 cases with a history of persecutory delusions. Whereas this subset showed strong association (odds ratio = 1.83 for the best marker), the remaining larger sample of 165 patients with no such history did not differ from comparison subjects, suggesting that the association between DAOA/G30 and bipolar affective disorder is due to persecutory delusions. This was confirmed in an independent study of 294 bipolar affective disorder patients and 311 comparison subjects from Poland, in which an association between bipolar affective disorder and DAOA/G30 was only seen when case definition was restricted to cases with persecutory delusions.

Conclusions: These data suggest that bipolar affective disorder with persecutory delusions constitutes a distinct subgroup of bipolar affective disorder that overlaps with schizophrenia.

The D-amino acid oxidase activator (DAOA)/G30 locus, formerly known as the G72/G30 locus, has been found to be associated with both schizophrenia and bipolar affective disorder (1, 2). We were able to replicate these findings for both disorders in a study of 299 patients with schizophrenia, 300 individuals with bipolar affective disorder (all bipolar type I), and 300 comparison subjects: a four-marker haplotype comprising markers M12 (rs1341402), M15 (rs2391191), M23 (rs3918342), and M24 (rs1421292) showed association with schizophrenia and bipolar affective disorder (3).

DAOA/G30, located on chromosome 13q34, was initially found through systematic fine-mapping (1) in a schizophrenia linkage region (4). This locus also shows linkage evidence for bipolar affective disorder (5). It is of interest that Potash et al. (6) found increased evidence of linkage with bipolar affective disorder in a neighboring region (13q31) in a conditional linkage analysis of bipolar affec-
TABLE 1. Subject Groups in the Exploratory and Replication Studies of Bipolar Affective Disorder Genotype-Phenotype Associations

<table>
<thead>
<tr>
<th>Group</th>
<th>Exploratory Study (German group)</th>
<th>Replication Study (Polish group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients with bipolar affective disorder</td>
<td>300</td>
<td>294</td>
</tr>
<tr>
<td>Subjects with definite yes/no ratings for all 21 OPCRIT symptoms of psychosis*</td>
<td>256</td>
<td>284</td>
</tr>
<tr>
<td>History of psychotic symptoms</td>
<td>173</td>
<td>121</td>
</tr>
<tr>
<td>No history of psychotic symptoms</td>
<td>83</td>
<td>163</td>
</tr>
<tr>
<td>Subjects with definite yes/no ratings for history of persecutory delusions</td>
<td>255</td>
<td>287</td>
</tr>
<tr>
<td>History of persecutory delusions</td>
<td>90</td>
<td>55</td>
</tr>
<tr>
<td>No history of persecutory delusions</td>
<td>165</td>
<td>232</td>
</tr>
<tr>
<td>Comparison subjects</td>
<td>300</td>
<td>311</td>
</tr>
</tbody>
</table>

* A definite "no" rating is only possible when all 21 OPCRIT symptoms of psychosis are rated negative with no missing values.

bipolar affective disorder that used a subset of families enriched with psychotic symptoms. Despite this region being 28 cM centromeric to the DAOA/G30 locus, this linkage peak may still represent the effect conferred by DAOA/G30, given the low resolution of linkage findings (7–9). Furthermore, proneness to psychotic symptoms appears to be an inherited predisposition common to both schizophrenia and bipolar affective disorder (10). Finally, previous findings have suggested an interaction between DAOA/G30 and the gene D-amino-acid oxidase (DAAO), which is involved in the glutamatergic signaling pathway (1) and has in turn been implicated in the etiology of affective disorders and psychotic symptoms (11).

The separation of psychotic syndromes into etiologically homogeneous subtypes has been controversial among psychiatrists since the first attempts to classify psychiatric disorders (12–19). Although bipolar affective disorder and schizophrenia are defined as distinct and exclusive diagnostic entities, they show great overlap of symptoms, particularly psychotic features. The diagnostic boundaries are justified mainly by clinical convenience; their biological validity is still limited. The recent detection of disease-associated risk haplotypes in several susceptibility genes for psychiatric disorders offers the chance to test whether such an association is stronger between the haplotype and the diagnostic entity or between the haplotype and specific symptoms.

On the basis of the clinical, genetic, and neurochemical findings, we hypothesized that the association between bipolar affective disorder and the schizophrenia-associated DAOA/G30 alleles/haplotypes could be explained by the presence of psychotic symptoms in bipolar affective disorder rather than with the diagnostic entity "bipolar affective disorder" alone.

We tested this hypothesis in our group of German patients in which an overall association between DAOA/G30 and bipolar affective disorder had been detected (3). A replication study was performed in an independent group of patients from Poland that had been gathered using the same phenotype characterization procedures.

Method

Subjects

**Exploratory study (German group).** This group comprised 300 patients (138 men and 162 women; mean age=42.3 years (SD=13.2)) with DSM-IV bipolar affective disorder (all bipolar type I) and 300 comparison subjects (121 men and 179 women; mean age=47.1 years (SD=15.2)) for whom we had genotype data available (3) (Table 1). Patients in this study were recruited from the same geographical area and were all of German descent. Patients were systematically recruited at the University of Bonn Department of Psychiatry. Subjects in the comparison group were anonymous blood donors of German descent recruited from the same geographical area as the patients. Written informed consent was obtained from all patients and comparison subjects. Of the 300 patients, 225 had been assessed by experienced psychiatrists with the Structured Clinical Interview for DSM-IV Disorders (SCID) (20), and 75 patients had been assessed with the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (21). Lifetime “best estimate” diagnoses according to DSM-IV criteria were based on multiple sources of information including the structured interviews, medical records, and family history method. Consensus diagnoses were performed by two psychiatrists, and additional psychiatrists were included in the decision process whenever necessary (22). Furthermore, for the detailed polydiagnostic documentation of symptoms, we used the OPCRIT system (23). OPCRIT allows for the assessment and documentation of lifetime psychopathology without any preference for a particular
classification system by decomposing diagnostic criteria into their component items (24).

**Replication study (Polish group).** This group consisted of 294 bipolar affective disorder patients (type I: N=259, type II: N=35; 128 men and 166 women; mean age=46.9 years [SD=13.7]) and 311 comparison subjects (115 men and 196 women; mean age=43.7 years [SD=9.5]) from the Wielkopolska region (Western Poland) (Table 1). All individuals were of Polish descent. Patients were systematically recruited at two psychiatric hospitals, the Department of Psychiatry of the Poznan University of Medical Sciences and the psychiatric hospital in Koscián. The same diagnostic procedures were applied; all patients were interviewed with the SCID (20). Comparison subjects were drawn from anonymous blood donors, hospital staff, and medical students. Written informed consent was obtained from all patients and comparison subjects.

**Assessment of Lifetime Psychotic Symptoms**

We defined lifetime psychotic symptoms as the occurrence of delusional or hallucinatory symptoms. Patients with bipolar affective disorder were classified as having a positive history of psychosis if a “yes” rating was given on at least one of the 21 OPCRIT symptoms of delusions or hallucinations (Table 2). Of the 300 patients in the exploratory study, we identified 173 individuals with a definite positive history and 83 with a definite negative history. The latter assignment was only made when all 21 OPCRIT symptoms of psychosis were rated negative with no missing values. Thus, for 44 patients, no clear assignment could be made. Of the 294 patients in the replication study, 121 patients with a definite positive history of psychosis and 163 patients with a definite negative history were identified (10 patients could not be classified).

**Genotyping**

The DAOA/G30 single nucleotide polymorphisms (SNPs) genotyped in the exploratory study were determined by Masscode Technology (QIAGEN Genomics). The DAOA/G30 SNPs analyzed in the replication study were genotyped using the MassARRAY system (Sequenom, San Diego) according to Ding and Cantor (25) with minor modifications. The genotyping quality between both techniques is comparable: two SNPs (rs7320 and rs2185740) were genotyped using both techniques, the Masscode and the Mass ARRAY technology, and no discrepancies in genotypes were observed. Genotype frequencies were in Hardy–Weinberg equilibrium for cases and comparison subjects in both study groups.

**Genetic Analyses**

We performed both single-marker and haplotype analyses with the program COCAPHASE 2.40 (http://www.mrc-bsu.cam.ac.uk/personal/frank/software/unphased/) (26). Using a standard unconditional logistic regression, this software package performs likelihood ratio tests under a log-linear model of the probability that an allele or a haplotype belongs to a case rather than a noncase; the expectation-maximization algorithm is used to resolve uncertain haplotypes and provide maximum-likelihood estimates of frequencies.

For the single-marker analyses, a permutation procedure was used to estimate the significance of the best results, correcting for all loci tested. For haplotype analyses, the global null hypotheses that all odds ratios are equal were tested by permutation, owing to the fact that estimated haplotype frequencies cannot be treated as observed data. The permutation method implemented in COCAPHASE randomly reassigns the “patient” and “comparison” labels in the actual data. Ten thousand permutations were performed.

Comparisons were performed across clinical subgroups by stratifying the patients and comparing allele and haplotype frequencies against the same comparison population.

**Phenotype-Genotype Association Analysis**

Statistical genotype-phenotype association analysis was performed by using logistic regression analysis as implemented in the SAS procedure PROC LOGISTIC. For this analysis, we chose the genotype of the DAOA/G30 marker M23, which had yielded the most marked result in our previous analysis (3), as the dependent variable with three categories (i.e., the genotypes TT, TC, CC). The 21 OPCRIT symptoms of psychosis (Table 2) were entered as explanatory variables in the model, as well as the variables age, gender, and age at onset. The logistic regression analysis was performed on a complete case basis including only those patients for whom information on all items was available (N=225). The logistic model was used in its generalized version allowing for dependent variables that take their values in a set of more than two ordered categories. This approach is based on the proportional odds assumption according to which the odds ratios related to all possible dichotomized versions of the dependent variable, except for the intercept terms, are the same function of the covariates for any choice of the cutoff. Generalized logistic regression was carried out for the 21 OPCRIT symptoms of psychosis both as a full set and in a stepwise manner selecting the symptoms that showed a significant contribution to the goodness of fit of the model.

**Empirical Significance for Clinically Defined Subgroups**

It has been suggested that, given a population with significant association, an improvement in p value may exist in random subsets of the population (27). Therefore, we established the empirical significance of any asymptotically significant finding by simulation. In 10,000 replicates, random subsets of the size of the actual, clinically defined subset were drawn from the overall group and analyzed.

**Power Calculations (Polish group)**

Power calculations were performed using the Genetic Power Calculator (http://statgen.iop.kcl.ac.uk/gpc/cc2.html) (28) and were based on the odds ratio of 1.33 for the best associated marker (M23) in the German sample. We used both a recessive and a dominant model, assuming equal allele frequencies for the disease and marker alleles, and a D’ of 0.8 between disease and marker locus.

**Results**

**Genetic Analysis of Bipolar Affective Disorder Patients With Psychosis**

In the German group of 300 patients and 300 comparison subjects, the association between bipolar affective disorder and markers and haplotypes at the DAOA/G30 locus yielded odds ratios of around 1.3 (Table 3 and Table 4). We investigated whether this finding was due to an association with the overall group or with the subset of patients displaying psychotic features.

For the analysis of the subgroup of patients with psychotic bipolar disorder, we chose the four markers that made up the risk haplotype for both schizophrenia and bipolar affective disorder in the entire group of patients with bipolar affective disorder, i.e., M12, M15, M23, and M24.

In the single marker analysis, only M23 showed a significant association (p=0.005) in bipolar disorder patients with psychotic symptoms, as was the case for the entire group of patients with bipolar affective disorder (p<0.02). The ro-
The global four-marker haplotype was significant for those patients with a history of psychotic symptoms (p < 0.01). The other markers showed no association, either in the single marker or in the full multivariate model (Table 3).

For the haplotype analyses (Table 4), significant associations were seen for the global four-marker haplotype (p = 0.04) and the individual haplotype G-G-T-A (p < 0.03), with the G-G-C-T haplotype approaching significance (p = 0.007), respectively.

The 83 patients with bipolar affective disorder and no lifetime history of delusional or hallucinatory symptoms showed no association, either in the single marker or in the haplotype analyses (Table 3 and Table 4).

**Further Phenotype-Genotype Analyses**

Given that the aforementioned stratification on psychotic features might still be too crude a procedure for refining phenotypes, we were interested in whether the association between bipolar affective disorder and DAOA/G30 was explained instead by an even more specific subset, defined by specific psychotic features. We performed a logistic regression in a model that included age, gender, age at onset, and the 21 OPCRIT symptoms of psychosis (Table 2). This analysis identified the variable “lifetime history of persecutory delusions” as the only significant (p < 0.005) explanatory variable for the M23 genotype. Individuals with a history of persecutory delusions were more likely to have genotypes containing the C allele than those with no such history. Generalized logistic regression was carried with the 21 OPCRIT symptoms of psychosis both as a full set and in a stepwise manner. Since both approaches led to the same qualitative conclusions, only the results of analyzing the full multivariate model are presented.

We thus divided our group of bipolar affective disorder patients for whom detailed information regarding the OPCRIT item “persecutory delusion” was available into those with (N = 90) and those without (N = 165) a history of persecutory delusions in order to perform two separate comparisons with the comparison group. When comparing the subset of 90 bipolar disorder patients with persecutory delusions versus comparison subjects, markers M12 and M15 did not yield significant results. As seen in Table 3, we observed significant association for markers M23 (p < 0.0004) and M24 (p < 0.007).

In a simulation analysis, p values < 0.0004 and < 0.007 were observed for, respectively, 24 and 67 out of 10,000 random subsets of 90 individuals, indicating that the association findings at these significance levels are very unlikely to occur in equally sized random subsets (p = 0.0024 and p = 0.0067).

In the haplotype analysis (Table 4), significant associations were seen for the global four-marker haplotype (p < 0.03) and the individual haplotypes G-G-T-A (odds ratio = 0.54, p < 0.006) and G-G-C-T (odds ratio = 1.54, p < 0.04). We also evaluated the empirical significance of these haplotype-based results: a p value smaller or equal to 0.006 would be seen in 1,360 out of 10,000 random subsets of 90 individuals (p = 0.136). Comparing the larger subsample of patients with bipolar disorder and no history of persecutory delusions (N = 165) with the comparison group (N = 300) yielded no association (odds ratios –1) (Table 3, Table 4).

**TABLE 3. Association Between Illness Phenotypes and Markers at the DAOA/G30 Locus in an Exploratory Study of German Bipolar Affective Disorder Patients**

<table>
<thead>
<tr>
<th>Marker</th>
<th>SNP</th>
<th>Rate</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>Rate</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>Rate</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>Rate</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>M12</td>
<td>G/A</td>
<td>0.61</td>
<td>0.86</td>
<td>0.91–1.47</td>
<td>0.61</td>
<td>0.89</td>
<td>0.68–1.19</td>
<td>0.57</td>
<td>0.75</td>
<td>0.52–1.08</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M15</td>
<td>G/A</td>
<td>0.61</td>
<td>0.86</td>
<td>0.91–1.47</td>
<td>0.61</td>
<td>0.87</td>
<td>0.66–1.15</td>
<td>0.60</td>
<td>0.83</td>
<td>0.58–1.19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M23</td>
<td>T/C</td>
<td>0.53</td>
<td>(C) 1.33**</td>
<td>1.06–1.68</td>
<td>0.56</td>
<td>(C) 1.46***</td>
<td>1.12–1.91</td>
<td>0.47</td>
<td>(C) 1.03</td>
<td>0.73–1.46</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M24</td>
<td>A/T</td>
<td>0.55</td>
<td>(T) 1.24*</td>
<td>0.98–1.56</td>
<td>0.56</td>
<td>(T) 1.29*</td>
<td>0.98–1.69</td>
<td>0.49</td>
<td>(T) 0.98</td>
<td>0.69–1.40</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Significant associations remained after adjustment for multiple testing (i.e., four markers) through permutation in the total group of bipolar affective disorder patients and the subgroups with psychotic symptoms and persecutory delusions. Significant associations also remained in the psychotic symptom and persecutory delusion subgroups after Bonferroni adjustment for testing multiple bipolar disorder diagnostic groups.

**TABLE 4. Association Between Illness Phenotypes and Haplotypes in an Exploratory Study of German Bipolar Affective Disorder Patients**

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>All Patients With Bipolar Affective Disorder (N=300)</th>
<th>Patients With a History of Psychotic Symptoms (N=173)</th>
<th>Patients With No History of Psychotic Symptoms (N=83)</th>
<th>Patients With a History of Persecutory Delusions (N=165)</th>
<th>Rate Among Comparison Subjects (N=300)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate</td>
<td>Odds Ratio</td>
<td>Rate</td>
<td>Odds Ratio</td>
<td>Rate</td>
</tr>
<tr>
<td>G-G-C-T</td>
<td>0.35</td>
<td>1.29*</td>
<td>0.35</td>
<td>1.33**</td>
<td>0.28</td>
</tr>
<tr>
<td>G-G-T-A</td>
<td>0.24</td>
<td>0.73**</td>
<td>0.24</td>
<td>0.68**</td>
<td>0.27</td>
</tr>
<tr>
<td>All others</td>
<td>0.41</td>
<td>0.41</td>
<td>0.45</td>
<td>0.42</td>
<td>0.43</td>
</tr>
</tbody>
</table>

The global four-marker haplotype was significant for those patients with a history of psychotic symptoms (p < 0.04) and persecutory delusions (p < 0.03) and approached significance for the entire bipolar affective disorder group (p < 0.08).

*p < 0.10. **p < 0.05. ***p < 0.01. †p < 0.001.
We also compared the comparison subjects with those 83 patients that had a history of psychotic symptoms but not of persecutory delusions (i.e., the 173 patients with psychosis minus the 90 patients with a history of persecutory delusions [see Table 1]). For all four markers, again, there was no association. Allele and haplotype frequencies were similar between this particular subset of cases and comparison subjects (odds ratios ranged from 0.86 to 1.14, p values ranged from 0.50 to 0.97 [data not shown]).

The subsample of patients with bipolar disorder with persecutory delusions did not differ from the entire sample of patients with bipolar disorder regarding gender (χ² = 0.37, p=0.54), age (t=0.26, p=0.79), or age at onset (t=0.62, p=0.536).

Given that only markers M23 and M24 showed association with bipolar affective disorder, we analyzed these in our replication study with the Polish group. As with the analysis of the German subjects, we performed single-marker and haplotype-based analyses, using three case definitions: all patients with bipolar affective disorder, a subgroup of those with a history of psychotic symptoms, and a subgroup of those with a history of persecutory delusions. In the single-marker analysis, neither M23 nor M24 showed significant association with bipolar affective disorder in any of the three sets (Table 5). However, for M23, we observed a nearly significant association (odds ratio=1.48, p<0.08) in the subset of bipolar disorder patients with persecutory delusions. Similar to the German group, the bipolar disorder patients with persecutory delusions were enriched with the C allele relative to the entire group of bipolar affective disorder patients (57% versus 49%). With regard to the haplotype analysis, no association was observed in the bipolar affective disorder patients and the bipolar affective disorder subgroup with a history of psychotic symptoms. When case definition was confined to those with persecutory delusions, however, we observed a significant association (Table 6): The C-T haplotype, which is part of the associated G-G-C-T haplotype in the German subjects, was similarly more frequent in patients than in comparison subjects (odds ratio=1.61*, p<0.04). We also evaluated the empirical significance of this haplotype-based result: a p value ≤0.04 would be seen in 220 out of 10,000 random subsets of 55 individuals (p=0.022). Thus, while there was no association when using the total group of patients with bipolar affective disorder or the subgroup with a history of psychotic symptoms, there was a significant one when cases were restricted to patients with persecutory delusions. The "protective" haplotype T-A did not show a significant association. It is interesting to note, however, that it showed...
DAOA/G30 LOCUS AND PERSECUTORY DELUSIONS

the same frequency in the total group of bipolar affective disorder patients, the subgroup of bipolar affective disorder patients with psychotic symptoms, and comparison subjects while being less frequent in bipolar disorder patients with persecutory delusions, as observed in the German subjects.

Discussion

We had previously reported an association between bipolar affective disorder and DAOA/G30 (3). Given that DAOA/G30 has also been shown to be associated with schizophrenia (1, 3), we were interested in whether bipolar affective disorder patients with a history of psychotic symptoms would differ from those with no such history. Restricting case definition to the subgroup of patients with a history of psychotic symptoms yielded no significant results. We were therefore interested in whether confining case definition to specific delusional or hallucinatory symptoms would be better at revealing a potential genotype-phenotype correlation between bipolar affective disorder and DAOA/G30.

Our analysis revealed that the association between bipolar affective disorder and the DAOA/G30 locus is an association involving those with a history of persecutory delusions rather than bipolar affective disorder in general. In fact, patients with no history of persecutory delusions did not differ at all from comparison subjects with regard to their distribution of DAOA/G30 marker alleles and haplotypes. These findings are supported by our analysis in an independent group of bipolar affective disorder patients and comparison subjects from Poland.

A general limitation of case/control analyses is the susceptibility to population stratification. The patients and comparison subjects investigated in the German and Polish samples were all of German and Polish descent, respectively, and were recruited from the same well circumscribed geographical areas (the cities of Bonn and Poznan and their vicinities). Preliminary results from large-scale genomic analyses in several population-based samples from different geographic German regions (National Genome Research Network [http://www.ngfn.de/]) suggest that population stratification is negligible in the German population (personal communication, M. Krawczak, June 2, 2004). Furthermore, an association between bipolar affective disorder and markers on or near to DAOA/G30 has now been shown in three independent samples from Germany (3) and the United States (2, 29), rendering the possibility of this being a mere artifact due to population stratification unlikely.

Our observations in the exploratory and replication studies suggest that the subgroup of patients with persecutory delusions represents a genetically more homogeneous group than patients with bipolar affective disorder as a whole. The intuitive approach to divide bipolar affective disorder patients into those with versus those without psychotic features might not be sufficient for determining biologically meaningful subtypes for genetic studies. Psychosis is perhaps too broad a concept; well-established clinical subtypes of psychosis might be more amenable to genetic study. The gene mapping efforts in inflammatory bowel disease—a group of genetically heterogeneous, complex phenotypes (i.e., Crohn’s disease, ulcerative colitis)—may serve as an example. For this condition, detailed phenotypic characterization and the establishment of fine-scaled diagnostic categories (according to, for example, anatomic location of disease, extent of disease, and disease behavior) helped to detect the underlying genetic factors (30).

The importance of such detailed refinement of phenotype is illustrated in the Polish study. In the overall group, no association between DAOA/G30 markers and bipolar affective disorder could be detected. This could be due to the limited power (less than 20%) of the Polish study. However, we were able to detect an association in the Polish subjects when only patients with persecutory delusions were considered, despite the even lower a priori power of this subset of less than 10%. To our knowledge, this is the first time in psychiatric genetics that an association between a genotype and a specific clinical feature of a broader phenotype could be replicated in an independent sample. Given the inconsistencies of genetic findings in the field of psychiatric association studies, our approach may serve as an example of how to identify more homogeneous samples, thus enhancing the chances of success in replication attempts (31).

Formal genetic analyses (10, 32–35) have suggested that psychotic symptoms are an inherited predisposition common to both schizophrenia and bipolar affective disorder. The observation in our study that the risk-conferring DAOA/G30 haplotype is the same in both bipolar affective disorder and schizophrenia indicates that not only the same gene but the same (hitherto undetected) variant contributes to both disorders. The reported genotype-phenotype correlation further pinpoints the nature of the DAOA/G30-mediated genetic overlap between schizophrenia and bipolar affective disorder.

While our findings support the idea of a genetic overlap between schizophrenia and bipolar affective disorder, the question remains whether the symptom “persecutory delusion” per se is important or rather some other trait that correlates with it. What could that be? A patient’s idea of future harm triggering anxiety-associated processes has been suggested as a key feature of persecutory delusions (36). One could speculate that a delusional patient with a genetic proneness to anxiety may be more likely to have delusions of a persecutory nature than a patient without this predisposition. Put another way, delusions of reference or influence that are accompanied by fear are more likely to be labeled as persecutory delusions. Clinical experience has long taught us about a connection between anxiety and persecutory delusions in the context of toxic...
psychoses such as PCP and amphetamine intoxication, where extreme anxiety, panic, and persecutory delusions usually occur together (37–39).

With this in mind, it is intriguing that we recently identified the same DAOA/G30 markers and haplotypes as potential risk factors for panic disorder (40).

The genetic overlap between schizophrenia and bipolar affective disorder hints at a weakness of specificity of the current classification systems, which are based merely on clinical symptoms. To our knowledge, our study is the first systematic genotype-phenotype analysis of a well-established susceptibility gene for schizophrenia and bipolar affective disorder and may be considered a first step toward a molecular genetic classification of psychiatric phenotypes.

References


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Reduced NAA Levels in the Dorsolateral Prefrontal Cortex of Young Bipolar Patients

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Objective: Converging evidence implicates prefrontal circuits in the pathophysiology of bipolar disorder. Proton spectroscopy studies performed in adult bipolar patients assessing prefrontal regions have suggested decreased levels of N-acetylaspartate (NAA), a putative marker of neuronal integrity. In order to examine whether such abnormalities would also be found in younger patients, a $^1$H spectroscopy study was conducted that focused on the dorsolateral prefrontal cortex of children and adolescents with bipolar disorder.

Method: The authors examined the levels of NAA, creatine plus phosphocreatine, and choline-containing molecules in the left dorsolateral prefrontal cortex of 14 bipolar disorder patients (mean age=15.5 years, SD=3, eight female) and 18 healthy comparison subjects (mean age=17.3, SD=3.7, seven female) using short echo time, single-voxel in vivo $^1$H spectroscopy. Absolute metabolite levels were determined using the water signal as an internal reference.

Results: Bipolar patients presented significantly lower NAA levels and a significant inverse correlation between choline-containing molecules and number of previous affective episodes. No differences were found for other metabolites.

Conclusions: These findings suggest that young bipolar patients have decreased NAA levels in the dorsolateral prefrontal cortex, similar to what was previously reported in adult patients. Such changes may reflect an underdevelopment of dendritic arborizations and synaptic connections. These neuronal abnormalities in the dorsolateral prefrontal cortex of bipolar disorder youth are unlikely to represent long-term degenerative processes, at least in the subgroup of patients where the illness had relatively early onset.

Bipolar disorder is a serious and chronic psychiatric illness whose neuropathology is still largely unknown. The involvement of prefrontal brain regions in bipolar disorder has been replicated by various research groups and is supported by several lines of evidence. In vivo structural neuroimaging studies have reported decreased prefrontal cortical volumes among bipolar patients (1–3). Postmortem analysis of this region has revealed specific abnormalities such as decreased neuronal and glial density (4). Investigations employing functional magnetic resonance imaging, positron emission tomography, or single photon emission computed tomography all have consistently reported decreased frontal glucose metabolism (5, 6) and lower frontal blood flow in bipolar patients, mostly during depressive episodes (3, 7).

Discrete prefrontal cortical regions have been investigated in bipolar disorder patients, with interesting although sometimes conflicting results. Drevets et al. (8) reported decreased volume and function of the subgenual prefrontal cortex among bipolar patients, familial subtype. A postmortem study (9) found subgenual abnormalities, mainly glial density reduction, in this same population. Our group, however, has failed to identify volumetric abnormalities in this region among mood disorder patients (10). Hypoactivation of orbital and rostral prefrontal cortices has been reported in manic patients (11), although other investigators have not found any rCBF abnormalities in bipolar disorder (12).

The dorsolateral region of the prefrontal cortex, encompassing Brodmann’s areas 9 and 46 (13), is believed to play a major role in decision making (14) and working memory (15, 16), acting as an interface between cognition and emotion (17–19). Utilizing proton magnetic resonance spectroscopy ($^1$H-MRS), a methodology that provides information on the brain content of several metabolites in vivo, Winsberg et al. (20) observed significantly decreased N-acetylaspartate (NAA) in the dorsolateral prefrontal cortex of unmedicated adult bipolar patients. NAA is found primarily in neurons (21) and is a nonspecific marker of neuronal integrity (22). On the other hand, Moore et al. (23) reported a significant increase in NAA levels after 4 weeks of lithium treatment in bipolar patients, possibly as a consequence of lithium’s neurotrophic actions (24). However, most neurobiological studies of affective disorder were conducted with adult patient groups. For instance, the average age of subjects in the Winsberg et al. (20) and Moore et al. (23) studies was 37.9 and 36.3 years, respectively. Therefore, it is not clear if the reported
abnormalities were present since the early stages of the illness or whether they might be related to illness progression or medication use.

The purpose of the present study was to investigate metabolite abnormalities in the dorsolateral prefrontal cortex of bipolar disorder youth. A younger patient population was chosen in order to minimize the effects of confounding variables such as long-term medication usage. We hypothesized that lower NAA levels would be found among patients with bipolar disorder, representing abnormal prefrontal processes of possible neurodevelopmental origin that are already present at the early stages of the disease. Moreover, levels of choline-containing compounds in this same region would allow us to indirectly evaluate membrane phospholipid metabolism and signaling of the phosphatidylcholine system, providing information on neuronal membrane functioning.

Method

Subjects

Thirty-two subjects were studied, of whom 14 were DSM-IV bipolar disorder patients (Table 1) and 18 were healthy comparison subjects (mean age=17.3 years [SD=3.7, median=18, range=11–21]; female: N=7, male: N=11; African American: N=3, Caucasian: N=15). After having understood all issues involved in participation in the study protocol, all subjects and their parents or legal representatives provided signed informed study consent. This research study was approved by the University of Pittsburgh Biomedical Institutional Review Board. The patients were recruited at the outpatient facilities of the University of Pittsburgh Medical Center or through advertisements in the local media. The inclusion criteria were age between 10 and 21 years and a diagnosis of bipolar disorder, any subtype, in any mood state. All patients met DSM-IV criteria for bipolar disorder. For patients 10–17 years old, diagnosis was determined with the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS-PL) (25). Patients 18–21 years old were assessed with the Structured Clinical Interview for DSM-IV (SCID), patient edition (26). Information about family history of psychiatric disorders, age at onset of illness, length of illness, number of previous DSM-IV affective episodes, number of weeks receiving lithium treatment, current lithium dose, and medication history was retrieved from psychiatric interviews with the patients and medical charts.

All subjects had normal physical examination results and no history of neurological problems. The patients did not have any comorbid psychiatric diagnoses with the exception of ADHD (five of 14), conduct disorder (one of 14) and oppositional defiant disorder (one of 14). At the time of the study, one patient was in a depressive episode and 13 were euthymic. Only two patients were drug-free, and 12 patients were receiving medication treatment at

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Race</th>
<th>Diagnosis and Current Mood Episode</th>
<th>Age at Onset (years)</th>
<th>Previous Antipsychotic Use</th>
<th>Comorbidity</th>
<th>Medications (daily oral dose)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>M</td>
<td>White</td>
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<td>Yes</td>
<td>Conduct disorder</td>
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<tr>
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<td>White</td>
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<td>Yes</td>
<td>ADHD</td>
<td>Lithium (1050 mg); methylphenidate (36 mg); levothyroxine (50 µg)</td>
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<tr>
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<td>Bipolar I disorder, euthymic</td>
<td>10</td>
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<td>N/A</td>
<td>Lithium (900 mg); valproate (750 mg)</td>
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<tr>
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<td>14</td>
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<td>Bipolar I disorder, euthymic</td>
<td>10</td>
<td>Yes</td>
<td>Oppositional defiant disorder</td>
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<td>N/A</td>
<td>Valproate (1000 mg)</td>
</tr>
<tr>
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<td>ADHD</td>
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<tr>
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<td>ADHD</td>
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<td>N/A</td>
<td>Valproate (1875 mg); levothyroxine (50 µg)</td>
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<tr>
<td>12</td>
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<td>F</td>
<td>White</td>
<td>Bipolar I disorder, euthymic</td>
<td>8</td>
<td>Yes</td>
<td>ADHD</td>
<td>Lithium (900 mg)</td>
</tr>
<tr>
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<td>17</td>
<td>No</td>
<td>N/A</td>
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<td>15</td>
<td>No</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

a Mean=15.5 years (SD=3).
study entry. Ten patients had a history of previous antipsychotic usage, whereas four patients had no such history. Only one patient did not have a positive family history of mood disorders in a first-degree relative. First-degree relatives were considered positive for mood disorders if they ever received a diagnosis of unipolar or bipolar disorder by a psychiatrist, as ascertained by patient and relative reports or available medical records. Furthermore, the patients did not have any current medical problems or alcohol/substance abuse in the 6 months preceding the study. One patient had a previous history of substance abuse (cannabis) that had been in remission for more than 6 months before the study, and no patient had a lifetime history of substance dependence (Table 1).

We could not ascertain the number of previous affective episodes for one patient. Our patient group had the following clinical characteristics: length of illness: mean=3.79 years (SD=2.39, median=3, range=1–10); age at first affective episode: mean=11.71 years (SD=3.24, median=11.5, range=6–17); number of previous affective episodes: mean=4.85 (SD=2.34, median=3, range=2–9).

Healthy subjects had no DSM-IV axis I disorders, as determined either with the SCID or K-SADS-PL depending on subject age. Comparison subjects also had no current medical problems, no lifetime history of substance dependence or substance abuse in the 6 months preceding the study, and no history of psychiatric disorders among first-degree relatives.

**MRS Method**

In vivo 1H MRS was conducted on a GE Signa Imaging System (General Electric Medical Systems, Milwaukee), at field strength of 1.5 T. A three-dimensional spoiled gradient-recall acquisition was performed in the coronal plane (TR=25 msec, TE=5 msec, flip angle=40°, field of view=24 cm, slice thickness=1.5 mm, number of excitations=1, matrix size=256×192) to obtain 124 images covering the entire brain. A double spin-echo sequence was also used to obtain T2 and proton density images in the axial plane to screen for neuroradiological abnormalities.

The single-voxel short TE MRS data were collected with a STEAM sequence (TE=20 msec, TM=13.6 msec, TR=1.5 seconds, bandwidth=2 kHz, 2,048 complex data points, 300 acquisitions, voxel dimension=2×2×2 cm3). This 8-cm3 voxel was placed in the left dorsolateral prefrontal cortex (Figure 1), which was identified on the set of sagittal and coronal MR images using standard anatomical atlases (28, 29). A second STEAM spectrum was performed in the coronal plane (TR=25 msec, TE=5 msec, flip angle=40°, field of view=24 cm, slice thickness=1.5 mm, number of excitations=1, matrix size=256×192) to obtain 124 images covering the entire brain. A double spin-echo sequence was also used to obtain T2 and proton density images in the axial plane to screen for neuroradiological abnormalities.

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Results

Bipolar disorder patients and healthy comparison subjects did not differ with regard to age (F=2.09, df=1, 30, p=0.14), gender (χ2=1.05, df=1, p=0.30), race (χ2=0.65, df=1, p=0.42), or handedness (χ2=1.81, df=1, p=0.18).

Within the 8-cm3 voxel, there were no significant differences between bipolar patients and healthy subjects in volumes of gray matter (mean=3.68 cm3 [SD=0.51] and 3.66 cm3 [SD=0.73], respectively; F=1.28, df=1, 29, p=0.91),...
white matter (mean=3.87 cm³ [SD=0.55] and 3.93 cm³ [SD=0.82]; F=1.56, df=1, 29, p=0.84), or CSF (mean=0.08 cm³ [SD=0.12] and 0.07 cm³ [SD=0.04]; F=1.05, df=29, p=0.73).

The 1H metabolite levels examined are presented in Table 2. When comparing the two groups, we found that bipolar patients had significantly decreased NAA levels relative to healthy subjects. Bipolar patients also tended to have decreased creatine plus phosphocreatine levels relative to healthy subjects (ANCOVA F=3.22, df=1, 28, p=0.08).

In contrast, no between-group differences were observed for glycerophosphocholine plus phosphocholine levels (ANCOVA F=0.002, df=1, 28, p=0.96).

No significant correlation was observed between age and any metabolite concentration in bipolar patients. Moreover, no significant correlation was found between any metabolite concentration and age at first affective episode, length of illness, lithium dose, or valproate dose. On the other hand, we observed a significant inverse correlation between number of previous affective episodes and glycerophosphocholine plus phosphocholine concentration (Figure 2).

**Discussion**

We report here having found significantly lower NAA levels in the left dorsolateral prefrontal cortex of bipolar disorder youth relative to healthy comparison subjects. Our results provide indirect support for the hypothesis that neuronal dysfunction, or decreased neuronal density, is present in the prefrontal cortex of bipolar patients already at early stages of the illness. On the basis of only cross-sectional MRS observations it is not possible to determine whether decreased NAA in the dorsolateral prefrontal cortex of young patients represents a general underdevelopment of dendritic arborizations and synaptic connections or degenerative/atrophic processes that may progress during the course of illness.

The results of this study are consistent with reports of decreased NAA levels in the dorsolateral prefrontal cortex of adult bipolar patients (20, 35) as well as postmortem data demonstrating decreased neuronal density in that region in adult mood disorder patients (4, 36). Furthermore, another MRS study of pediatric bipolar patients who were children of a bipolar parent, reported by Chang et al. (37), also showed similar findings, although only for the right dorsolateral prefrontal cortex. Some important differences between our study and the one by Chang et al. (37) must be pinpointed. First, our patients were older (mean age=15.5 [SD=3] versus 12.6 years [SD=2.9]), more evenly distributed regarding gender (percentage of girls was 57% versus 13%), and presented less comorbidity (36% versus 87% for comorbid ADHD) than their bipolar disorder patients. On the other hand, Chang et al. (37) included only patients with bipolar I disorder and a history of bipolar disorder in at least one first-degree relative, whereas our inclusion criteria was less stringent. Our study group included patients with bipolar disorder type II or not otherwise specified, and patients who had either unipolar or bipolar disorder diagnosed in a first-degree relative were considered to have a positive family history. There were also considerable technical differences between our protocols. First, we measured absolute metabolite levels instead of Cr ratios, which might have helped us to minimize potential confounders. Second, we utilized STEAM instead of PRESS to acquire the MRS data and ended up with reliable spectra for only three peaks (NAA, creatine plus phosphocreatine, glycerophosphocholine plus phosphocholine), whereas Chang et al. (37) also measured myo-inositol levels in addition to those three metabolites. Last, and most important, we did not measure the level of any metabolites in the right dorsolateral prefrontal cortex, whereas Chang et al. (37) examined both right and left dorsolateral prefrontal cortex. Thus, we were not able to report in our study whether decreased NAA in the dorsolateral prefrontal cortex was a bilateral phenomenon or restricted to the left side only. It is not clear if any of the differences in patient selection or data acquisition might account for the differences in the final results between our study and the one by Chang et al. (37). In any case, the lack of...
of a bilateral dorsolateral prefrontal cortex measurement is one of the main limitations of our study.

Some other limitations should also be considered. It is difficult to examine the influence of clinical variables on prefrontal NAA levels, mostly due to our reduced study group size. For instance, our bipolar group had only three bipolar II patients, which limited our ability to compare whether the changes in NAA concentration were related to any specific bipolar subtype. Furthermore, we did not identify in the bipolar subjects any correlation between NAA levels and age, length of illness, or number of previous affective episodes. Along the same lines, other phenomenological characteristics that might have influenced our final results (e.g., history of psychotic symptoms or suicide attempts) were not addressed given our small patient group size. Moreover, the large majority of our patients were taking mood stabilizers and other medications such as antidepressants and stimulants, restricting our capacity to rule out possible pharmacological effects. Studies with a larger number of subjects, a prospective design, and larger numbers of untreated subjects will be needed to address the influence of medications on NAA levels in bipolar patients.

Another limitation of our study concerns the lack of other comparable brain structures. It is believed that mood regulation involves several cortical and subcortical regions and that dysfunction in one area might lead to abnormalities in other connected structures. Since we examined only a single region, we were not able to verify if decreased NAA is also found in other brain structures of interest in child and adolescent bipolar patients.

Our method did not allow a reliable quantification of other metabolites reported in previous proton MRS studies, such as myo-inositol, glutamate, and glutamine. On the other hand, we were able to obtain absolute concentration of NAA, creatine plus phosphocreatine, and choline-containing compounds (glycerophosphocholine plus phosphocholine), which represents an advantage over ratios in terms of sensitivity and eliminates an important confounding factor. $^1$H MRS, in contrast with $^{31}$P-MRS, is limited when discriminating the specific components that contribute to the choline peak. Nonetheless, it is believed that glycerophosphocholine plus phosphocholine reflects either membrane phospholipid metabolism or the rate of signaling of the phosphatidylyceroline system (38). There are reports of increased choline in the anterior cingulate (39) and basal ganglia (40–42) among adult bipolar patients and also increased choline in the left dorsolateral prefrontal cortex (43) and orbitofrontal cortex (44) in depressed adolescent patients. On the other hand, Castillo et al. (45) have not found any temporal or frontal changes in choline-containing molecules or NAA in children with bipolar disorder, and Cecil et al. (35) reported decreased choline concentration in the frontal lobe of adult bipolar patients.

We did not find any significant difference in glycerophosphocholine plus phosphocholine concentration between bipolar patients and healthy subjects, but we observed a significant negative correlation between choline-containing molecules and the number of previous affective episodes. There is a possible bias that may explain these findings. Patients with several previous affective episodes were potentially exposed to different classes of medication and probably were treated for longer periods. Thus, patients with multiple affective episodes have a pharmacological history that is substantially distinct from patients with only a few illness episodes. However, there is evidence that lithium does not alter the brain concentration of choline-containing molecules (41, 46, 47), although response to antidepressants seems to be related to changes in the brain levels of this metabolite (48). Moreover, it is not clear if other medications such as antipsychotics, stimulants, and anticonvulsants exert any influence on the levels of choline-containing molecules. Thus, we are not able to rule out medication effects as an alternative explanation for such findings. Nonetheless, an inverse correlation of choline-containing molecules and number of affective episodes may represent neurodegenerative processes occurring in the prefrontal cortex. To the best of our knowledge, this is the first time such a relationship has been reported. Replication in larger samples with stricter medication profiles is needed to assess whether these findings have relevance for illness progression.

Children and adolescent patients have been largely overlooked in MRS investigations. Fortunately, this trend has started to change in recent years, since the examination of younger patients allows us to minimize potentially confounding factors commonly found in adult patients, such as long-term medication effects. Nonetheless, we wish to underscore the preliminary nature of the present study. A replication in a larger study group with medication-naive or first-break bipolar patients is warranted. Nevertheless, in the context of most other MRS studies that investigated only older subjects, our report suggests that youth with bipolar disorder exhibit abnormalities in the dorsolateral prefrontal cortex that are similar to those found in adult patients.
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Risk Factors for Suicide Completion in Major Depression: A Case-Control Study of Impulsive and Aggressive Behaviors in Men

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Objective: Major depression is a major risk factor for suicide. However, not all individuals with major depression commit suicide. Impulsive and aggressive behaviors have been proposed as risk factors for suicide, but it remains unclear whether their effect on the risk of suicide is at least partly explained by axis I disorders commonly associated with suicide, such as major depression. With a case-control design, a comparison of the level of impulsive and aggressive behaviors and the prevalence of associated psychopathology was carried out with control for the presence of primary psychopathology.

Method: One hundred and four male suicide completers who died during an episode of major depression and 74 living depressed male comparison subjects were investigated with proxy-based interviews by using structured diagnostic instruments and personality trait assessments.

Results: The authors found that current (6-month prevalence) alcohol abuse/dependence, current drug abuse/dependence, and cluster B personality disorders increased the risk of suicide in individuals with major depression. Also, higher levels of impulsivity and aggression were associated with suicide. An analysis by age showed that these risk factors were more specific to younger suicide victims (ages 18–40). A multivariate analysis indicated that current alcohol abuse/dependence and cluster B personality disorder were two independent predictors of suicide.

Conclusions: Impulsive-aggressive personality disorders and alcohol abuse/dependence were two independent predictors of suicide. A developmental hypothesis of suicidal behavior, with impulsive and aggressive behaviors as the starting point, is discussed.

Several lines of evidence confirm the strong association between major depressive disorder and completed suicide (1–4). More specifically, estimates indicate that approximately 60% of suicide victims suffered from major depressive disorder and other mood disorders (3, 5–7). On the other hand, most subjects affected with major depressive disorder do not die by suicide. The lifetime mortality risk by suicide of subjects with major depressive disorder who have been inpatients has usually been reported at around 15% (8). This was revised to 3.4%, with a higher risk in men (7%) than in women (1%) (9). Regardless of the exact suicide mortality risk faced by subjects affected with major depressive disorder, it is clear that this figure is substantial. Why some patients with major depressive disorder die by suicide while others with seemingly the same disorder do not, is a question of enormous clinical relevance.

Among sociodemographic risk factors, gender, marital status, and migration are those most strongly associated with suicide in patients with major depressive disorder (10, 11). Issues related to social and/or medical support, such as discharge from psychiatric care (12) and certain clinical symptoms, have also been identified as predictors of suicide. In addition, a positive history of suicide attempts seems to be a powerful predictor identified by some studies (13–15). Furthermore, investigators have reported that various clinical symptoms of depression, such as insomnia, memory problems, self-neglect, anhedonia, hopelessness, and comorbidity with alcohol dependence/abuse, increase the risk of suicide (11, 16–19).

There has been growing evidence to support the role of impulsive and aggressive behaviors in the risk of suicide. Studies assessing living patients with major depressive disorder have indicated that suicide attempters have higher levels of impulsive and aggressive behaviors (20–24). Similarly, studies looking at the prevalence of these traits in other diagnostic categories have also suggested that attempters are more likely to be impulsive and aggressive (25–29). However, data on impulsive and aggressive behaviors in suicide completers are limited and based primarily on indirect evidence, such as the prevalence of diagnostic categories associated with aggressive and impulsive traits. These studies showed that substance use disorders (1) and borderline personality disorders (30) are associated with an increased risk of suicide when they are
comorbid with major depressive disorder. The few studies that carried out direct personality trait assessments remain controversial. Two studies found an association between aggression and suicide (31, 32), but one recent study in adults ages 50 and over showed that the association between aggression and suicide was no longer significant when the authors controlled for psychopathology (33). Therefore, it remains unclear whether the association between impulsive and aggressive behaviors and the risk of suicide is at least partly explained by axis I disorders that are commonly associated with suicide, such as major depressive disorder. This issue has not been properly addressed because almost all previous studies of suicide have exclusively investigated unselected suicide victims in relation to normal comparison subjects and lacked a psychiatric comparison group. Thus, the purpose of our study was to investigate impulsive and aggressive behaviors and associated psychopathology while we directly controlled for major depressive disorder. More specifically, we investigated subjects who committed suicide in the context of a major depressive episode and compared them to a group of age- and gender-matched living subjects with a current major depressive episode of sufficient severity to warrant treatment in a specialized psychiatric outpatient clinic but without a history of medically serious suicide attempts. A key methodological innovation in this study was the use of a proxy informant for both the suicide group, when it was necessary, and also for the living depressed comparison subjects to prevent a reporting artifact because of the method of data collection.

Method

Subjects

Patients used for this study were 104 men ages 18 years and over who committed suicide, as determined by the Quebec Coroner’s Office, and who met DSM-IV diagnostic criteria for major depressive disorder or depression not otherwise specified in the 6 months before their death. Individuals with depression not otherwise specified (operationally defined as depressed mood or lack of interest most of the time for at least 2 weeks and four symptoms of depression) were selected for this study because these patients most likely had major depressive disorder. They were not recognized as having such because of the reduced sensitivity of the psychological autopsy procedure, particularly for conditions present immediately before death (34). The subjects who met criteria for bipolar or any psychotic disorder were excluded to increase comparability between groups. Our subjects were consecutive male suicide victims (representative of male suicide cases in the general population) who were recruited primarily from 2000 to 2004. The acceptance rate of participation by the families of the suicide victims was 75%. Suicide cases from families who did not agree to participate were not different from those included in the study with regard to age, race, or method of suicide.

The comparison subjects were 74 living men, age-matched (within 2 years) to the cases, who met criteria for major depressive disorder with a condition severe enough to require follow-up in a specialized psychiatric outpatient clinic. The acceptance rate of participation was 90%, and those who did not agree to participate had similar demographic characteristics to those who accepted. To ensure comparability of the two groups, all comparison subjects were diagnosed by proxy-based interviews carried out on average 5 months after recruitment. This project was approved by our local institutional review board and the families of the suicide victims; comparison subjects and informants signed written informed consents.

Diagnoses

Psychiatric diagnoses in suicide victims were made by means of the psychological autopsy method. This technique, which has been validated for axis I and II diagnoses (32, 35, 36), consists in part of selecting a family member who was best acquainted with the deceased to serve as an informant for the interview process. In our study, the informants included a mother, father, sibling, significant other, friend, or other relative. We have previously shown that the type of informant makes no significant difference in the rate of specific disorders identified (3). The families were recruited at the Montreal Morgue and were interviewed, on average, 4 months after the suicide.

Psychiatric diagnoses were obtained by using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (37), in addition to the Structured Clinical Interview for DSM-IV Personality Disorders (SCID-II) (38). The SCID was used to investigate 71 suicide victims and all comparison subjects. Before the SCID, we used the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) (39), an interview modified to include questions adapted from the Interview Schedule for Children (40), to assess personality disorders. As reported elsewhere (7), the diagnoses obtained using these two different methods had excellent concordance rates. Information collected through the SCID or the K-SADS interviews and from the coroner’s notes and medical records was used by the interviewers to write a case history for each subject. These case histories were reviewed by a clinical panel to reach a consensus regarding DSM-IV diagnoses for each subject.

Interrater Reliability

Two or more interviewers were asked to separately rate the same subject, and kappa coefficients for key diagnoses were excellent: major depression, 0.96; alcohol abuse/dependence, 0.98; drug abuse/dependence, 1.00; bipolar disorder, 1.00; schizophrenia, 1.00, and cluster B personality disorders, 1.00. These excellent concordance rates are consistent with previous analyses by our group (3) and are probably a consequence of substantial clinical training of the interviewers, who were all clinical psychologists, and of regular training sessions carried out by our clinical coordinator to avoid drifting.

Personality Trait Assessments

The Brown-Goodwin History of Aggression (41) is an 11-item interview that assesses lifetime aggressive behaviors across three separate stages of life (childhood, adolescence, and adulthood). The Barratt Impulsiveness Scale (42) has been commonly used in the investigation of impulsive behaviors and consists of 30 items. Finally, the Temperament and Character Inventory (43) was used to collect data by assessing four basic temperament and three character dimensions. The estimate for internal consistency was excellent overall with the informant version of the Brown-Goodwin History of Aggression (alpha=0.88), the Barratt Impulsiveness Scale (alpha=0.89), and the Temperament and Character Inventory (alphas between 0.73 and 0.88 for the four temperament and three character scales).

Validity of Proxy-Based Personality Assessments

We compared personality trait assessments by means of the instruments listed and scored them using two different informants for each subject. No significant differences were found for any of
the comparisons (p values between 0.25 and 0.94), which had good measures of symmetry (gamma values between 0.40 and 0.68). Furthermore, with living subjects, we compared information obtained with the same instruments with an informant and the subject and found no significant differences (p values between 0.67 and 0.98 for all comparisons) and also good measures of symmetry (gamma values between 0.46 and 0.75). These findings are consistent with the literature on the validity of behavioral assessments with informants (32, 35, 36).

In addition, the validity of impulsive and aggressive measures was supported by the finding of a positive correlation between disorders that are characterized by high levels of these behaviors. A positive correlation was found between levels of impulsivity (Barratt Impulsiveness Scale) and aggression (Brown-Goodwin History of Aggression) (r=0.36, p<0.001). Moreover, high levels of impulsivity and high levels of lifetime aggression were correlated with severity of alcohol and drug abuse/dependence, as well as with cluster B personality disorders (r values between 0.17 and 0.58 for all tested correlations). These findings are consistent with previous reports (31, 44).

Classification of Suicide
Suicide cases were classified as violent and nonviolent, according to the classification system used in other studies (45–47). Poisoning, gas, and drowning were classified as nonviolent, whereas all other suicide methods were classified as violent.

Statistical Analysis
Statistical analyses were performed with SPSS version 11.5 (SPSS, Chicago) and Epi-Info version 6 (Centers for Disease Control, Atlanta). Chi-square analyses, Fisher’s exact test (two-tailed), and odds ratios (with the exact limit test to evaluate the 95% confidence interval [CI]) were used to compare categorical variables, and Student’s t test was used to analyze continuous variables. The joint effect of the independent variables, including age and the interactions of age and independent variables, were then analyzed with stepwise logistic regression.

Results
Study Group Characteristics
One hundred four depressed male suicide completers and 74 living depressed men were included in this study. Their ages (suicide victims: mean=40.6, SD=14.4; comparison subjects: mean=43.0, SD=10.8), working status (employed—suicide victims: N=52, 60%; comparison subjects: N=26, 61%), and education levels (completed college—suicide victims: N=17, 20%; comparison subjects: N=15, 24%) were similar between the groups. In addition, a similar proportion of suicide victims and comparison subjects had at least one or more children (suicide victims: N=53, 59%; comparison subjects: N=36, 62%). Almost all suicide cases and comparison subjects were from the same ethnic and cultural/religious backgrounds (N=57 and 66, 98%, in both groups were French Canadian, and N=55 and 63, 95%, in both groups were Catholic). There were no significant differences between groups in family history of suicide or in history of physical and/or sexual abuse.

Axis I Disorders
The prevalence rates of alcohol abuse/dependence and drug abuse/dependence in the last 6 months were significantly higher in depressed suicide completers than in depressed comparison subjects. No significant differences were found in the prevalence rates of other major axis I diagnoses in the last 6 months (Table 1). In addition, although a higher proportion of depressed suicide completers had a positive lifetime history of substance-related disorders, no significant differences were found for any lifetime axis I diagnosis (Table 1). Finally, two or more comorbid axis I disorders were more prevalent in depressed suicide completers (N=38, 37%) than in depressed comparison subjects (N=8, 11%) (odds ratio=4.75, 95% CI=1.97–12.60).

Axis II Disorders
The prevalence rates of cluster B personality disorders were significantly higher in depressed suicide victims than in depressed comparison subjects (Table 1). On the other hand, the prevalence rates of cluster A and cluster C personality disorders were comparable between suicide victims and comparison subjects. Finally, two or more comorbid axis I and axis II disorders were more prevalent in depressed suicide completers (N=54, 50%) than in depressed comparison subjects (N=14, 21%) (odds ratio=3.87, 95% CI=1.85–8.29).

Behavioral Measures
Mean scores on measures of impulsive behaviors obtained by using the total score on the Barratt Impulsiveness Scale were comparable between groups. Nevertheless, the prevalence rates of highly impulsive individuals (those scoring 75 and higher, as suggested by Barratt [48]) were significantly higher in depressed suicide completers than in depressed comparison subjects (p=0.001) (Table 2). In addition, mean scores on lifetime aggressive behavior measures obtained by using the total score on the Brown-Goodwin History of Aggression were significantly higher (p<0.02) in depressed suicide completers than in depressed comparison subjects. However, measures on the Temperament and Character Inventory were not statistically different between groups (Table 2).

Analysis by Age
To explore the possible effect of age, we decided to separate the groups by using 40 years as the cutoff point (18–40 years and ≥41). This point was chosen primarily because it was the mean and median age of our study group and because this is the age up to which suicide is the leading cause of death for men in Canada (49).

The prevalence rates of alcohol abuse/dependence in the last 6 months were significantly higher in younger depressed suicide completers than in younger depressed comparison subjects, and a nonsignificant higher proportion of younger depressed suicide completers had a positive history of drug abuse/dependence during the 6 months before their deaths. No other significant differences were found on current axis I diagnoses between younger and older depressed suicide completers (Table 3).
Lifetime prevalence rates of drug abuse/dependence were significantly higher in younger depressed suicide completers than in younger depressed comparison subjects but not in older depressed suicide completers compared to older depressed comparison subjects. There was a nearly significant difference between alcohol abuse/dependence among depressed suicide completers older than 40 compared to older depressed comparison subjects. No other significant differences were found on lifetime axis I diagnoses in younger or older depressed suicide completers (Table 3).

The prevalence rates of cluster B personality disorders were significantly higher in younger depressed suicide victims than in depressed comparison subjects only in the younger age group (Table 2).

Finally, we found that suicide completers 40 years and younger were using marginally more violent suicide methods (N=41, 85%) than suicide cases older than 40 (N=27, 66%) (odds ratio=3.04, 95% CI=0.98–10.00).

**Predictors of Suicide**

A stepwise logistic regression that included all significant variables and their interaction with age showed that cluster B personality disorders and alcohol abuse/dependence in the last 6 months were two independent predictors of suicide in major depressive disorder. The adjusted odds ratio for cluster B personality disorders was 16.59 (95% CI=2.02–136.24), and the adjusted odds ratio for alcohol abuse/dependence for the last 6 months was 4.08 (95% CI=1.38–12.06). No interaction term was a significant predictor of suicide outcome. Figure 1 illustrates the major predictors of suicide and other variables that significantly correlated with these predictors.

**Discussion**

One hundred four men who committed suicide during an episode of major depressive disorder were compared to
a group of 74 living men with major depressive disorder. Both groups were similar in terms of age, marital and parental status, education level, race, and religion. To our knowledge, this is the first study that has used a design that allowed direct control for the effect of major depressive disorder during an investigation of risk factors for suicide. In addition, there are only a few studies of suicide completers (31–33) that investigated impulsive and aggressive behaviors using a case-control design and standardized interviews to retrieve information on personality disorders and personality traits of the deceased.

### Axis I Disorders

Alcohol abuse/dependence during the 6 months preceding death increased the likelihood of dying by suicide in patients with major depressive disorder. A logistic regression analysis with control for the effects of age showed that the presence of alcohol abuse/dependence in the last 6 months was a good predictor of suicide, with an adjusted risk of 4.08. On the other hand, the prevalence rates of alcohol abuse/dependence in the last 6 months did not remain significant when we controlled for other significant factors. This finding is probably attributable to the fact that among those with drug abuse/dependence in the month preceding death, many (N=11, 52%) had also concomitant alcohol abuse/dependence. These findings confirm previous studies that showed the importance of substance abuse/dependence as a risk factor for suicide in adolescents and suicide attempters when it was comorbid with major depression (50–57).

Comorbidity with anxiety disorder does not appear to be a major risk factor for suicide in major depressive disorder in men. More specifically, panic disorder, when co-

### Axis II Disorders

Our analysis showed that cluster B personality disorders were major independent predictors of male suicide in major depressive disorder. Primarily, personality disorders characterized by the presence of impulsive/aggressive personality traits (borderline and antisocial) were observed as cluster B personality disorders in our study group, with 43% of them (N=13) having both diagnoses. This finding is consistent with previous studies of patients with major depression that reported no relationship between comorbidity with panic disorder and increased risk for lifetime suicide attempts (60). Nevertheless, it is possible that we failed to see an effect of anxiety disorders on suicide risk because we focused on male major depressive disorder in this study, and comorbidity with panic disorder has been reported to be more common in female suicide victims than in male suicide victims (61).

### Table 2. Measures of Impulsivity, Aggressive Behavior, Temperament, and Character in Depressed Suicide Victims and Depressed Comparison Subjects

<table>
<thead>
<tr>
<th>Measure</th>
<th>Depressed Suicide Victims</th>
<th>Depressed Comparison Subjects</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
<td>N</td>
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<tr>
<td>Total on Barratt Impulsiveness Scale</td>
<td>69</td>
<td>67.37</td>
<td>69</td>
</tr>
<tr>
<td>Total on Brown-Goodwin History of Aggression</td>
<td>55</td>
<td>13.75</td>
<td>62</td>
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<tr>
<td>Temperament and Character Inventory</td>
<td>Novelty seeking</td>
<td>73</td>
<td>60.54</td>
</tr>
<tr>
<td></td>
<td>Harm avoidance</td>
<td>73</td>
<td>53.67</td>
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<tr>
<td></td>
<td>Reward dependence</td>
<td>73</td>
<td>39.82</td>
</tr>
<tr>
<td></td>
<td>Persistence</td>
<td>73</td>
<td>15.56</td>
</tr>
<tr>
<td></td>
<td>Self-directedness</td>
<td>73</td>
<td>63.02</td>
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<td></td>
<td>Cooperativeness</td>
<td>73</td>
<td>57.90</td>
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<td></td>
<td>Self-transcendence</td>
<td>73</td>
<td>52.92</td>
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<tr>
<td>Age ≤ 40 years</td>
<td>Total on Barratt Impulsiveness Scale</td>
<td>33</td>
<td>70.63</td>
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<tr>
<td></td>
<td>Total on Brown-Goodwin History of Aggression</td>
<td>23</td>
<td>18.72</td>
</tr>
<tr>
<td>Age ≥ 41 years</td>
<td>Total on Barratt Impulsiveness Scale</td>
<td>36</td>
<td>64.37</td>
</tr>
<tr>
<td></td>
<td>Total on Brown-Goodwin History of Aggression</td>
<td>23</td>
<td>10.18</td>
</tr>
<tr>
<td>Total score ≥ 75 on the Barratt Impulsiveness Scale</td>
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<td>39.1</td>
<td>69</td>
</tr>
<tr>
<td>Subjects ages ≤ 40 years</td>
<td>33</td>
<td>45.5</td>
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<tr>
<td>Subjects ages ≥ 41 years</td>
<td>36</td>
<td>33.3</td>
<td>44</td>
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analysis showed that this seems to be particularly the case for younger suicide completers.

On the other hand, we found that cluster C personality disorders were not associated with an increased risk of suicide when we directly controlled for major depressive disorder. This result contrasts with findings from Foster et al. (65) and Cheng et al. (30) and suggests that cluster C personality disorders may be more directly related to the risk of major depressive disorder than to the risk of suicidal behavior.

**Impulsive and Aggressive Behaviors**

We found that impulsive and aggressive behaviors were associated with the risk of suicide in depression and that this effect was more important among younger cases (18 to 40 years). On the other hand, impulsive and aggressive behaviors were not direct predictors of suicide. It seems that these personality traits probably underlie the main predictors. This vision is supported by the positive correlation found between impulsive and aggressive behaviors and cluster B personality disorder and alcohol and drug abuse/dependence. It is possible to speculate that a developmental cascade may start with a biological predisposition to higher levels of impulsive and aggressive behavior. Having a higher level of impulsive and aggressive behavior may, in turn, increase the risk of developing a cluster B personality disorder that, per se, could lead to an increased risk of substance abuse/dependence (66–68). This developmental hypothesis of suicidal behavior is also supported by at least one other study showing that borderline personality disorder alone was not a risk factor for suicide (30), but when it was comorbid with severe depression, the risk of dying by suicide was increased close to 450 times.

**Age Effects**

The effect of age on the mediating role of impulsive and aggressive behaviors and substance abuse/dependence on the risk of suicide was suggested by the stratified analyses. We have further explored this effect by investigating how these risk factors interacted with age in the regression model; however, the interactions were not retained in the final model. This is explained by the fact that although impulsive and aggressive behaviors and substance abuse/dependence are not significant risk factors in subjects older than 40, their effect is in a similar direction. In other words, these variables do not have opposite effects according to age.

### TABLE 3. Lifetime and 6-Month Prevalence Rates of Comorbid Axis I and Axis II Disorders in Depressed Suicide Victims and Depressed Comparison Subjects by Age

<table>
<thead>
<tr>
<th>Age Group and Diagnosis</th>
<th>Depressed Suicide Victims</th>
<th>Depressed Comparison Subjects</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Subjects With a Diagnosis</td>
<td>Subjects With a Diagnosis</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>Age ≤40 years</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Last 6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol abuse/dependence</td>
<td>55</td>
<td>19</td>
<td>34.5</td>
</tr>
<tr>
<td>Drug abuse/dependence</td>
<td>55</td>
<td>15</td>
<td>27.3</td>
</tr>
<tr>
<td>Anxiety disorder(a)</td>
<td>55</td>
<td>13</td>
<td>23.6</td>
</tr>
<tr>
<td>Lifetime</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol abuse/dependence</td>
<td>55</td>
<td>20</td>
<td>36.4</td>
</tr>
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<td>Drug abuse/dependence</td>
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<td>19</td>
<td>34.5</td>
</tr>
<tr>
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<td>27.3</td>
</tr>
<tr>
<td>Personality disorders(b)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<tr>
<td>Cluster B</td>
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<td>22</td>
<td>41.5</td>
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<tr>
<td>Cluster C</td>
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</tr>
<tr>
<td>Age ≥41 years</td>
<td></td>
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<td>Last 6 months</td>
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<tr>
<td>Cluster C</td>
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<td>6</td>
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</tr>
</tbody>
</table>

\(a\) Panic disorder, social phobia, specific phobia, obsessive-compulsive disorder, generalized anxiety disorder, anxiety disorder not otherwise specified, agoraphobia without panic disorder, and posttraumatic stress disorder.

\(b\) Cluster A=paranoid, schizoid, schizotypal; cluster B=borderline, antisocial, narcissistic, histrionic; cluster C=avoidant, dependent, obsessive-compulsive, passive-aggressive, and depressive.

\(c\) Nonsignificant difference between groups (\(p=0.16, \text{Fisher's exact test, two-tailed}\)).

\(d\) Significant difference between groups (\(\chi^2=15.96, \text{df}=1, p=0.00006\)).

\(*p<0.05\).
**Limitations**

The limitations associated with the methods employed in this study are inherent to postmortem studies involving proxy-based interviews. However, the validity of such procedures, particularly with regard to the use of observable behaviors, has been well demonstrated (32), and our comparisons of data obtained using two different informants on the same subject, as well as comparisons between the comparison subject and his or her informant, further support its use on behavioral measures. On the other hand, the major problem of proxy-based interviews seems to be at the level of sensitivity (34). Nevertheless, using proxy-based techniques in both groups, we controlled for this possible bias.

Another important limitation of this study is that we focused on male subjects. How generalizable are the risk factors identified in this study to female depressed patients is an issue that deserves investigation. Of particular interest will be to investigate whether or not impulsive and aggressive behaviors play a similar role in mediating suicide in depressed women as they seem to play in depressed men.

**Conclusions**

This study was the first to our knowledge to investigate suicide completers in a specific diagnostic category by using a case-control design. Thus, 104 male depressed suicide completers and 74 living depressed male comparison subjects were investigated by means of the psychological autopsy method to better define the risk factors for suicide in major depressive disorder. We found that current alcohol abuse/dependence and the presence of a cluster B personality disorder were two independent risk factors for suicide among depressed individuals. In addition, we found that impulsive and aggressive behaviors were associated with suicide, but this association was not independent of cluster B and alcohol abuse in relation to suicide. These risk factors seem to play a larger role in younger suicide victims (ages 18–40). Further studies should be carried out to investigate the external validity of these findings, particularly among women and in other diagnostic categories associated with suicide, such as schizophrenia.

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**References**

Association of Resolution of Major Depression With Increased Natural Killer Cell Activity Among HIV-Seropositive Women

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Objective: Depression is a potential risk factor for morbidity and mortality among HIV-seropositive women, improvements in the diagnostic status of major depression are related to increases in NK cell activity among HIV-seropositive women.

Method: HIV-seropositive women were recruited as part of a longitudinal cohort study and underwent comprehensive medical and psychiatric evaluations during a 2-year period. Fifty-seven women had complete NK cell activity and depression data measured at two time points and were examined for associations between changes in depression status and alterations in NK cell activity over time.

Results: Among the 57 HIV-seropositive women, improvements in the diagnostic status of depression and decreases in scores on the 17-item Hamilton Depression Rating Scale were significantly associated with increases in NK cell activity over time, as measured in lytic units. Eleven women (19.3%) had a major depression diagnosis that resolved over time, and this group also had a significant increase in cell activity measured in lytic units during this period.

Conclusions: This study suggests that depression may impair certain aspects of innate cellular immunity relevant to delaying the progression of HIV disease and that these alterations are reversible with the resolution of a depressive episode. These findings support an examination of NK cell activity in assessments of the relationship between depression and morbidity and mortality in HIV disease.

(Depression is potential risk factor for increased morbidity and mortality among patients with numerous medical conditions (1), including HIV and AIDS (2–4). In chronic HIV disease, depression may adversely affect quality of life and adherence to medication regimens (5, 6), which may subsequently affect disease progression and health outcomes. Our work has suggested that killer lymphocytes may be altered during depression and subsequently affect the HIV viral load (7), although the exact mechanisms involved are not yet delineated.

Depressive symptoms are frequently reported among HIV-seropositive individuals, and several studies have documented elevated rates of major depression and subclinical depressive symptoms among HIV-seropositive homosexual men (8–12), although these rates are similar to those of HIV-seronegative homosexual men in the general population. The majority of these early studies of the prevalence of depression focused almost exclusively on men because of the demographics of HIV disease at the time. However, women now account for just over 50% of those infected with HIV globally, and the rates of new HIV cases among women in the United States and many other nations are rising (13). Because medically healthy women in the general population are also diagnosed with depression more often than men (14), it is increasingly salient to study the prevalence and effects of depression among HIV-seropositive women as well.

Recent studies have reported increased rates of the prevalence of depression and other mood disturbances among HIV-seropositive women. Morrison and colleagues (15) examined the prevalence of depressive disorders among 93 HIV-seropositive and 62 HIV-seronegative women and found that HIV-seropositive women without an active substance abuse problem had a significantly higher prevalence rate of major depressive disorder (19.4%) than HIV-seronegative women (4.8%). In a prospective longitudinal cohort study of 765 HIV-seropositive women, 42% reported chronic depressive symptoms, and 35% had intermittent depressive symptoms (2). In this study, depression was also associated with markers of the progression of HIV disease and mortality. Although the exact mechanisms underlying the association between depression and disease morbidity and mortality are unknown, the effects of depression on the immune system may represent a key mechanistic pathway (16, 17).

Associations between depression and immune system impairments among medically healthy individuals have...
been observed. The severity of depression has been associated with decrements in several in vitro measures of immunity (e.g., lower CD8+ T [antigenic marker on suppressor/cytotoxic T] cells and natural killer [NK] cell numbers and activity) in a large-scale meta-analysis (18). Patients diagnosed with depression, especially severe depressive states, also have pronounced decrements in immunity (19). Evans et al. (20) examined the effects of major depression on peripheral blood NK cell phenotypes and NK cell activity among depressed and nondepressed comparison participants. Depressed subjects exhibited significant reductions in NK effector cell numbers, Leu-11 (CD16) and Leu-7 (HNK-1), and NK cell activity.

Studies examining the association between depression and immunity, particularly CD4+ T lymphocyte counts, in HIV disease have reported both positive and negative findings (21–26). These results may be due to differences in psychiatric assessments or the patient samples studied or perhaps to a reliance on broad indices of immune status (e.g., CD4+ T cell counts), which may not be the most sensitive or reliable indicators of immunity. Depression is associated with alterations in more specific measures of immune function among HIV-seropositive women. For example, depression was associated with decrements in killer lymphocyte function among a group of 63 HIV-seropositive women (7). These measures are a specific indicator of innate immunity, which may be relevant to the progression of HIV disease; however, to our knowledge, no study to date has examined the association between changes in depression status and NK cell activity over time among HIV-seropositive women.

Irwin and colleagues (27) assessed NK cell lytic activity at intake and at a 6-month follow-up among medically healthy depressed individuals and comparison subjects in a longitudinal case-control design and found that as depression scores decreased, NK cell activity increased in the depressed subjects, but neither changed in the comparison subjects. Frank et al. (28) examined medically healthy depressed individuals and found that 4 weeks of fluoxetine treatment was associated with augmented NK cell activity in a subgroup of subjects that initially exhibited low NK cell activity. Schleifer and colleagues (29), however, found no change in NK cell numbers or cell activity among 21 medically healthy adults with major depression after 6 weeks of antidepressant treatment, although they did find both decreased NK cell numbers and function during initial depressive states. One way to reconcile these differences is to investigate subjects over longer time intervals with more specific immune assays, which may allow for more opportunities to observe alterations in depression and more precise changes in immunity.

In the current study, we assessed the status of a diagnosis of major depression and immune system functioning in a group of HIV-seropositive women over a period of up to 2 years. We predicted that resolution of the major depression and improvement in acute depressive symptoms would be significantly associated with increases in NK cell activity over time. We further hypothesized that a subgroup of women who showed significant improvements in mood (as indicated by a resolution of a major depression diagnosis) over time would also show improvements in immune functioning, as measured by the specific functional measure of innate immunity, NK cell activity. We also predicted that a subgroup of HIV-seropositive women who did not meet the diagnostic criteria for major depression would show no significant changes in NK cell activity.

Method

The data for this study were collected from two sites (Gainesville, Fla., and Philadelphia) as part of a prospective, longitudinal cohort study investigating the neuropsychiatric, endocrine, and immune aspects of HIV infection in women (7). The current study specifically examines the association between depression and immune data obtained across a 2-year period.

Participants

HIV-seropositive women were recruited from outpatient clinics, public health departments, and other organizations focused on HIV disease and care through a combination of community presentations, clinician referrals, word of mouth, and media advertisements. The specific inclusion and exclusion criteria were detailed in a previous report (7). Fifty-seven HIV-seropositive women had complete depression and immune data measured from at least two time points during the study period and thus were available for inclusion in the current main analyses. These 57 women were comparable to women without such matched data on relevant demographic, medical, and depression data (7). To further understand whether NK cell activity, measured in lytic units (LU), changes with resolution in the clinical diagnosis of major depression, we examined participants who experienced a change in diagnosis over the follow-up period. Eleven of the 57 women were diagnosed with major depression either at study entry or early on (i.e., within the first year of the study), but they did not meet criteria for major depression at the follow-up assessment. Forty-three women did not meet the criteria for major depression at the follow-up assessment. Forty-three women did not meet the criteria for major depression at the follow-up assessment.

HIV serostatus was confirmed by using an enzyme-linked immunosorbent assay with Western blot analysis for confirmation of the presence of anti-HIV-1 antibodies. All women were fully aware of their HIV-seropositive status at study entry.

Procedures

The institutional review boards of the University of Pennsylvania and the University of Florida approved the protocol. The participants were assessed at baseline and followed up every 6 months across the 2-year period. All participants provided written informed consent and were reimbursed for their time, travel expenses, and child-care expenses.

Psychiatric and Medical Assessments

Each participant received a thorough outpatient assessment at study entry and at follow-up over a 2-year period, which included a physical examination and a structured psychiatric interview. Current and lifetime DSM axis I diagnoses, including major depressive disorder, were assessed by a psychiatric clinician with a modified version of the Structured Clinical Interview for DSM-III-R (SCID) (30). Consensus diagnoses were determined at team
meetings; the clinicians’ rating/diagnosing was blind to patient immune status, and all immune assessments were performed with blinding for rating/diagnostic status. We also assessed acute symptoms of depression with the 17-item Hamilton Depression Rating Scale (31). HIV medication status was coded as a categorical variable pertaining to whether or not the woman was taking antiretroviral medication or protease inhibitors.

**Immune Assessments**

To control for potential circadian effects on immunity, all participants were evaluated at the same time of day. Specifically, the participants were placed in a recumbent position, an intravenous line was started at approximately 9:00 a.m., and intravenous line patency was maintained with a slow normal saline drip. Blood was obtained approximately 1 hour later. Blood cell counts and flow cytometry panels were performed on peripheral blood samples, as detailed previously (7). NK cell activity was assessed by using standard techniques established in our laboratory (32). Lytic units/107 of peripheral blood mononuclear cells and lytic units/107 of NK cells were calculated with the method of Bryant et al. (33) and Friberg et al. (34). By measuring the percentage of CD16+/CD56+ cells in the preparation of peripheral blood mononuclear cells, we determined the lytic units of NK activity (LUNK) per NK cell (35). Expressing the NK data as LUNK cell adjusts for differences in the percentage of NK cells (CD16+/CD56+) in the effector cell population. Thus, our primary outcome measure of innate immunity was expressed as LUNK cell activity. We took the log of LUNK to make the distribution more symmetric and to equalize variances for group comparisons.

**Viral Assessments**

Serum HIV RNA viral load was determined from archived samples with the Amplicor Monitor assay (Roche Diagnostics, Branchburg, N.J.). The lower limit of quantification for this assay is 400 copies per milliliter of blood. Because approximately half the group measured at this lower limit and standard transformations, such as the log, would not normalize the distribution, we analyzed viral load as a dichotomous variable. Thus, viral load was quantified as either nondetectable (less than or equal to 400 copies/ml) or detectable (greater than 400 copies/ml) in the current study.

**Statistical Analyses**

Two different analyses were performed to evaluate the overall association between different depression measures as the time-varying covariate and log (LUNK) cell activity over time as the longitudinal dependent variable. First, to analyze such associations, we included as fixed effects to account for significant heterogeneity among the subjects with respect to both LUNK and the depression measure, which would cause confounding under a random effects model. The estimate of the longitudinal correlation was obtained from the estimated regression slope divided by the model-based standard deviations for log (LUNK) cell activity and the depression measure. Second, for the analysis of the 11 women who exhibited a change in depression status, we used Wilcoxon’s signed rank tests to examine whether there were changes in LUNK cell activity during the period depression resolved. Similar tests were performed for the remaining women across an equivalent period of time. Finally, we used Spearman’s r for continuous and ordinal outcomes and chi-square tests for binary outcomes to compare different groups of subjects with respect to demographic and medical variables. In all analyses, we adjusted for baseline viral load, antiretroviral medication use, antidepressant treatment status, and time interval (in months) between assessments.

**Results**

The demographic and behavioral characteristics of the 57 HIV-seropositive women with depression and immune data that were available from at least two time points were obtained from each site (Gainesville, Fla., and Philadelphia) and were comparable, as reported in our earlier work (7, 15). The mean age of the women was 39.7 years (SD=7.1). About 58% of the women were African American, and 35% were Caucasian. The majority of the women (81%) were taking an established regimen of HIV medications, and half of the group had a viral load in the detectable range. CD3+/CD4+ T cell counts averaged 521.6 (SD=7.1) for the entire group. Thirty-seven (65%) of the 57 women had a prior history of major depression, as assessed by the SCID at the initial assessment. Nineteen percent of the women reported that they were given a prescription for an antidepressant medication at the initial assessment. There were no significant differences between the groups on the relevant demographic and medical variables examined in this study.

The average time interval (in months) between the initial assessment and the final assessment for the group of 57 woman was 12.74 months (SD=5.79), with an average time interval of 13.64 months (SD=6.62) for the group of 11 women who were depressed and later had a resolution and 12.28 months (SD=5.70) for the group of 43 nondepressed women. There was no significant difference in time interval between the groups (t2=0.36, df=1, p=0.55).

By employing linear regression with the subject as a fixed effect to evaluate associations between depression and immunity in the entire group (Table 1), improvements in the diagnostic status of depression (r=-0.258, p<0.006) and decreases in Hamilton depression scale scores (r=-0.234, p<0.05) were significantly associated with increases in log (LUNK) cell activity over time. These associations were significant, even when we controlled for initial depression diagnostic status or Hamilton depression scale scores, respectively, as well as viral load, HIV medication status,

<table>
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<th>Score, and Viral Load</th>
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antidepressant medication status, and the time interval between assessments.

Hamilton depression scale scores paralleled major depression diagnostic status over time, improving significantly (mean=17.8, SD=6.5, to mean=5.9, SD=5.7) in the 11 women with a resolution of their major depression diagnosis (z=−32, p=0.002) and showing no significant change (mean=6.7, SD=5.9, to mean=5.7, SD=5.7, in the 43 women who were nondepressed (z=−53, p=0.42). In the group with improved depression, eight (73%) of the 11 women had remitted depression, as defined by a Hamilton depression scale score of 7 or less; one woman met criteria for dysthymic disorder but not major depression at the final assessment.

LUNK cell activity of the group with resolved depression (N=11) and the nondepressed group (N=43) of HIV-seropositive women over time is presented in Figure 1. In the resolution group (11 of 57, 19.3%), representing women whose depression diagnostic status improved, there was also a significant increase (mean=5.6, SD=1.4, to mean=7.0, SD=1.0) in log (LUNK) cell activity over time (z=28, p=0.009). In fact, 82% (nine of 11) of the women in this group had improvement in log (LUNK) cell activity that paralleled resolution of their major depression diagnostic status. If we include the three women who entered the study as nondepressed but became depressed by their final assessment, along with the 11 women with a resolution of their depression diagnostic status, there remains a significant absolute change in log (LUNK) cell activity among these 14 women (z=43.5, p=0.004) over time. Of these 14 women who experienced a change in their major depression diagnostic status in either direction, 11 (79%) had a significant parallel change in log (LUNK) cell activity over time. In the nondepressed group (43 of 57, 75.4%), however, there were no significant changes (mean=6.6, SD=1.6, to mean=6.6, SD=1.4) in log (LUNK) cell activity (z=18, p=0.83) during an equivalent period.

Discussion

This study examined the association between the diagnostic status of major depression, acute depressive symptoms, and a specific measure of innate immunity—LUNK cell activity—over time among a contemporary group of HIV-seropositive women. The women whose depression diagnostic status resolved over time also showed a significant increase in LUNK cell activity across this same period. However, the women who did not meet the diagnostic criteria for major depressive disorder did not show a significant change in immunity during an equivalent period. This study is one of the first to demonstrate that an improvement in depression diagnostic status results in a parallel change in a specific indicator of immune system functioning relevant to progression of HIV disease. These findings extend our previous work demonstrating significant inverse relationships between depression and NK cell activity in a cross-sectional study (7).

To our knowledge, this is also the first study in HIV disease to show that change in the diagnostic status of major depression and reduction in acute depressive symptoms are significantly associated with increases in LUNK cell activity over time. This association was observed even though the Hamilton depression scale scores of the women in our depressed group were in the moderate range, as observed in our earlier studies of HIV-seropositive women (7, 15), which indicates that this association may be even stronger in more severely depressed groups. Our more direct measure of NK cell functional activity (LUNK) may be an underlying mechanism of the effects of depression on HIV morbidity and mortality observed in previous studies (2–4). Prior HIV studies relating depression and immunity have reported mixed results when the authors used more global indices of immune status, such as CD4+ T cell counts (21–26). The results of the current study point to the benefits of employing more specific indicators of immunity, such as LUNK cell activity, which are potentially relevant to the progression of HIV disease.

Clinical studies of depression in subjects without other medical illness have demonstrated significant alterations in NK cells (20), a cellular immune population that may play a key role in regulating HIV infection. There is mounting evidence that NK cells exert anti-HIV effects by both
classic killing activity as well as the production of HIV-suppressive factors. Specifically, NK cells may be involved in a natural resistance against viral infection and may have the capacity to lyse HIV-1 infected cells (36–40). In our studies of HIV-infected men, alterations of NK lymphocytes associated with stress and depression were observed (23, 24), suggesting that killer lymphocytes mediate the effects of depression in the earlier stages of the progression of HIV disease. Ironson et al. (41) observed that NK cell number and function are preserved among AIDS patients with low CD4+ T cell counts and stated that these immune factors may be important in maintaining the health and well-being of these individuals. Thus, the mechanism underlying the impact of depression on the progression of HIV disease may operate in part by altering NK cell numbers and activity.

There are a number of limitations to the current study. The design was a prospective cohort study and not a population-based study, and thus, a sampling bias may have resulted. Although recruitment was open to women of all races and ethnic backgrounds, African American and Caucasian participants comprised the majority of the participants. Thus, these findings may not be generalizable to Hispanic or Asian populations. We also excluded women who were currently abusing alcohol or other substances to reduce the confounding effects of these substances on depression and immunity. This may also limit the generalizability of our findings. This was an observational study, not a treatment study, so we did not have complete data on adherence to specific antidepressant treatment (either pharmacological or psychological), and thus, it is difficult to ascertain whether the alterations in depression observed were due to a specific treatment or simply to the passage of time. Regardless of how depression improved in these women, the associated enhancement in immunity is noteworthy and warrants more extensive clinical evaluation in future studies.

In conclusion, our findings provide the first evidence that resolution of major depression is associated with significant increases in NK cell activity over time in HIV-seropositive women. These results extend previous findings demonstrating depression-associated decrements in NK cell numbers and function and suggest that these alterations are reversible with the resolution of the depressive episode. Increasing evidence suggests that depression may have a negative impact on the progression of HIV disease, and chronic depression has been associated with mortality in HIV-seropositive women. Given the role that innate immunity plays in the host’s defense against HIV infection, future studies assessing antidepressant treatment effects could shed light on the relationship and underlying mechanisms of depression, immunity, and the progression of HIV disease.

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DEPRESSION AND HIV-SEROPOSITIVE WOMEN

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Treatment Matching in the Posthospital Care of Depressed Patients

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Objective: This study assessed the efficacy of 1) matching patients to treatments and 2) adding additional family therapy or cognitive therapy in a group of recently discharged patients with major depression.

Method: Patients with major depression were recruited during a psychiatric hospitalization. After discharge, they were randomly assigned to one of four treatment conditions that were either “matched” or “mismatched” to their pattern of cognitive distortion and family impairment. The four treatment conditions were 1) pharmacotherapy alone; 2) combined pharmacotherapy and cognitive therapy; 3) combined pharmacotherapy and family therapy; and 4) combined pharmacotherapy, cognitive therapy, and family therapy. Randomly assigned treatment continued for 24 weeks on an outpatient basis.

Results: Among patients with at least moderate depressive symptoms at hospital discharge, low rates of remission (16%) and improvement (29%) were obtained. Matched treatment led to a significantly greater proportion of patients who improved and greater reductions over time in interviewer-rated depressive symptoms than mismatched treatment. However, matched treatment did not produce greater change in self-reported depression or interviewer-rated suicidal ideation. Treatment that included a family therapy component also led to a greater proportion of patients who improved and to significant reductions in interviewer-rated depression and suicidal ideation than treatment without family therapy.

Conclusions: These results suggest that 1) current treatments are not very efficacious in the aftercare of hospitalized depressed patients, 2) treatment matching moderately improves outcome for patients who are symptomatic at hospital discharge, and 3) inclusion of family therapy improves the outcome of posthospital care for depressed patients.

Recognition of the prevalence and seriousness of depressive disorders has led to the development of numerous treatments for depression, including medications, individual psychotherapies, marital/family therapy, as well as combinations of pharmacological and psychosocial treatments. In general, all of these treatments have been found to be efficacious. However, there has been considerable variability in absolute response rates. Conclusions about possible differences between treatments are unclear, with the most common finding being equivalence among active treatments (1).

Our knowledge about treatments for depression has a number of significant additional limitations. First, there is a high degree of heterogeneity among individuals labeled “depressed,” with descriptions ranging from the mildly depressed “worried well” to psychotic, suicidal patients. Despite this heterogeneity, a majority of treatment research in depression has been conducted on a relatively homogeneous group of moderately depressed outpatients. Patients whose depression was severe enough to require hospitalization, who had a significant risk of suicide, or who had psychiatric or medical comorbidity typically have been excluded.

Second, we have little knowledge of what type of treatment works best for which patient. Although clinicians make decisions about matching treatment to patient characteristics on a daily basis, virtually all research studies have treated patients as if they were homogeneous and have not investigated how to best match the large number of available treatments for depression to the needs of individual patients.

Third, despite the common use of combined psychosocial and pharmacological treatments in clinical practice, compared to studies of pharmacotherapy or psychotherapy alone, relatively few studies have investigated the efficacy of combined treatments for depression (2). Furthermore, reviews of this literature have reached conflicting conclusions regarding the benefits of combined treatments (2).

Fourth, although most researchers would accept that depression is a “biopsychosocial” disorder and that there is evidence that family dysfunction is predictive of treatment response and course of illness (3), there have been few studies investigating the efficacy of family treatments for depression (4–7) and virtually none that have integrated family interventions with pharmacological and individual treatments.
The present study was designed to address these limitations. More specifically, the goals of the current study were 1) to investigate the efficacy of matching treatments to patient characteristics in the posthospital outpatient care of a group of depressed hospitalized patients and 2) to investigate the efficacy of adding cognitive or family therapy to pharmacotherapy in this group.

Our primary a priori hypothesis was that patients receiving "matched" treatment would have better outcomes than those receiving "mismatched" treatment. We had two secondary hypotheses. First, the patients receiving additional cognitive therapy would have better outcomes than the patients who did not. Second, the patients receiving additional family therapy would have better outcomes than the patients who did not.

Method

Participants

A total of 121 patients were initially recruited from the inpatient or partial hospital units of a private psychiatric hospital if they met all of the following criteria: 1) currently living with one or more family members, 2) a DSM-III-R diagnosis of major depressive disorder according to the Structured Clinical Interview for DSM-III-R—Patient Version (SCID) (8, 9) a score greater than 17 at admission on the 17-item Modified Hamilton Rating Scale for Depression (9), and a score greater than 17 on the Beck Depression Inventory (10), 4) ages 18 to 65 years, 5) sufficient English reading skills to complete questionnaires, and 6) informed consent provided by the patient and family to participate in the project. Patients were excluded from the study if they 1) met DSM-III-R criteria for a current episode of bipolar disorder, alcohol or drug dependence, somatization disorder, or schizophrenia, 2) had significant cognitive impairment, or 3) had medical illness severe enough to contraindicate antidepressant medication.

The patients’ levels of depression and suicidal ideation were reassessed within 2 days of discharge from the hospital. Forty-five (37%) of the 121 patients did not have clinically significant levels of depression (a modified Hamilton depression scale score ≤14 or a Beck Depression Inventory score ≤16) before discharge. In fact, the mean level of depression for this group was in the nondepressed range (a modified Hamilton depression scale score=6.8, SD=3.5; a Beck Depression Inventory score=8.6, SD=4.9). Because hospital treatment was not controlled and the goal of this study was to evaluate different strategies for treating depression, these patients with low levels of symptoms before treatment assignment were excluded, leaving a group of 76 patients to be included in this report. All participants received a complete explanation of the study and provided written informed consent.

Stratification

The patients who met these criteria were grouped according to two classes of variables: 1) cognitive distortion and 2) family impairment. The procedures used for this grouping were as follows.

Consistent with our previous studies (11, 12), the subgroup with high cognitive distortion was defined by scores on two measures of cognitive distortion: 1) the Dysfunctional Attitude Scale (13) and 2) the Cognitive Bias Questionnaire (14). A patient was included in the subgroup with high cognitive distortion if he or she scored greater than one standard deviation above a mean derived from previously published reports for nondepressed subjects on both the Dysfunctional Attitude Scale (mean=119) (13) and the Cognitive Bias Questionnaire (mean=3) (14).

High and low family impairment was determined on the basis of the general functioning subscale of the interviewer-rated McMaster Clinical Rating Scale (15, 16). Because a majority of families with a depressed member will manifest some dysfunction, particularly during an acute episode, we used the median score of 3.0 for depressed families on the general functioning subscale of the McMaster Clinical Rating Scale from our previous studies of hospitalized depressed patients as a cutoff score.

Based on these criteria for cognitive distortion and family impairment, the patients were classified into one of four subgroups: 1) high cognitive distortion and high family impairment, 2) high cognitive distortion and low family impairment, 3) low cognitive distortion and high family impairment, and 4) low cognitive distortion and low family impairment.

Description of Treatment Conditions

All study treatments began after discharge from the hospital and continued for a 24-week period.

Pharmacotherapy. The pharmacotherapy condition consisted of a semistructured medication protocol and clinical management sessions with one of two board-certified psychiatrists. The medication protocol required prescription of an antidepressant approved by the Food and Drug Administration at recommended therapeutic dosages for at least a 4-week trial. The treating psychiatrist chose the specific antidepressant. This flexibility was particularly useful, given that many of the patients had previous medication trials. If the patient did not respond to the first trial of medication, subsequent trials with different antidepressants were initiated. The clinical management sessions with the psychiatrist followed the clinical management guidelines, as described by Fawcett et al. (17). The scheduling of the psychiatric visits was determined by the clinical judgment of the psychiatrist, with a maximum of 10 visits during the 24-week treatment period.

Combined cognitive therapy. The combined cognitive therapy condition consisted of pharmacotherapy, as described, plus individual cognitive therapy administered according to the manual by Beck et al. (18). The scheduling of cognitive therapy visits was determined by the clinical judgment of the cognitive therapist, with the goal of 20–24 therapy sessions.

The cognitive therapy was provided by one of three Ph.D. clinical psychologists with at least 5 years of clinical experience who had been trained as cognitive therapists. Before treating patients in the study, all of the therapists were certified as competent by an external cognitive therapy expert (Dr. Margorie Weishaar). In addition, all of the therapists received ongoing supervision from another highly experienced cognitive therapist (Dr. Stephen Bishop).

Combined family therapy. The combined family therapy condition consisted of pharmacotherapy plus family therapy based on the problem-centered systems therapy of the family (19). The problem-centered systems therapy of the family model is a short-term multidimensional family treatment that focuses on comprehensive assessment, problem identification, and task-oriented problem solving. The scheduling of sessions was at the discretion of the family therapist, with the goal of 8–10 therapy sessions.

The family therapy was provided by one of two M.S.W. family therapists with at least 5 years of clinical experience who were certified as competent in problem-centered systems therapy of the family by one of the developers of the model (Dr. Duane Bishop). In addition, both family therapists received ongoing supervision from this same family therapy expert.

Combined cognitive and family therapy. The combined cognitive and family therapy condition consisted of pharmacotherapy plus cognitive therapy plus family therapy, as described previously.
FIGURE 1. Treatment Matching Study Design for Recently Discharged Patients With Major Depression

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Cognitive distortion</td>
<td>Family impairment</td>
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<td>High</td>
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<td>Low</td>
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**Assignment to Treatment**

The patients were randomly assigned to a treatment condition that was theoretically “matched” or “mismatched” to the patients’ pattern of deficits. The matching was based on a “deficit remediation” model; that is, it was hypothesized that patients with deficits in a specific area would benefit most from a treatment that directly addressed those deficits. Based on this model, a matched and mismatched treatment condition was derived for each of the four patient subgroups. Thus, patients with high levels of cognitive distortion were hypothesized to respond best to a treatment that included cognitive therapy. Similarly, patients from highly impaired families were hypothesized to respond better to a treatment condition that included family therapy. The matching algorithm can be seen in Figure 1. It should be noted that this design was only 50% of a full factorial (four-by-four [patient group-by-treatment]) design. Thus, although the design allowed an efficient test of the matching hypotheses, comparisons between individual treatment conditions were confounded with patient groupings (see Data Analysis).

An urn randomization procedure (20) was used to balance the matched and mismatched conditions for potentially confounding variables, including gender, patient role in family, severity of depression (Modified Hamilton Rating Scale for Depression score ≥23), axis I disorder in a family member, presence of comorbid dysthymic disorder or personality disorder in the patient, and recruitment site (inpatient versus partial hospitalization). As expected, there were no differences in these variables between treatment groups.

**Assessments**

Upon admission to the hospital, the patients were administered the patient version of the SCID (8), the Dysfunctional Attitude Scale (13), the Cognitive Bias Questionnaire (14), the McMaster Clinical Rating Scale (15), the Modified Hamilton Rating Scale for Depression (9), the Beck Depression Inventory (10), the Modified Scale for Suicidal Ideation (21), as well as other measures not included in this report. The measures of depressive symptoms (the Modified Hamilton Rating Scale for Depression, the Beck Depression Inventory, and the Modified Scale for Suicidal Ideation) were readministered in person at discharge from the hospital and at week 12 and week 24 of outpatient treatment. The assessors were clinical raters trained to at least 0.80 reliability who were blind to the match/mismatch status of the patients but not to assignment to cognitive or family therapy.

**Data Analysis**

**Treatment discontinuation.** We categorized patients who dropped out of randomly assigned treatment as either “treatment failures” or “dropouts.” “Treatment failures” were defined as patients who manifested significant symptom deterioration or constituted a serious suicide risk and were removed from the study by the investigators. This decision was made at a weekly meeting attended by all study clinicians and investigators. Any clinician could recommend that a patient be removed from the study. If such a recommendation were made, the patient’s progress and assessment data would be discussed by the clinical team, who were blind to matched/mismatched assignment. A patient was declared a treatment failure based on a consensus judgment of the team that the patient was exhibiting a high suicide risk or clinical deterioration and that the current treatment was not adequately mitigating these risks.

“Dropouts” were defined as patients who left randomly assigned treatment for any other reason (were noncompliant, withdrew consent, moved away).

**Treatment response.** Treatment response was measured by scores on the Modified Hamilton Rating Scale for Depression, the Beck Depression Inventory, and the Modified Scale for Suicidal Ideation as assessed at hospital discharge, week 12, and week 24. In addition to continuous measures of symptom change, we also defined two treatment-response categories as follows: 1) remission was defined as a Modified Hamilton Rating Scale for Depression score <7, a Beck Depression Inventory score <9, and remaining in treatment; and 2) improvement was defined as ≥50% improvement on both the Modified Hamilton Rating Scale for Depression and the Beck Depression Inventory and remaining in treatment.

**Analyses.** Hierarchical linear modeling (22, 23) was used to analyze change in depressive symptoms and suicidal ideation. Hierarchical linear modeling is ideal for these analyses because it accommodates missing data among repeated measurements by using empirical Bayesian estimates. We first examined overall change for the entire group, not accounting for treatment group (i.e., null models). This allowed us to estimate overall symptom change and to determine whether change varied across individuals.

In a second set of analyses, we examined whether treatment assignment accounted for differential symptom change over time. For these analyses, total linear change (β11) consists of three parameters: 1) linear change for individuals, with a treatment value of 0 (β0b); 2) linear change for individuals, with a treatment value of 1 (γ11); and 3) unexplained error (μ1). Of importance, significance tests of γ11 indicate whether the average change for individuals with a treatment value of 1 is statistically different from the average change for individuals with a treatment value of 0. Because of space limitations, we report only tests of γ11.

To extend these hierarchical linear modeling analyses, chi-square comparisons were also conducted to assess differences in categorical variables (noncompletion, treatment response). All statistical tests were conducted with a two-tailed alpha level of 0.05,
with intent-to-treat groups. Effect sizes (Cohen’s d) were calculated on the basis of the hierarchical linear modeling and chi-square values and degrees of freedom. It should be noted that different statistical software packages calculate degrees of freedom differently; thus generalization of these effect size estimates of hierarchical linear modeling across studies should be done cautiously.

**Results**

**Treatment Received**

Overall, during the 24 weeks of the study, the patients received a mean of 8.4 clinical management sessions with a psychiatrist (SD=4.3). An “adequate” trial of medication was defined as a period of 4 weeks or longer of at least the minimum targeted dose of a medication (e.g., 150 mg/day of imipramine, 20 mg/day of fluoxetine) (24). With these criteria, 61 (80%) of the 76 patients received at least one adequate medication trial. Eight (11%) of the 76 patients dropped out of treatment before receiving an adequate trial. All of the remaining seven patients received between one and four trials of antidepressants, but because of side effects and/or noncompliance, they were not receiving the criterion dose for a 4-week period. Of the patients who re-

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**TABLE 1. Baseline, Discharge, and Week-24 Demographic and Clinical Characteristics of Recently Discharged Patients With Major Depression**

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<td>39.1</td>
<td>11.9</td>
<td>35.6</td>
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<td>Education (years)</td>
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<td>2.5</td>
<td>12.7</td>
<td>2.5</td>
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<td>Age at illness onset (years)</td>
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<td>12.9</td>
<td>28.0</td>
<td>13.6</td>
<td>23.1</td>
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<td>4.3</td>
<td>25.4</td>
<td>4.2</td>
<td>25.7</td>
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<td>24.9</td>
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<td>8.5</td>
<td>36.9</td>
<td>8.9</td>
<td>34.3</td>
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<td>12.7</td>
<td>19.7</td>
<td>12.4</td>
<td>23.5</td>
<td>13.0</td>
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<td>162.0</td>
<td>38.5</td>
<td>175.6</td>
<td>46.3</td>
<td>168</td>
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<td>3.3</td>
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<td>4.7</td>
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<td>2.7</td>
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<td>1.0</td>
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<td>Adequate medication triala</td>
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<td>38</td>
<td>84</td>
<td>23</td>
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<td>8</td>
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<td>18</td>
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<td>Patients with remitted depression</td>
<td>12</td>
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<td>9</td>
<td>20</td>
<td>3</td>
<td>10</td>
<td>6</td>
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<tr>
<td>Patients with improved depression</td>
<td>22</td>
<td>29</td>
<td>17</td>
<td>38</td>
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<td>Week-24 scores</td>
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<tr>
<td>Beck Depression Inventory Modified Scale for Suicidal Ideation</td>
<td>17.9</td>
<td>13.6</td>
<td>15.7</td>
<td>12.2</td>
<td>21.4</td>
<td>15.3</td>
<td>17.7</td>
</tr>
</tbody>
</table>

a Four weeks or longer of taking at least the minimum targeted dose of a medication.
received at least one adequate trial, 48% (N=29) received one trial, 25% (N=15) received two trials, and the remaining 27% (N=17) had three or more medication trials. There were no significant differences between any treatment groups in the proportion of patients who received an “adequate” medication trial. The patients in the combined cognitive therapy plus pharmacotherapy and the combined cognitive plus family therapy conditions received a mean of 13.0 cognitive therapy sessions (SD=6.0), whereas the patients in the combined family therapy plus pharmacotherapy and the combined cognitive plus family therapy conditions received a mean of 5.1 family therapy sessions (SD=4.3).

**Overall Group**

Study results can be seen in Table 1. Twenty-one percent of the group (N=16) dropped out of treatment, and 24% (N=18) were removed from the study as “treatment failures.” There was a significant linear decrease in Modified Hamilton Rating Scale for Depression scores from discharge to week 24 (γ10=−2.96, t=−5.23, df=75, p<0.001). Furthermore, there was moderate variability in Modified Hamilton Rating Scale for Depression change in score over time (μ1=2.63, χ²=83.61, df=69, p=0.11), suggesting differentiation in score change across individuals. A significant linear decrease in Beck Depression Inventory scores was also observed (γ10=−2.31, t=−2.97, df=75, p<0.01). This decrease also had significant variability (μ1=3.64, χ²=98.88, df=69, p<0.01). Finally, scores on the Modified Scale for Suicidal Ideation did not significantly change over time (γ10=0.73, t=1.13, df=75, p=0.26). Despite this overall stability, there was significant variance in linear change (μ1=2.85, χ²=97.50, df=69, p=0.05). This suggests that scores on the Modified Scale for Suicidal Ideation increased for some individuals and decreased for others, leading to relatively small change overall. Noncompleters reported higher levels of suicidal ideation during hospital admission than completers (γ10=−4.54, t=−5.51, df=74, p<0.05). However, the completers and the noncompleters did not differ in their rates of change in suicidal ideation during the course of treatment (γ11=−0.13, t=−0.10, df=74, n.s.). At the end of treatment, 29% of the group (N=22) met the criteria for improvement, and 16% (N=12) met the criteria for remission.

To summarize, substantial proportions of the patients did not complete the 6-month treatment. Depression scores significantly decreased over time. Not everyone changed similarly because change parameters had moderate variability. Suicidal ideation did not significantly change over time. However, there was significant variability in change in scores on the Modified Scale for Suicidal Ideation, indicating that suicidal ideation changed differently across individuals. Overall rates of improvement and remission were low. We next examined whether treatment allocation could account for individual differences in response over time.

**Primary Hypothesis: Matched Treatment**

Our primary set of analyses compared the matched and the mismatched subjects across all treatment conditions (cells 1, 3, 6, 8 against cells 2, 4, 5, 7; see Figure 1). As can be seen in Figure 1, these comparisons used the entire group, with the two conditions (matched and mismatched) taking equivalent proportions of each patient subgroup (high versus low cognitive dysfunction, high versus low family impairment) and type of treatment (cognitive therapy, family therapy, and pharmacotherapy alone).

There were no significant differences in Modified Hamilton Rating Scale for Depression scores, Beck Depression Inventory scores, or Modified Scale for Suicidal Ideation scores at discharge between the matched and mismatched groups. Similarly, there were no significant differences between the matched and the mismatched groups in the proportions of treatment failures or dropouts.

---

**FIGURE 2. Proportion of a Group of 76 Recently Discharged Patients Who Improved or Whose Depression Remitted After 24 Weeks**

- **Matched:**
  - Improved: 45%
  - Remitted: 40%
- **Mismatched:**
  - Improved: 35%
  - Remitted: 30%
- **Received Family Therapy:**
  - Improved: 50%
  - Remitted: 45%
- **Did Not Receive Family Therapy:**
  - Improved: 30%
  - Remitted: 25%
- **Received Cognitive Therapy:**
  - Improved: 40%
  - Remitted: 35%
- **Did Not Receive Cognitive Therapy:**
  - Improved: 25%
  - Remitted: 20%

* p<0.05. ** p<0.10.
Matched treatment led to significantly greater change in score on the Modified Hamilton Rating Scale for Depression than mismatched treatment ($\chi^2_{11}=–2.12, t=1.95, df=74, p=0.05, d=0.45$). However, treatment matching did not lead to significantly different change in Beck Depression Inventory scores compared to mismatched treatment ($\gamma_{11}=–2.10, t=–1.38, df=74, p=0.58, d=0.32$). Similarly, treatment matching did not produce greater change in scores on the Modified Scale for Suicidal Ideation compared to mismatched treatment ($\gamma_{11}=–1.06, t=–0.86, df=74, p=0.39, d=0.20$).

At the end of treatment, the matched condition had a significantly higher proportion of patients who improved ($\chi^2=3.9, df=1, p<0.05, d=0.47$), but there were no significant differences in the proportion whose illness remitted (Figure 2).

**Secondary Hypotheses**

The secondary hypotheses investigated the more specific efficacy of different treatment approaches by comparing the outcome of the patients who received 1) cognitive therapy versus no cognitive therapy (cells 1, 3, 5, 7 versus cells 2, 4, 6, 8) and 2) family therapy versus no family therapy (cells 1, 4, 6, 7 versus cells 2, 3, 5, 8). These comparisons also included the entire group, with each comparison (cognitive therapy versus no cognitive therapy; family therapy versus no family therapy) taking equivalent proportions of each patient subgroup and other types of treatments. We do not report analyses of specific treatment conditions—pharmacotherapy, combined cognitive therapy and pharmacotherapy, etc. Although the data are potentially interesting, these comparisons between individual treatment conditions either 1) are completely confounded with patient grouping and/or 2) are composed of only two of the four patient groups (Figure 1).

**Family therapy.** There were no significant differences in Modified Hamilton Rating Scale for Depression, Beck Depression Inventory, or Modified Scale for Suicidal Ideation scores at discharge between the groups with family therapy and no family therapy. The patients who received family therapy had a significantly lower proportion who were treatment failures ($\chi^2=5.8, df=1, p<0.05, d=0.57$) than those who did not. But the two groups did not differ in the proportion who were dropouts.

Linear change in Modified Hamilton Rating Scale for Depression scores was significantly greater for family therapy than for no family therapy ($\gamma_{11}=–2.19, t=–2.05, df=74, p=0.04, d=0.48$). Family therapy also produced a significantly greater decrease in scores on the Modified Scale for Suicidal Ideation across time compared to no family therapy ($\gamma_{11}=–2.70, t=–2.36, df=74, p=0.02, d=0.55$). However, inclusion of family therapy produced only a nonsignificant tendency for change in Beck Depression Inventory scores ($\gamma_{11}=–2.58, t=–1.71, df=74, p=0.09, d=0.40$).

At the end of treatment, the patients receiving family therapy had significantly higher proportions of patients who improved ($\chi^2=10.1, df=1, p<0.01, d=0.78$) and showed a nonsignificant tendency to have higher proportions whose illness remitted ($\chi^2=2.7, df=1, p=0.10, d=0.38$) (Figure 2).

**Cognitive therapy.** There were no significant differences in Modified Hamilton Rating Scale for Depression, Beck Depression Inventory, or Modified Scale for Suicidal Ideation scores at discharge between groups with and without cognitive therapy. The patients receiving cognitive therapy had significantly fewer members who were treatment failures than the patients who did not receive cognitive therapy ($\chi^2=7.5, df=1, p<0.05, d=0.66$). There were no significant differences in proportions of dropouts. Hierarchical linear modeling analyses indicated no significant differences between cognitive and noncognitive treatments on scores on the Modified Hamilton Rating Scale for Depression, the Beck Depression Inventory, and the Modified Scale for Suicidal Ideation. Similarly, there were no significant differences in the proportion of patients who improved or whose illness remitted (Figure 2).

**Discussion**

Our study found inconsistent evidence for the effects of matching patients to type of treatment. Although the matching procedure did result in a higher proportion of patients who improved and a faster decrease in interviewer-rated depression scores, we found no differences in self-reported depression, suicidal ideation, or the percentage of patients whose illness remitted. Thus, matching patients to treatments on the basis of their types of deficits produced a moderate gain in overall treatment efficacy.

Further analyses indicated that the patients who received additional family therapy had significantly better outcomes than those who did not. The patients receiving family therapy had a significantly faster decrease in depressive symptoms and suicidal ideation, significantly higher rates of improvement, a nonsignificant tendency toward lower self-reported depression, and a greater proportion of patients whose illness remitted. This overall pattern of results suggests that adding family therapy to pharmacotherapy substantially improves the outcome of severely depressed patients. These results mirror studies of other major psychiatric disorders (bipolar disorder, schizophrenia) that also have found evidence for significant benefits of additional family therapy (25–27). They are also congruent with previous studies suggesting that family or marital treatments may be effective as standalone treatments for depression (5–7). It is particularly noteworthy that the results of this study were obtained with relatively few family therapy sessions (mean=5). Thus, our results suggest that inclusion of a brief family therapy intervention as part of a treatment package for severely depressed patients may have significant benefits.

Our results do not provide strong support for the efficacy of the addition of individual cognitive therapy. Although the patients receiving additional cognitive therapy
did have lower rates of treatment failures (the patients were removed because of suicide risk), we found less support for the efficacy of additional cognitive therapy in producing better depression outcomes. These results are contrary to previous research (including our own studies) that has suggested that combined pharmacotherapy plus individual cognitive therapy is more effective than pharmacotherapy alone for severely depressed patients (28–30).

There are several possibilities why the addition of cognitive therapy was not efficacious in this study. First, in one of our previous studies (29), cognitive therapy began while the patients were in the hospital, and the patients received an average of 10 inpatient sessions. With changes in the health care system, the hospital stay was reduced to the extent that beginning therapy in the hospital was not logistically feasible. It is possible that beginning cognitive therapy while in the hospital is more beneficial than delaying initiation until discharge.

Second, despite the fact that our protocol specified 20–24 sessions of cognitive therapy, the actual mean number of therapy sessions received was substantially fewer (mean=13) than in both our previous study and in usual cognitive therapy protocols. The major reason for this reduced number of sessions was patient compliance. A substantial proportion of the patients assigned to cognitive therapy missed a number of scheduled sessions. As noted previously, because of the typical history of treatment noncompliance, we did not remove patients for noncompliance, except under extreme circumstances. Thus, the patients assigned to the cognitive therapy condition were not removed from treatment if they attended a minimal number of sessions and/or were compliant with other assigned treatments. It may be that the reduced number of cognitive therapy sessions adversely affected treatment efficacy. However, although the correlation between the number of cognitive therapy sessions and Modified Hamilton Rating Scale for Depression scores at the end of treatment was significant (r=0.45, p<0.05), these correlations were positive, suggesting that a greater number of cognitive therapy sessions was associated with a greater level of depressive symptoms. Although a complete analysis and description of these effects are beyond the scope of the current article, it appears as if the patients who were doing relatively well choose not to attend as many therapy sessions.

In summary, although the matching hypotheses of the study received modest support, the secondary analyses strongly suggested that a treatment approach that includes family therapy was more efficacious than one that did not. These results emphasize the importance of operationalizing the biopsychosocial model when providing treatment to this severely impaired population of depressed patients.

References

Depressive Symptoms and 24-Hour Urinary Norepinephrine Excretion Levels in Patients With Coronary Disease: Findings From the Heart and Soul Study

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Objective: Depressive symptoms are associated with an increased risk of cardiac events in patients with heart disease. Elevated catecholamine levels may contribute to this association, but whether depressive symptoms are associated with catecholamine levels in patients with heart disease is unknown.

Method: The authors examined the association between depressive symptoms (defined by a Patient Health Questionnaire score ≥ 10) and 24-hour urinary norepinephrine, epinephrine, and dopamine excretion levels in 598 subjects with coronary disease.

Results: A total of 106 participants (18%) had depressive symptoms. Participants with depressive symptoms had greater mean norepinephrine excretion levels than those without depressive symptoms (65 µg/day versus 59 µg/day, with adjustment for age, sex, body mass index, smoking, urinary creatinine levels, comorbid illnesses, medication use, and cardiac function). In logistic regression analyses, participants with depressive symptoms were more likely than those without depressive symptoms to have norepinephrine excretion levels in the highest quartile and above the normal range. Depressive symptoms were not associated with dopamine or epinephrine excretion levels.

Conclusions: In patients with coronary disease, depressive symptoms are associated with elevated norepinephrine excretion levels. Future longitudinal studies are needed to determine whether elevations in norepinephrine contribute to adverse cardiac outcomes in patients with depressive symptoms.

(Cor)onary disease and major depression are the two leading causes of disability worldwide (1). Depressive symptoms occur in about 20% of patients with coronary disease (2, 3) and are associated with an increased risk of future cardiac events and mortality (4–7). However, the mechanisms linking depressive symptoms with subsequent cardiac events are unknown (8).

Enhanced activity of the sympathetic nervous system with increased concentrations of catecholamines has been proposed as one possible mechanism by which depressive symptoms may increase morbidity and mortality (7–9). This hypothesis is based on evidence suggesting that depressed patients without heart disease have elevated catecholamine levels (10–12). Previous studies have also found alterations of the sympathetic nervous system in depressed patients with coronary heart disease, including increased heart rate (13) and decreased heart rate variability (14). High catecholamine levels can damage cardiac myocytes (15, 16) and have been associated with cardiac events and mortality in a variety of clinical and population-based samples (17–22). Thus, altered autonomic tone may contribute to adverse cardiac outcomes in patients with depression.

The Heart and Soul Study is an ongoing prospective cohort study of psychosocial factors and health outcomes in patients with coronary disease (3). We examined the association of depressive symptoms with 24-hour levels of urinary norepinephrine, epinephrine, and dopamine excretion at baseline. We hypothesized that depressive symptoms would be associated with increased levels of excretion of urinary catecholamines.

Method

Participants

Details regarding our recruitment procedures have been published previously (3). In brief, we used administrative databases to identify outpatients with documented coronary disease at two Veterans Affairs (VA) Medical Centers (the San Francisco VA Medical Center and the VA Palo Alto Health Care System, California), one university medical center (the University of California, San Francisco), and nine public health clinics in the Community Health Network of San Francisco. The patients were eligible to participate if they had at least one of the following: a history of myocardial infarction, angiographic evidence of ≥50% stenosis in one or more coronary vessels, prior evidence of exercise-induced ischemia by treadmill or nuclear testing, a history of coronary revascularization, or a diagnosis of coronary disease by an internist.
or cardiologist (based on a positive angiogram or an exercise treadmill test >98% of the cases). The subjects received a nominal reimbursement for their participation.

Between September 2000 and December 2002, a total of 1,024 participants enrolled and completed a day-long study appointment at the San Francisco VA Medical Center. Of these, we evaluated the association between depressive symptoms and 24-hour urinary catecholamine excretion levels in the participants whose urine collection we verified as having been refrigerated during the 24-hour collection. Refrigeration is important for the preservation of catecholamines. Although all participants were instructed to refrigerate their urine, we verified urine refrigeration for only the last 630 study participants. Of these 630 subjects, we further excluded 24 participants whose 24-hour urine collections were deemed inadequate (because of incomplete collection), seven participants with low urine volumes (<500 ml), and one participant with pheochromocytoma, leaving 598 participants for the analysis. Our protocol was approved by the appropriate institutional review boards, and all participants provided written informed consent.

**Depressive Symptoms**

We measured depressive symptoms by using the 9-item Patient Health Questionnaire (20), a self-report checklist of depressive symptoms derived from the well-validated Primary Care Evaluation of Mental Disorders interview (23). When compared with a structured psychiatric interview by mental health professionals as a criterion standard, a score on the Patient Health Questionnaire ≥10 has been reported to be 88% sensitive and 80% specific for major depression (24). We used this standard cutoff point of ≥10 to define depressive symptoms. We also categorized scores on this scale as representing none to minimal depressive symptoms (Patient Health Questionnaire score=0–3), mild to moderate depressive symptoms (score=4–9), and symptoms consistent with major depression (score ≥10). The participants found to have high levels of depressive symptoms were informed that they may be suffering from depression, were instructed to discuss these symptoms with their primary care provider, and were provided a list of local resources available for further evaluation and treatment.

**24-Hour Urinary Catecholamine Measures**

To ensure urine collection during a typical day under typical circumstances, the participants were asked to collect urine in their home environments. They were instructed to collect all urine for 24 hours between the end of their study appointment and the time when a researcher visited their house the next day and to keep the urine collection jugs refrigerated at all times. In our pilot testing, we found that this procedure was more likely to yield complete 24-hour collections than asking participants to start their 24-hour collection at 8 a.m. the next day. No preservatives were added to the urine jugs.

The subjects were instructed to void immediately before leaving the study appointment and beginning the urine collection. Research personnel arrived at the patients’ homes exactly 24 hours after their study appointments ended to ensure accurately timed specimens and to enhance compliance with the protocol, including verifying that the urine jugs were stored in the refrigerator. If more than 1 hour had passed since the participants’ last void, the subjects were asked to void again to complete the collection.

All participants were asked whether they were able to collect all urine or if some fraction had been inadvertently discarded. If the sample was reported to be incomplete, if it was not refrigerated throughout the procedure, or if the volume was less than 1 liter, the subjects were asked to repeat the collection, and research personnel returned 24 hours later to recollect the urine. Similarly, if the 3-liter collection jugs were completely full, the subjects were given two new jugs and asked to repeat the collection to ensure that no urine had been inadvertently discarded. If the subjects were unable to collect all urine for any reason or had urinary incontinence, their samples were deemed inadequate, and no urinary catecholamine data were recorded for these subjects.

Urinary catecholamine excretion levels (norepinephrine, epinephrine, and dopamine) were measured with gas chromatography-mass spectrometry at the Associated Regional and University Pathologists laboratories, with headquarters in Salt Lake City (25). The normal reference range for these assays is 60–440 µg/day for dopamine, 0–25 µg/day for epinephrine, and 0–100 µg/day for norepinephrine. Because the detection limit was 1.0 µg/dl, catecholamine levels for the participants whose excretion level was below this detection limit were coded as 1.0 µg/dl. To ensure adequate sampling, we measured urinary creatinine levels in parallel and included only the participants who had a urinary creatinine value within the normal range (0.8–2.1 g/day).

**Potential Confounding Variables**

Self-reported age, gender, medical history (with a checklist of 30 common medical disorders), smoking, and alcohol use were determined by questionnaire. Body mass index was calculated as weight in kilograms divided by the square of height in meters, and obesity was defined as a body mass index ≥30 kg/m² (26). To assess physical activity, we asked the participants, “Which of the following statements best describes how physically active you have been during the last month?” Those who answered fairly, quite, very, or extremely active (versus not at all or a little active) were considered physically active. The participants received written instructions and were reminded by telephone the night before their appointments to bring their medication bottles to the study appointments, and study personnel carefully recorded all current medications.

We assessed cardiac function by using a resting ECG for the measurement of left ventricular ejection fraction, an exercise treadmill test for the measurement of exercise capacity, and a stress ECG for the assessment of ischemia. We measured resting blood pressure with a standard sphygmomanometer and performed a symptom-limited, graded exercise treadmill test according to standard Bruce protocol. We defined exercise capacity as the total number of metabolic equivalents and calculated the wall motion score index at the peak of exercise as our measure of ischemia (27).

**Statistical Analysis**

The goal of this study was to examine the association between depressive symptoms and 24-hour urinary catecholamine excretion levels in patients with coronary heart disease. Differences in characteristics between participants with and without depressive symptoms were compared by using t tests (or a nonparametric equivalent) for continuous variables and chi-square tests for dichotomous variables. Analysis of covariance was used to compare mean levels of catecholamine excretion in participants with and without depressive symptoms.

To determine the unadjusted and adjusted associations between depressive symptoms and catecholamine levels, we used logistic regression analyses with depressive symptoms (Patient Health Questionnaire score ≥10) as the predictor variable. Our dichotomous outcome variables were 1) highest quartile of catecholamine levels and 2) catecholamine value above the normal range. To obtain adjusted risk estimates, we entered all variables from Table 1 into a backward-elimination logistic regression model, with depressive symptoms forced into the model. The variables that were associated with elevated levels of catecholamine excretion at p<0.15 were retained in the models so as not to miss any associations between potentially confounding variables and the variables of interest. The likelihood ratio test was used to assess the fit of the model and to determine if additional variables should be dropped from the models. We also tested for interactions between depressive symptoms and all other variables that
were associated with elevated levels of catecholamine excretion. The analyses were performed with Statistical Analysis Software, version 8 (SAS Institute, Cary, N.C.).

**Results**

Of the 598 participants, 106 (18%) had depressive symptoms (Patient Health Questionnaire score ≥10). Compared with the participants who did not have depressive symptoms, those with depressive symptoms were younger, more likely to be female, and more likely to have hypertension, diabetes, or congestive heart failure (Table 1). The participants with depressive symptoms were more likely to be using antidepressant medications, to have a lower exercise capacity, and to smoke. There was no difference in 24-hour levels of urine creatinine excretion between the participants with and without depressive symptoms. The proportion with depressive symptoms was similar to the Heart and Soul Study participants who were included or excluded from the analysis (18% versus 19%) ($\chi^2=0.28$, df=1, p=0.74).

**Mean Levels of Catecholamine Excretion**

The participants with depressive symptoms had greater 24-hour levels of urinary free norepinephrine excretion than the patients without depressive symptoms (Table 2). This difference in levels of norepinephrine excretion persisted after we adjusted for age, sex, body mass index, smoking, urinary creatinine level, comorbid illnesses, medication use, physical activity, and cardiac function (Table 2). We observed no interactions between depressive symptoms and the other variables that entered the model (all p values for interaction >0.05). The participants with depressive symptoms also had greater levels of dopamine excretion than those who did not have depressive symptoms, but this difference did not persist after adjustment for age, sex, body mass index, smoking, urinary creatinine level, comorbid illnesses, medication use, physical activity, and cardiac function. We did not observe an association between depressive symptoms and epinephrine levels (Table 2).

### Table 1. Demographic and Clinical Characteristics of Patients With Coronary Heart Disease by the Presence of Depressive Symptoms

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients With Depressive Symptoms (N=106)</th>
<th>Patients Without Depressive Symptoms (N=492)</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62</td>
<td>10</td>
<td>67</td>
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<tr>
<td>Cardiac function</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Wall motion score index</td>
<td>1.2</td>
<td>0.4</td>
<td>1.2</td>
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<tr>
<td>Exercise capacity (metabolic equivalents)</td>
<td>6.8</td>
<td>3.6</td>
<td>8.0</td>
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<tr>
<td>Ventricular ejection fraction (%)</td>
<td>61</td>
<td>11</td>
<td>62</td>
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<tr>
<td>Resting heart rate (bpm)</td>
<td>67.3</td>
<td>13.5</td>
<td>68.3</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>29</td>
<td>6</td>
<td>28</td>
</tr>
<tr>
<td>Urine creatinine level (mg/day)</td>
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<td>321</td>
<td>1350</td>
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<tr>
<td>Male sex</td>
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<tr>
<td>White ethnicity</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Diabetes</td>
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<td>128</td>
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<tr>
<td>Myocardial infarction</td>
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<td>58</td>
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<tr>
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<tr>
<td>Medication use</td>
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<tr>
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<td>Selective serotonin reuptake inhibitors</td>
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<tr>
<td>Tricyclics</td>
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<td>8</td>
<td>17</td>
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<tr>
<td>Other antidepressants</td>
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<tr>
<td>Angiotensin receptor blockers</td>
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<tr>
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<td>Antiarrhythmics</td>
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<td>Hypoglycemic agents</td>
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<tr>
<td>Antiparkinsonian agents</td>
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<td>5</td>
<td>11</td>
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<tr>
<td>Anorexiants/stimulants</td>
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<td>0.9</td>
<td>1</td>
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<td>85</td>
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<tr>
<td>Physically activeb</td>
<td>47</td>
<td>44</td>
<td>337</td>
</tr>
<tr>
<td>Regular alcohol use</td>
<td>26</td>
<td>25</td>
<td>142</td>
</tr>
</tbody>
</table>

*Patient Health Questionnaire score ≥10.
*See Methods section.
Depressive symptoms were not associated with elevated levels of epinephrine or dopamine excretion. However, depressive symptoms were strongly associated with elevated levels of norepinephrine excretion. Among the participants with depressive symptoms, 32% (34 of 106) had a norepinephrine excretion level in the highest quartile (>65 µg/day), compared with 23% (112 of 492) of the participants who did not have depressive symptoms (odds ratio = 1.6, 95% confidence interval [CI] = 1.0–2.5, p = 0.04). This association remained after we controlled for comorbid illnesses, medication use, cardiac function, physical activity, and urinary creatinine level (adjusted odds ratio = 1.6, 95% CI = 1.0–2.7, p = 0.06), although the confidence interval overlapped one. There were no interactions between depressive symptoms and other predictors of elevated levels of norepinephrine excretion (all p values for interaction > 0.05).

Abnormal Levels of Catecholamine Excretion

Depressive symptoms were not associated with abnormal levels of epinephrine or dopamine excretion. However, 9.4% (10 of 106) of the participants with depressive symptoms had a norepinephrine value above the normal range (>100 µg/day), compared with 3.3% (16 of 492) of the participants who did not have depressive symptoms (odds ratio = 3.1, 95% CI = 1.4–7.0, p = 0.007) (Figure 1). Again, this association persisted after adjustment for comorbid illness, medication use, physical activity, and urinary creatinine level (adjusted odds ratio = 2.9, 95% CI = 1.2–6.9, p = 0.02).

Norepinephrine and Cardiac Function

Norepinephrine excretion level (entered either as the highest quartile (>65 µg/day), compared with 23% (112 of 492) of the participants who did not have depressive symptoms (odds ratio = 1.6, 95% confidence interval [CI] = 1.0–2.5, p = 0.04). This association remained after we controlled for comorbid illnesses, medication use, cardiac function, physical activity, and urinary creatinine level (adjusted odds ratio = 1.6, 95% CI = 1.0–2.7, p = 0.06), although the confidence interval overlapped one. There were no interactions between depressive symptoms and other predictors of elevated levels of norepinephrine excretion (all p values for interaction > 0.05).

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Norepinephrine and Cardiac Function

Norepinephrine excretion level (entered either as the highest quartile or as a continuous variable) was not associated with systolic blood pressure, diastolic blood pressure, diabetes, congestive heart failure, exercise capacity, or ischemia. Likewise, the highest quartile level of norepinephrine was not associated with left ventricular ejection fraction. However, when entered as a continuous variable, each standard deviation increase in norepinephrine level (25 µg/day) was associated with a 1% decrease in left ventricular ejection fraction (parameter estimate = −0.04, SE=...
Discussion

We found that depressive symptoms were associated with elevated levels of norepinephrine excretion in 598 subjects with coronary heart disease. The participants with depressive symptoms were more likely than those without to have increased levels of 24-hour mean norepinephrine excretion, to have norepinephrine excretion levels in the highest quartile, and to have norepinephrine excretion levels above the normal range. The presence of depressive symptoms was not associated with 24-hour urinary epinephrine or dopamine levels.

Because a high norepinephrine level is an established risk factor for cardiac events and mortality (17–22), our findings suggest that elevated norepinephrine may contribute to the increased risk of cardiac events associated with depressive symptoms (7). It is well known that norepinephrine is increased in patients with heart failure, correlates with the severity of heart failure, and is associated with increased mortality in cardiac patients (28). In our sample, a high level of norepinephrine excretion was associated with the lower left ventricular ejection fraction. These adverse effects of norepinephrine levels have been shown not only in patients with heart failure (21, 28, 29) but also in population-based samples of apparently healthy elderly subjects (20, 22), in asymptomatic patients without clinically relevant heart failure (18), in patients with end-stage renal disease without heart failure (19), and in patients with tachyarrhythmias without heart failure (17, 30). These findings argue for a more causative role of norepinephrine in increasing the risk for cardiac events and mortality. Possible mechanisms include direct toxic effects of norepinephrine on cardiocytes (16, 31), its ability to trigger tachyarrhythmia (17, 30), and its role in the promotion of platelet aggregation and platelet thrombi formation (18).

To our knowledge, only one previous study has examined the association between depressive symptoms and norepinephrine levels in patients with coronary heart disease (13). Carney et al. (13) measured plasma norepinephrine levels in 50 depressed and 39 nondepressed subjects with coronary heart disease but did not find an association between depressive symptoms and plasma norepinephrine levels. Unlike our study, their measurement of norepinephrine was based on a series of plasma norepinephrine levels at baseline and at three time points within 10 minutes after orthostatic challenge. It is possible that integrated 24-hour urinary measurement of norepinephrine is a more sensitive measure for the detection of differences in norepinephrine levels.

The causal direction between depressive symptoms and norepinephrine levels cannot be determined by our cross-sectional study. However, a plausible mechanism linking depressive symptoms with increased sympathetic activity is the enhanced activity of hypothalamic and extrahypothalamic corticotropin-releasing factor (CRF) in depressed patients. It is well established that CRF is increased in medically healthy patients with depressive symptoms (10, 32), leading to increased cortisol levels (33–35). Moreover, a large body of evidence suggests that both hypothalamic and extrahypothalamic CRF activate the locus ceruleus in the brain, leading to an increase in norepinephrine (36–39).

Accordingly, earlier studies have found that depressed patients who were cortisol nonsuppressors after receiving dexamethasone had higher norepinephrine levels. Moreover, administration of a CRF antagonist led to a diminished norepinephrine response to stress in primates (40). Thus, high CRF activity may simultaneously lead to elevated cortisol and norepinephrine levels (41). Moreover, levels of CSF norepinephrine and plasma cortisol were increased and highly correlated in depressed patients, which is also consistent with the increased CRF activity causing these alterations (11). In turn, norepinephrine enhances forebrain CRF activity, possibly closing a feed-forward loop leading to higher activity of both norepinephrine and CRF in depressed patients (37). Indeed, in this study group, we also found increased cortisol levels in depressed patients (42), consistent with this model of norepinephrine-CRF interaction (10).

We did not find an association between depressive symptoms and epinephrine or dopamine levels in this group, which is in accordance with an earlier study that also found increased norepinephrine but similar epinephrine levels in depressed patients (12). This might suggest that depressive symptoms are more closely related to increased sympathetic nervous system activity, as reflected in increased norepinephrine levels compared with the adrenomedullary system and reflected levels of epinephrine excretion. Indeed, it has been shown that there is a differential response of the sympathetic nervous and adrenomedullary hormonal systems, depending on the type and severity of a stressor (43).

Several limitations should be considered in interpreting the results of our study. Only 58% (598 of 1,024) of the Heart and Soul Study participants were included in this analysis. However, the prevalence of depressive symptoms was similar in the participants who were included or excluded from the analysis. Although we made every effort to systematically assess medication use and to ensure complete urine collection, our results were limited by self-reported medication use and compliance with the urine collection procedure. Only 17% of our participants were women, thereby reducing our power to detect interactions by gender and limiting the generalizability of our results. Finally, most of the catecholamine values in our group were within the normal range, and their clinical significance is unclear. However, the Heart and Soul Study is an...
ongoing prospective study that will follow patients to determine whether greater norepinephrine levels at baseline contribute to the association of depressive symptoms with worse outcomes in patients with coronary heart disease.

In summary, we found that depressive symptoms are associated with elevated levels of norepinephrine excretion but not with epinephrine or dopamine excretion levels in medical outpatients with heart disease. Increased levels of norepinephrine excretion may contribute to an increased risk of future cardiac events in patients with depressive symptoms.

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References


Objective: This study estimated the proportion of patients attending an urban general medical practice with current major depression and a history of bipolar disorder and compared the history, presentation, and treatment of patients with unipolar and bipolar depression.

Method: A group of 1,143 patients was assessed with measures of past and current mental health and treatment. Patients were partitioned into bipolar and unipolar groups based on a predefined cutoff on the Mood Disorder Questionnaire. The groups were compared on sociodemographic characteristics, depressive symptoms, comorbid mental disorders, and mental health treatment.

Results: Approximately one-quarter of the patients with major depression had lifetime bipolar depression. Patients with unipolar and bipolar depression did not significantly differ on background or health characteristics. Patients with bipolar depression were significantly more likely to report hallucinations, current suicidal ideation, and low self-esteem than patients with unipolar depression but less likely to report disturbed appetite. Patients with bipolar depression were significantly more likely to have an alcohol use disorder and to report inpatient psychiatric care and antipsychotic treatment during the past month than patients with unipolar depression. Nearly one-half of the patients with bipolar depression had taken an antidepressant in the last month, but most were not also being treated with an antipsychotic or mood stabilizer.

Conclusions: Bipolar depression is common in urban general medicine practice. When patients took antidepressants, they seldom received concurrent antimanic medications. Because of the risks of treating bipolar disorder with antidepressant monotherapy, physicians should assess their depressed patients for mania before prescribing antidepressants.
have bipolar depression, defined as current major depression and a positive screen for a lifetime history of bipolar disorder, tended to appear with different symptoms or impairments than those with unipolar depression. If patients with bipolar and unipolar depression have different clinical presentations, this information could be used to alert primary care physicians to the need for referral to a psychiatrist before they initiate pharmacological treatment. We also evaluated the extent to which patients with bipolar depression from the practice under study were treated with antidepressant medications without antipsychotic medications or mood stabilizers.

Method

The study was conducted at the Associates in Internal Medicine practice of New York–Presbyterian Hospital (Columbia University Medical Center). Associates in Internal Medicine is the faculty and resident group practice of the Division of General Medicine at the College of Physicians and Surgeons of Columbia University. Associates in Internal Medicine provides primary care to approximately 18,000 adult patients from the surrounding northern Manhattan community each year.

The institutional review boards of Columbia Presbyterian Medical Center and the New York State Psychiatric Institute approved the study protocol, including the Spanish translation of data forms. All participants provided informed consent.

Participant Recruitment

A systematically selected group of consecutive adult patients seeking primary care at the Associates in Internal Medicine practice were invited to participate. The patients were approached to determine eligibility based on the seat they freely selected in the waiting rooms. Eligible patients were ages 18 to 70 years, had made at least one prior visit to the practice, could speak and understand Spanish or English, and were waiting for scheduled face-to-face contact with their primary care physician. Patients were excluded from the study if their current health status prohibited completion of the survey forms.

Because one aim of the study was to examine clinical detection and management of primary care patients with bipolar depression, we sought to limit the group to returning patients because these patients were likely to be better known to the primary care physicians than patients making their first clinic visit. There was also a concern that because of the substantial patient burden of the routine clinical intake procedures, patient fatigue during the first visit might compromise the quality of the research assessment.

The study focused on patients scheduled to see their primary care physician. We excluded the substantial number of waiting room patients who were scheduled to see other health care professionals. Examples of such patients included patients treated with oral anticoagulation therapy who were scheduled for prothrombin time measurements, patients scheduled to see nurse practitioners for routine Pap smears, and patients of a memory disorders clinic, a podiatry clinic, and other subspecialty clinics that share waiting rooms with the primary care practice.

A total of 3,807 patients were approached, 169 of whom (4.4%) refused solicitation. Of the 3,638 who were prescreened, 2,291 (63.0%) were ineligible to participate. Inclusion criteria most frequently unmet were 1) not being scheduled for face-to-face contact with a primary care physician (56.5%), 2) not being between 18 and 70 years old (33.5%), and 3) not having made a previous visit to the practice (16.7%). Less commonly, patients were excluded because they were unable to complete the survey forms because of poor physical health (3.3%) or cognitive impairment (1.6%). Of the 1,347 who met the eligibility criteria, 1,157 (85.9%) consented to participate, and of these, 1,143 (98.8%) provided sufficient information to be classified with respect to the Mood Disorder Questionnaire, a brief self-report assessment of lifetime bipolar disorder (20).

Sociodemographic and Clinical Assessment

The survey forms were translated from English to Spanish and back-translated by a bilingual team of mental health professionals. All participants completed a sociodemographic history form to assess age, sex, race/ethnicity, marital status, educational achievement, and annual household income. The participants also completed the Mood Disorder Questionnaire, a 15-item self-report assessment of lifetime bipolar disorder based on DSM-IV criteria (20). The standard Mood Disorder Questionnaire scoring for bipolar disorder requires endorsement of ≥ 7 total lifetime manic symptoms with two or more co-occurring symptoms resulting in moderate or serious functional impairment (20, 21). At this cutoff point, the Mood Disorder Questionnaire was reported to have a sensitivity of 0.281 and a specificity of 0.972 in a community sample (20) and a sensitivity of 0.73 and a specificity of 0.90 in an outpatient psychiatric sample (21) with a Structured Clinical Interview for DSM-IV (SCID) (22) diagnosis of bipolar I and bipolar II disorders as the criterion standard. In the current analysis, the participants who met or exceeded the standard Mood Disorder Questionnaire scoring algorithm were considered to have screened positive for a lifetime history of bipolar disorder.

The DSM-IV Primary Care Evaluation of Mental Disorders (PRIME-MD) Patient Health Questionnaire (23) was used to assess current symptoms of major depression, panic disorder, general anxiety disorder, and past-year alcohol use disorder. Drug use disorders were assessed with a module patterned after the PRIME-MD alcohol use disorder module.

Health functioning was evaluated with the physical and mental health component summary scores of the Medical Outcomes Study 12-Item Short-Form Health Survey (24). Impairment was evaluated with the 10-point self-rated social life and family life/home responsibilities subscales of the Sheehan Disability Scale (0=none, 1–3=mild, 4–6=moderate, 7–9=marked, 10=extreme) (25). Because only 12.4% of the study patients were gainfully employed, the work subscale of the Sheehan Disability Scale was not used. Items from the psychotic disorders section of the Mini International Neuropsychiatric Interview (26) were administered to assess lifetime and current history of hallucinations.

Self-report information was collected concerning mental health treatment history, including lifetime hospitalization for psychiatric care and past-month use of antidepressant, antianxiety, and antipsychotic medications.

Analytic Strategy

The patients with current DSM-IV/PRIME-MD major depressive disorder were first partitioned on the basis of Mood Disorder Questionnaire screening status into those with unipolar (negative screening on the Mood Disorder Questionnaire) and bipolar (positive screening on the Mood Disorder Questionnaire) depression. These two patient groups were compared with respect to sociodemographic characteristics, depressive symptoms, comorbid mental disorders and symptoms, health functioning, and mental health treatment, including use of antidepressant, antipsychotic, and antianxiety medications. Comparisons between patient groups on categorical variables were made with the chi-square test, except when the expected count fell below 5 in at least 20% of the cells, in which case, Fisher’s exact test was used. Student’s t test was used for comparisons involving continuous variables. The alpha was set at 0.05 (two-tailed).
BIPOLAR DEPRESSION AND LOW INCOME

Results

Sociodemographic Characteristics

In the study sample (N=1,143), the prevalence of unipolar depression was 15.1% (N=173), and the prevalence of bipolar depression was 4.6% (N=53). Both groups were predominantly women, Hispanic, not married or cohabiting, had received less than a high school education, and had a total family income of less than $12,000 per year. There were no significant group differences in age, sex, race/ethnicity, marital status, educational attainment, or household income (Table 1). In addition, 23.5% (N=53) of the patients with current major depression were classified as having bipolar depression, and 76.5% (N=173) were classified as having unipolar depression.

Psychiatric Symptoms and Mental Disorders

The study groups were compared with respect to the frequency of current depressive symptoms, defined as occurring on one-half or more of the days during the past 2 weeks, and for suicidal ideation on any days during the past 2 weeks. Compared with the patients with unipolar depression, the patients with bipolar depression were significantly more likely to report low self-esteem and suicidal ideation but were less likely to report an appetite disturbance (Table 2).

Comorbid generalized anxiety disorder occurred in more than one-third of each group. In addition, the patients with bipolar depression were significantly more likely than their counterparts with unipolar disorder to meet criteria for current alcohol use disorder and to report a lifetime history of auditory or visual hallucinations (Table 2).

Health Functioning

A substantial majority of the patients with bipolar and unipolar depression reported that their current general health and mental health were fair or poor rather than good, very good, or excellent. There were no significant group differences on the two-factor Sheehan Disability Scale score or on the physical or mental health components of the Medical Outcomes Study 12-Item Short-Form Health Survey (Table 2). For both groups, the Medical Outcomes Study 12-Item Short-Form Health Survey scores reflected substantially lower health-related quality of life than general community samples (27).

Mental Health Care

Roughly one-half of the patients with bipolar depression and unipolar depression reported having been given a prescription for a psychotropic medication in the last month. In both groups, antidepressants were the most frequently reported psychotropic medication, followed
by antipsychotic and antimanic medications. During the past month, a significantly greater proportion of bipolar than unipolar patients were treated with an antipsychotic medication (Table 3). However, most of the patients with bipolar depression (N=17, 70.8%) who were treated with antidepressant medications were not concurrently treated with either an antipsychotic or antimanic medication.

The patients with bipolar depression were significantly more likely than the patients with unipolar depression to report a past psychiatric hospitalization (Table 3).

Discussion

In an urban general medicine practice that serves a predominantly low-income immigrant population, approximately one-quarter of the patients with current major depressive disorder screened positive for a lifetime history of bipolar disorder. This represented 4.6% of the participating patients. In a previous study (28), 2.8% of the adult patients in a suburban private family practice center with an anxiety or depressive disorder had a history of bipolar I disorder, and 18.5% had a history of bipolar II disorder.

In the current study, adult outpatients with bipolar depression (a positive screening for current major depression and lifetime for bipolar disorder) were more likely than those with unipolar depression to report suicidal ideation, low self-esteem, a comorbid alcohol use disorder, and a lifetime history of hallucinations and inpatient psychiatric care. Suicidal behavior (29–31), substance use (8), psychotic symptoms (8), and a history of inpatient psychiatric treatment (32) have been previously reported to be common in patients with bipolar disorder. The observed constellation of clinical characteristics in the current study provides construct validity for the Mood Disorder Questionnaire, which was used to screen for lifetime bipolar disorder. However, because each of these characteristics is nonspecific, none could be used to establish a lifetime diagnosis of bipolar depression.

Approximately one-half (49.0%) of the patients with bipolar depression reported recent treatment with an antidepressant medication. Roughly similar rates of use of antidepressant medications among bipolar patients has been reported in a large voluntary registry of adults with bipolar disorder (33) during the month before registration.

### TABLE 2. Clinical Characteristics of Patients With Unipolar or Bipolar Depressiona in an Urban General Medicine Practice

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients With Unipolar Depression (N=173)b</th>
<th>Patients With Bipolar Depression (N=53)c</th>
<th>Analysis (Unipolar Versus Bipolar Depression)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Depressive symptomsd</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anhedonia</td>
<td>152</td>
<td>87.9</td>
<td>43</td>
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<tr>
<td>Depressed mood</td>
<td>164</td>
<td>94.8</td>
<td>51</td>
</tr>
<tr>
<td>Insomnia or hypersomnia</td>
<td>157</td>
<td>91.3</td>
<td>49</td>
</tr>
<tr>
<td>Low energy</td>
<td>156</td>
<td>91.2</td>
<td>46</td>
</tr>
<tr>
<td>Anorexia or overeating</td>
<td>144</td>
<td>83.7</td>
<td>35</td>
</tr>
<tr>
<td>Low self-esteem</td>
<td>120</td>
<td>70.2</td>
<td>44</td>
</tr>
<tr>
<td>Poor concentration</td>
<td>123</td>
<td>71.1</td>
<td>43</td>
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<tr>
<td>Psychomotor agitation or retardation</td>
<td>97</td>
<td>56.1</td>
<td>34</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>21</td>
<td>12.1</td>
<td>16</td>
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<tr>
<td>Comorbid mental disordersd</td>
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<tr>
<td>Panic disorder</td>
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<td>Generalized anxiety disorder</td>
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<tr>
<td>Alcohol use disorder</td>
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<td>Hallucinationsf</td>
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<tr>
<td>Current auditory or visual</td>
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<tr>
<td>Lifetime auditory or visual</td>
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<td>Health functioning</td>
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<tr>
<td>General health is poor or fairg</td>
<td>144</td>
<td>83.7</td>
<td>44</td>
</tr>
<tr>
<td>Emotional health is poor or fairg</td>
<td>142</td>
<td>82.6</td>
<td>41</td>
</tr>
</tbody>
</table>

Mean  SD Mean  SD t  df  p

| Physical component summary score | 36.3| 10.6 | 34.4| 10.5| 1.11 | 219 | 0.27 |
| Mental component summary score   | 33.6| 11.0 | 32.6| 9.5 | 0.59 | 219 | 0.56 |
| Sheehan Disability Scale score   | 10.3| 5.4  | 11.7| 4.8 | 1.46 | 194 | 0.15 |

a Based on patient self-report.
b Number range is 168–173 owing to missing data.
c Number range is 51–53 owing to missing data.
d Based on positive screening on the Primary Care Evaluation of Mental Disorders.
e Fisher's exact test, used when any cell had an expected count <5.
f Based on the Mini International Neuropsychiatric Interview.
g Compared with good, very good, or excellent (self-report).
A major limitation of the current study is the failure to obtain accurate data on the use of mental health services. The study relied on self-report of mental health treatment, which is known to be subject to recall bias and underreporting. Additionally, the study did not include data on the use of mental health services from sources other than the primary care setting, such as specialty clinics or hospital records. This limitation may have resulted in an underestimate of the true prevalence of bipolar depression in the study population.

In an urban general medicine practice, evidence of a lifetime history of bipolar disorder was relatively common among adult patients with current major depressive disorder. Although patients with bipolar depression had some indications of greater illness severity, they did not report significantly more impairment. Because it may be difficult to distinguish patients with bipolar depression from unipolar depression during the routine delivery of primary care, a careful systematic assessment of lifetime manic symptoms is urged before the initiation of antidepressant medications for all patients presenting with a current major depressive episode.

The current study has several limitations. First, the study was conducted in an urban general medical practice that serves a predominantly low-income urban immigrant population, so the findings may not generalize to primary care settings that serve other socioeconomic populations. Second, the study excluded several patient groups that may limit the generalizability of the findings and introduce selection biases into the estimated prevalence and clinical characteristics of bipolar depression in this clinic. Because patients over 70 years of age were excluded, the results cannot be safely extended to older adult primary care patients. Systematically excluding patients not scheduled to see their primary care physician and patients there for their first visits may have further biased the study results. If, for example, patients with bipolar disorder were overrepresented among patients having their first visit because of disorder-related interruptions in continuity of care, this exclusion would reduce the estimated prevalence of bipolar depression. Third, the lifetime bipolar disorder screening was based on self-reports of past symptoms rather than expert-administered diagnostic interviews of current and past symptoms that would have likely yielded more accurate clinical information. Fourth, it is not possible with the administered instruments to distinguish bipolar I from bipolar II depression. Finally, the mental health treatment data were based on self-reports rather than administrative or pharmacy records that would likely have provided a more accurate representation of the actual use of mental health services.
References


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OLFSON, DAS, GAMEROFF, ET AL.
A 20-Month, Double-Blind, Maintenance Trial of Lithium Versus Divalproex in Rapid-Cycling Bipolar Disorder

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Objective: The authors tested the hypothesis that divalproex would be more effective than lithium in the long-term management of patients with recently stabilized rapid-cycling bipolar disorder.

Method: A 20-month, double-blind, parallel-group comparison was carried out in recently hypomanic/manic patients who had experienced a persistent bimodal response to combined treatment with lithium and divalproex. Sixty patients were randomly assigned to lithium or divalproex monotherapy in a balanced design after stratification for illness type (bipolar I versus bipolar II disorder).

Results: Of the 254 patients enrolled in the open-label acute stabilization phase, 76% discontinued the study prematurely (poor adherence: 28%; nonresponse: 26% [of whom 74% remained depressed and 26% remained in a hypomanic/ manic/mixed episode], intolerable side effects: 19%). Of the 60 patients (24%) randomly assigned to double-blind maintenance monotherapy, 53% relapsed (39% into depression and 41% into a hypomanic/ manic/mixed episode), 22% completed the study, 10% had intolerable side effects, and 10% were poorly adherent. The rates of relapse into any mood episode for those given lithium versus divalproex were 56% and 50%, respectively; the rates were 34% and 29% for a depressive relapse and 19% and 22% for a hypomania/mania relapse. There were no significant differences in time to relapse. The proportion discontinuing prematurely because of side effects was 16% for lithium and 4% for divalproex.

Conclusions: The hypothesis that divalproex is more effective than lithium in the long-term management of rapid-cycling bipolar disorder is not supported by these data. Preliminary data suggest highly recurrent refractory depression may be the hallmark of rapid-cycling bipolar disorder.

The rapid-cycling variant of bipolar disorder has been estimated to occur in 14%–53% of patients (1–5). Its prevalence appears to be as low as 4% in bipolar I disorder and as high as 31% in bipolar II disorder in one study (4). Of these patients, 72%–82% have been reported to exhibit poor response to lithium (1, 2). Thus, a substantial percentage of poor response to lithium has been associated with rapid cycling.

In an attempt to develop alternative treatments for patients with rapid-cycling bipolar disorder, we previously evaluated the spectrum of acute and prophylactic efficacy of divalproex in 131 patients who received divalproex (either in monotherapy or in combination with other psychotropic drugs) in a prospective, naturalistic, 17-month open-label trial. Sixty percent of these patients were either lithium-resistant or intolerant. The data from this preliminary study suggested that divalproex possessed marked acute and prophylactic antimanic efficacy as well as moderate acute and prophylactic antidepressant efficacy in lithium-naive patients as well as those who had previously not responded to adequate trials of lithium (6). We hypothesized that divalproex would be more effective than lithium in the long-term treatment of rapid-cycling bipolar disorder and conducted a random assignment, 20-month, double-blind, parallel-group comparison of divalproex and lithium to test this hypothesis.
propranolol concurrently, experienced intolerable side effects to documented lithium levels of 0.8 meq/liter or valproate levels of 50 µg/ml, were pregnant or planning to become pregnant, were taking exogenous steroids, had met criteria for alcohol or drug abuse or dependence within the preceding 6 months, or were actively suicidal as evidenced by a score ≥3 on that item from the Hamilton Depression Rating Scale (7). After complete description of the study to the subjects, written informed consent was obtained.

Screening
Screening occurred in the 2 weeks preceding the patient’s entry into the open-label phase. Psychiatric and medical histories were obtained, physical examinations including clinical laboratory tests were performed, scores on psychiatric rating scales (including the 24-item Hamilton depression scale, Young Mania Rating Scale [8], and the Global Assessment Scale [GAS] [9]) were obtained, and then a retrospective mood chart was completed over 1–2 months to confirm the existence of four mood episodes in the preceding 12 months (10). Eligible patients were then enrolled in the open-label acute stabilization phase.

Open-Label Acute Stabilization Phase
During this phase, patients were seen by a psychiatrist every 2 weeks and treated with the combination of lithium and divalproex sodium. For patients who had been receiving no medication, lithium carbonate monotherapy was initiated at 300 mg twice daily and titrated over 4–6 weeks to minimum blood levels of 0.8 meq/liter. Divalproex augmentation was then initiated at 250 mg twice daily and then increased over 4–6 weeks to minimum blood levels of 50 µg/ml. If patients were already taking psychotropic medications other than lithium and divalproex, these medications were gradually weaned over 3 months as lithium and divalproex were concurrently initiated and titrated as described above. Patients who had previously been treated with lithium or divalproex were allowed into this study as long as they tolerated the medication regimen and had never previously taken both medications concurrently. If patients were already taking lithium, but not valproate, divalproex was then initiated as described. If patients were already taking divalproex, but not lithium, lithium was then initiated and titrated as described. All psychotropic medications other than lithium and divalproex were discontinued a minimum of 4 weeks before random assignment to a double-blind maintenance monotherapy condition.

At each visit, the same psychiatric evaluations administered at the screening visit were administered, and patients were assessed for adverse events. Beginning at week 12 of the open-label acute stabilization phase, patients who met the criteria for entry into the next treatment phase for a minimum of 4 consecutive weeks were eligible to be randomly assigned to a double-blind maintenance monotherapy condition. Entry criteria were a 24-item Hamilton depression scale score ≤20, Young Mania Rating Scale score ≤12, GAS score ≥51, lithium levels ≥0.8 meq/liter, and valproate levels ≥50 µg/ml. Patients not meeting these criteria after 20 weeks were discontinued from the study.

Patients who did not achieve a score of 20 on the 24-item Hamilton depression scale over 4 consecutive weeks during weeks 12–24 while receiving the combination of lithium and divalproex were classified as having refractory depression. Patients who did not achieve a score of 12 or less on the Young Mania Rating Scale over 4 consecutive weeks during weeks 12–24 while receiving the combination of lithium plus divalproex were classified as having refractory hypomania/mania/mixed state.

Patients who missed a total of two visits during the open-label phase met criteria for lack of adherence and were discontinued from the study. Patients not meeting criteria for entry into the maintenance phase and those meeting refractory criteria were discontinued from the study, given six gratis clinical visits over a 3-month period, and were offered either follow-up care within another research study at the investigating site or routine clinical care.

Double-Blind Maintenance Monotherapy Phase
At the beginning of the maintenance phase, patients were assigned 1:1 to treatment with lithium or divalproex monotherapy after stratification for illness type (bipolar I versus bipolar II disorder). Double-blind, double-substitution methodology was used to transition patients from open-label combination therapy with both medications to double-blind monotherapy. Patients were started on equal numbers of capsules of double-blind active lithium 300-mg capsules and matching (in color, taste, and size) lithium placebo capsules, and equal numbers of double-blind active divalproex capsules of 250-mg capsules and matching divalproex placebo capsules.

Patients randomly assigned to monotherapy had one blinded active capsule replaced with a matching placebo capsule once every 2 weeks for as long as necessary. The process of tapering to monotherapy took place over an average of 6 weeks if patients were taking 1200 mg of lithium or 1500 mg of divalproex—longer if the doses of either were higher and more quickly if the doses of either were lower. After the taper was completed, matching placebo for the drug that was discontinued was discontinued for the rest of the maintenance phase. This slow, gradual process of transitioning patients to monotherapy obscured the progress of the taper until completed. The maintenance phase began at the beginning of the taper, and the survival analysis began at that time as well.

After the taper was completed, the number of capsules of active compound and placebo was unchanged for the rest of the maintenance phase, except for adjustments made to both by the unblinded medical monitor when blood levels decreased to less than 0.8 meq/liter for lithium and 50 µg/ml for valproate. Dosing of the active compound could be decreased if patients were believed to be experiencing dose-related side effects (such as tremors) as long as minimum blood levels were maintained. If this was not possible, patients reached study endpoint due to intolerable side effects.

Trough divalproex and lithium levels were performed bi-monthly during the first 3 months of the maintenance phase and monthly thereafter. Dose adjustments were made according to blood levels. To maintain the blind and the exact number of capsules being administered during the maintenance phase, each change in the dose of the active compound was accompanied by a matching change in the placebo dose. The number of placebo capsules was decreased commensurately if the number of capsules of the active compound was increased, and vice versa for decreases.

Patients were seen by the research psychiatrist every 2 weeks during the first 3 months of the maintenance phase and monthly thereafter for up to 20 months. At each visit, psychiatric evaluations from the screening visit were repeated, and adverse events were assessed. For patients who experienced no mood episodes for a minimum of 6 months, monthly assessments were continued, but they were then allowed to have assessments conducted over the telephone every other month. Patients could receive lorazepam in doses up to 4 mg/day for anxiety, agitation, and insomnia; as an alternative, adjunctive alprazolam in doses up to 2 mg/day was permitted to treat lorazepam nonresponders. Initiation of psychotherapy was not permitted during the maintenance phase, but patients were permitted to continue any ongoing psychotherapy that had begun before study entry.

Time to treatment for a mood episode, i.e., time to treatment for emerging symptoms of a relapse at the discretion of the investigators or time to a full relapse was the primary outcome measure for the study. Patients who met criteria for mania (a total
Young Mania Rating Scale score ≥ 20 for up to 8 weeks) or depression (a 24-item Hamilton depression scale score ≥ 20 for 8 weeks) were considered to have relapsed.

If patients opted for follow-up by the investigators after premature study discontinuation or study completion, they were offered six gratis visits over a 3-month period and then offered routine clinical care or follow-up within another research study at the investigating site. Double-blind study medications were abruptly discontinued and replaced with half the doses of lithium and divalproex prescribed at the end of the open-label acute stabilization phase and then increased to full dosing as tolerated. If patients preferred treatment with the monotherapy provided during the maintenance phase, study medications were continued until an appointment was scheduled with a community psychiatrist who was informed by the unblinded medical monitor of the identity of the medication prescribed during the maintenance phase. Study medications were then abruptly discontinued by the community psychiatrist at the time of this appointment and replaced with the open-label medication the patient was randomly assigned to during the blinded phase of the study.

### Data Analysis

The intent-to-treat population included all patients who were randomly assigned to a study treatment condition. Secondary outcome analyses for the maintenance phase were performed on data from all patients who received at least one dose of study drug and had at least one postbaseline outcome assessment during the maintenance phase. The outcome measures included time to additional pharmacotherapy for emerging mood symptoms or full relapse, time to study discontinuation for any reason, time to relapse into depression, and time to relapse into a hypomanic/manic/mixed episode. Kaplan-Meier methodology was used to plot the survival data, and median survival times were calculated. A log-rank test at an alpha=0.05 level of significance was employed to evaluate differences between survival curves. A Cox regression was performed evaluating the following predictors of outcome: treatment arm assignment, type of bipolar diagnosis (bipolar I or bipolar II), and index episode at study entry.

Prior to study initiation, it was estimated that a minimum of 30 patients per arm would be required to detect a minimum hazard ratio of at least 0.36 at a power of 0.80 and an alpha level of 0.05.
For each study phase, the safety population comprised all patients who received at least one dose of study drug. Safety was assessed by summarizing treatment-emergent adverse experiences and determining changes from the screening visit in clinical laboratory test results, including white blood cell count, platelet count, free thyroxine index, thyroid stimulation hormone, and liver functions tests (ALT and AST).

**Results**

**Patients**

Patients enrolled into this study included more women than men and more with bipolar II disorder than bipolar I (Table 1). Study patients exhibited very severe illness as reflected by the number of mood episodes in the last 12 months, high rates of polypharmacy at the time of study entry, and 93% cycling without full interepisode recoveries (Table 1 and Table 2). Sixty-nine percent had axis I lifetime comorbidity (56% co-occurring substance use disorders), 44% had past psychiatric hospitalizations, 39% had past suicide attempts, 35% had past psychotic symptoms, 34% had past physical abuse, and 30% had past sexual abuse.

Less than half had been previously diagnosed and treated for bipolar disorder, and the majority of the rest had been incorrectly treated for unipolar depression despite the presence of syndromal hypomania or mania. The numbers of years elapsed between onset of symptoms and treatment, including patients diagnosed at study entry for the first time, was 16 years (SD=11.4).

Treatment history is summarized in Table 2. Depending on the phase and treatment groups, 34%–38% of patients had received prior lithium treatment at some point; 37%–46% had been previously treated with divalproex at some point. Demographics, illness characteristics, and treatment history were comparable across treatment groups (Table 1 and Table 2). Predictors of response analyses will be the focus of a separate study.

Of 254 patients enrolled into the open-label acute stabilization phase, 28% exited because of poor adherence, 26% exhibited nonresponse to the combination of lithium plus divalproex and exited because of the need for additional treatment, 19% exited because of adverse events, and 24% completed this phase and were randomly assigned to a double-blind maintenance monotherapy condition for up to 20 months (lithium: N=32, divalproex: N=28). Of the 65 not responding to the combination of lithium and divalproex, 74% exhibited refractory depression, 12% refractory hypomania, 8% refractory mania, and 6% refractory mixed state (Table 3). In addition to lithium and divalproex, other psychiatric medications were prescribed during the initial part of the open-label phase for 59% of all patients and 22% of those who eventually entered the maintenance phase of the study. Medications used by 10% or more of patients during the open-label acute stabilization phase included benzodiazepines (28%), antidepressants (30%), antipsychotics (19%), nonbenzodiazepines (14%), and other mood stabilizers (12%); these drugs were
comparably distributed across the double-blind treatment groups.

Of the 254 subjects enrolled into this study, 54 (21%) were exposed to antidepressant medications during the open-label acute stabilization phase; 53 were receiving at least one antidepressant medication at the time of study entry and one had an antidepressant regimen started. Of these 54, 12 were randomly assigned to a double-blind maintenance condition: eight to lithium and four to divalproex. For these 12 patients, the mean duration of concurrent antidepressant use during the open-label phase was 7.76 weeks (range=0.43–21.57) (no significant differences between groups). The mean duration of the antidepressant washout before entry into the maintenance phase was 13.58 weeks (range 0.86–23.71) (no significant differences between groups). Predictors of response analyses were conducted, and antidepressant exposure during the open-label acute stabilization phase did not predict response during the double-blind maintenance phase.

Of 60 patients entering the 20-month double-blind maintenance phase, 22% completed the phase, 53% required treatment for a mood episode, and 25% discontinued prematurely (Table 3).

The mean dose of lithium during the double-blind maintenance monotherapy phase was 1359 mg/day (range=900–2100), and the mean lithium level was 0.92 meq/liter. The mean dose of divalproex was 1571 mg/day (range=750–2750), and the mean valproate level was 77 µg/ml.

Lorazepam/alprazolam use during the double-blind maintenance phase occurred in seven of 32 patients assigned to lithium and seven of 28 patients assigned to divalproex.

**Time to Event Data**

There were no significant differences in time to treatment for a mood episode, time to premature discontinuation for any reason, time to treatment for depression, and time to treatment for a hypomanic/manic/mixed episode (Figure 1 and Figure 2). The Cox regression predictors of outcome analysis yielded no effect for treatment arm assignment, type of bipolar diagnosis (bipolar I or bipolar II), or index episode at study entry.

**Changes in Symptom Severity and Overall Function**

For those patients who entered the study while in a depressed episode and who were eventually assigned to a double-blind maintenance monotherapy group, Hamilton depression scale-based symptom severity at baseline diminished substantially by the time of random assignment, as did GAS-based functional impairment (Table 4). For those patients who entered the study hypomanic, Young Mania Rating Scale-based symptom severity at baseline diminished by the time of random assignment. For those patients who entered the study while in a mixed episode, Young Mania Rating Scale-based symptom severity at baseline also diminished substantially by the time of random assignment. The observed difference in worsening symptom severity and function during the maintenance phase did not achieve statistical significance.

**Adverse Events**

Table 5 summarizes the adverse events that were observed in at least 5% of patients during the open-label acute stabilization phase and the double-blind maintenance monotherapy phase. Of the 254 enrolled, 48 (19%) discontinued during the open-label phase because of adverse events. The most common adverse events leading to premature discontinuation from the open-label phase were gastrointestinal discomfort (69%), tremors (25%), polyuria and polydipsia (25%), sleeping difficulties (21%), dizziness (17%), headaches (15%), slowed movement (13%), and cognitive difficulties (13%). Of the 60 patients who entered the double-blind maintenance phase, six
(10%) discontinued because of adverse events, with the most common reasons being gastrointestinal discomfort (100%), polyuria and polydipsia (50%), and tremors (50%). Tremors and polyuria/polydipsia were significantly more common in those patients randomly assigned to lithium than divalproex. The proportion of patients discontinuing prematurely because of adverse events was not significantly different between lithium (16%) and divalproex (4%). There were no significant differences in changes in laboratory values during the double-blind maintenance phase.

**Discussion**

This maintenance monotherapy comparison of lithium and divalproex joins our previous double-blind, long-term evaluation of a population of prospectively defined patients with rapid-cycling bipolar disorder (11) and is the longest double-blind study conducted in this subgroup of patients.

The 254 patients enrolled in this study experienced very severe illness. Only 24% met the rigorously defined response criteria necessary to enter the double-blind maintenance monotherapy phase, which required 4 consecutive weeks of improvement. Of the 65 patients that were not responsive to the treatment combination of lithium plus divalproex, 74% exhibited refractory depression, which suggests that depression while receiving lithium plus divalproex treatment may be a common presentation of patients with rapid cycling.

After random assignment, there were no significant differences in rates of relapse into mood episodes or premature discontinuations. The observed differences in survival favoring divalproex over lithium in time to treatment never reached statistical significance. Despite a lifetime of significant morbidity, depressive and manic symptom severity at the time of study entry was only mild to moderate, and there were no significant differences in the worsening of symptom severity and function. Divalproex was significantly better tolerated than lithium as reflected by lower rates of tremors and polyuria/polydipsia, but premature discontinuations due to adverse events did not differ between treatment arms.
These findings do not support the a priori hypothesis that divalproex monotherapy is significantly better than lithium monotherapy for the treatment of rapid-cycling bipolar disorder. Further, the use of the combination of lithium plus divalproex during the open-label acute stabilization phase was only effective in 24% of the intent-to-treat sample, suggesting that three medications or a different combination of two medications may be necessary in the majority of patients with a recent history of rapid cycling.

Several aspects of the design of this study were innovative. First, the open-label acute stabilization phase of this study extended up to 6 months, which is longer than any of the previously conducted maintenance studies in bipolar disorder (11–15). Valuable information was obtained on over 250 patients regarding the magnitude and the spectrum of response to the combination of lithium plus divalproex. Second, patients were stabilized with the combination of divalproex and lithium, which are two commonly used treatments for bipolar disorder. As a result, the findings of this study are likely to be meaningful and generalizable. In addition, exposing patients to both agents being compared during the experimental phase of a maintenance study improves generalizability and diminishes bias inherent in comparisons of safety and tolerability, since all subjects had been previously shown to be tolerant of both study medications. Third, entry into the double-blind maintenance monotherapy phase of the study required evidence of improvement over 4 consecutive weeks. While this criterion increased the design's ability to uncover new mood episodes, it is likely to have been a contributing factor in the study's low rate of initial phase completion. The criteria to enter the maintenance phase were also rigorous in that they not only concurrently assessed depressive and manic symptom severity but also function. In order to be assigned to a double-blind maintenance monotherapy condition, patients were required to have few or no symptoms of hypomania, but mild symptoms of depression and moderate functional impairment were permitted because of prior data suggesting that the combination of lithium and divalproex would be more effective in managing the symptoms of mania than symptoms of depression (6). Fourth, the duration of the maintenance phase of this study was 20 months, which is longer than any of the recently conducted maintenance studies in bipolar disorder (11–15). As a result, the design assessed rates of relapse over clinically meaningful periods of time.

The design of this study had several methodological limitations. First, the patient group size employed in this study was modest, and as a result it is possible that divalproex may be associated with slightly better prevention of relapse into a syndromal mood episode. The estimated hazard ratio was 0.74, indicating that patients randomly assigned to divalproex had a tendency toward lower risk of relapse (95% CI=0.36 to 1.49). If this estimate were an accurate description of the advantage in preventing a mood episode, then a study would need 364 patients per arm in order to achieve statistical power of 0.80 with alpha set at 0.05, two-tailed. Divalproex showed a tendency toward a larger advantage when both side effects and mood symptoms were considered, with a hazard ratio of 0.68 (95% CI=0.38 to 1.21). If this estimate were accurate, then a study would need to enroll 234 patients per arm to achieve power of 0.80. Second, the design required the unblinded medical monitor to keep lithium levels at a minimum of 0.8 meq/liter and valproate levels at a minimum of 50 µg/ml. This may have disadvantaged the divalproex arm, since recent data suggest that there is a linear relationship between valproate levels and response for acute mania, with the range starting at 71 µg/ml and extending to at least 94 µg/ml (16). Third, soon after the initiation of this trial it became apparent that the combination of lithium plus divalproex possessed better acute and continuation
efficacy for episodes of mania/hypomania than depression. As a result, patients with depressive episodes not responsive to the combination were excluded from the maintenance phase, which limits generalizability. Fourth, although maintenance monotherapy comparisons are a necessary first step in treatment trials, combination therapy designs are needed.

The results from this trial are consistent with rapid cycling being a nonspecific predictor of poor outcome to treatment. The hypothesis that divalproex monotherapy is more effective than lithium monotherapy in the long-term management of rapid-cycling bipolar disorder is not supported by the findings from this maintenance study. These findings suggest that there exists a need for maintenance study designs that combine mood stabilizers possessing a complementary spectrum of activity, including at least one agent that stabilizes mood from below baseline (17).

### TABLE 4. Clinical Ratings Over the Course of the Study for Rapid-Cycling Bipolar Disorder Patients Treated With a Lithium/Divalproex Combination Regimen Followed by Double-Blind Maintenance Monotherapy Upon Stabilization

<table>
<thead>
<tr>
<th>Patient Group and Assessment</th>
<th>Double-Blind Maintenance Monotherapy (N=60)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lithium (N=32)</td>
<td>Divalproex (N=28)</td>
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</tr>
<tr>
<td></td>
<td>N</td>
<td>Mean Score</td>
<td>SD</td>
</tr>
<tr>
<td>Patients depressed at study entry</td>
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<td></td>
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<tr>
<td>Hamilton Depression Rating Scale</td>
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<td></td>
<td></td>
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<tr>
<td>Acute phase baseline</td>
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<tr>
<td>Maintenance phase baseline</td>
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<tr>
<td>Maintenance phase endpoint</td>
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<tr>
<td>Young Mania Rating Scale</td>
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<tr>
<td>Acute phase baseline</td>
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<td>Maintenance phase baseline</td>
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<tr>
<td>Maintenance phase endpoint</td>
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<tr>
<td>Global Assessment Scale</td>
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<tr>
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<td>Maintenance phase baseline</td>
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<td>Maintenance phase endpoint</td>
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<td>Patients hypomanic at study entry</td>
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<tr>
<td>Hamilton Depression Rating Scale</td>
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<tr>
<td>Acute phase baseline</td>
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<td>Maintenance phase baseline</td>
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<td>Maintenance phase endpoint</td>
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<tr>
<td>Young Mania Rating Scale</td>
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<tr>
<td>Acute phase baseline</td>
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<td>Maintenance phase baseline</td>
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<td>Maintenance phase endpoint</td>
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<td>Global Assessment Scale</td>
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<td>Acute phase baseline</td>
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<td>Maintenance phase baseline</td>
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<tr>
<td>Maintenance phase endpoint</td>
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<tr>
<td>Patients manic at study entry</td>
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<tr>
<td>Hamilton Depression Rating Scale</td>
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<td>Acute phase baseline</td>
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<td>Young Mania Rating Scale</td>
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<tr>
<td>Maintenance phase endpoint</td>
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<td></td>
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<tr>
<td>Patients in mixed episode at study entry</td>
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<td>Hamilton Depression Rating Scale</td>
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<td></td>
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<td>Acute phase baseline</td>
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<tr>
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</tbody>
</table>

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TABLE 5. Common Adverse Events of Rapid-Cycling Bipolar Disorder Patients Treated With a Lithium/Divalproex Combination Regimen Followed by Double-Blind Maintenance Monotherapy Upon Stabilization

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>N</th>
<th>%</th>
<th>N</th>
<th>%</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal discomfort</td>
<td>146</td>
<td>58</td>
<td>5</td>
<td>16</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Tremor</td>
<td>110</td>
<td>43</td>
<td>9*</td>
<td>28</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Polyuria and polydipsia</td>
<td>115</td>
<td>45</td>
<td>11**</td>
<td>34</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>62</td>
<td>24</td>
<td>2</td>
<td>6</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Headache</td>
<td>41</td>
<td>16</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>Weight gain</td>
<td>33</td>
<td>13</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Balance</td>
<td>31</td>
<td>12</td>
<td>2</td>
<td>6</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Cognitive difficulties</td>
<td>22</td>
<td>9</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>19</td>
<td>7</td>
<td>3</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fluid retention</td>
<td>16</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>15</td>
<td>6</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Speech</td>
<td>13</td>
<td>5</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*p<0.02. **p=0.001.

The data from this study suggest that refractory depression is probably the most common presentation of rapid-cycling bipolar disorder, even when treated with the combination of lithium plus divalproex. Data from the open-label acute stabilization phase of this study suggest that combination therapy with lithium and divalproex results in marked antimanic but modest antidepressant efficacy. Since the use of antidepressants has been discouraged in the recent treatment guidelines (18), an alternative study design for future consideration would include the use of a medication such as lamotrigine. Lamotrigine has been shown to stabilize mood, both short-term (19) and long-term (13, 14), particularly in patients exhibiting depression with a recent history of rapid cycling (11). Such a design could compare the efficacy of lithium plus lamotrigine versus divalproex plus lamotrigine. Another possibility would be to consider a design that evaluated the safety and efficacy of trimethylamin vs. lithium, divalproex, and lamotrigine versus lithium, divalproex, and a conventional antidepressant.

References


Lithium Placental Passage and Obstetrical Outcome: Implications for Clinical Management During Late Pregnancy

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Adele C. Viguera, M.D., M.P.H.
Aquila J. Beach, B.A.
James C. Ritchie, Ph.D.
Lee S. Cohen, M.D.
Zachary N. Stowe, M.D.

Objective: Lithium has been used during pregnancy for more than four decades, but quantification of fetal lithium exposure and clinical correlations of such exposure are limited. The study objectives were to 1) quantify the rate of lithium placental passage, 2) assess any association between plasma concentration of lithium at delivery and adverse perinatal events, and 3) determine whether lithium concentrations can be reduced by briefly suspending therapy proximate to delivery.

Method: Maternal blood and umbilical cord blood were obtained at delivery for assay of lithium concentrations, and obstetrical outcome data were collected prospectively for 10 participants. These data were combined with results from MEDLINE and PsycINFO searches that identified 32 cases in which maternal lithium was administered throughout delivery. Statistical analysis of the pooled data was conducted.

Results: The ratio of lithium concentrations in umbilical cord blood to maternal blood (mean=1.05, SD=0.13) was uniform across a wide range of maternal concentrations (0.2–2.6 meq/liter). Significantly lower Apgar scores, longer hospital stays, and higher rates of CNS and neuromuscular complications were observed in infants with higher lithium concentrations (>0.64 meq/liter) at delivery. Withholding lithium therapy for 24–48 hours before delivery resulted in a 0.28 meq/liter reduction in maternal lithium concentration.

Conclusions: Lithium completely equilibrates across the placenta. Higher lithium concentrations at delivery are associated with more perinatal complications, and lithium concentrations can be reduced by brief suspension of therapy proximate to delivery. Treatment guidelines are proposed to improve neonatal well-being when lithium use is indicated in late pregnancy.

The management of bipolar disorder during pregnancy remains one of the most daunting challenges of psychiatric practice. Although the risk for relapse of bipolar disorder during gestation is poorly characterized, and evidence is conflicting as to whether pregnancy alters such risk favorably or unfavorably (1–13), several studies have indicated that, in the absence of continued pharmacotherapy, 50%–60% of women with bipolar disorder will relapse during pregnancy (2, 14, 15). Relapse rates are higher after abrupt cessation of lithium therapy, and relapse rates have been poorly evaluated after abrupt discontinuation of other mood stabilizers (2). Postpartum recurrence of bipolar disorder is especially common (2–4, 12, 16–21), and postpartum psychosis is more common among women with bipolar disorder, demonstrating a 100-fold increase over the background rate of 0.05% (22–24). This vulnerability to perinatal relapse, coupled with evidence that maternal psychiatric illness carries untoward risks for fetal development (25–27), underscores the need for effective clinical management during gestation.

There are, however, numerous reproductive safety concerns regarding the medications used to treat bipolar disorder. Psychotropic agents used to manage bipolar disorder are either known teratogens or have limited reproductive safety data that preclude sound risk estimates (27). Since the 1950s, lithium has been the cornerstone of pharmacotherapy for bipolar disorder. Its use in pregnancy has garnered considerable attention. Initial retrospective analyses suggested that lithium exposure was associated with a 400-fold increase in the rate of Ebstein’s anomaly, a tricuspid valve malformation (28, 29), but subsequent meta-analyses indicated that the risk ratio for cardiac malformations after lithium exposure is only 1.2 to 7.7 (30) and the risk for Ebstein’s anomaly rises from 1 in 20,000 to 1 in 1,000 (31). It has been argued, however, that these revised estimates could be low as an artifact of study methods, because Ebstein’s anomaly may have been underrecognized in previous reports as a result of the inconsistent use of fetal echocardiography (32). These revised estimates of lithium teratogenicity are considerably lower than estimates of the teratogenic risks of valproate and carbamazepine (27). Furthermore, lithium is the only mood stabilizer for which published neurodevelopmental outcome data show a lack of adverse effects among prenatally exposed children (33).
Early findings from a lamotrigine pregnancy registry are promising, compared to findings for other anticonvulsants (34), but additional cases and infant follow-up studies are needed.

Although lithium is not devoid of prenatal safety concerns, and its use during lactation has been widely discouraged (35), it continues to be favored by many clinicians for use during pregnancy, given its favorable safety profile relative to other mood stabilizers. Nevertheless, lithium use during late pregnancy is associated with particular clinical concerns that have not been systematically investigated, and the literature includes numerous reports of neonatal complications in association with lithium treatment during late pregnancy, including cardiac dysfunction (36–47), diabetes insipidus (37, 38, 48, 49), hypothyroidism (37, 48, 49), low muscle tone (36–40, 42–44, 46, 48, 50, 51), lethargy (36, 48, 52, 53), hepatic abnormalities (36–39, 42, 45, 46), and respiratory difficulties (36–40, 42–46, 48). Recognizing lithium’s low therapeutic index, it seems plausible that such complications are related to the level of lithium exposure proximate to delivery, although some reviewers contend that the occurrence of such effects is independent of lithium concentration (38, 42).

The objective of the present study was to address this deficiency in lithium’s reproductive safety data by 1) extending data quantifying the rate of lithium placental passage, 2) testing for an association between infant lithium concentration at delivery and the incidence of perinatal adverse events, and 3) determining whether lithium concentrations can be reduced by briefly suspending treatment immediately before delivery.

Method

Subjects

Participants were recruited from patients who were referred to the Emory Women’s Mental Health Program for the perinatal management of bipolar disorder and were enrolled in a prospective observational study of the clinical course of bipolar disorder during pregnancy and the postpartum period. Subjects were informed of the risks associated with fetal and infant exposure to lithium as well as the risks of untreated maternal bipolar disorder. In addition, the risks and benefits of alternative treatment options, including other mood stabilizers, psychotherapy, and electroconvulsive therapy, were reviewed. In an effort to reduce the potential for lithium-associated complications at delivery, Women’s Mental Health Program patients are empirically advised to suspend lithium administration 1–2 days before a scheduled delivery or at the onset of labor in the event of spontaneous delivery. Dose suspension is a standard of care at the Women’s Mental Health Program clinic that was not randomly assigned or in any respect dictated by study participation. Data are presented for 10 study participants who elected to continue lithium therapy during late pregnancy. Each participant fulfilled the DSM-IV criteria for bipolar I disorder or bipolar II disorder. The Institutional Review Board of the Emory University School of Medicine approved the study.

Data Collection

Study data included prospective documentation of prenatal psychiatric treatment, obstetrical outcome as recorded on the Women’s Mental Health Program Delivery Information Sheet and the hospital delivery record, and assays of maternal and umbilical cord blood samples collected during gestation and at delivery. Blood samples were collected in chilled EDTA-containing tubes, placed on ice, and centrifuged at 4°C for 10 minutes at 3,000 rpm. Plasma was coded and stored at −80°C until assay.

Laboratory personnel who were blind to the subjects’ demographic characteristics and to the source of the blood samples conducted lithium assays with an ion-selective electrode instrument (Beckman Coulter, Inc., Fullerton, Calif.).

Study data were extended by incorporating findings from previous reports of fetal and maternal lithium concentrations and obstetrical outcome among women taking lithium at delivery. The previous reports were identified through a search of the English-language literature by using MEDLINE and PsycINFO databases.

Data Analysis

A descriptive analysis was performed to characterize the placental passage of lithium. The ratio of lithium concentration in infant (umbilical cord) plasma to that in maternal plasma was calculated for each maternal-infant pair as an index of lithium placental passage, and a scatterplot was constructed of the calculated ratios. This analysis was performed by using data for each dyad from the Women’s Mental Health Program participants and data from previous published studies that reported both infant and maternal lithium concentrations.

The hypothesis that higher infant lithium concentrations at delivery are associated with increased vulnerability to perinatal complications was tested by using data for the infants in the Women’s Mental Health Program group and data from previous studies that reported both infant lithium concentrations at delivery and obstetrical outcomes. The median neonatal lithium concentration was calculated, and infants whose lithium concentration at delivery was greater than the median were assigned to the high lithium exposure group. The remaining infants were assigned to the low lithium exposure group. Hypothesis testing to assess group differences with respect to various complications was performed by using frequency tests (Fisher’s exact test) for nominal variables and one-sample t tests for continuous variables.

Finally, the hypothesis that lithium concentrations at delivery could be significantly reduced by suspending treatment within 48 hours of anticipated delivery was tested by using a paired t test of maternal lithium concentrations at delivery and earlier measures during pregnancy for the participants from the Women’s Mental Health Program. All statistical tests were two-tailed.

At relevant points in the analysis, findings from the Women’s Mental Health Program group were compared to those from previous reports to assess the validity of the pooled analysis.

Results

The demographic and clinical characteristics of the Women’s Mental Health Program participants are presented in Table 1. Lithium concentrations were determined for the 10 umbilical cord samples and nine of the 10 maternal samples (one sample was lost). In addition to the Women’s Mental Health Program participants, 32 fetal-maternal pairs exposed to lithium at delivery were identified from published reports (36–60). Lithium concentrations were reported for 18 of these 32 dyads (38–40, 48, 52, 53, 55–58).

The mean infant-mother lithium ratio at delivery for the 27 pairs was 1.05 (SD=0.13). A scatterplot of the ratios is depicted in Figure 1. For these 27 pairs, the mean infant lithium concentration at delivery was 0.72 meq/liter (SD=0.57,
**TABLE 1. Clinical and Demographic Characteristics of Mothers With Bipolar Disorder (N=10) Who Continued Lithium Therapy in Late Pregnancy and of Their Infants at Delivery**

<table>
<thead>
<tr>
<th>Mother-Infant Pair</th>
<th>Plasma Concentration of Lithium at Delivery (meq/liter)</th>
<th>Maternal Dose of Lithium (mg/day)</th>
<th>Treatment</th>
<th>Demographic Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Umbilical Cord</td>
<td>Mother</td>
<td>Ratio</td>
<td>Therapy Duration</td>
</tr>
<tr>
<td>1</td>
<td>0.20</td>
<td>0.20</td>
<td>1.00</td>
<td>300</td>
</tr>
<tr>
<td>2</td>
<td>0.26</td>
<td>0.26</td>
<td>1.00</td>
<td>1200</td>
</tr>
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<td>3</td>
<td>0.33</td>
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<td>1.10</td>
<td>1200</td>
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<td>4</td>
<td>0.38</td>
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<td>1.15</td>
<td>1350d</td>
</tr>
<tr>
<td>5</td>
<td>0.45</td>
<td>——</td>
<td>——</td>
<td>900</td>
</tr>
<tr>
<td>6</td>
<td>0.47</td>
<td>0.63</td>
<td>0.75</td>
<td>900</td>
</tr>
<tr>
<td>7</td>
<td>0.47</td>
<td>0.43</td>
<td>1.09</td>
<td>1200</td>
</tr>
<tr>
<td>8</td>
<td>0.52</td>
<td>0.65</td>
<td>0.80</td>
<td>600</td>
</tr>
<tr>
<td>9</td>
<td>0.72</td>
<td>0.59</td>
<td>1.22</td>
<td>900d</td>
</tr>
<tr>
<td>10</td>
<td>1.02</td>
<td>1.03</td>
<td>0.99</td>
<td>1800</td>
</tr>
</tbody>
</table>

a. Mother-infant pairs were recruited from the Emory Women's Mental Health Program.
b. Weeks of pregnancy during which the mother received lithium.
c. Data not available.

**TABLE 2. Clinical Characteristics of Infants With Low Versus High Lithium Exposure at Delivery**

<table>
<thead>
<tr>
<th>N (N=12)</th>
<th>Mean</th>
<th>95% CI</th>
<th>N (N=12)</th>
<th>Mean</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants With High Lithium Exposure</td>
<td>Infants With Low Lithium Exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma lithium concentration at delivery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant (meq/liter)</td>
<td>12</td>
<td>1.68</td>
<td>1.02–2.34</td>
<td>12</td>
<td>0.40</td>
</tr>
<tr>
<td>Mother (meq/liter)</td>
<td>8</td>
<td>1.64</td>
<td>0.58–2.70</td>
<td>10</td>
<td>0.42</td>
</tr>
<tr>
<td>Infant/mother ratio</td>
<td>7</td>
<td>1.07</td>
<td>0.94–1.19</td>
<td>10</td>
<td>1.00</td>
</tr>
<tr>
<td>Maternal lithium dose (mg/day)</td>
<td>8</td>
<td>1110</td>
<td>654–1566</td>
<td>11</td>
<td>941</td>
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<tr>
<td>Pregnancy complications</td>
<td></td>
<td></td>
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<tr>
<td>Gestational diabetes</td>
<td>10</td>
<td>10</td>
<td>11</td>
<td>18</td>
<td></td>
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<tr>
<td>Polyhydramnios</td>
<td>10</td>
<td>30</td>
<td>11</td>
<td>9</td>
<td></td>
</tr>
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<td>Preeclampsia</td>
<td>10</td>
<td>10</td>
<td>11</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Any complication</td>
<td>10</td>
<td>60</td>
<td>11</td>
<td>27</td>
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<tr>
<td>Obstetrical outcomes</td>
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<tr>
<td>Apgar score</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1 minute</td>
<td>9</td>
<td>4.3</td>
<td>2.2–6.6</td>
<td>9</td>
<td>7.00</td>
</tr>
<tr>
<td>5 minutes</td>
<td>7</td>
<td>7.6</td>
<td>5.9–9.3</td>
<td>8</td>
<td>8.50</td>
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<tr>
<td>Estimated gestational age (weeks)</td>
<td>12</td>
<td>37.3</td>
<td>35.5–39.2</td>
<td>12</td>
<td>38.9</td>
</tr>
<tr>
<td>Infant weight (kg)</td>
<td>10</td>
<td>3.08</td>
<td>2.54–3.62</td>
<td>10</td>
<td>3.48</td>
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<td>Hospital stay (days)</td>
<td>7</td>
<td>10.1</td>
<td>5.0–15.3</td>
<td>8</td>
<td>4.3</td>
</tr>
<tr>
<td>Preterm delivery</td>
<td>12</td>
<td>33</td>
<td>12</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Low birth weight</td>
<td>10</td>
<td>40</td>
<td>10</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Neonatal complicationsd</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>11</td>
<td>45</td>
<td>11</td>
<td>18</td>
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<td>CNS</td>
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<td>90</td>
<td>11</td>
<td>18</td>
<td></td>
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<tr>
<td>Hepatic</td>
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<td>30</td>
<td>11</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Neuromuscular</td>
<td>8</td>
<td>100</td>
<td>12</td>
<td>25</td>
<td></td>
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<tr>
<td>Renal</td>
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<td>33</td>
<td>10</td>
<td>10</td>
<td></td>
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<tr>
<td>Respiratory</td>
<td>9</td>
<td>67</td>
<td>12</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td>10</td>
<td>20</td>
<td>11</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Any complication</td>
<td>12</td>
<td>100</td>
<td>12</td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>

a. Infants were assigned to study groups on the basis of a median split. Infants whose lithium concentration at delivery was greater than the median (0.64 meq/liter) were assigned to the high lithium exposure group. The remaining infants were assigned to the low lithium exposure group.
b. For continuous data, the difference between means and 95% confidence interval are reported. For nominal data, the calculated risk ratio and 95% confidence interval (CI) are reported. A one-sample t test was used to test group differences in continuous variables. Fisher's exact test was used to test group differences in nominal variables.
c. The risk ratio is not available if either of the group percentages equals 0% or 100%.
NEWPORT, VIGUERA, BEACH, ET AL.

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range=0.20–2.80), and the mean maternal concentration was 0.71 meq/liter (SD=0.59, range=0.20–2.60). Although infant (0.49 versus 0.84 meq/liter) and maternal (0.49 versus 0.82 meq/liter) concentrations were lower in the Women’s Mental Health Program group than in the infant-mother pairs from previous reports, infant-mother lithium ratios were remarkably similar (1.01 versus 1.06) between the two samples. Despite the lower lithium concentrations at delivery, daily lithium doses in the Women’s Mental Health Program mothers (mean=1050 mg/day, SD=437) were marginally higher than those in the mothers described in earlier publications (mean=1013 mg/day, SD=493).

Lithium concentrations and obstetrical outcomes were available for the 10 infants in the Women’s Mental Health Program group and for 14 of the 32 infants described in earlier reports (36, 38–40, 48, 52, 53, 55–58). In the resulting group of 24 infants, 12 with lithium concentrations below the median of 0.64 meq/liter were assigned to the low lithium exposure group (range=0.20–0.58 meq/liter), and 12 with lithium concentrations above the median were assigned to the high lithium exposure group (range=0.70 to >4.0 meq/liter). The results of hypothesis testing are presented in Table 2. The mean infant-mother lithium ratio at delivery was virtually identical between the low lithium exposure and high lithium exposure groups, indicating that the degree of placental passage does not vary with maternal plasma lithium concentration within the clinical range of concentrations encountered.

Apgar Score | Infant Estimated Gestational Age at Delivery (weeks) | Infant Weight (kg) | Neonatal Complications
--- | --- | --- | ---
1 Minute | 5 Minutes
--- | --- | --- | ---
8 | 9 | 38.9 | 3.42 | None
19 | 22 | 37.6 | 3.63 | None
8 | 9 | 38.9 | 3.00 | None
7 | 8 | 38.6 | 3.29 | None
8 | 9 | 40.1 | 3.80 | None
7 | 8 | 39.6 | 3.00 | None
6 | 8 | 37.0 | 3.20 | Hypotonia, lethargy
9 | 9 | 38.0 | 3.70 | Slight jaundice
2 | 7 | 40.9 | 3.62 | Hypotonia, lethargy, cyanosis

Risk Ratio | 95% CI | p
--- | --- | ---
0.50 | 0.04–6.55 | 0.42
4.29 | 0.37–50.20 | 0.23
--- | --- | ---
4.00 | 0.64–25.02 | 0.13

Risk Ratio | 95% CI | p
--- | --- | ---
3.75 | 0.54–26.04 | 0.15
40.50 | 3.09–530.29 | <0.002
1.93 | 0.25–14.89 | 0.33
--- | --- | ---
4.50 | 0.31–65.23 | <0.002
10.04 | 1.28–78.12 | 0.22
--- | --- | ---
<0.0002

Complications for particular body systems included bradycardia, cardiomegaly, and systolic murmur (cardiovascular); lethargy and “depression” (CNS); hepatomegaly and jaundice (hepatic); hypotonia, “flaccidity,” diminished deep tendon reflexes, and poor suck or Moro reflexes (neuromuscular); polyuria and diabetes insipidus (renal); apnea, cyanosis, labored breathing, and need for intubation (respiratory), and goiter (thyroid).

FIGURE 1. Concentrations of Lithium in Plasma Samples From Mothers With Bipolar Disorder Who Continued Lithium Therapy in Late Pregnancy and From Their Infants at Delivery

For data from mother-infant pairs recruited from the Emory Women’s Mental Health Program (current study) and from mother-infant pairs described in the literature (36–48, 51, 52, 53, 55–58), range=0.20–2.80), and the mean maternal concentration was 0.71 meq/liter (SD=0.59, range=0.20–2.60). Although infant (0.49 versus 0.84 meq/liter) and maternal (0.49 versus 0.82 meq/liter) concentrations were lower in the Women’s Mental Health Program group than in the infant-mother pairs from previous reports, infant-mother lithium ratios were remarkably similar (1.01 versus 1.06) between the two samples. Despite the lower lithium concentrations at delivery, daily lithium doses in the Women’s Mental Health Program mothers (mean=1050 mg/day, SD=437) were marginally higher than those in the mothers described in earlier publications (mean=1013 mg/day, SD=493).

Lithium concentrations and obstetrical outcomes were available for the 10 infants in the Women’s Mental Health Program group and for 14 of the 32 infants described in earlier reports (36, 38–40, 42, 44, 48, 49, 51, 52, 53, 56, 57, 59). In the resulting group of 24 infants, 12 with lithium concentrations below the median of 0.64 meq/liter were assigned to the low lithium exposure group (range=0.20–0.58 meq/liter), and 12 with lithium concentrations above the median were assigned to the high lithium exposure group (range=0.70 to >4.0 meq/liter). The results of hypothesis testing are presented in Table 2. The mean infant-mother lithium ratio at delivery was virtually identical between the low lithium exposure and high lithium exposure groups, indicating that the degree of placental passage does not vary with maternal plasma lithium concentration within the clinical range of concentrations encountered.
The rate of all complications, with the exception of gestational diabetes, was consistently higher in the high lithium exposure group. In particular, the rates of CNS and neuromuscular complications were significantly higher, the duration of infant hospital stays was significantly longer, and 1-minute Apgar scores were significantly lower in the high lithium exposure group. The rates of preterm delivery, low birth weight, and infant respiratory complications were higher in the high lithium exposure group than in the low lithium exposure group, but the differences only approached significance. Even when the data for five infants in the high lithium exposure group who...
had lithium concentrations at delivery in the “toxic” range (>1.2 meq/liter) were omitted from the analysis, the rates of CNS complications (83%) (p<0.04, Fisher’s exact test) and neuromuscular complications (100%) (p<0.01, Fisher’s exact test) remained significantly higher in the high lithium exposure group, and this group had longer infant hospital stays (mean=10.0 days) than the low lithium exposure group, although the difference only approached significance. Because the Women’s Mental Health Program participants had been instructed to suspend lithium treatment before delivery, these participants’ infants are over-represented in the low lithium exposure group (eight of 12), compared to the high lithium exposure group (two of 12), and had a lower rate of complications than the mother-infant pairs from previous reports.

Although maternal lithium concentrations at delivery were subtherapeutic (<0.5 meq/liter) for five of the nine women in the Women’s Mental Health Program group (mean=0.49 meq/liter, SD=0.26, range=0.20–1.03), they were in the therapeutic range for all Women’s Mental Health Program participants when sampled at the most recent prenatal visit (mean=0.79 meq/liter, SD=0.19, range=0.50–1.10). A paired t test indicated that maternal lithium concentrations at delivery were significantly lower than those during pregnancy (mean difference=0.28 meq/liter, 95% confidence interval [CL]=0.08–0.49; t=3.38, df=6, p<0.02), with a mean of 20.6 hours (SD=19.2) having elapsed since the last lithium dose when the delivery sample was collected. Despite the brief interruption in lithium therapy, only one of the 10 Women’s Mental Health Program participants was symptomatic in the perinatal period. That patient experienced a depressive episode with psychotic features that began 2 weeks before delivery, prior to any suspension of lithium therapy.

### Discussion

To our knowledge, this study is the first to examine systematically the clinical relevance of lithium placental passage at delivery. The study’s findings are as follows:

1. Lithium demonstrates complete placental passage as evidenced by the mean infant-mother lithium ratio of 1.05.

2. Lithium ion equilibration across the placental barrier is remarkably uniform across a wide range of maternal concentrations (0.2–2.6 meq/liter), suggesting that lithium equilibrates between maternal and fetal circulation much as it does across the total body water space in an individual. This finding is consistent with the results of preclinical studies demonstrating minimal transplacental differences in electric potential after acute lithium administration (60, 61).

3. Adverse perinatal outcomes are more extensive in the setting of higher lithium concentrations at delivery as evidenced by the consistently higher rate of varied complications among infants in the high lithium exposure group.

4. Lithium delivery concentrations can be significantly reduced at delivery without compromising pharmacotherapeutic efficacy by briefly withholding lithium therapy.

This constellation of findings bears important implications for treatment guidelines, now woefully inadequate, when lithium administration is indicated during late gestation. Conflicting recommendations have been proposed regarding lithium’s use in late pregnancy, with some experts urging lithium dose reduction or discontinuation long before delivery to avoid neonatal toxicity (36, 47) and others advocating the reinstitution of lithium therapy before delivery to avoid the high risk of postpartum relapse in patients with bipolar disorder (62). Moreover, despite its use for more than five decades, no guidelines have been established for therapeutic monitoring of lithium concentrations during pregnancy or potential adverse effects beyond surveillance for cardiac teratogenicity (63). Because poor outcomes in this study were predicted by higher infant lithium concentrations at delivery, and neonate concentrations invariably approximated maternal concentrations, infant well-being can be enhanced by monitoring maternal lithium concentrations as delivery approaches. Furthermore, the ability to lower maternal concentrations expeditiously by suspending lithium therapy for 24–48 hours before delivery might improve obstetrical outcome as neonatal concentrations can be reduced without unduly compromising treatment efficacy.

Neonatal effects of lithium exposure are of gravest concern when maternal toxicity arises before delivery. Although lithium toxicity did not complicate the pregnancies of the Women’s Mental Health Program participants, earlier reports indicate that maternal toxicity during late gestation warrants concern. Of seven reported cases of prenatal lithium toxicity (39, 44, 46, 50, 52–54), the etiology is identifiable in only three. In two cases, toxicity arose iatrogenically after the institution of diuretic therapy and a sodium-restricted diet to manage edema (44, 54). Toxicity occurred in another case when a sodium-restricted diet was initiated to manage preeclampsia (52), a condition that decreases the glomerular filtration rate (64–66) and, ostensibly, lithium clearance. The cause of lithium toxicity in the remaining cases (39, 46, 49, 50) is unclear. Toxicity may have been a consequence of intentional or accidental overdose, although this cause was not explicitly stated, and pregnancy-specific causes, such as abrupt fluid loss during labor, cannot be eliminated.

From these findings, we propose the following guidelines for lithium administration during late pregnancy:

1. Maintain a target lithium concentration at the minimum effective level for the individual. Although lithium levels of 0.8–1.0 meq/liter are widely cited as the ideal...
LITHIUM PLACENTAL PASSAGE

for maintenance therapy, some individuals can be successfully maintained at lower concentrations (67).

2. Periodically monitor lithium concentrations during pregnancy, particularly during late gestation when marked changes in glomerular filtration rate can alter lithium clearance (66, 68, 69).

3. Avoid pregnancy treatment modalities that increase the potential for lithium toxicity (Table 3). However, if such measures are obstetrically warranted, more frequent lithium monitoring and dose reduction are indicated.

4. Lower maternal lithium dose in the event of pregnancy complications such as preeclampsia (64–66) or polyhydramnios (38, 39, 47, 48) (Table 3) that might predispose the patient or her child to lithium toxicity. Similarly, any abnormality in amniotic fluid volume, including oligohydramnios, could be the result of and/or could increase the likelihood of lithium-associated fetal nephrotoxicity.

5. Suspend lithium administration 24–48 hours before a scheduled Cesarean section or induction, or suspend lithium administration at the onset of labor in the event of spontaneous delivery.

6. Check the maternal lithium concentration at the patient’s presentation to the hospital for delivery.

7. Administer oral and/or intravenous fluids throughout the labor and delivery process, and check maternal lithium concentration in the event of clinical signs of toxicity.

8. Reinstitute lithium therapy as soon as the patient is medically stabilized after delivery. Use the preconception dose, because the maternal glomerular filtration rate rapidly returns to pregravid levels after delivery.

This study is not without shortcomings. The small number of participants limited the statistical power to elucidate fully the association between clinical outcome and lithium concentration. Another limitation is the demographic homogeneity of the 10 Women’s Mental Health Program participants, which limits the generalizability of the study results. It can also be argued that the dependency of the study findings is weakened by the inclusion of case data from earlier reports that in some instances were incomplete. Conversely, the consistent character of the findings when the data are analyzed across so many reports, despite probable differences in data collection, serves to reinforce the reliability and potential generalizability of the findings.

In summary, given the considerable morbidity of untreated bipolar disorder and the significant risk of perinatal relapse in the absence of continued pharmacotherapy, prolonged discontinuation of treatment is seldom a viable option. Despite documented concerns about effects of lithium in reproduction, this medication remains the preferred alternative during gestation for many women with bipolar disorder. When lithium is used during late pregnancy, infant and maternal well-being can be maximized by maintaining maternal concentrations at the minimal effective level, suspending lithium therapy 24–48 hours before delivery to reduce neonatal concentrations further, and avoiding inadvertent or iatrogenic lithium toxicity during gestation.

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References


LITHIUM PLACENTAL PASSAGE

Neuropsychological studies of major depressive disorder have demonstrated that depressed patients show impairment relative to healthy subjects on some tests of attention (1), memory (2), and emotional processing (3). However, most of these studies assessed patients taking psychotropic medications, confounding interpretation of these results. For example, a previous study applying the Affective Go/No-Go Task of Murphy et al. (3) found that medicated depressed patients were impaired in their ability to shift attention from one affective valence to another, suggesting a mood-congruent affective bias for negative stimuli in major depressive disorder. The current study investigated performance on this task of unmedicated subjects with major depressive disorder. The primary hypothesis tested was that unmedicated depressed patients would require less time to respond to mood-congruent sad words than to happy words, while healthy comparison subjects would show the opposite bias (3).

Method

Twenty currently depressed subjects (10 men and 10 women) were selected who met DSM-IV criteria for recurrent major depressive disorder and had illness onset before age 40 years. Subjects had not received psychotropic medications within 3 weeks of testing. Four depressed patients were naive to psychotropic medications, and 11 had been medication free for 1 to 8 years. Depression severity was rated by using the Montgomery-Åsberg Depression Rating Scale (4). Twenty medically healthy comparison subjects with no history of psychiatric disorders and no first-degree relatives with a psychiatric disorder were matched to the subjects with major depressive disorder for gender, age, and intelligence. Subjects were excluded if they 1) had ever met DSM-IV criteria for alcohol or substance dependence, 2) met criteria for alcohol or substance abuse within 1 year, 3) had a history of hypomanic episodes, 4) demonstrated full-scale IQ below 85, measured with the Wechsler Abbreviated Scale of Intelligence (5), or 5) had clinically significant abnormalities on physical or laboratory examination. Written informed consent was obtained from each subject following full description of the study.

Three CANTAB subtests (6) were used. The rapid visual information processing task, a continuous performance test, was used to evaluate attentional processing. The pattern recognition memory test was employed to assess encoding, retrieval, and recognition of nonverbal material. The spatial working memory test was administered to assess nonverbal short-term working memory.

The Affective Go/No-Go Task (3) required subjects to respond to either happy or sad words. Eight word blocks, each containing 18 affectively valenced words (nine happy, nine sad), were presented. Single words appeared on a computer screen, and subjects were initially instructed to press the space bar for happy words (e.g., hopeful, serene) but not for sad words (e.g., glum, mistake). After two word blocks requiring responses to happy words, the instructions changed so that the space bar was to be pressed for sad words. Conditions were alternated in an HHSSHHSS pattern to create shift and nonshift response blocks. Each word was presented for 300 msec, followed by a 900-msec interstimulus interval.

Variables extracted from this task were target (omission) errors (e.g., failing to respond to sad words during sad word blocks) and distractor (commission) errors (e.g., responding to happy words during sad word blocks) during happy and sad word blocks, and during shift and nonshift blocks. Reaction times were recorded for correct responses.

Two-tailed repeated-measures analyses of variance (ANOVAs) were used to compare performances on the Affective Go/No-Go Task across groups. The within-group repeated measures were valence (happy versus sad word blocks) and shift (shift versus nonshift blocks). Two-way ANOVAs were used to compare performance between groups on the CANTAB subtests.

References

1. [Provide references here]

Conclusions: Unmedicated depressed patients do not show a pattern of generalized cognitive impairment but, rather, specifically display an attentional deficit and a mood-congruent bias toward salient stimuli.
Depressed patients and healthy subjects showed different patterns of performance on the Affective Go/No-Go Task. Depressed patients made more omission errors when responding to happy than to sad words, and they responded more quickly to sad targets than to happy targets. Healthy subjects showed the opposite pattern for both error and response time variables. The mood-congruent processing bias was previously reported in medicated depressed patients, who also required more time to respond to positive words than healthy subjects (3). Our results thus extend this finding in unmedicated depressed patients. Taken together, the two studies suggest preservation of a mood-congruent attentional bias despite pharmacological treatment.

The specificity of performance deficits on the Affective Go/No-Go Task was assessed with attention and memory tests. Attentional performance indicated more omission errors by depressed patients than by healthy subjects. No other significant differences between healthy subjects and depressed patients were found on CANTAB test performance, indicating that differences between groups on the Affective Go/No-Go Task were not accounted for by nonspecific cognitive impairment, although the number of subjects and statistical power were not large in this study. It has been assumed that cognitive deficits in depression are due to generalized cognitive slowing, but studies reporting such nonspecific impairment included depressed patients taking psychotropic medications. In contrast, studies of unmedicated depressed patients (7, 8) indicated that cognitive deficits in depression are not associated with nonspecific changes in cognitive performance but, instead, implicate specific attentional processes.

On the Affective Go/No-Go Task, healthy subjects had longer latencies and made more omission errors in response to sad words than to happy words; these data suggest that the normative state is characterized by a positive bias. This phenomenon may conceivably confer resilience against the psychological impact of negative life events. In contrast, unmedicated depressed patients responded more slowly to happy than to sad words and made more omission errors during happy than sad word blocks. Large numbers of omission errors on the rapid visual information processing test suggest a generalized deficit in attention; therefore, this mood-congruent attentional bias occurs within the context of an attention deficit. However, the larger numbers of omission errors on the Affective Go/No-Go Task were not wholly attributable to an attention deficit, because omission errors were not extended across affective valence. Equivalent performance by depressed patients and healthy subjects in response to sad words but impaired performance in response to happy words by de-

**Results**

Mean age and full-scale IQ scores of the patients and comparison subjects are presented in Table 1. Two-way ANOVAs indicated that the subjects with major depressive disorder made more omission errors than healthy subjects on the rapid visual information processing test subtest (Table 1).

Two-way repeated-measures ANOVA indicated a significant valence-by-diagnosis interaction for target errors (Table 1); subjects with major depressive disorder made more target errors during happy than sad word blocks. Healthy subjects showed the opposite pattern, making more target errors during sad than happy word blocks. Both groups made more distractor errors during shift blocks than nonshift blocks (Table 1). No significant diagnosis or gender effects were observed for distractor errors. Mean reaction time scores revealed a significant valence-by-diagnosis interaction (Table 1); subjects with major depressive disorder required more time to respond to happy than to sad words, and healthy subjects required more time to respond to sad than to happy words.

**Discussion**

Depressed patients and healthy subjects showed different patterns of performance on the Affective Go/No-Go Task. Depressed patients made more omission errors when responding to happy than to sad words, and they responded more quickly to sad targets than to happy targets. Healthy subjects showed the opposite pattern for both error and response time variables. The mood-congruent processing bias was previously reported in medicated depressed patients, who also required more time to respond to positive words than healthy subjects (3). Our results thus extend this finding in unmedicated depressed patients. Taken together, the two studies suggest preservation of a mood-congruent attentional bias despite pharmacological treatment.

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pressed patients indicates that salient stimuli affect attentional processing in depression.

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Brief Report

Emergent Suicidality in a Clinical Psychotherapy Trial for Adolescent Depression

Jeffrey A. Bridge, Ph.D.
Rémy P. Barbe, M.D.
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Objective: The authors’ goal was to examine the incidence and predictors of emergent suicidality that occurred during a clinical trial of psychotherapy for adolescent depression.

Method: The rates and predictors of emergent suicidality in 88 medication-free depressed adolescent outpatients who reported no current suicidality during an intake interview were assessed over 12 to 16 weeks of psychotherapy treatment.

Results: The incidence of emergent suicidality was 12.5% (11 of 88 subjects). Self-reported suicidal thoughts at intake were a significant predictor of emergent suicidality, even when suicidality was denied at intake interview.

Conclusions: Emergent suicidality is a common occurrence in psychosocial treatment of adolescent depression, with rates similar to those reported recently in antidepressant trials. To evaluate accurately the role of treatment in emergent suicidality, it is important to assess self-reported suicidality at intake and to balance treatment groups on this key predictor of emergent suicidality.

The U.S. Food and Drug Administration (FDA) issued a public health advisory on Oct. 15, 2004, ordering manufacturers of all antidepressant drugs to adopt a boxed warning to alert doctors of a greater risk of suicidal thinking and behavior in children and adolescents being treated with these medications (1).

The aim of the present study was to place the concerns raised by the FDA and other regulatory agencies (2) in context. We report on the incidence and predictors of emergent suicidality in a randomized psychotherapy treatment trial of adolescent depression in which no subjects received pharacootherapy but were otherwise comparable to participants in previous clinical trials of depression in adolescents used to assess risk of emergent suicidality (1, 2).

Method
Subjects were participants in a clinical trial of psychotherapy for adolescent depression. All had normal intelligence, were between 13 and 18 years of age, had a DSM-III-R diagnosis of major depressive disorder, and had an intake Beck Depression Inventory (3) score of 13 or higher (4). Subjects with ongoing physical or sexual abuse, psychosis, or bipolar, obsessive-compulsive eating, or substance abuse disorder were excluded. Of 122 eligible participants, 107 were recruited. The subjects’ median socioeconomic score was 40 (class IV) (4), and 81 (75.7%) were girls. Approximately 22%, 32%, and 21% of the
pressed patients indicates that salient stimuli affect attentional processing in depression.

References
5. Wechsler D: Wechsler Abbreviated Scale of Intelligence. San Antonio, Tex, Psychological Corp, 1999

Brief Report

Emergent Suicidality in a Clinical Psychotherapy Trial for Adolescent Depression

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patients had comorbid dysthymia, anxiety, and disruptive disorders, respectively. About one-third of the patients were recruited through advertisement, and the rest were recruited from a child psychiatry outpatient clinic in a university setting. Once the patient and family had given informed consent, they were randomly assigned to receive cognitive behavior therapy, systemic behavioral family therapy, or nondirective supportive therapy. Treatment consisted of two phases: 1) an active phase, in which patients received 12 to 16 sessions provided in 12 to 16 weeks, and 2) a booster phase, in which patients received two to four sessions in as many months. In this report, we focus exclusively on the active phase. Four of the randomly assigned participants never came for treatment and were not included in any of the present analyses.

On the basis of the assumption that interview, rather than self-report, is the best way to assess suicidality, we focus on the 88 participants who at the intake interview denied clinically significant suicidality during the week before evaluation. This interview used the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS) (5). Clinically significant suicidality was defined as a rating of 4 or higher on the K-SADS suicide ideation item, corresponding to suicidal ideation with a plan or an actual suicide attempt.

Patients were classified regarding history of suicidality before the week preceding intake according to all available interview data from the K-SADS and the Suicide Circumstances Schedule (6), a semi-structured interview for the assessment of precipitants, suicidal intent, and lethality of a suicidal episode. Twenty-two patients were classified as nonsuicidal; they had no past history of suicidal ideation or behavior. Sixty-six patients had past but not current suicidality, and 19 of these patients (28.8%) reported a history of suicide attempt. Self-reported thoughts of killing oneself in the week before intake were measured by using item 9 of the Beck Depression Inventory (3), dichotomized as present or not present; information on this item was missing for two subjects.

The primary outcome variable was the emergence of suicidality during the 12 to 16 weeks of active treatment. Emergent suicidality, coded on a 5-point scale (0 = no suicidality, 1 = ideation without plan, 2 = ideation with plan, 3 = suicide gesture [i.e., episode in which a subject had suicidal intent and means at hand but did not attempt suicide], 4 = suicide attempt), was assessed at each session by the treating therapist.

Potential demographic predictors of emergent suicidality included age, race, sex, referral source (clinical versus advertisement), family constellation, and socioeconomic status. Intake clinical predictors included interview and self-rated suicidality, comorbid disorders, age at onset, duration and severity of depressive episode, functional status, level of cognitive distortion, hopelessness, family discord, and parental depressive symptoms (4).

Factors that distinguished the groups were examined by using standard parametric and nonparametric statistics. Time to emergent suicidality was compared between groups with Kaplan-Meier survival analyses, and differences were tested by using the log-rank statistic. The survival time began with the first treatment session following the intake assessment and continued until a suicidal event occurred, withdrawal from the study due to either dropping out or entering open treatment, or the end of the trial. Alpha was set at 0.05 (two-tailed) for all comparisons.

Results

Of 88 depressed subjects who denied current suicidality on interview, 11 (12.5%) developed suicidality during treatment (10 had ideation without a plan; one made a suicide attempt). With respect to timing of emergent suicidality, eight (72.7%) of 11 episodes occurred within 3 weeks of beginning treatment. There were no completed suicides during the study period.

The majority (N=53 [61.6%]) of the 86 subjects classified as nonsuicidal endorsed item 9 of the Beck Depression Inventory, reporting that they had thoughts of killing themselves. All 10 patients classified as nonsuicidal who developed emergent suicidality during active treatment endorsed this item, reporting suicidal thoughts at intake, compared with 43 (56.6%) of the 76 nonsuicidal patients who did not become suicidal during treatment (p=0.01, Fisher's exact test). Of the 10 cases of emergent suicidality, none was identified by interview alone, four were identified by self-report alone, and six were identified by both interview and self-report. There was no significant difference in the rate of emergent suicidality between patients with (N=66) and without (N=22) a past history of suicidality at intake (nine [13.6%] versus two [9.1%]) (p=0.72, Fisher's exact test). Among patients with a past history of suicidality, there was a nonsignificant trend for a previous suicide attempt to predict emergent suicidality, both in terms of rate (five [26.3%] of 19 versus four [8.5%] of 47) (p=0.11, Fisher's exact test) and in terms of time to emergent suicidality (log-rank χ²=3.75, df=1, p=0.06).

Subjects with and without emergent suicidality were similar with regard to treatment assignment, age, sex, race, socioeconomic status, and referral by advertisement (7). With respect to clinical predictors, patients who developed emergent suicidality had lower overall scores on the Children's Negative Cognitive Errors Questionnaire (7) (mean=67.1, SD=18.3, versus mean=84.0, SD=18.5) (t=2.71, df=85, p=0.008), reflecting greater cognitive distortion, and higher Beck Depression Inventory scores (not including item 9) (mean=30.5, SD=8.9, versus mean=21.8, SD=6.9) (t=3.62, df=84, p=0.001). However, the only significant predictor of emergent suicidality in a multivariate Cox regression model was self-reported suicidality on Beck Depression Inventory item 9.

Discussion

In this clinical trial, which enrolled subjects similar to those enrolled in pharmacotherapy clinical trials, rates of emergent suicidality in patients receiving psychotherapy but no pharmacotherapy were comparable to rates observed in antidepressant trials (1, 2). Self-reported suicidality in the week before intake predicted the onset of emergent suicidality to a much greater extent than did interview-rated suicidality, indicating that self-report may be a necessary component to the assessment of adolescent suicidal risk.

These findings raise methodological issues for the design and interpretation of psychotherapy and pharmacotherapy treatment trials of depression in young patients. Notably, emergent suicidality, even in those patients who did not report suicidality during the intake interview, occurred fairly commonly. In the case of psychotherapy, the emergence of suicidality is probably not easily attribut-
able to treatment. In our study, the detection of emergent suicidality could be increased by its specific and systematic assessment, whereas in previous clinical trials of depression among young patients, adverse events were reported by participants or observed by investigators. Self-reported suicidality in the week before intake predicted the onset of emergent suicidality to a much greater extent than did interview-rated suicidality, treatment assignment, cognitive distortions, and depression severity. Therefore, it is important to assess intake suicidality by self-report and to consider balancing treatment groups on this key predictor of emergent suicidality.

Received July 19, 2004; accepted Sept. 24, 2004. From Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center. Address correspondence and reprint requests to Dr. Brent, Western Psychiatric Institute & Clinic, Child and Adolescent Psychiatry, 3811 O’Hara St., BFT 311, Pittsburgh, PA 15213-2592; brentda@upmc.edu (e-mail). Supported by NIMH grants T32 MH-18951, R01 MH-46500, P30 MH-66371, and K01 MH-69948.

The authors thank their colleagues who aided in the conduct of this study and, above all, the patients and families for their participation in this study.

References

1. FDA Public Health Advisory: Suicidality in children and adolescents being treated with antidepressant medications. www.fda.gov/cder/drug/antidepressants/SSRIPHA200410.htm


Several studies have shown that symptoms of complicated grief are distinct from symptoms of bereavement-related depression and anxiety (1). A limitation of earlier studies is that they relied on exploratory factor analysis to evaluate the latent structure of postloss symptoms, a method that does not allow for the comparative evaluation of the fit of competing models of the latent structure. Furthermore, earlier studies have hardly addressed whether the distinctiveness of the three symptom clusters holds across subgroups of bereaved individuals.

Using data from Dutch mourners, the current study aimed to extend earlier findings on this topic, using confir-
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References
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Complicated Grief, Depression, and Anxiety as Distinct Postloss Syndromes: A Confirmatory Factor Analysis Study

Paul A. Boelen, M.A.
Jan van den Bout, Ph.D.

Objective: The authors used confirmatory factor analysis to replicate earlier findings that complicated grief, depression, and anxiety are distinct syndromes.

Method: Data were derived from 1,321 bereaved individuals. Complicated grief was measured with the Inventory of Traumatic Grief. Depression and anxiety were measured with the SCL-90.

Results: A model in which symptoms of complicated grief, depression, and anxiety loaded on separate factors was superior to a one-factor model, revealed good model fit, and was invariant across subgroups.

Conclusions: Previous findings of a distinction among complicated grief, depression, and anxiety were confirmed.

Several studies have shown that symptoms of complicated grief are distinct from symptoms of bereavement-related depression and anxiety (1). A limitation of earlier studies is that they relied on exploratory factor analysis to evaluate the latent structure of postloss symptoms, a method that does not allow for the comparative evaluation of the fit of competing models of the latent structure. Furthermore, earlier studies have hardly addressed whether the distinctiveness of the three symptom clusters holds across subgroups of bereaved individuals.

Using data from Dutch mourners, the current study aimed to extend earlier findings on this topic, using confir-
BRIEF REPORTS

Among 1,321 Bereaved Individuals

<table>
<thead>
<tr>
<th>Measure and Symptom</th>
<th>Factor 1: Complicated Grief</th>
<th>Factor 2: Depression</th>
<th>Factor 3: Anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inventory of Traumatic Grief</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. I think about [... ] so much that it can be hard for me to do the things I normally do</td>
<td>0.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. I feel myself longing for [...]</td>
<td>0.60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. I feel drawn to places and things associated with [...]</td>
<td>0.42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. I feel lonely ever since [...] died</td>
<td>0.74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. I feel like the future holds no meaning or purpose without [...]</td>
<td>0.80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. I feel like I have become numb since the death of [...]</td>
<td>0.77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. I feel disbelief over [...]’s death</td>
<td>0.57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. I feel that life is empty or meaningless without [...]</td>
<td>0.77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. I feel that a part of myself died along with [...]</td>
<td>0.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. I feel that the death of [...] has changed my view of the world</td>
<td>0.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. I have pain in the same area of my body, or some of the same symptoms as [...] had</td>
<td>0.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. I am bitter over [...]’s death</td>
<td>0.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SCL-90 anxiety subscale</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Feeling no interest in things</td>
<td></td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>2. Feeling blue</td>
<td></td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>3. Poor appetite</td>
<td></td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>4. Feeling low in energy or slowed down</td>
<td></td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td>5. Feelings of worthlessness</td>
<td></td>
<td>0.66</td>
<td></td>
</tr>
<tr>
<td>6. Blaming yourself for things</td>
<td></td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>7. Thoughts of ending your life</td>
<td></td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td><strong>SCL-90 depression subscale</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Nervousness or shakiness inside</td>
<td></td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td>2. Suddenly scared for no reasons</td>
<td></td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>3. Feeling fearful</td>
<td></td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>4. Heart pounding or racing</td>
<td></td>
<td>0.62</td>
<td></td>
</tr>
<tr>
<td>5. Spells of terror or panic</td>
<td></td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>6. The feeling that something bad is going to happen</td>
<td></td>
<td>0.65</td>
<td></td>
</tr>
<tr>
<td>7. Thoughts and images of a frightening nature</td>
<td></td>
<td>0.71</td>
<td></td>
</tr>
</tbody>
</table>

Method

Data were available from 1,321 individuals originally recruited—along different pathways—for a research program on cognitive variables in complicated grief (2). The first group was recruited through grief counselors, therapists, clergy, and other people who met bereaved individuals through their work-related or voluntary activities. They handed out 1,128 questionnaire packets to mourners, 492 (43.6%) of which were returned. The other participants were recruited through an advertisement on a Dutch Internet site with information about grief. Information generally encompassed references to self-help literature, addresses for support, and stories of visitors. The advertisement explained that the research program was aimed at enhancing knowledge on grief and variables that influence the mourning process and invited people to participate by filling in questionnaires. People could choose to fill in questionnaires through the Internet or send an e-mail with the request to have the questionnaires sent to their homes; 260 (53.1%) of the mailed questionnaires were returned. Questionnaires differed slightly across the three groups, but all included symptom measures of complicated grief, depression, and anxiety. Participants younger than 18 years (N=31) were excluded. The final study group thus comprised 1,321 individuals. Written informed consent was obtained from all participants. Typewritten name and e-mail address in the Internet group (N=600) replaced the handwritten signature of the mailed consent forms.

The mean age of the participants was 43.2 years (SD=14.3). Most were female (N=1,084 [82.1%]), and 573 (43.4%) had lost a spouse, 187 (14.2%) a child, and 561 (42.4%) someone else. Losses occurred on average 32.5 months (SD=42.0) before the survey. Causes were nonviolent in 1,075 (81.4%) of the cases and violent in 246 (18.6%).

Items for the factors were selected before any model was tested. Theoretical considerations guided choices. Items for the complicated grief factor were taken from the Dutch version of the Inventory of Traumatic Grief (3), a 29-item questionnaire covering all symptoms of the refined consensus criteria for complicated grief and other problematic grief reactions. It is an extended version of the 19-item Inventory of Complicated Grief used in many earlier studies on complicated grief (1). We selected 12 items from the inventory that resembled the four separation distress and eight traumatic distress symptoms of the refined consensus criteria (Table 1). Items for the depression factor were taken from the 16-item depression subscale of the Dutch SCL-90 (4). We selected seven items corresponding closely to DSM-IV criteria of a major depressive episode, excluding items that were not part of these criteria (e.g., “crying easily”) and items that were ambiguous in the light of subjects’ circumstances (e.g., “thoughts of death”). Striving for an equal number of items in the anxiety factor, we selected seven items closely related to anxious states in DSM-IV from the 10-item anxiety subscale of the SCL-90.

AMOS 5.0 (5) was used to conduct confirmatory factor analyses. Goodness of fit was evaluated by using the comparative fit index, the Tucker-Lewis index (values >0.90 indicate good fit), and the root mean square error of approximation (values <0.08 indi-
cate acceptable fit). Chi-square difference tests were used to evaluate the relative fit of competing models.

Results

First, a one-factor model was tested. This model did not fit the data (comparative fit index=0.733, Tucker-Lewis index=0.709, root mean square error of approximation=0.111). Next, a three-factor model was examined with symptoms loading on three distinct but correlated factors. This model fit significantly better than the unitary model (difference $\chi^2=2956.75$, df=3, $p<0.001$). Fit estimates reflected an acceptable model fit (comparative fit index=0.896, Tucker-Lewis index=0.886, root mean square error of approximation=0.069). Modification indexes indicated that correlations existed between the error terms of complicated grief items 5 and 8 and depression items 5 and 6. Because both complicated grief items reflected hopelessness and both depression items reflected negative self-view, we assumed that these correlations reflected non-random measurement error stemming from content overlap. Accordingly, we tested the fit of an adjusted three-factor model in which these error terms were allowed to be correlated. This model was a significant improvement over the second model (difference $\chi^2=351.81$, df=2, $p<0.001$) and had good fit estimates (comparative fit index=0.916, Tucker-Lewis index=0.907, root mean square error of approximation=0.063). Table 1 shows its factor loadings. Correlations between factors were 0.78 for complicated grief with depression, 0.58 for complicated grief with anxiety, and 0.78 for depression with anxiety.

Multiple group analyses examined the invariance of this last three-factor model across subgroups. In all analyses, restrictive models were tested with factor loadings, factor variances, and factor covariances, and residuals were constrained to be equal across subgroups. We tested the equivalence of the structure across the three groups included in this study (model 4), men and women (model 5), victims of violent versus nonviolent losses (model 6), mourners more than 1 year versus less than 1 year removed from their loss (model 7), and those who lost a partner, child, or other relative (model 8). All multiple group analyses revealed adequate fit: for model 4, comparative fit index=0.901, Tucker-Lewis index=0.903, root mean square error of approximation=0.037; for model 5, comparative fit index=0.912, Tucker-Lewis index=0.903, root mean square error of approximation=0.044; for model 6, comparative fit index=0.913, Tucker-Lewis index=0.913, root mean square error of approximation=0.044; for model 7, comparative fit index=0.913, Tucker-Lewis index=0.912, root mean square error of approximation=0.043; for model 8, comparative fit index=0.899, Tucker-Lewis index=0.901, root mean square error of approximation=0.037.

The structure was invariant across groups does not mean that complicated grief levels were equal. The grief scores of victims of violent losses (mean=81.01, SD=21.33) on the Inventory of Traumatic Grief were slightly but signifi-
Suicide rates in many Western countries have increased considerably in recent decades, causing much concern. Bereavement places people at a high risk of psychological and mental deprivations, including mortality (1). Suicide rates are higher among bereaved people (particularly early in bereavement) than for nonbereaved persons, and suicide is one of the most excessive causes of death among the bereaved (2–4). Thus, it is important to identify the mediators and moderators of suicidal behavior in bereavement. The suicidal ideation domain provides potentially useful information for understanding why bereaved persons attempt or actually commit suicide. Although few of those with suicidal ideation will act on their thoughts, ideation would seem a precursor to suicidal acts. Furthermore, suicidal ideation reflects thoughts of desperation in grieving that need to be comprehended. However, investigations of suicidal ideation in bereavement are rare.

Prigerson and colleagues examined relationships among “complicated grief,” depression, and suicidal ideation in bereaved persons, including young adults (5) and elderly persons (6). Complicated grief emerged as an independent predictor of suicidal ideation. Rosengard and Folkman (7) investigated suicidal ideation among partners of men with AIDS. Over 50% experienced suicidal ideation; the rates were even higher in bereaved than in nonbereaved men. These studies suggest high suicidal ideation among the bereaved and associated complications in grieving. However, information is limited. The studies by Prigerson et al. (5) and Szanto et al. (6) did not focus on comparing suicidal ideation between bereaved and nonbereaved persons. Although the study by Rosengard and Folkman (7) did so, many nonbereaved partners may have already been anticipating bereavement and even their own mortality. Overall, information is still lacking. Are the rates for ideation, as for suicide, really higher among the bereaved? Are there gender differences? Does social support reduce suicidal ideation, as Durkheim (2) suggested?

Studies of social support in bereavement have not confirmed the stress-theory assumption that social support buffers persons against the deleterious effects of bereavement (8). This finding is consistent with the attachment-theory assumption that loss of an attachment figure results in emotional loneliness (a sense of utter aloneness, whether or not the companionship of others is accessible), which cannot be reduced by the social support of family or friends (9). We used data from an earlier study of ours (8) to assess the impact of marital bereavement and social support on suicidal ideation and the mediating role of emotional loneliness.

**Method**

The participants were 30 widows and 30 widowers (mean age = 53.05 years, SD = 6.81) and 60 individually matched (by age, gender, socioeconomic status, and number of children), married individuals (mean age = 53.75, SD = 6.83) who were under retirement age. The prospective participants were sent a letter asking for their participation. Those who did not decline by mail or telephone were contacted a few days later to ask for an interview. To achieve a study group of 60 widowed individuals, 217 persons were approached. This rather low acceptance rate is typical for bereavement research.

The data for the present analysis, collected 4–7 months postbereavement, were obtained from questionnaires given personally to participants and returned by mail. We did not consider it ethically appropriate to ask recently bereaved spouses a battery of questions about suicidal ideation. Rosengard and Folkman (7) asked a single question on a 3-point scale. We followed a similar procedure, deriving our measure from the Beck Depression Inventory (10). Four statements (e.g., “I don’t have any thoughts of killing myself,” “I would like to kill myself”) were presented in an alternative-choice format. Perceived social support was assessed with the Perceived Social Support Inventory, a 20-item questionnaire (8) measuring four typical functions of social support (e.g., instrumental: “If I couldn’t go shopping, I’d have somebody to shop for me”; appraisal: “If I need advice on financial matters, I’d have someone to rely on”; emotional: “I have nobody to talk to about my feelings and problems”; contact: “I have hardly any friends who share my interests”). It has high internal consistency (alpha = 0.90). Emotional loneliness was
assessed by using two items: “I feel lonely even when I am with other people,” and “I often feel lonely” (alpha=0.78).

Results

Figure 1 presents mean suicidal ideation scores of married and widowed individuals who rated above and below the median scores on the Perceived Social Support Inventory. A two-by-two-by-two (marital status-by-social support-by-gender) analysis of variance on suicidal ideation yielded a marginally significant main effect of marital status (F=3.16, df=1, 111, p<0.10), a main effect of social support (F=12.71, df=1, 111, p<0.01), a main effect of gender (F=11.58, df=1, 111, p<0.01), and an interaction of gender and social support (F=4.12, df=1, 111, p<0.05). The bereaved had higher levels of suicidal ideation than the married people; women had higher scores than men. High levels of social support were associated with lower levels of suicidal ideation. This effect was stronger for women than for men. The introduction of emotional loneliness as a covariate into this analysis eliminated the effect of bereavement on suicidal ideation (F=0.10, df=1, 107, n.s.), leaving all the other effects practically unchanged.

To examine the relationship of suicidal ideation to criteria for potential psychiatric diagnosis, suicidal ideation scores (for widows only) were analyzed by using the cutoff point on the Beck Depression Inventory for severe depression (score of ≥19). The mean suicidal ideation value with a severe depression score (mean=1.13, SD=0.99) was significantly higher than for those with a low depression score (mean=0.14, SD=0.35) (t=−5.46, df=57, p<0.001). Correlations between suicidal ideation and scores on the Beck Depression Inventory were much lower for those with a Beck Depression Inventory score <19 (Pearson correlation: r=0.28, p=0.05) than for those with a Beck Depression Inventory score ≥19 (Pearson correlation: r=0.92, p<0.01). Thus, suicidal ideation seems closely related to severe depressive symptoms among the bereaved.

Discussion

Loss of a partner, perception of low levels of social support, and being a woman were associated with increased suicidal ideation. Women are frequently found to have higher suicidal ideation and rates of suicide attempts than men, but our results indicated more excessive risk of suicidal ideation among widows than either widowers or nonbereaved women/men. This suggests that bereavement puts women at a worrisome high risk of suicidal ideation (particularly given the results showing a close relationship with severe depressive symptoms), although we must remember that—paradoxically—the prevalence of completed suicides is typically higher in (bereaved) men than in (bereaved) women (11). Although lack of social support appears to have a more deleterious effect (its association with higher suicidal ideation for women than for men), again, there is no evidence of a buffering effect. Social support reduces suicidal ideation equally for both marital status categories.

The reason for the failure of social support to buffer the bereaved against the deleterious impact of loss of a partner became apparent from our analysis of covariance. Statistical control for differences in emotional loneliness eliminated the association between suicidal ideation and marital status, although it did not affect either the effects of social support or gender. This pattern is consistent with the attachment-theory assumption that the effects of loss of a partner and lack of social support are mediated by different mechanisms. Thus, uniquely, the impact of bereavement on suicidal ideation seems to be due to intense emotional loneliness, fitting the notion of “the broken heart.”

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Suicide Attempters’ Reaction to Survival as a Risk Factor for Eventual Suicide

Gregg Henriques, Ph.D.
Amy Wenzel, Ph.D.
Gregory K. Brown, Ph.D.
Aaron T. Beck, M.D.

Objective: The authors’ goal was to evaluate whether suicide attempters’ reaction to surviving their attempt predicted eventual suicide.

Method: Three hundred ninety-three suicide attempters were categorized on the basis of their reaction to having survived their attempt (i.e., glad to be alive, ambivalent, wished they were dead) and were followed for 5 to 10 years to determine whether they completed suicide.

Results: A survival analysis found that subjects who said that they wished they had died after a suicide attempt were 2.5 times more likely to commit suicide eventually than those who were glad they survived and those who were ambivalent about the attempt.

Conclusions: Suicide attempters’ reaction to surviving is an important clinical variable that is easily assessed in evaluations that occur following a suicide attempt. (Am J Psychiatry 2005; 162:2180–2182)
Suicide Attempters’ Reaction to Survival as a Risk Factor for Eventual Suicide

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Conclusions: Suicide attempters’ reaction to surviving is an important clinical variable that is easily assessed in evaluations that occur following a suicide attempt.

The identification of patients who are most likely to kill themselves following a suicide attempt presents a serious challenge to clinicians (1). To examine risk factors for eventual suicide, a prospective study that involved 499 suicide attempters who were recruited from a large public hospital was conducted between 1970 and 1975 (2). Beck and Steer (3) examined 413 of these attempters, 20 (4.8%) of whom committed suicide during the follow-up period. Of several clinical and demographic variables considered (i.e., age, gender, race, marital status, employment status, presence of a depressive diagnosis, presence of a schizophrenia diagnosis, history of drug abuse, presence of an alcoholism diagnosis, previous suicide attempt, Beck Depression Inventory [4] score, Beck Hopelessness Scale [5] score, and Suicide Intent Scale [6] score), only a diagnosis of alcoholism, unemployment, and score on the precautions subscale of the Suicide Intent Scale accounted for significant variance in predicting eventual suicide.

It was surprising that hopelessness did not predict eventual suicide because Beck et al. (7) found that hopelessness was one of the most robust predictors of suicide in hospitalized patients with suicidal ideation. Beck and Steer (3) noted that hopelessness was assessed after the attempt rather than before and that “its predictive validity may be obscured by the psychological aftermath of the attempt” (p. 208). This interpretation suggests that characteristics of the aftermath of a suicide attempt might have relevance in predicting ultimate suicide. Beautrais (1) found that reactions to the attempt (e.g., hoping to die before making the attempt, failing to be relieved by survival) contributed modestly in predicting eventual suicide in 302 suicide attempters.

The purpose of the current study was to reanalyze the suicide attempters studied by Beck and Steer (3) to determine if their reaction to surviving the suicide attempt predicted eventual suicide. We hypothesized that individuals who wished they were dead following the suicide attempt would be at greater risk for killing themselves than those who were glad to be alive or ambivalent.
Method

The present analysis was based on 393 patients drawn from a group of 499 patients who had been admitted for recent suicide attempts to Philadelphia General Hospital between 1970 and 1975. Following the strategy of Beck and Steer (3), we identified 413 patients who had completed the Beck Depression Inventory, Beck Hopelessness Scale, and Suicide Intent Scale and eliminated 20 of them from analysis because participants failed to respond to the reaction to suicide item. There were 167 men (42.5%) and 226 women (57.5%). The racial composition was 51.4% Caucasian (N=202), 47.1% African American (N=185), and 1.5% from other backgrounds (N=6). The mean age was 30.12 years (SD=10.93). Of the 393 attempters, 20 (5.1%) eventually committed suicide.

Beck and colleagues obtained the initial study group by screening the admissions of suicide attempters to Philadelphia General Hospital from 1970 to 1975. Within 24–48 hours of admission, eligible patients were asked for their consent to participate in a longitudinal study of suicidal behavior, were interviewed by a clinical psychologist or psychiatrist to establish psychiatric diagnoses, and were administered standardized assessment instruments. Attempts were made to follow these patients through 1980, and 95% were successfully followed. Whenever possible, patients themselves were contacted semiannually for the first 2 years and then annually by telephone. Other means of contact included collateral informants, first-class or certified mail, and home visits.

If the follow-up indicated that the patient was deceased, appropriate agencies were contacted to verify cause of death, mode of death, and circumstances surrounding death. In addition, the death records of the Philadelphia Medical Examiner’s Office were scanned daily to determine whether any of the patients were on the list. When a patient died, the relevant medical examiner’s or coroner’s records were requested so that the cause of death could be verified.

The variable of interest for the present study is an item that asked about the individual’s reaction to the suicide attempt. Reactions were classified as to whether respondents endorsed that they regretted the attempt and were glad to be alive, or ambivalent about the attempt, or regretted the failure of the attempt and wished they had died. All analyses compared respondents who regretted the attempt and were glad to be alive, 168 (42.7%) were classified as wishing the attempt had succeeded. There were substantial differences among those who wished they had died and those who were glad to be alive or ambivalent on each of the following measures: Beck Depression Inventory score (t=7.64, df=382, p<0.03), Beck Hopelessness Scale score (t=11.01, df=379, p<0.001), and Suicide Intent Scale score (t=9.05, df=391, p<0.001). In all cases, subjects in the group who wished they had died scored higher on these measures than those in the other two groups.

We performed a Cox regression survival analysis to examine whether the two groups of attempters differed in the likelihood of eventually committing suicide. Results indicated that attempters who wished they had died were more than twice as likely to commit suicide than those who were glad to be alive or who were ambivalent (hazard ratio=2.56, 95% CI=1.06–6.34, Wald χ²=4.34, df=1, N=393, p=0.03). Forty percent of those who committed suicide had endorsed that they wished they had died in their previous attempt (N=8), compared with 21% of those who did not eventually complete suicide (N=77). However, results from a logistic regression analysis indicated that this variable did not predict eventual suicide better than the factors identified by Beck and Steer (3).

Discussion

Consistent with findings reported by Beautrais (1), results from this investigation suggest that a suicide attempter’s reaction to surviving the attempt may be an important risk factor in predicting eventual suicide. Those individuals who wished they had died following their suicide attempt were significantly more likely to kill themselves eventually than those who were glad to be alive or ambivalent about the suicide attempt. In addition, individuals who wished they were dead following the attempt were more depressed and hopeless and had more suicidal intent than those who were glad to be alive or ambivalent about the attempt.

These findings are of particular import because an individual’s reaction to having survived a suicide attempt may be assessed easily and documented during a psychiatric evaluation. Although this variable did not predict eventual suicide beyond other established risk factors, it is valuable in that it is easier to determine in an emergency setting than it is to administer an entire self-report inventory, such as the precautions subscale of the Suicide Intent Scale. Moreover, unlike demographic variables that also predict eventual suicide (e.g., employment status), this variable is one that has been documented as modifiable with appropriate intervention, such as cognitive therapy (8). Thus, individuals who indicate that they wished they had died after a suicide attempt may be monitored and receive interventions to reduce the likelihood that they will attempt suicide again.

References


Confirmation of Association Between Autism and the Mitochondrial Aspartate/Glutamate Carrier SLC25A12 Gene on Chromosome 2q31

Ricardo Segurado, B.A., Ph.D.
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Michael Fitzgerald, M.B. B.Ch., M.D.
Michael Gill, M.B. B.Ch., M.D.
Louise Gallagher, M.B. B.Ch., Ph.D.

Objective: Autism is a neurodevelopmental disorder with childhood onset and a known major genetic component. A recent study identified a highly significant association between autism and a two-single-nucleotide-polymorphism haplotype in the SLC25A12 gene, with a homozygote genotype relative risk between 2.4 and 4.8. The authors’ goal was to investigate this association with autism in Irish affected child-parent trios because replication in an independent sample is essential in the validation of such potentially important findings.

Method: Markers rs2056202 and rs2292813 were genotyped in a total of 158 trios (442 individuals). The Transmission Disequilibrium Test was used to examine these markers for association with autism.

Results: In agreement with the recent study, the authors found significant association between autism and the C alleles of both rs2056202 and rs2292813 as well as the two-marker haplotype.

Conclusions: These findings provide replication of the association between autism and SLC25A12.
Confirmation of Association Between Autism and the Mitochondrial Aspartate/Glutamate Carrier SLC25A12 Gene on Chromosome 2q31

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Conclusions: These findings provide replication of the association between autism and SLC25A12.

(Am J Psychiatry 2005; 162:2182–2184)
Markers were examined for genotype errors and Mendelization inconsistencies with the PedCheck software program (12) in 158 affected trios. Allele and genotype frequencies from parents were calculated, tested for Hardy-Weinberg equilibrium, and examined for linkage disequilibrium \((D', r^2)\) by using the EMPLD program (https://epi.mdanderson.org/~qhuang/Software/pub.htm). The markers and the two-marker haplotype were examined for association by using the Extended Transmission Disequilibrium Test program (13) and the TDTPHASE function of the UNPHASED package, which compensates for missing information and reconstructs haplotype phase where ambiguous, using an expectation-maximization algorithm (14).

**Results**

Genotypes at both markers were shown to follow the expected Hardy-Weinberg distribution. The markers were verified to be in linkage disequilibrium \((D'=1.0, r^2=0.57)\). For markers rs2056202 and rs2292813, 64 and 50 families, respectively, had at least one affected child and one heterozygous parent. Association was detected at each marker individually with the Transmission Disequilibrium Test and, when examined as a haplotype, with TDTPHASE (Table 1).

The associated alleles were identical to those reported by Ramoz et al. (9) as showing biased transmission to affected children. Sample size and minor allele frequencies were insufficient for useful estimation of genotype relative risks.

**Discussion**

The association between autism and SLC25A12 was originally reported by Ramoz et al. (9) in 411 families, 197 of which had at least one affected child and one parent heterozygous for the marker. If the reported relative risk estimates in this association are accurate, we expect our study to have good power to detect such an association, if disease allele frequency is approximately equal to that of the risk C alleles \((0.8–0.9)\) (15). Our estimates of the effect size are of similar magnitude to those detected by Ramoz et al., suggesting that the risk factor may be the same in both studies.

The SLC25A12 gene comprises a 2,037-base-pair open-reading frame, encoding the 678 amino acid mitochondrial aspartate/glutamate carrier, which resides in the mitochondrial inner membrane and is involved in the respiratory chain (16). It is difficult to hypothesize a model by which variation in this protein may contribute to the cause of autism because it is expressed predominantly in muscle and at lower levels in the brain (16). One could speculate that a defect in this gene could be compensated for by up-regulation or functional redundancy in some tissues, but that lack of compensatory mechanisms in tissues such as brain may lead to greater sensitivity to a slight deficiency in respiratory efficiency.

A functional role for the polymorphisms examined would be purely speculative because they are at opposite ends of the gene \((\text{approximately } 68.3 \text{ kilobases [kb] apart})\), although they are in strong linkage disequilibrium with each other. The possibility remains that another functional variant exists elsewhere, in linkage disequilibrium with the SNPs examined, possibly in an adjacent gene or regulatory site. Examination of the HapMap (http://www.hapmap.org) data across the gene and adjacent areas shows that strong linkage disequilibrium relationships between markers extend across the entire gene as well as the adjacent DNCI2, HAT1, and MAP1D genes in a linkage disequilibrium block of approximately 370 kb, although these data are still relatively sparse. The exact location of any functional polymorphism responsible for susceptibility to autism, therefore, remains uncertain. However, given that we were testing a strong a priori hypothesis, we believe that the present study represents a confirmation of the association between autism and the C alleles at the rs2056202 and rs2292813 SNPs in the SLC25A12 gene.

**References**

Impulsivity, defined as a predisposition to rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions to the impulsive individual or to others (1), is a core feature of many psychiatric disorders, including attention deficit hyperactivity disorder, bipolar disorder, and substance use disorders. Disorders characterized by an impaired ability to resist impulses to engage in ultimately self-destructive behavior (or behavior with deleterious long-term consequences) have been categorized in DSM as impulse control disorders not elsewhere classified. These disorders, currently including pathological gambling, kleptomania, intermittent explosive disorder, trichotillomania, pyromania, and impulse control disorder not otherwise specified,
Impulse Control Disorders in Adult Psychiatric Inpatients

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Laura Levine, M.D.
Daniel Kim, M.D.
Marc N. Potenza, M.D., Ph.D.

Objective: The authors' goal was to examine the prevalence of impulse control disorders in psychiatric inpatients.

Method: They used the Minnesota Impulsive Disorders Interview, a semistructured clinical interview assessing pathological gambling, trichotillomania, kleptomania, pyromania, intermittent explosive disorder, compulsive buying, and compulsive sexual behavior, to screen 204 consecutively admitted psychiatric inpatients. One hundred twelve of the inpatients were women (54.9%), and the mean age of the 204 inpatients was 40.5 years (SD=13.2, range=18–83). Patients whose screen was positive for an impulse control disorder were evaluated with structured clinical interviews.

Results: Sixty-three patients (30.9%) were diagnosed with at least one current impulse control disorder. The most common impulse control disorders were compulsive buying (N=19 [9.3%]), kleptomania (N=16 [7.8%]), and pathological gambling (N=14 [6.9%]). Patients with and without co-occurring impulse control disorders did not differ significantly from each other on demographic measures or number or type of psychiatric disorders other than impulse control disorders.

Conclusions: Impulse control disorders appear common among psychiatric inpatients. Additional, larger studies are needed to examine the prevalence of impulse control disorders in the general population and specific psychiatric groups.

Impulsivity, defined as a predisposition to rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these reactions to the impulsive individual or to others (1), is a core feature of many psychiatric disorders, including attention deficit hyperactivity disorder, bipolar disorder, and substance use disorders. Disorders characterized by an impaired ability to resist impulses to engage in ultimately self-destructive behavior (or behavior with deleterious long-term consequences) have been categorized in DSM as impulse control disorders not elsewhere classified. These disorders, currently including pathological gambling, kleptomania, intermittent explosive disorder, trichotillomania, pyromania, and impulse control disorder not otherwise specified,
have historically received little clinical and research attention. Diagnostic criteria for compulsive sexual behavior and compulsive buying have been proposed because preliminary data suggest that these behaviors may be linked to other impulse control disorders (2, 3).

Data suggest that impulse control disorders are relatively common, carry substantial morbidity and mortality, and may be treated effectively with behavioral and pharmacological therapies (4). Although pathological gambling has prevalence estimates similar to those for bipolar disorder and schizophrenia (5), few investigations have examined the prevalence of other impulse control disorders. Two French studies involving 107 depressed and 79 alcoholic inpatients (6, 7) found that 19% and 38%, respectively, had positive screens for a co-occurring impulse control disorder.

The co-occurrence of impulse control disorders and other psychiatric disorders has treatment implications. Individuals with co-occurring impulse control disorders and other psychiatric disorders generally have more severe symptoms, suggesting that untreated impulse control disorders may complicate treatment of the identified psychiatric disorder (8). Since empirically validated treatments for impulse control disorders are available, it is important for psychiatrists to identify and treat people with these disorders.

Our goal in this study was to examine the frequency of co-occurring impulse control disorders in voluntarily hospitalized psychiatric patients using structured diagnostic measures. On the basis of earlier studies, we hypothesized that impulse control disorders would be common.

Method

The study and consent forms were reviewed and approved by the institutional review boards of the two hospitals whose patients were studied. All patients provided written informed consent. Two hundred four consecutive patients presenting for admission to an inpatient unit at a private psychiatric (N=103) or public university (N=101) hospital participated. The group included 112 women (54.9%), and the mean age of the 204 patients was 40.5 years (SD=13.2, range=18–83).

Inclusionary criteria included voluntary admission and ability to read and understand the consent form. To avoid possible consent under duress, patients admitted involuntarily were not approached for participation. No patient refused participation. Demographic variables (age, gender, race, ethnicity, marital status, and education) and admission psychiatric diagnoses were taken from patients’ charts.

Two psychiatrists trained on the study instruments and in the phenomenology of impulse control disorders (L.L. and D.K.) evaluated all subjects for current and lifetime impulse control disorders with the Minnesota Impulsive Disorders Interview (9). This instrument is used to screen for pathological gambling, trichotillomania, kleptomania, pyromania, intermittent explosive disorder, compulsive buying, and compulsive sexual behavior (9–12). It evaluates each disorder beginning with a general question, which, if answered affirmatively, allows the interviewer to ask a series of questions mirroring DSM criteria. For compulsive buying and compulsive sexual behavior, the questions in the Minnesota Impulsive Disorders Interview reflect the impulse control disorder criteria of increasing tension before the related act followed by relief after act performance and subsequently evaluate related distress and impairment. A subject’s Minnesota Impulsive Disorders Interview screen is positive for a disorder if all questions are answered affirmatively (except the pathological gambling screen, which requires five positive responses, and compulsive sexual behavior screen, which requires an affirmative answer to one of two questions). The psychiatrist performing the screening interview scored the instrument.

Subjects with a positive screen for an impulse control disorder were evaluated in a structured clinical interview conducted by a different psychiatrist with expertise in impulse control disorders (J.E.G.), who was unaware of the impulse control disorder(s) for which the subject had a positive screen. This second assessment involved administration of all of the following instruments: the Structured Clinical Interview for Pathological Gambling (13), a valid and reliable diagnostic instrument based on the Structured Clinical Interview for DSM-IV (SCID); proposed diagnostic criteria for compulsive buying (2) and compulsive sexual behavior (3); the Structured Clinical Interview for Kleptomania (14), a diagnostic interview with good psychometric properties; and SCID-compatible modules based on DSM-IV diagnostic criteria for pyromania, trichotillomania, and intermittent explosive disorder.

The percentages of patients with current and lifetime impulse control disorders were determined, along with 95% confidence intervals. Between-group differences were tested by using Pearson chi-square tests and two-sided Fisher exact tests for categorical variables and two-tailed independent samples t tests for continuous variables. Because multiple pairwise comparisons were made, a Bonferroni correction was used, resulting in a significance threshold of p=0.008.

Results

Frequencies of individual impulse control disorders are presented in Table 1. Compulsive buying was the most common current and lifetime impulse control disorder and trichotillomania the least common. Sixty-three (30.9%) of the 204 patients were diagnosed with at least one impulse control disorder. Forty-two patients (20.6%) reported current symptoms of two impulse control disorders, 20 (9.8%) three impulse control disorders, and one (0.5%) more than three impulse control disorders. Sixty-seven patients (32.8%) were diagnosed with at least one lifetime impulse control disorder. Only four patients had a previous impulse control disorder; they reported no symptoms of an impulse control disorder within the last year.

Participants were admitted for multiple psychiatric reasons. Only three of the patients were admitted for an impulse control disorder (two for pathological gambling and

### TABLE 1. CURRENT AND LIFETIME PREVALENCE OF IMPULSE CONTROL DISORDERS AMONG 204 PSYCHIATRIC INPATIENS

<table>
<thead>
<tr>
<th>Impulse Control Disorder</th>
<th>Current Prevalence</th>
<th>Lifetime Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Compulsive buying</td>
<td>19</td>
<td>9.3</td>
</tr>
<tr>
<td>Kleptomania</td>
<td>16</td>
<td>7.8</td>
</tr>
<tr>
<td>Pathological gambling</td>
<td>14</td>
<td>6.9</td>
</tr>
<tr>
<td>Intermittent explosive disorder</td>
<td>13</td>
<td>6.4</td>
</tr>
<tr>
<td>Compulsive sexual behavior</td>
<td>9</td>
<td>4.4</td>
</tr>
<tr>
<td>Pyromania</td>
<td>7</td>
<td>3.4</td>
</tr>
<tr>
<td>Trichotillomania</td>
<td>7</td>
<td>3.4</td>
</tr>
</tbody>
</table>
one for intermittent explosive disorder). One hundred ten patients (53.9%) suffered from two or more psychiatric disorders, not including an impulse control disorder. Mood disorders, seen in 148 patients (72.5%), were the most common. Other psychiatric disorders included substance use disorders (N=90 [44.1%]), anxiety disorders (N=27 [13.2%]), psychotic disorders (N=23 [11.3%]), eating disorders (N=9 [4.4%]), adjustment disorders (N=7 [3.4%]), and somatization disorders (N=2 [1.0%]).

Patients with co-occurring impulse control disorders did not significantly differ from those without impulse control disorders on demographic measures (Table 2). The two groups also did not differ significantly with respect to the number or type of other psychiatric diagnoses, although the group with impulse control disorders was marginally more likely than those without to report two or more psychiatric diagnoses other than impulse control disorders (Table 2). No significant differences in demographic or diagnostic characteristics were observed between patients admitted to the private versus public hospitals (data not shown).

The Minnesota Impulsive Disorders Interview demonstrated classification accuracy based on the subsequent structured clinical interviews as follows: compulsive buying (sensitivity 100%, specificity 96.2%); kleptomania (sensitivity 89.5%, specificity 93.0%); pathological gambling (sensitivity 100%, specificity 98.4%); intermittent explosive disorder (sensitivity 100%, specificity 97.4%); compulsive sexual behavior (sensitivity 80.0%, specificity 96.9%); pyromania (sensitivity 100%, specificity 100%); and trichotillomania (sensitivity 100%, specificity 98.5%).

**Discussion**

We found that approximately one-third of the adult patients admitted for inpatient psychiatric treatment suffered from a co-occurring impulse control disorder. Only 1.5% of the inpatients carried an admission diagnosis for an impulse control disorder, however, suggesting that these disorders frequently go unrecognized. The current and lifetime estimates found here (30.9% and 32.8%, respectively) are consistent with findings of two earlier French studies that assessed impulse control disorders in

**TABLE 2. Characteristics of 204 Psychiatric Inpatients With or Without a Co-Occurring Lifetime Impulse Control Disorder**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Any Lifetime Impulse Control Disorder (N=67)</th>
<th>No Lifetime Impulse Control Disorder (N=137)</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean 38.7 SD 12.2</td>
<td>Mean 41.3 SD 13.6</td>
<td>t 1.34</td>
</tr>
<tr>
<td></td>
<td>N 67 % 52.2 SD 77 % 56.2</td>
<td>N 137 % 56.2 SD 60 % 43.8</td>
<td>df 202</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>p &lt;0.19</td>
</tr>
<tr>
<td>Male</td>
<td>35 52.2</td>
<td>77 56.2</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>32 47.8</td>
<td>60 43.8</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>28 41.8</td>
<td>50 36.5</td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>16 23.9</td>
<td>35 25.5</td>
<td></td>
</tr>
<tr>
<td>Divorced</td>
<td>21 31.3</td>
<td>49 35.8</td>
<td></td>
</tr>
<tr>
<td>Separated</td>
<td>2 3.0</td>
<td>7 5.1</td>
<td></td>
</tr>
<tr>
<td>Widowed</td>
<td>0 0.0</td>
<td>1 0.7</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>58 86.6</td>
<td>121 88.3</td>
<td></td>
</tr>
<tr>
<td>Nonwhite</td>
<td>9 13.4</td>
<td>16 11.7</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>12 17.9</td>
<td>22 16.1</td>
<td></td>
</tr>
<tr>
<td>High school graduate</td>
<td>33 49.3</td>
<td>62 45.3</td>
<td></td>
</tr>
<tr>
<td>Some college</td>
<td>13 19.4</td>
<td>33 24.1</td>
<td></td>
</tr>
<tr>
<td>College graduate</td>
<td>6 9.0</td>
<td>13 9.5</td>
<td></td>
</tr>
<tr>
<td>More than college</td>
<td>3 4.5</td>
<td>7 5.1</td>
<td></td>
</tr>
<tr>
<td>Psychiatric diagnoses other than an impulse control disorder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One</td>
<td>25 37.3</td>
<td>69 50.4</td>
<td></td>
</tr>
<tr>
<td>Two or more</td>
<td>42 62.7</td>
<td>68 49.6</td>
<td></td>
</tr>
<tr>
<td>Admission diagnoses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mood disorder</td>
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<td>96 70.1</td>
<td></td>
</tr>
<tr>
<td>Substance use disorder</td>
<td>33 49.3</td>
<td>57 41.6</td>
<td></td>
</tr>
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<td>6 9.0</td>
<td>21 15.3</td>
<td></td>
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<td>Psychotic disorder</td>
<td>10 14.9</td>
<td>13 9.5</td>
<td></td>
</tr>
<tr>
<td>Eating disorder</td>
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<td>6 4.4</td>
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<tr>
<td>Personality disorder</td>
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<td>4 2.9</td>
<td></td>
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<td>Adjustment disorder</td>
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<td></td>
</tr>
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<td>Cognitive disorder</td>
<td>0 0.0</td>
<td>3 2.2</td>
<td></td>
</tr>
<tr>
<td>Somatization disorder</td>
<td>1 1.5</td>
<td>1 0.7</td>
<td></td>
</tr>
</tbody>
</table>

* Fisher’s exact test used because of low expected cell frequencies.
smaller groups of psychiatric inpatients with alcohol use disorders and depression (6, 7). Together, the findings suggest that impulse control disorders occur commonly across cultures in inpatient psychiatric populations. Unlike the studies in France, the results from our larger study also suggest that impulse control disorders are common among psychiatric inpatients with a broad range of disorders, including anxiety disorders and psychotic disorders. Prevalence estimates of impulse control disorders did not differ between patients admitted to the private and public hospitals, suggesting that impulse control disorders are common in different inpatient treatment settings.

The range of impulse control disorders identified extends beyond those currently included in the DSM category of impulse control disorders not otherwise classified. Compulsive buying, currently not a formal DSM-IV-TR diagnosis, was the most common current and lifetime impulse control disorder, suggesting the need for consideration of formal criteria for the disorder in the next DSM revision. Previous studies (15, 16) have suggested that kleptomania and pyromania are rare. This study, however, found kleptomania to be one of the most common lifetime impulse control disorders; estimates of pyromania were only slightly less than those for pathological gambling, an impulse control disorder that has received more clinical and research attention.

Because impulse control disorders appear common in inpatients with other psychiatric disorders, it seems important to screen for impulse control disorders in this population. The fact that estimates of lifetime impulse control disorders (32.8%) were not notably different from those of current impulse control disorders (30.9%) suggests that these disorders may become chronic if left untreated. Treatment of either an impulse control disorder or another psychiatric disorder could be complicated or compromised by the presence of the other untreated condition. Treating one disorder alone may not be effective if a co-occurring disorder is exerting a causal or maintaining influence on the treated condition. To our knowledge, no research has been published on the treatment of co-occurring impulse control disorders in patients with other psychiatric disorders. Research on effective treatments for psychiatric patients with co-occurring impulse control disorders is needed.

This study has several limitations. First, impulse control disorder diagnoses were based on subject report—supporting collateral information was not obtained. Because behaviors associated with impulse control disorders are often denied, the observed frequencies probably underestimate those of actual impulse control disorders among psychiatric inpatients. Second, other disorders characterized by impaired impulse control (compulsive computer use, binge eating disorder) were not assessed; consequently, the rates of impulse control disorders might be higher than reported here. Conversely, studies done in clinical settings bias toward finding high rates of co-occurrence (due to Berkson’s bias [17] and clinical biases). Third, it is unclear how generalizable our results are to patients admitted to psychiatric facilities against their will, psychiatric outpatients, or individuals in the community. Fourth, the instruments used to screen for and diagnose impulse control disorders (Minnesota Impulsive Disorders Interview, Structured Clinical Interview for Pathological Gambling, Structured Clinical Interview for Kleptomania, criteria for compulsive buying and compulsive sexual behavior, and the SCID-compatible modules for pyromania, trichotillomania, and intermittent explosive disorder) lack rigorously tested psychometric properties, particularly when used as a group. Comprehensive testing of a diagnostic battery of impulse control disorders is needed.

Although impulse control disorders appear common among psychiatric inpatients, these results should be considered tentatively and as preliminary. No empirically validated diagnostic instruments for these disorders currently exist, and this represents a research need. Additional research requirements include large prevalence investigations, identification of clinical correlates of impulse control disorders in psychiatric groups, studies on the relationship between impulse control disorders and other disorders, and treatment trials to identify safe and efficacious treatments for patients with both impulse control disorders and other psychiatric disorders.

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Clinical Presentations and Treatment Outcomes of Peacekeeper Veterans With PTSD: Preliminary Findings

David Forbes, Ph.D.
Neanne Bennett, M.A.
Dirk Biddle, B.Sc.
David Crompton, M.B.B.S.
Tony McHugh, M.A.
Peter Elliott, Ph.D.
Mark Creamer, Ph.D.

Objective: Despite evidence of potential psychiatric sequelae following peacekeeping operations, no data have appeared on treatment outcome for this population. This study examined intake and treatment outcome data for a group of peacekeepers with posttraumatic stress disorder (PTSD).

Method: Participants were 63 Australian Vietnam veterans and 66 Australian peacekeepers attending specialized PTSD treatment units. Measures of PTSD, depression, anxiety, alcohol use, and anger were obtained at intake and 3-month follow-up.

Results: PTSD scores were more severe for peacekeepers than Vietnam veterans at intake, primarily in reexperiencing symptoms. In terms of comorbidity, only anger was higher among peacekeepers. No differences were apparent in treatment outcome. Initial anger predicted change in PTSD severity for peacekeepers.

Conclusions: The finding of differences between peacekeepers and Vietnam veterans in anger and reexperiencing symptoms, in addition to the attenuating role of anger on treatment outcome, suggests that modification to standard PTSD treatment models may be warranted for peacekeepers.

(Despite mounting evidence of psychiatric morbidity following peacekeeping operations (1), to our knowledge no data have appeared on clinical profiles of peacekeepers who seek treatment or on their response to standard intervention models. Given increasing deployments of defense forces on peacekeeping missions, it is important to better understand the needs and treatment responses of these veterans. In the absence of such data, assumptions that peacekeepers will benefit from the same models of treatment as those used for chronic posttraumatic stress disorder (PTSD) in combat veterans should be questioned.

Treatment programs for Australian Vietnam veterans with PTSD have existed for several years. These programs report modest but clinically significant improvements, with gains maintained to 9-month follow-up (2, 3). Although the programs are designed primarily for Vietnam combat veterans with chronic PTSD and considerable comorbidity, Australian veterans of peacekeeping deployments are increasingly participating in these programs. Differences in clinical presentation and outcome between Vietnam and peacekeeper veterans may be expected given the different nature of peacekeeping stressors (which may include witnessing violence while prohibited from intervening), the more recent onset of disorder among peacekeepers, and the differences in life stages (many peacekeepers have young families and associated stressors).
BRIEF REPORTS


Brief Report

Clinical Presentations and Treatment Outcomes of Peacekeeper Veterans With PTSD: Preliminary Findings

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This study compares initial symptom profiles and treatment outcomes of peacekeepers and Vietnam veterans attending PTSD treatment programs. The findings may inform tailoring of treatment to the veteran’s presentation and operational history, helping to clarify the appropriateness of programmatic treatment models for peacekeeper veterans.

Method

Participants were a convenience sample of 63 Vietnam veterans and 66 peacekeeper veterans attending PTSD treatment programs. Peacekeeping deployments included Timor, Cambodia, Rwanda, and Somalia. At intake, all participants met PTSD criteria on the Clinician-Administered PTSD Scale (4) administered by trained clinical staff.

Peacekeepers (mean age=35.68, SD=7.05) were younger than the Vietnam veterans (mean age=52.69, SD=3.02) and reported more recent symptom onset (mean=72.00 months, SD=48.45, versus mean=278.12 months, SD=130.43) (F=123.04, df=1, 127, p<0.001). As part of a standardized assessment at intake and 3 months after treatment (6 months after intake), participants completed self-report questionnaires including the PTSD Checklist (5), Hospital Anxiety and Depression Scale (6), Alcohol Use Disorders Identification Test (7), and the anger items of the War Stress Inventory used by the U.S. Department of Veterans Affairs in their PTSD programs (8). These measures are valid and reliable and have been used in other studies. Details of these measures and the treatment programs have been reported elsewhere (2).

The study group comprised veterans who completed treatment in groups of six to eight at one of three facilities. The treatment protocol in all programs followed a set of guidelines established by the Australian Centre for Posttraumatic Mental Health. Approximately 61% of the peacekeepers participated in programs where they represented the entire treatment group, and 39% participated in mixed treatment groups with Vietnam veterans. For treatment groups comprising only peacekeepers, the same number of Vietnam veterans from the following treatment group at the same facility were selected for comparison. For treatment groups comprising both peacekeepers and Vietnam veterans, an equal number of randomly selected veterans from the same treatment group were chosen for comparison. After complete description of the study to participants, written informed consent was obtained from all.

Multivariate analysis of variance (MANOVA) was used to compare symptom profiles of peacekeepers and Vietnam veterans at intake. Treatment effects by group were examined by using repeated-measures MANOVA and effect sizes (Cohen’s d). Finally, a hierarchical linear regression was used to explore predictors of treatment outcome for the peacekeeper group.

Results

All participants completed the treatment program, although 3-month follow-up data were missing for 17 (26%) peacekeepers and 13 (21%) Vietnam veterans. For both groups, there were no significant differences on intake measures between those who were missing or present at 3 months. Missing data were imputed by using the last observation carried forward. Application of an alternative imputation method based on pattern matching procedures (9) did not substantively change the outcome of any analysis.

Clinician-Administered PTSD Scale severity scores were significantly higher for peacekeepers than Vietnam veterans (mean=89.73, SD=17.83, versus mean=81.70, SD=18.46) (F=5.10, df=1, 127, p<0.03). Of the three symptom clusters, only reexperiencing was significantly more severe for peacekeepers (mean=25.09, SD=7.11, versus mean=20.96, SD=8.28) (F=9.05, df=1, 125, p=0.003). This difference was not significant after symptom duration was controlled for (F=2.45, df=1, 126, p>0.05).

Clinical profiles from the self-report measures are shown in Table 1. MANOVA identified no significant overall difference between groups on the five self-report intake measures (F=2.09, df=5, 115, p=0.07). Examination of univariate analyses, however, identified a significant difference for anger, with peacekeepers reporting more severe symptoms (F=7.31, df=1, 119, p<0.01). This difference was not maintained after age was controlled for (F=0.245, df=1, 118, p>0.05). Age was significantly correlated with anger (r=−0.25, p<0.01) but not with any other symptom measure. Greater age was associated with less anger.

The repeated-measures MANOVA indicated a significant main effect for time (F=8.45, df=5, 115, p<0.001) but no group-by-time interaction effect (F=0.81, df=5, 115, p=0.54), suggesting that both groups responded equally well to treatment. Controlling for age had little impact on the interaction effect. Effect size analyses using Cohen’s d identified moderate clinical improvements in PTSD, depression, and anxiety for both groups, as well as for anger in Vietnam veterans (Table 1). Negligible change occurred for anger in peacekeepers or for harmful alcohol use in both groups.

The hierarchical regression revealed that anger but not duration of illness, alcohol use, depression, or anxiety, was a significant predictor of 3-month PTSD (controlling for

### Table 1. Intake Scores on Self-Report Measures of PTSD, Alcohol Use, Depression, Anxiety, and Anger for 66 Peacekeepers and 63 Vietnam Veterans Attending a Programmatic Intervention for PTSD

<table>
<thead>
<tr>
<th>Measure</th>
<th>Peacekeepers</th>
<th>Vietnam Veterans</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTSD Checklist</td>
<td>Intake Score</td>
<td>3-Month Score</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td></td>
<td>69.19</td>
<td>8.94</td>
</tr>
<tr>
<td>Depression</td>
<td>13.44</td>
<td>3.47</td>
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<tr>
<td>Anxiety</td>
<td>15.50</td>
<td>3.35</td>
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<tr>
<td>Alcohol Use Disorders Identification Test</td>
<td>12.97</td>
<td>9.97</td>
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<tr>
<td>War Stress Inventory (anger)</td>
<td>4.22</td>
<td>1.99</td>
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</table>

<table>
<thead>
<tr>
<th>Measure</th>
<th>Vietnam Veterans</th>
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<tr>
<td>PTSD Checklist</td>
<td>Intake Score</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
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<tr>
<td></td>
<td>67.83</td>
</tr>
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</table>

PTSD at intake) for the peacekeeper group (F change = 6.01, df=1, 50, B=1.56, SE=0.64, β=0.27, t=2.45, p<0.05), accounting for an additional 3% of the variance. Lower anger levels were associated with better outcomes.

Discussion

We found that the reexperiencing component of clinician-rated PTSD was more severe for peacekeepers than for their Vietnam veteran counterparts. This difference was a function of more recent symptom onset. No differences were apparent on the PTSD self-report measure. Of the two instruments, however, the Clinician-Administered PTSD Scale is considered the more reliable and valid measure.

Of the self-reported comorbidity, only anger was significantly more elevated for peacekeepers. Both groups reported improvement following treatment, albeit with relatively modest gains. These data are consistent with previous reports for Vietnam veterans (e.g., references 3, 4), but to our knowledge this is the first report on treatment effects for peacekeepers with PTSD. The outcomes remain somewhat disappointing; it had been anticipated that shorter duration of illness in peacekeepers would result in a better prognosis.

Several of the differences seem to relate to anger. Peacekeepers reported greater anger at intake and less change in anger following treatment. Of the four comorbid features examined as predictors of PTSD symptom change, only anger was significant.

There are two key implications of these findings for treatment of peacekeepers. First, treatment should ensure that adequate attention is directed at addressing reexperiencing symptoms through trauma-focused interventions. Second, improved results may result from focusing on anger before initiating PTSD treatment or in the early stages of treatment.

Clearly, the current results should be interpreted cautiously and are presented purely as a starting point for clinical research with this population. Numbers were small, precluding use of more sophisticated data analytic approaches and potentially masking important differences (such as across specific deployments). Absence of a measure for use of drugs other than alcohol is problematic given anecdotal reports of widespread use of illicit drugs among peacekeepers. Nevertheless, the findings are a crucial starting point in developing best-practice treatment models with this growing population of veterans.

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References

Tardive Dystonia Associated With Ziprasidone

To the Editor: Although the new atypical neuroleptics have held the promise of fewer extrapyramidal signs, there have been several reports of tardive movement disorders associated with their use. Ziprasidone-associated tardive dyskinesia has been rarely described (1). However, to our knowledge, there have been no reports of tardive dystonia caused by ziprasidone.

Ms. A, a 56-year-old woman, was seen with a chief complaint of involuntary jaw movements. She had a 35-year history of migraines for which she had received a number of treatments (triptans, beta-blockers and calcium channel blockers, antiepileptics, antidepressants, and clonazepam) with limited success. Her first trial with an atypical neuroleptic was 2.5 years before her presentation, when she was administered ziprasidone (80 mg/day). Ms. A experienced a moderate decrease in the frequency and severity of her migraine attacks. Eleven months later, she started noticing mild involuntary movements of her tongue, and ziprasidone was gradually discontinued. Within 2 weeks, involuntary movements involving jaw opening were superimposed on the involuntary movements of her tongue. Gradually, her symptoms intensified, causing eating difficulties accompanied by weight loss (5–6 kg). She also experienced occasional tongue and oral mucosa injuries. Her past medical history was remarkable only for a hysterectomy performed for an ovarian cyst.

A neurological examination revealed frequent, sustained jaw opening, with occasional tongue protrusions and rare dystonic furrowing of her eyebrows. No other abnormalities were noted; brain magnetic resonance imaging was normal. Ms. A had already received botulinum toxin type A injections without success and declined repeat injections.

Tardive dystonia is a late-onset complication of treatment with dopamine-blocking agents consisting of persistent dystonic movements of focal onset involving mainly the cranio-cervical region. It usually appears while receiving a stable dose, but it may manifest while tapering the dose or even 1–3 weeks after discontinuation (as in our case) (2). In many patients, tardive dystonia is combined with the classic tardive oral-buccal-lingual dyskinesias (3). Tardive dystonia is very resistant to treatment and can occur in patients with psychiatric as well as other conditions (in our case, migraine headaches) (2). Although very rare, tardive dystonia has been reported with the use of other atypical neuroleptics, including clozapine, risperidone, and olanzapine (4).

We found no reports of tardive dystonia occurring with ziprasidone on PubMed. Although our patient's clinical diagnosis was unequivocally tardive dystonia, with its time course consistent with ziprasidone monotherapy as the precipitant, the remote possibility of dystonia due to other causes (i.e., idiosyncratic, psychogenic) may be considered. Clinicians should keep in mind that there is no “absolutely safe” atypical neuroleptic since there is always a potential for the appearance of extrapyramidal signs.

References

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Memantine for Treatment-Resistant OCD

To the Editor: Current options for treatment-resistant obsessive-compulsive disorder (OCD) include switching to an alternative selective serotonin reuptake inhibitor or augmentation with dopamine antagonists or other agents (1). Evidence from genetic, behavioral, and neuroimaging studies have indicated glutamatergic alteration in OCD (2). In pediatric OCD patients, the glutamate caudate concentration was abnormally increased, but it decreased after paroxetine treatment (3). Thus, attenuating glutamatergic hyperactivity might be beneficial in OCD. We report a therapeutic effect of add-on memantine, an N-methyl-D-aspartic acid glutamatergic receptor antagonist, in treatment-resistant OCD.

Ms. A, a 34-year-old woman, was seen with incapacitating ego-dystonic obsessions, including fear of harm to her daughter and of losing her mind. She developed compulsive checking behavior to decrease the associated anxiety. Obsessive-compulsive symptoms, initially detected at age 16, remitted spontaneously 2 years later. Subsequent postpartum exacerbation of DSM-IV OCD symptoms associated with major depression occurred at age 30. She also met DSM-IV criteria for schizotypal personality disorder.

Subsequent adequate trials with paroxetine and sertraline were ineffective. Add-on risperidone caused marked akathisia and was discontinued. At her presentation, oral clomipramine was initiated and titrated to 300 mg/day; however, 10 weeks later, there was no significant clinical improvement (Yale-Brown Obsessive Compulsive Scale [4] score=35). Addition of a selective dopamine D2 antagonist, sulpiride (up to 400 mg/day for 4 weeks), was also ineffective (Yale-Brown Obsessive Compulsive Scale score=34). At this point, adding memantine to Ms. A’s regimen of clomipramine (300 mg/day) and sulpiride (400 mg/day) was suggested, and she signed informed consent after explanation of this off-label therapy. Memantine was started at 5 mg/day and titrated to 20 mg/day within 2 weeks. Ms. A reported initial relief on day 7 of combined treatment, and a significant decrease in symptom severity was noted 3 weeks later (Yale-Brown Obsessive Compulsive Scale score=22). There was a substantial reduction in the time occupied by OCD and distress, followed by increased control over obsessions. No clinically significant side effects were noted. Improvement was maintained after 3 months.

Add-on memantine was well tolerated and resulted in clinically significant reduction of OCD symptom severity. Prior treatment resistance and the proximity between symptomatic improvement and the initiation of memantine point to its
possible attenuating effect on the symptoms of OCD. The association of OCD-schizotypal comorbidity with the beneficial effect of memantine is noteworthy in view of a pertinence of glutamatergic dysfunction in both OCD and schizophrenia spectrum disorders (5). Our case suggests that memantine may be an option for treatment-resistant OCD, but controlled studies are needed to substantiate this observation.

References

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Deep Brain Stimulation for OCD and Major Depression

To the Editor: Deep brain stimulation has been proposed to alleviate treatment-resistant obsessive-compulsive disorder (OCD) (1). We examined the long-term efficacy of deep brain stimulation of the ventral caudate nucleus in a case of primary, severe, and intractable OCD with concomitant major depression.

We previously reported the case of Mr. A, a 56-year-old man suffering from a severely disabling and refractory form of OCD that began over 4 decades before (2). He mainly experienced obsessive obsessions concerning potential disturbances in bodily functioning, especially regarding his arms, fingers, legs, and gastrointestinal tract, and his mental capacities, with compulsive verification of functioning, comprising repetitive voluntary movements, controlled intake of foods according to their purgative properties, and repeated mental acts of questioning. Aggressive obsessions with fear of embarrassing thoughts about his children occurred, although considerably less frequently. OCD coexisted only with a lifetime history of recurrent major depression. Mr. A’s written informed consent had been obtained before his participation in the study. Psychiatric assessments included the Yale-Brown Obsessive Compulsive Scale, the Hamilton Depression Rating Scale, the Hamilton Anxiety Rating Scale, and the Global Assessment of Functioning (GAF) scale. Neuropsychological assessments consisted of a wide range of tests primarily exploring memory and executive functions (2).

These evaluations were performed independently and blindly, regarding stimulation settings. No pharmacological and/or psychological treatment was administered postoperatively.

We previously reported that deep brain stimulation of the ventral caudate nucleus progressively improved Mr. A’s depressive and anxiety symptoms until remission was achieved at 6 months (Hamilton depression scale ≤7 and Hamilton anxiety scale ≤10) (2). There was also a marked but delayed reduction in OCD symptom severity on the Yale-Brown Obsessive Compulsive Scale from a baseline score of 25 to 10 and 14 at 12 and 15 months after deep brain stimulation, respectively. His level of functioning on the GAF scale gradually increased from 35 to 60 over the first 15 months of the postoperative period (2). Failure of the pulse generator battery, which was discovered after a clinical impairment, did not affect depressive and anxiety symptom intensity but worsened his obsessive-compulsive manifestations, especially his somatic preoccupations and the related checking compulsions (Yale-Brown Obsessive Compulsive Scale score=21), with a slight deterioration of global functioning (GAF scale score=55) at 18 months. A return to remission levels of OCD (Yale-Brown Obsessive Compulsive Scale score <16) was observed 3 months after replacement of the generator and remained stable until the end of the 27-month follow-up (final Yale-Brown Obsessive Compulsive Scale score=12). This was paralleled by an improvement in psychosocial functioning (final GAF scale score=65). Of interest, no neuropsychological alteration or any adverse clinical effect was reported.

Thus, this finding strengthens our previous report, suggesting that deep brain stimulation of the ventral caudate nucleus could be a promising strategy for the treatment of refractory cases of both OCD and major depression.

References

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Therapeutic Brain Stimulation and Cortical Excitability in Depressed Patients

To the Editor: Changes in central cortical inhibitory pathways, especially associated with γ-aminobutyric acid (GABA) neurotransmission, have been widely implicated in the pathogenesis of major depressive disorder. Furthermore, a
number of studies have supported the view that response to antidepressant interventions is accompanied by an increase in GABA-ergic neurotransmission. In accordance, there is evidence that antidepressant therapeutic brain stimulation techniques, such as vagus nerve stimulation and ECT may act via GABA-ergic pathways (1, 2). Transcranial magnetic stimulation is a noninvasive investigational tool that has been extensively used over recent years to assess human motor cortex excitability (3).

After approval by a local ethics committee and receipt of written informed consent, we tested the motor threshold, postexcitatory inhibition, and intracortical excitability to clarify the influence of vagus nerve stimulation and ECT on motor cortex excitability with transcranial magnetic stimulation in two female patients with unipolar major depressive disorder (40 and 65 years old); each received two different antidepressant stimulatory interventions. In the premenopausal patient, each of the three assessments was performed within the follicular phase of her menstrual cycle. Antidepressant medication (tranylcypromine, 40 mg/day, and venlafaxine, 150 mg/day) was kept constant at least 4 weeks before the first stimulation treatment and throughout the whole treatment. Response was defined as a 50% reduction in score on the 21-item Hamilton Depression Rating Scale.

Ms. A did not respond to 12 sessions of right unilateral ECT (her Hamilton depression scale score dropped only 1 point, from 27 to 26) and was then successfully treated with vagus nerve stimulation (her Hamilton depression scale score dropped from 26 to 12). Ms. B did not respond to 10 weeks of vagus nerve stimulation (her Hamilton depression scale score increased by 2 points, from 29 to 31) and was then successfully treated with 12 sessions of ECT (her Hamilton depression scale score dropped from 31 to 10). In both patients, measurements of motor cortical excitability were performed at baseline, after completion of the first unsuccessful intervention, and after the completion of the second (successful) intervention. Regardless of the type of intervention, all parameters remained unchanged after the first therapeutic trial. After the second therapeutic intervention (vagus nerve stimulation in Ms. A and ECT in Ms. B), both patients showed a treatment response and an increase in cortical silent-period duration and intracortical inhibition.

To our knowledge, this is the first report of an increase in motor cortical inhibition in depressed patients receiving vagus nerve stimulation and ECT. The data suggest that a common GABA-ergic pathway is activated in both vagus nerve stimulation and ECT responders. Furthermore, the data indicate that measurement of motor cortical excitability may be a useful tool for investigating and monitoring inhibitory brain effects of different antidepressant stimulation techniques. In the future, further studies with larger groups are needed.

References

Understanding the Heterogeneity of OCD

TO THE EDITOR: I read with interest the excellent review of dimensional approaches to understanding obsessive-compulsive disorder (OCD) heterogeneity by David Mataix-Cols, Ph.D., and colleagues (1). I agree with the authors that OCD heterogeneity is an important issue and that failure to identify differences within the condition has significantly hindered advances in theory and treatment. My comments focus on the authors’ contention that a dimensional approach to understanding OCD heterogeneity is an inherently superior method.

There have been three recent approaches to understanding OCD symptom heterogeneity. Some researchers have focused on patients’ dominant compulsive behavior to form symptom subgroups (e.g., washers versus checkers). This approach is limited and fails to capture most cases in which patients are seen with multiple classes of symptoms. In recent investigations, the diversity and complex patterns of symptoms seen in clinical presentations have been characterized with multivariate statistical analyses. Factor analysis has been used to identify the latent dimensions of several comprehensive OCD symptom measures. Alternatively, symptom measures have been subjected to cluster analysis to form symptom-based subgroups of individuals. In cluster analysis, individuals are assigned to groups created by maximizing between-group differences and minimizing within-group variability on a set of measures (2).

Cluster analysis may offer several advantages over factor analysis in characterizing OCD heterogeneity, and this categorical approach is not limited in some of the ways Dr. Mataix-Cols et al. implied. In cluster analysis, individuals are unambiguously assigned to unique groups, whereas in factor analysis, each individual is assigned a score on all of the identified latent dimensions. Thus, the factor scores estimated for individuals may not connect the person to a specific dimension. As Dr. Mataix-Cols et al. pointed out, hoarding symptoms have emerged as a symptom dimension that predicts unresponsiveness to current pharmacotherapy and standard behavior therapy. Although there has been limited study, similar results have been reported with a cluster analysis approach in which the hoarding subgroup was less responsive to behavior treatment (3). The results of several recent cluster analyses (e.g., reference 4) suggest that complex symptom presentations can be captured with a cluster analysis approach and that resultant clusters are far from monosymmetric.

The relative merits of categorical and dimensional approaches to psychiatric classification have long been debated. The use of each of these approaches to understanding OCD heterogeneity warrants further investigation.


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LETTERS TO THE EDITOR

Dr. Mataix-Cols and Colleagues Reply

To the Editor: We were pleased to read Dr. Calamari’s letter in relation to our recently published review. It highlights methodological and conceptual issues that are unlikely to be easily resolved. Rather than diametrically opposite techniques, factor analysis and categorical approaches, such as cluster analysis, are likely to be complementary because they constitute different ways of looking at the same phenomenon—the heterogeneity of OCD (1). Both have demonstrated their usefulness. For example, tic-related OCD and early-onset OCD both appear to be overlapping and valid subtypes (2). Our preference for factor analytical techniques to address the classic symptoms of OCD is twofold.

First, our model hypothesizes that obsessive-compulsive phenomena are normally distributed in the general population (3, 4) and are not limited to the traditional diagnostic boundaries of OCD, i.e., they may be present in many other neurological and psychiatric conditions. Conceptually, a dimensional approach seems to reflect this more accurately. Second, if one adopts a strictly categorical approach, patients need to be unequivocally allocated to only one subtype: a patient is either in cluster X or in cluster Y but not both. We doubt that nature is so exact regarding these symptoms. This is one of the main limitations of the DSM-IV multiaxial system and has been heavily criticized. Along with other theoreticians (5, 6), we propose that a dimensional approach can better deal with the problem of comorbidity or the coexistence of various symptom types in OCD. In short, we reiterate the idea that different methods of analysis are probably likely to yield complementary results. We are glad that Dr. Calamari concurs that considering the heterogeneity of OCD is the direction to take in this important area of research.

References

JOHN E. CALAMARI, Ph.D.
North Chicago, Ill.

Heart Transplantation in a Schizophrenia Patient

To the Editor: Mr. A, in the clinical case conference by Stephanie M. Le Melle, M.D., M.S., and Charles Entelis, M.D. (1), is one of many patients with schizophrenia, schizoaffective disorder, and bipolar disorder who have undergone heart transplantation at New York Presbyterian Hospital–Columbia University Medical Center. The case conference provided an opportunity to reflect on what psychiatric consultants to heart transplant programs have learned about helping patients with severe mental illness and other psychosocial risk factors achieve successful heart transplant outcomes.

First, some psychiatric disorders and psychosocial variables do have an effect on transplant outcomes. Recent substance abuse, severe personality disorders, poor global function, and an avoidant coping style predict worse outcomes (2, 3). Second, in some cases, even high-risk patients can do well with expert management. Third, especially in such cases, good family support is invaluable. Fourth, a longitudinal relationship with the transplant team provides an opportunity to assess and modify psychosocial risks much better than evaluation at a single moment in time. Mr. A was undoubtedly a high-risk patient, but he had the benefit of devoted and expert psychiatric care, time to develop a relationship with his transplant cardiologist, and superb support from his family.

I would demur on one point made in the report. There has been no shortage of previous experiences with the development or exacerbation of psychosis in patients after transplantation who were receiving a high dose of corticosteroid immunosuppressant therapy. The role of steroids in precipitating psychosis and mood disorders in heart transplant recipients has been described repeatedly since the late 1960s (4–6).

As we noted previously (2), the presence of psychosocial risk factors should not be reason to prejudicially deny care; rather, it should stimulate efforts to mitigate these risks to provide the best possible care and outcome.

References

References

JOHN E. CALAMARI, Ph.D.
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References

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References

JOHN E. CALAMARI, Ph.D.
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Insight and Aggression in Schizophrenia

To the Editor: The research literature on the association between deficits in awareness and aggression in patients diagnosed with schizophrenia is limited; therefore, it was pleasing to read the article by Peter F. Buckley, M.D., and colleagues (1). Their findings highlighted the legal dilemma that mental health experts are faced with in many competency-to-stand trial evaluations. If a schizophrenic patient who physically assaults another person during a psychotic episode lacks insight into his or her mental illness and does not understand the implications of the violent act, is he or she then mentally fit to be held accountable and to stand trial? The authors briefly discussed this sensitive topic but did not elaborate on an answer.

It is not entirely clear, however, why the authors chose an outpatient population, rather than a forensic or an inpatient population, as the nonviolent control group. The outpatients displayed more insight and less psychopathology than the physically violent patients in a forensic setting (jail or court psychiatric clinic). One might argue, however, that the forensic population displayed symptom profiles similar to those of an institutionalized population because both are involuntarily “locked up” and unable to function in society. The significantly higher scores on the Positive and Negative Syndrome Scale (2) total score in the violent group appear to support this view. Consequently, the insight data might simply be a reflection of the clinical difference between outpatients and institutionalized patients that is unrelated to violent behavior. In other words, an outpatient control group, whether violent or not, would always display higher insight into their mental illness because better awareness is what characterized this group as being able to function in society. In support, the authors reported on the results of Arango et al. (3), who found that lack of awareness predicted violent behavior in inpatients with schizophrenia. The authors, however, did not discuss other studies that have failed to find a relationship between insight and violence in severely mentally ill forensic patients (4), outpatients (5), and inpatients (6). Preliminary analyses of insight data from our inpatient unit at the Nathan Kline Institute for Psychiatric Research–Rockland Psychiatric Center suggest that inpatients with schizophrenia tend to score high on lack of insight—whether violent or not.

References


Dr. Buckley and Colleagues Reply

To the Editor: We appreciate the insightful (no pun intended) comments on our recent publication examining the relationship between violence, psychopathology, and insight in schizophrenia by Mr. Antonius. His point regarding the differential severity of illness across treatment settings is well taken, and we agree that an acute or long-term inpatient comparison group may have been more apt. He concurs with our statement that research on this patient population is difficult to conduct and, consequently, the population is underrepresented in the psychiatric literature. Because our article was limited in scope by the Brief Report format, we are pleased that the citations of Mr. Antonius in this correspondence further detail the literature on this topic. We have provided more lengthy discussions on the medical-legal implications of lack of insight and the treatment implications thereof in other publications (1).

Reference


Conclusions Inconsistent With Results With Citalopram

To the Editor: In their article, Eric J. Lenze, M.D., et al. (1), after noting three limitations of their trial (its small size, problems with random assignment, and diagnostic heterogeneity in their study groups) reported positive summary statements in their conclusions and elsewhere. For example, they wrote, “Notwithstanding these limitations, this study suggests that, as in younger people, SSRIs [selective serotonin reuptake inhibitors] are efficacious and well tolerated in the treatment of anxiety disorders in elderly persons” (p. 149).
The authors’ statements regarding the efficacy/tolerability of citalopram in geriatric anxiety disorders may be true, but their published repetitive positive conclusions are not consistent with their evidence. For example, the Results section demonstrated that 11 members of a treatment group of 17 subjects experienced less anxiety than a placebo group. However, 88% of the treatment group were women, and 47% received various doses of lorazepam while they received various doses of citalopram (according to their clinical response). This treatment group was compared to an unmatched placebo group, 65% of whom were men and (only) 24% of whom were administered various doses of lorazepam.

The treatment group experienced more adverse side effects (intolerable sedation, nausea, and fatigue) and had a higher dropout rate than the members of the placebo group, who experienced fewer side effects and had a lower dropout rate. Furthermore, despite random assignment, the placebo group—when evaluated for mean scores for anxiety and depression—was more symptomatic than the treatment group before the initiation of any “treatment,” and conversely, the “treatment” group was less symptomatic at baseline on both measures, skewing the statistical endpoint contrasts of “treatment effect.”

Design difficulties and the questionable interpretation of results were distorted by graphical analysis. In Table 1, the mean baseline rating of anxiety for the placebo group is 23.1 whereas the corresponding number for the citalopram group is 21.4. However, despite the apparent use of data from Table 1 as the basis for Figure 1, the graphical analysis shows that the subjects taking citalopram began with a higher anxiety score than the placebo group, creating the impression that the citalopram “treatment” group had a more pronounced decrease in anxiety after treatment than it, in fact, did.

The evidence shows that the citalopram group did not tolerate its treatment as well as the placebo group, nor did the authors establish the efficacy of treatment since the groups were not comparable. Unmatched intergroup mean baseline scores for the symptoms of anxiety or depression skewed the statistical analysis, and inaccurate graphical representation of the results distorted the findings. The conclusions of this research effort, funded by Forest Pharmaceuticals and three grants from the National Institute of Mental Health, are misleading and inconsistent with the authors’ data.

Reference

STEFAN P. KRUSZEWSKI, M.D.
Harrisburg, Pa.

Dr. Lenze and Colleagues Reply

TO THE EDITOR: We are pleased that Dr. Kruszewski took interest in our study, but we respectfully disagree with his assertion that our study conclusions are misleading or inconsistent with our results. Our conclusion was that citalopram was efficacious and well-tolerated in elderly persons with anxiety disorders. We are happy to respond to some of his specific concerns. Dr. Kruszewski notes that the placebo and citalopram groups had unequal gender proportions, with more men in the placebo arm. We commented that this was a limitation, but we also mentioned on page 148 that we controlled for gender and found no change in the significantly higher rate of response to citalopram compared to placebo. Thus, the gender proportions did not appear to account for our efficacy finding.

Dr. Kruszewski also notes that the subjects in both groups also received lorazepam. However, there are two important reasons why it is unlikely that lorazepam co-administration could have accounted for our efficacy finding. First, the subjects were taking low doses (the median dose was 0.75 mg/day for the subjects in the citalopram arm). Second, the subjects were required to have been taking a fixed dose of this medication for at least 2 weeks before their random assignment, with no changes in their dosage during the study, and no subjects were administered benzodiazepines during the trial (they kept taking the medication if they were already taking it to avoid the added confounder of benzodiazepine withdrawal during the treatment study). Thus, the subjects still met entry criteria for significant anxiety symptoms despite taking a low dose of lorazepam.

Dr. Kruszewski states that the citalopram group experienced more adverse side effects and had a higher dropout rate than the placebo group. This is not really correct. In fact, a majority of the subjects in both the citalopram and placebo arms mentioned at least one side effect, and the difference in the proportions who reported any side effects was small and statistically insignificant ($\chi^2=1.12$, df=1, N=24, exact $p=0.48$; effect size: $\phi=0.18$). The difference in dropout rates was also small and insignificant ($\phi^2=1.13$, df=1, N=24, exact $p=0.29$; effect size: $\phi=0.18$). Figure 2 on page 148, with the Udvalg for Kliniske Undersøgelser Side Effect Rating Scale, shows that the subjects who were randomly assigned to citalopram tended to have lower side effect scores during treatment. As a whole, these data support the tolerability of citalopram in this population.

Finally, Dr. Kruszewski notes that the Hamilton Anxiety Rating Scale score and Hamilton Depression Rating Scale score were higher at baseline in the placebo groups, but he fails to state that these differences were not statistically reliable. Moreover, the sizes of the effects were small (for the Hamilton depression scale, effect size: $d=0.37$) to extremely small (the Hamilton anxiety scale, effect size: $d=0.06$). In practical terms, a difference of 1.7 points on the Hamilton anxiety scale and 1.1 points on the Hamilton depression scale are not clinically meaningful. Thus, despite Dr. Kruszewski’s assertion, we would have been remiss to conclude that the placebo group was more symptomatic than the treatment group before the initiation of treatment. He also notes that the baseline Hamilton depression scale and Hamilton anxiety scale scores were not the same as the week-0 scores in Figure 1 on page 148, which shows the course of symptoms over 8 weeks of treatment. This difference is because the subjects’ baseline assessment was not on the same day as their week-0 random assignment. The subjects were assessed at baseline to determine inclusion into the study. As is typical of medication studies, they were again assessed with the outcome measure at week 0 (the day of random assignment). The week-0 Hamilton anxiety scale scores shown in Figure 1 demonstrate that
the groups were similar in anxiety severity at the point of random assignment.

Thus, we believe that our conclusions were neither misleading nor inconsistent with the results. Despite the study's limitations owing to the small group size, this is, to our knowledge, the first prospective randomized, controlled study that demonstrates the efficacy of a serotonergic antidepressant medication for late-life anxiety disorders. We are currently confirming and extending the results in a larger clinical trial funded by the National Institute of Mental Health that focuses on late-life generalized anxiety disorder.

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Conclusions Inconsistent With Results With Amphetamines and Divalproex

To the Editor: In their article, Russell E. Scheffer, M.D., et al. (1) reported in their conclusions and elsewhere positive summary statements that included the following: “Pediatric patients with bipolar disorder and concurrent ADHD [attention deficit hyperactivity disorder] can be safely and effectively treated with mixed amphetamine salts after their manic symptoms are stabilized with divalproex sodium” (p. 58).

These ambitious claims were made by the authors after noting what they suggested to be these limitations of their brief trial: 1) ineffectively low doses of mixed amphetamine salts, 2) a failure to increase the divalproex doses to assess greater possible response, 3) the small group size, 4) a study protocol limited to a single academic center, and 5) a failure to address long-term outcomes and safety.

The authors’ statements regarding the efficacy/tolerability of mixed amphetamine salts/divalproex might be true, but their repetitively positive published conclusions are not consistent with their evidence. The announced conclusions, likewise, that appeared in the official publication of APA that reiterated this positive news (2) failed to disclose serious research limitations.

The expressed concerns of Dr. Scheffer and colleagues regarding the limitations of their study, while justified, did not address the serious problems in their research design and reporting:

1. Twenty-five percent of the original subjects (N=40) did not have postrandomization data.
2. At least four individuals in the study became manic, three of whom required hospitalization.
3. The “treatment” period with mixed amphetamine salts was limited to a brief 14 days.
4. An individual could be a positive responder with only one follow-up visit, despite being lost to follow-up thereafter.
5. The 80% positive response rate reported with divalproex was unblinded and open label.

6. The authors failed to disclose which treatment groups experienced “transient” side effects of “low to moderate severity and frequency.”
7. At least one person treated with mixed amphetamine salts became manic.
8. The authors included a misleading statement regarding the absence of worsening manic symptoms with treatment, and their Results section failed to provide information about other serious adverse reactions.

Published positive conclusions of this research effort, funded in part by a grant from the Stanley Medical Research Institute to Dr. Rush, are misleading. The Journal and Psychiatric News must be cautious about favorable generalizations from brief trials whose data from partially unblinded and open-label design do not include results from the research itself that demonstrate serious injuries (e.g., rehospitalizations and induction of mania) as a likely byproduct of the protocol. Representations of preliminary results should not suggest “safety and efficacy” when the data are limited and inconclusive.

References
2. Levin A: Kids with bipolar + ADHD respond to added stimulant. Psychiatr News, Jan 21, 2005, p 46

STEFAN P. KRUSZEWSKI, M.D.
RICHARD PACZYNSKI, M.D.
Harrisburg, Pa.

Dr. Scheffer and Colleagues Reply

To the Editor: In reply to Drs. Kruszewski and Paczynski’s comments, let us consider each point.

1. The doses of mixed amphetamine salts were not ineffective. In fact, the study revealed efficacy for mixed amphetamine salts for the doses used compared to placebo. It is true that higher doses might have been even more effective.
2. We agree that higher doses of divalproex might have led to even greater benefits, although the doses and serum levels used were associated with a substantial rate of response of 80%.
3 and 4. We agree that the small group size and a study conducted at only one site, by definition, limited generalizability and also recommend replication studies. However, we demonstrated strong statistical significance with the group we used.
5. We agree that longer-term studies are needed to best evaluate long-term safety and outcome.

That 20% of the patients with bipolar disorder could not be stabilized while taking open-label divalproex is not particularly surprising. The response rate of 80% with open-label divalproex was substantial, however, and similar to what has been found in other open-label studies (1). The 14-day treatment with mixed amphetamine salts and placebo was long enough to establish clinical statistical significance. Most patients (23 of 29) did elect open treatment with mixed am-
Pharmacologic adverse event reported in their review of the database of though psychosis was found to be the most frequent psychiatric complication that is highly likely to be recognized as an adverse event by clinicians (whether for FDA reporting or for the purposes of medical literature), but addiction is not—despite its more long-lasting, well-documented, and devastating personal and societal consequences. Moreover, be aware that ephedra products have been aggressively marketed as legal alternatives to illegal stimulants, with some ephedra products testing positive for controlled substances of abuse (4). Thus, these products are perhaps more likely to be consumed by those at risk of developing substance use disorders. Since our original case report was published in Psychosomatics (5), I have encountered two additional cases of ephedra dependence.

My own experience with the FDA's Internet and telephone-based reporting "portholes" during attempts to report a highly detailed case report of an ephedra addiction/adverse event led only to dead ends and no returned calls, despite three attempts. My best recourse was to publish this case in the medical literature (5). This data input access issue further complicates the FDA's well-intended data, data that may only represent 1% of the actual adverse event reports in society.

Thus, I hypothesize that ephedra abuse/dependence is a more common adverse event than FDA data indicate, and quite possibly more common than psychosis. Nevertheless, this article summarizing the FDA data and alerting clinicians cannot be overstated in terms of its value and practical worth to psychiatrists and general practitioners. I am very thankful for the authors' product.

References

Shannon C. Miller, M.D., F.A.S.A.M.
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Psychiatric Effects of Ephedra: Addiction

To the Editor: I wish to extend my support to Margaret Maglione, M.P.P., et al. (1) for their article. The issue of the safety of dietary supplements, and specifically ephedra alkaloids, has been long problematic but only recently addressed (2). Although psychosis was found to be the most frequent psychiatric adverse event reported in their review of the database of the Food and Drug Administration (FDA), I offer that substance (ephedra) abuse, and sometimes dependence, is a more frequent occurrence in society.

As addressed in their article, this is known to occur (FDA data: 8.6%) but is only rarely reported in the medical literature (3). This may be due, in part, to the possibility that psychosis is highly likely to be recognized as an adverse event by clinicians (whether for FDA reporting or for the purposes of medical literature), but addiction is not—despite its more long-lasting, well-documented, and devastating personal and societal consequences. Moreover, be aware that ephedra products have been aggressively marketed as legal alternatives to illegal stimulants, with some ephedra products testing positive for controlled substances of abuse (4). Thus, these products are perhaps more likely to be consumed by those at risk of developing substance use disorders. Since our original case report was published in Psychosomatics (5), I have encountered two additional cases of ephedra dependence.

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Thus, I hypothesize that ephedra abuse/dependence is a more common adverse event than FDA data indicate, and quite possibly more common than psychosis. Nevertheless, this article summarizing the FDA data and alerting clinicians cannot be overstated in terms of its value and practical worth to psychiatrists and general practitioners. I am very thankful for the authors' product.

References

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The Multiple Sleep Latency Test in the Diagnosis of Narcolepsy

To the Editor: We read with interest the clinical case conference by Lois E. Krahn, M.D., and Heydy L. Gonzalez-Arriaza, M.D. (1). Excessive daytime sleepiness is a common symptom of many sleep disorders, including narcolepsy. It can be difficult to make a firm diagnosis of narcolepsy, especially when the pathognomonic symptom of cataplexy is absent. Even when present, cataplexy rarely occurs in a physician's office.
As mentioned by the authors, some drug abusers fabricate sleep symptoms to obtain psychostimulants. Although narcolepsy cannot be diagnosed based on the Multiple Sleep Latency Test alone, a properly performed Multiple Sleep Latency Test can help to confirm the diagnosis (2). Drs. Krahn and Gonzalez-Arriaza discussed some of the challenges of performing the Multiple Sleep Latency Test in a suspected narcoleptic patient. For example, in the excellent case presented, the authors appropriately adjusted the timing of the Multiple Sleep Latency Test and the preceding polysomnogram to accommodate the patient’s delayed sleep phase (3). However, their patient also had a short habitual total sleep time of approximately 5 hours, as documented by 1 week of wrist actigraphy. The fact that the patient was able to obtain 7.2 hours of sleep during the nocturnal polysomnogram suggests that he may have insufficient sleep syndrome, possibly associated with inadequate sleep hygiene.

At the University of Mississippi Sleep Disorders Center, we emphasize to our patients the importance of allowing sufficient time for sleep by spending at least 8 hours per night in bed in the week preceding a Multiple Sleep Latency Test. Usually a sleep log is used to document the preceding week’s sleep. We commend the authors on the use of more objective wrist actigraphy, which documented a chronically insufficient sleep time but question assigning the diagnosis of narcolepsy to a patient with apparent chronically insufficient sleep.

As Drs. Krahn and Gonzalez-Arriaza illustrated in this case, the diagnosis of narcolepsy must be based on a combination of history, examination, and overnight polysomnogram findings, in addition to the Multiple Sleep Latency Test. As is known, the results of a Multiple Sleep Latency Test are influenced by the quantity and quality of the preceding 7 nights of sleep (3). Chronic sleep deprivation can mimic narcolepsy on a Multiple Sleep Latency Test. Accordingly, we wonder about the possibility that the Multiple Sleep Latency Test results in the case presented were affected by an accumulated sleep debt that could not be more than partially compensated for by the 7.2 hours of nocturnal sleep preceding the test.

References


Drs. Krahn and Gonzalez-Arriaza Reply

To the Editor: We appreciate the comments of Dr. Rack and colleagues that remind us of the importance of interpreting sleep laboratory test results in a clinical context. We agree that the Multiple Sleep Latency Test is a valuable diagnostic tool. Nonetheless, the role of the clinician is to correlate the Multiple Sleep Latency Test findings with the patient’s clinical presentation. In this instance, the presence of long-standing excessive daytime sleepiness, spells consistent with clear-cut cataplexy, sleep paralysis, and vivid dreams greatly increased the likelihood of narcolepsy. We concur that the sleep testing was performed under less-than-optimal conditions in view of the patient’s delayed sleep phase and chronic partial sleep deprivation. If the patient’s symptoms had been limited to excessive daytime sleepiness, the Multiple Sleep Latency Test findings would have been less persuasive. In the presence of the classic tetrad of narcoleptic symptoms and given that the Multiple Sleep Latency Test results were dramatically abnormal (mean initial sleep latency of 30 seconds and sleep onset of REM sleep at all four naps), we believe that this test confirmed the clinical diagnosis of narcolepsy with cataplexy (1).

Many patients with narcolepsy are now recognized to have sleep maintenance difficulties, which sometimes makes performing a Multiple Sleep Latency Test under optimal conditions, while desirable, at times difficult to achieve. Relying solely on the clinical assessment for establishing the diagnosis of narcolepsy, in our opinion, is not sufficient. The relative lack of physician education regarding narcolepsy, the wide range of cataplectic spells, and the potential need after diagnosis to provide lifelong treatment with medications with abuse potential underscore the need for as much objective data as possible.

Reference

1. Aldrich MS, Chervin RD, Malow BA: Value of the Multiple Sleep Latency Test (MSLT) for the diagnosis of narcolepsy. Sleep 1997; 20:1012–1020

Lois E. Krahn, M.D.
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Suicide Among Physicians

To the Editor: The article by Eva S. Schernhammer, M.D., and Graham A. Colditz, M.D., D.P.H. (1), is the first meta-analysis of suicide rates among physicians, to our knowledge, and is therefore most welcome.

The authors conducted electronic searches in four databases: MEDLINE, PsycINFO, AARP Ageline, and EBM Reviews Cochrane Database of Systematic Reviews. To conduct a comprehensive and systematic literature search, several databases should be used. In psychiatry, it is recommended to include at least Embase (Excerpta Medica) and Biosis (Biological Abstracts) in addition to MEDLINE (Index Medicus) and PsycInfo/PsycINFO (Psychology Abstracts) (2). We would also recommend the Web of Science (http://www.isinet.com/products/citation/wos). Variations in the overlap between databases and the high proportion of journals indexed in only one of the databases emphasize the importance of searching all that we mentioned to ensure optimal coverage of the relevant literature (2, 3).

Drs. Schernhammer and Colditz concluded that since many studies were conducted more than a generation ago, there was a need for more recent studies. We recently published a nationwide study from Norway covering the period 1960–2000 (4). A total of 98 suicides among male physicians and 13 suicides among female physicians were studied. Suicide rates among physicians increased from the 1960s to the
1980s. However, in the 1990s, the rates were significantly lower than in the 1980s among male physicians, other university graduates, and the general population. Nevertheless, in the 1990s, physicians still had a higher suicide rate than other university graduates and the general population, both among men (43.0 per 100,000 person-years; 95% confidence interval [CI]=35.3–52.5) and women (26.1 per 100,000 person-years; 95% CI=15.1–44.9) compared to 23.5 per 100,000 person-years (95% CI=23.1–24.0) and 8.0 per 100,000 person-years (95% CI=7.8–8.3) among male and female nongraduates, respectively.

The suicide rate among female physicians was twice as high as that of the general population as well as other female graduates, even in the 1990s. Of interest, suicide rates increased steeply by age among physicians and other graduates, whereas for nongraduates, the rate was highest among those ages 40–60 years. Drs. Schernhammer and Colditz emphasized the elevated suicide rates among female physicians. However, the higher suicide rates among elderly physicians are also of concern and warrant further investigation.

References

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Reprints are not available; however, Letters to the Editor can be downloaded at http://ajp.psychiatryonline.org.
GENETICS AND NEUROSCIENCE


In the introduction to this book, Larry Squire, Ph.D., points out that the first book called Mechanisms of Memory, by the neuroscientist E. Roy John, was published in 1967 (1). Squire highlights the considerable progress that has been made in understanding memory systems, including a host of new tools, ideas, and discoveries, by comparing the foundation from which Dr. John wrote with the state of the field in the 2000s. Dr. John’s book was based on localization of function, information provided by assemblies of neurons, and electrophysiological correlates of learning and memory. The current volume is based on the development of animal model systems for studying the genetics and synaptic changes underlying behavioral memory, the discovery of long-term potentiation, the concept of multiple memory systems, and delineation of both cellular and molecular contributions to neural plasticity.

The book is organized in a way that provides a foundation for thinking about the molecular and cellular underpinnings of synaptic plasticity and information storage, with particular emphasis on the hippocampus and its role in declarative and spatial learning. Examples from other anatomical and behavioral systems are also included. Dr. Sweatt progresses from well-established facts and background, to a description of current work and thinking in each area, to a final section he clearly indicates should be considered “speculation.” Thus, after a brief introduction to the basics of learning and memory at the psychological level, chapters focus on rodent behavioral learning and memory models (chapter 2), the role of the hippocampus in multimodal information processing and memory consolidation (chapter 3), aspects of long-term potentiation (chapters 4–6 and 9), biochemical mechanisms for short- and long-term information storage at the cellular level (chapters 7 and 8), inherited and acquired disorders of memory (chapters 10 and 11), and the chemistry of perpetual memory (chapter 12). Thus, the reader goes from a basic background of learning theory and synaptic physiology, to a detailed discussion of the biochemical mechanisms of long-term changes in synaptic function and information storage, to consideration of the molecular basis of learning and memory disorders.

The intended users of this book include advanced undergraduates, graduate students, and researchers interested in learning, and it is well designed as a textbook to be used in psychology, biology, and neuroscience programs. Dr. Sweatt’s goal that the book be targeted to active researchers in the fields of learning and memory, at all stages of their career development, may be somewhat ambitious. One unique aspect of this book is that it surveys learning and memory from a molecular level through complex behavioral levels, but this means that it is best viewed as a survey tool. Dr. Sweatt provides an organizational framework for thinking about synaptic plasticity and memory that incorporates biochemical complexity into our conceptualization and understanding. He clearly articulates throughout the book why an understanding of the molecular basis of memory is important to those of us working in the field, since all biological processes are subserved by biochemical phenomena.

The book is well written and includes interesting and illustrative text inserts as well as colorful figures with detailed explanations. Mechanisms of Memory is a successful integration of recent discoveries and technological advances applied to learning and memory at many different levels that will appeal to its target audience of advanced undergraduates and graduates across a number of disciplines.

Reference


LAURA A. FLASHMAN, Ph.D.
Lebanon, N.H.


The advent of the genomic era and recent progress in the fields of statistics and computation methodology are neatly balanced with the traditional cornerstones of psychiatric genetics, such as twin and adoption studies, in this impressive text on psychiatric genetics and genomics. The book has an impressive list of contributors; the editors selected from an exciting range of experts. The text diligently explores its subjects in four sections: Basic Principles, Genetics of Normal and Abnormal Development, Genetics of Abnormal Behaviour in Adult Life, and Applications and Implications.

The first section covers basic molecular genetics, quantitative genetics, linkage, and association. The chapter authors recognize that their audience’s principal realm of experience is in psychiatry and psychology and take pains to ensure that the molecular and quantitative concepts presented are accessible to all levels of expertise. This section also contains many additional suggestions on further reading for those interested in understanding more than just the basics.

The second section includes chapters on personality and cognitive abilities, genetics of mental retardation, reading and language disorders, and childhood disorders. The third section covers personality disorders, affective disorders, schizophrenia, substance misuse, anxiety and eating disorders, and the dementias. Detailed coverage is provided of the major psychiatric syndromes in adult life, with explanations offered for both quantitative and molecular findings. The latest research is discussed and critically reevaluated, and current findings are compared with more traditional methods for a fair and accurate assessment of both systems.

The final section focuses on psychopharmacogenetics, genetic counseling, ethical considerations in psychiatric genetics, and the future and postgenomic psychiatry. Clinical, academic, and ethical perspectives provide a balanced view of the possible future paths for psychiatric genetics.
PROFESSIONAL ISSUES IN PSYCHOLOGY


This tidy, somewhat brief book is made up of 10 chapters devoted to the issue of unity in psychology. A broad range of perspectives is represented—from Sternberg’s opening chapter, suggesting unity in multiple domains, to Kimble’s chapter, reflecting a career-long attempt to formulate an overarching theory of human behavior that could serve as a consensus-building focal point. Others propose social relevance (Levant), diversity (Denmark and Krauss), and methodology (Fishman and Messer; Rychlak) as unifying themes. The final chapter, by Staats, is a cogent summary of the differences between preunified science (psychology in its present state) and unified science (toward which psychology will probably move, although, as in all other sciences, this will take a very long time).

The chapters are uniformly well written, clear, and sensible. Indeed, I found myself swayed by arguments internal to each chapter. Gardner’s reprise of his 1992 article asking whether we should bury psychology or praise it is a genuine delight. He suggests, by the way, that much of psychology is being “cannibalized” by other sciences, perhaps leaving psychology with the study of a “person-centered trio” of personality, self, and will.

At the core of this book is a decades-long soul-searching (or “brain-searching,” according to one colleague) journey seeking to answer the question of whether psychology is a “real” science. Unlike psychiatry, which appears to have largely resolved its identity crisis by out-sourcing psychoanalysis to the humanities, at least some groups within psychology continue to wonder if we measure up to the “hard sciences.” (I must confess to a strong urge to slip into analytic interpretation here.) Departments of psychology have morphed into departments of psychological sciences, brain sciences, cognitive sciences, behavioral sciences, or some permutation thereof, the unifying theme being “science.”

Do read this book, although not for the goal of reaching an answer. It is inevitable that by the end of the 10 chapters you will conclude that unity is hopeless. As Staats points out, the road to unity was much easier at a time when there were fewer scientists, less information, and less sophisticated technology. The increase in all three will make unity less and less likely over time. There is more to the agenda, however, than scientific unity. There are also professional issues that speak to status, money, and power. This facet of unity is best captured in the chapter by Fowler (former Executive Director of the American Psychological Association) and Bullock. It seems to me that this form of unity, although of substantial importance to the guild of psychology, does not befit the remaining chapters’ focus on the science of psychology. Then again, this entire edited volume is about the many faces of psychology.

Two of psychology’s most revered clinical scientists—Paul Meehl and Phil Holzman—were trained analysts who maintained active therapy practices while simultaneously conducting rigorous research in other areas. They seemed not to be bothered by the “lack of unity” in their understanding of psychology but, rather, appreciated that some complexities are resistant to unified views. For my own position, therefore, I can only conclude that what was good enough for them will be good enough for me.

RICHARD R.J. LEWINE, Ph.D.
Louisville, Ky.

LAW AND ETHICS


This volume takes its place as the 23rd in a series that is planned, eventually, to acquaint mental health professionals in each of the 50 states, the District of Columbia, and the federal jurisdictions with a comprehensive yet concise outline and review of the laws that affect these professionals in each respective jurisdiction.

The author has identified and summarized the legal and regulatory issues that have an impact on mental health practice in Kentucky—each broad topic identified is a chapter in the book. Each chapter both describes the specific legal and/or regulatory standards currently in force and outlines the specific areas in which the mental health professional can legally carry out his professional responsibilities. Inasmuch as this volume constitutes, specifically, an identification and brief discussion of the laws and regulations governing the conduct and practice of medical professionals in the state of Kentucky, it will prove to be most relevant to the mental health professional working in that state. The sources of state law reviewed in the book include the Kentucky State Constitution as well as state statutes, administrative rules, judicial decisions, and judicial rules.

The editors note that this series is conceptualized as an easily accessible resource for mental health professionals who do not “know about, much less understand, most of the laws that affect their practice, the services they provide, and the clients they serve.” This volume corrects that lack of knowledge by providing a concise and easily readable over-
view of the current laws and regulations affecting the professional life and work of mental health professionals practicing in the state of Kentucky.

The legal topics covered in this book are organized along a continuum, beginning with a summary of the laws and regulations that cover licensure and certification, third-party reimbursement, and professional incorporation. This is followed by a review of the different issues at the legal-behavioral science interface: the areas in which mental health professionals are asked to provide such services as evaluations of the mental status of litigants, the preparation and presentation of expert testimony in court, and the delivery of psychotherapy services to court-referred juveniles and adults. The more indirect ways in which the mental health professional can be involved and in which mental status issues are, on occasion, prominent (e.g., divorce proceedings or termination of parental rights) are also identified and summarized.

In addition to providing a good reference compendium of the laws and regulations in force in the state of Kentucky (current as of February 2004), this volume also represents a contribution to an ongoing series that the editors envision as establishing a database for comparative interjurisdictional studies. The planned database will "allow for nationally oriented policy studies to identify the variety of legal approaches that are currently in use nationwide and to assess the validity of the behavioral assumptions underlying each variant and, ultimately, lead to a conclusion as to the relative desirability of alternate approaches." This process could be useful in improving future laws in the interests of increasing the effective delivery of high-quality mental health services.

C. ROBERT SHOWALTER, M.D.
Harrisonburg, Va.


This review of ECT and the ethics of ECT enjoys the authorship of well-known, established scholars and practitioners of ECT, with the added advantage of a European as well as an American perspective. This is an overview treatment, encyclopedic in some ways, of the issues of ECT. The authors do a credible job of pulling together a disparate set of fields and perspectives on the use (or lack of use) of ECT in the modern Western world. The tone is even and objective, but what comes through in the content are the voices of advocates, two men who have devoted much of their careers to the robust use of ECT.

The premise of the book is to examine ECT through the lens of modern biomedical ethics. The authors begin with a chapter on the stigmatization of ECT, citing different theories of the origin and maintenance of this stigmatization. The next chapter, an overview of the principles of medical ethics (based on the work of Beauchamp and Childress), identifies the four principles of medical ethics of the "Georgetown" group, namely, beneficence, nonmaleficence, autonomy, and justice. This is a competent overview of these issues; however, in presenting their synthesis on bioethics, the authors manage to give very positive views of ECT, which seems a little bit like editorializing in the news, or giving an opinion before all the facts are presented. Chapter 3 is a history of previous ethical approaches to ECT, and chapters 4 through 7 address the topics of beneficence, nonmaleficence, autonomy, and justice in terms of the specifics of the practice of ECT. These chapters could be called "Efficacy" for beneficence, "Side Effects" for nonmaleficence, "Consent" for autonomy, and "Access" for justice. The authors make the point strongly that the existing literature supports these four principles of biomedical ethics.

The chapter on beneficence addresses the evidence for the efficacy and/or effectiveness of ECT in a variety of disorders, including depressive mood disorders, psychotic depression, mania, postpartum psychosis, schizophrenia, malignant catatonia, and parkinsonian disorder. Also described are the salient features of the effectiveness of ECT, namely, the provocation of convulsive activity and the continuation of treatment. This chapter, in many ways the center of the book, might be expected to be the most important, but it has some weaknesses. It tends to be encyclopedic, and there is no critical differentiation among the studies reported. Furthermore, there are several personal attestations, and these are, to my mind, a bit too much oriented toward celebrities and, for that matter, too celebratory of ECT. However, the basic content is important, namely, that the existing literature supports ECT as an effective treatment for many illnesses, particularly for severe depression when other treatment approaches fail and as a frontline treatment given at the beginning of an episode.

Chapter 5, "Nonmaleficence," basically deals with the side effects of ECT and rightly emphasizes the cognitive effects. The authors give a very nice account of retrograde and antegrade amnesia as well as other memory dysfunctions. They appropriately note that, in many instances, it is very difficult to disentangle the cognitive distortions brought on by the illness itself as opposed to side effects from ECT. One disappointing aspect of this discussion is that the issue of the memory defect is dealt with more anecdotally than through systematic studies. Perhaps the systematic studies do not exist.

The chapter on autonomy thoroughly addresses the idea of consent. The authors do a particularly good job of discussing the subtle ethics of getting consent from someone who is mentally ill and who may have thought disorder as a result. Their views are practical, humane, and well considered ethically.

The chapter on justice addresses the issue of availability of ECT. The authors argue that ECT is an effective treatment with a low incidence of serious side effects that is also cost-effective; however, ECT is not widely available. They discuss the availability of ECT in several Western countries and point out that refusing to give, abstaining from, or being prejudiced against ECT are, perhaps, unethical in themselves. This chapter is passionately written; the authors make their case quite well.

The strength of this small offering is its encyclopedic account of efficacy and outcome studies. It has the advantage of a multicultural perspective, and it strives to give an adequate overview of ethical practice in psychiatry. There are elements that are particularly strong, such as the chapters on autonomy (consent) and justice (access).

The weakness is the authors’ unabashed advocacy for ECT. It is not so much that they say anything that seems to be erroneous or misleading, but their enthusiasm raises the prospect that they might be overly zealous. The vignettes are always positive and always show how ECT saved the person’s life or the absence of ECT may have contributed to someone’s de-
to contain increasing use of brain stimulation in the treatment of mental illness. The book is well written and highly informative. It is fully appropriate that as the elderly proportion of our population increases, we should have a book that addresses the elderly person with psychosis. Schizophrenia in Late Life is an excellent reference book. Dr. Harvey is a psychologist by training and has excellent experience in the study of chronic mental illness. The book is well written and highly informative.

Older people with schizophrenia are an often neglected group. The author describes the history of these patients and gives detailed information about their condition over the past 15 years. For example, elderly people with psychosis have long been shuffled into poorhouses, county farms, and nursing homes. This has made the study of this group difficult. As the asylums expanded into state hospitals, the accounting of elderly people with schizophrenia continued to be difficult, due to overcrowding and poor diagnostic techniques. Only in the last 20 years has operational study of the elderly subgroup of chronically mentally ill people been possible.

We have learned a fair amount about this condition. We see that these people are poorly equipped for the problems of later life. They have seldom been employed as young people and hence have no savings to “retire” on. Similarly, the condition of chronic psychosis usually means that no retirement contributions have been made to government programs by these individuals. As a result, the elderly person with schizophrenia is at the mercy of the least expensive care available, which sometimes results in no care at all.

Cognitive decline is often seen in schizophrenia. This is a common diagnostic problem once the person has become elderly. Many older people have dementia. This can be very difficult to sort out in the elderly person with schizophrenia if the history is unavailable. The cohabitation of demented elders and cognitively impaired elders with psychosis is commonly seen in nursing homes. In this setting, misdiagnosis and the subsequent incorrect treatment of elderly patients causes a multitude of problems.

Even before coming to old age, the elderly person with schizophrenia has had a number of treatments not shared by elderly people without chronic mental illness. Neuroleptic use (with possible tardive dyskinesias) is common, and ECT and even psychosurgery occur often in the histories of elderly patients with schizophrenia. Many former treatments lead to complications in the assessment of cognitive decline. As these people come into treatment settings, triage and care must be provided.

This is a complex group of patients. They bring histories of unemployment, family chaos, and serious medical problems. They need treatment, housing, and care, but they have limited resources of their own. The huge cohort of elderly mentally ill is growing and will do so for several decades. They produce a challenge for the geriatrician and for society in general. Dr. Harvey articulates this topic very well. This is quite a good book and we recommend it.

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strong and almost exclusive affinity to dopamine receptors while behaving clinically like an atypical antipsychotic. The authors posit that amisulpride, which is widely used in Europe but unavailable in North America, could offer some advantage in the treatment of negative symptoms in maintenance therapy. Furthermore, an inspiring reflection about a probable genetic mechanism of risk for schizophrenia, involving variations in the COMT gene, is put forward by Weinberger in chapter 7.

The dopamine hypothesis may also offer an understanding of clinical phenomena, as outlined by Kapur and, albeit in a wider frame, Spitzer. The dopamine system plays a central role in the attribution of salience, a psychological mechanism by which the brain filters and labels important information. Chapter authors stress the idea that dopamine dysfunction, for this reason, could constitute a primary mechanism for the elaboration of delusions and delusional perceptions, eloquently bridging the apparent gap between neuroscience and psychology. Stahl provides an inspiring conclusion that reviews the unmet needs in the treatment of schizophrenia.

Overall, this is a very instructive piece of work, successfully depicting the current state of knowledge regarding the dopamine hypothesis and opening avenues of research and reflection. Exhaustiveness has been preferred to uniformity, making it a heterogeneous work. However, one could argue that it is representative of our relative ignorance on the matter, where there is ample space for controversy and generation of new hypotheses eliciting original and diversified angles of approach. Although some chapters may seem at first glance tedious to the neophyte, this book is undoubtedly a must-read for clinicians and researchers alike who want to better their knowledge of dopamine’s role in schizophrenia.

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Reprints are not available; however, Book Forum reviews can be downloaded at http://ajp.psychiatryonline.org.

Correction

In the article “Impairment of Executive Function But Not Memory in First-Degree Relatives of Patients With Bipolar I Disorder and in Euthymic Patients With Unipolar Depression” (Am J Psychiatry 2005; 162:1980–1982), the name of the second author should be listed as Antonina Scarná, Ph.D.
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Highlights of the 2005 Annual Meeting

The 158th Annual Meeting of the American Psychiatric Association was held in Atlanta, May 21–26, 2005. The total registration was 17,545, compared to 26,728 in 2004. This total includes 5,281 members (17% of the APA membership of 30,579); 8,189 nonmembers, of whom 1,344 were spouses, other family members, and guests; 3,670 exhibitors; 231 members of the media; and 174 staff members. This total also includes 5,423 international registrants, of whom 790 were members and 4,633 were nonmembers.

Business Meeting

The annual business meeting was called to order by Steven S. Sharfstein, M.D., APA President-Elect, in the Georgia World Congress Center on Sunday, May 22, at 12:30 p.m. Michelle Riba, M.D., President, was unable to attend.

First Session

Dr. Sharfstein opened the business meeting and then asked the audience to observe a moment of silence in memory of all members and fellows who passed away during the last year. Dr. Sharfstein noted in particular the passing of Dr. Donald Langsley, past President, and Jay Cutler, past APA Director of Government Relations and Special Counsel. Liza H. Gold, M.D., chairperson of the Committee of Tellers, was unable to attend the meeting, so in her absence, Dr. Sharfstein announced the results of the 2005 election of officers and trustees. Reports to the membership were presented by Nada L. Stotland, M.D., Secretary; Carolyn B. Robinowitz, M.D., Treasurer; James E. Nininger, M.D., Speaker of the Assembly; Joseph E. Rubin, M.D., Speaker-Elect of the Assembly; Yvonne B. Ferguson, M.D., chairperson of the Elections Committee; and Mary K. Marrocco, M.D., chairperson of the Membership Committee. Derek Puddester, M.D., chairperson of the Bylaws Committee, was unable to attend, but the committee’s report was included in the packet distributed at the meeting. James H. Scully, Jr., M.D., presented the annual Medical Director’s report. Reports of all the councils were also available in the packet distributed at the meeting. Dr. Sharfstein then recessed the first session of the business meeting.

Second Session

Following the business meeting, Dr. Sharfstein called to order the annual Forum for all voting members. At the Forum, several members expressed concerns about issues in the field of psychiatry. The annual business meeting and Forum were adjourned by Dr. Sharfstein at 1:00 p.m.

Opening Session

The opening session was called to order by Michelle B. Riba, M.D., 131st President of the Association, at 5:00 p.m., Sunday evening, May 22, in the Georgia World Congress Center. Dr. Riba introduced those seated on the stage with her: members of the Board of Trustees, past Presidents, Assembly officers, chairperson of the Scientific Program Committee, the people introducing the President and President-Elect, the APA Medical Director, the President of the World Psychiatric Association, and the President of the Georgia Psychiatric Physicians Association. Dr. Riba then recognized Ms. Cathy L. Nash, C.M.P., Director of APA’s Annual Meetings Department, for her 25 years of dedication and commitment to the annual meeting and to APA.

Dr. Riba then thanked the members of the Assembly for their hard work and dedication.

Marian I. Butterfield, M.D., chairperson of the Scientific Program Committee, was introduced and thanked by Dr. Riba; Dr. Butterfield then presented a brief report.

Dr. Riba then thanked and recognized the distinguished representatives of psychiatric and other related organizations from the United States and abroad.

John F. Greden, M.D., introduced Dr. Riba, who gave the Presidential Address (printed elsewhere in this issue of the Journal). Lawrence Hartmann, M.D., introduced Steven S. Sharfstein, M.D., President-Elect of the Association, who gave the Response to the Presidential Address, "Advocacy for Our Patients and Our Profession" (printed elsewhere in this issue). Dr. Riba then adjourned the opening session at 6:15 p.m.

Convocation

The 49th Convocation of Distinguished Fellows was held at the Georgia World Congress Center beginning at 5:30 p.m. on Monday, May 23, 2005. Dr. Riba presided. After the processional march, Dr. Riba called the convocation to order. President-Elect Steven S. Sharfstein, M.D., led the ceremony conferring Distinguished Life Fellowship and the induction of Distinguished Fellows of the Association.


**Special Presidential Commendations** were presented to Richard Balon, M.D., in recognition of his distinguished work, efforts, and leadership on behalf of medical student and resident education; Leah J. Dickstein, M.D., in recognition of her leadership as chairperson of the Scientific Program Committee (1995–1996) and as a superb mentor and role model for students, residents, early-career psychiatrists, and colleagues; John F. Greden, M.D., in recognition of his leadership as chairperson of the Council on Research (2000–2005) and of his dedication to increasing and improving the quality of research training for students and residents; Alfred Herzog, M.D., in recognition of his years of devoted service to APA and of his activities as a great clinical role model, teacher, and mentor; JoAnn Macbeth, J.D., in recognition of her dedication and ongoing devotion and service to APA, its members, and the patients and families they serve; Philip R. Muskin, M.D., in recognition of his leadership as chairperson of the Scientific Program Committee (2001–2002) and as chairperson of the Council on Psychosomatic Medicine (2004–2005);
John M. Oldham, M.D., in recognition of his leadership as chairperson of the Scientific Program Committee (1993–1995), as Senior Editor of the American Psychiatric Publishing, Inc. (APPI), Review of Psychiatry series, and chairperson of the APA Council on Quality Care (1999–2005); Allan Tasman, M.D., in recognition of his distinguished service to APA and to the profession of psychiatry; and Cathy Tasman in recognition of her work with the APA Alliance and her diligence, perseverance, and advocacy in support of the mission of APA, its members and their families, and the patients they serve.

The Distinguished Service Award was presented to Thomas N. Wise, M.D., Medical Director of Behavioral Services at the Inova Health System in Falls Church, Va.; Professor of Psychiatry at the Johns Hopkins University School of Medicine as well as Georgetown University and Virginia Commonwealth University; and Editor of Psychosomatics and Advances in Psychosomatic Medicine. Dr. Wise also serves on the editorial board of Psychosomatic Medicine. In relation to APA, Dr. Wise has been President of the APPI Board of Directors, co-chairperson of the DSM-IV for Primary Care project, chairperson of the Committee on Primary Care and Consultation Psychiatry, chairperson of the Task Force on Medical Staff Privileges, and APA liaison to the American College of Physicians. He is a Distinguished Fellow of APA, a fellow of the American College of Psychiatrists, Academy of Psychosomatic Medicine, and American College of Physicians, and past president of both the Academy of Psychosomatic Medicine and the American Psychosomatic Society. Dr. Wise has authored or co-authored 285 articles and book chapters.

The Organizational Distinguished Service Award, which was established by the Board of Trustees in 1964 to be given to any group that has benefited APA, the field of psychiatry, or the mentally ill, was presented to the American Foundation for Suicide Prevention.

After recognizing and acknowledging the work of the Membership Committee and the chairpersons of the award committees, Dr. Riba presented the following additional awards.

The APA/Lilly Resident Research Award, established in 1985 to honor psychiatry residents for excellence in research undertaken during residency, was presented to Eran Chemerinski, M.D., a psychiatry resident in postgraduate year 4 (PGY-4) at the Mount Sinai School of Medicine; Joseph B. Holmgren, M.D., a PGY-4 psychiatry resident at New York University; Soo-Jeong Kim, M.D., a first-year child and adolescent psychiatry fellow at the University of Chicago; Michael S. Marcin, M.D., a second-year child and adolescent psychiatry fellow at Emory University; and Marc J. Miresco, M.D., a PGY-4 psychiatry resident at McGill University.

The Human Rights Award was given to Carola Eisenberg, M.D., who received her medical degree from the University of Buenos Aires and took psychiatric training at Hospicio De Las Mercedes, the University of Maryland, and Johns Hopkins Hospital. She served as Assistant Professor of Psychiatry at Johns Hopkins, staff psychiatrist at the Massachusetts Institute of Technology, Dean for Student Affairs at the Massachusetts Institute of Technology, and Dean for Student Affairs at Harvard Medical School. Dr. Eisenberg was one of five founding members of Physicians for Human Rights, which shared in the 1997 Nobel Peace Prize for its campaign to ban land mines. She has been a member of Physicians for Human Rights missions to El Salvador, Chile, and Paraguay. She served on the Committee on Women in Science and Engineering of the National Research Council and co-chaired the National Institutes of Health (NIH) Conference on Women in Biomedical Careers in 1992. She received the History Maker Award for Women in Medicine from the Association of American Medical Colleges in 2001. In 2002 she received the Morani Renaissance Woman Award from the Foundation for the History of Women in Medicine at Drexel Medical School.

The Human Rights Award was also given to Leon Eisenberg, M.D., who received his medical degree from the University of Pennsylvania, completed his residency at the Sheppard and Enoch Pratt Hospital, completed a fellowship in child psychiatry at Johns Hopkins Hospital, and has been Chief of Child Psychiatry at Johns Hopkins, Chief of Psychiatry at the Massachusetts General Hospital, and chairperson of the Department of Social Medicine and Health Policy at Harvard. In July 1993 he became emeritus, but he continues to serve as consultant to the Division of Mental Health at the World Health Organization in Geneva, where he has chaired many working groups since 1964. He has received the Thomas Salmon Medal from the New York Academy of Medicine (1995), the Rhoda and Bernard Sarnat prize for mental health from the Institute of Medicine of the National Academies of Science (1996), the Institute of Medicine’s Walsh McDermott Medal (2003), and the Ruane Prize for Child and Adolescent Psychiatric Research from the National Alliance for Research in Schizophrenia and Depression (2003). He is an honorary fellow of the Greek Society of Neurology and Psychiatry, the Ecuadorian Academy of Neuroscience, and the Royal College of Psychiatrists (U.K.).

The Human Rights Award was also given posthumously to David Lozovsky, M.D., Ph.D., D.Sci., who passed away in March 2004. Dr. Lozovsky was committed to research on the mental health of citizens of the Soviet Union. As chief of the Section of Biochemistry, Institute of Psychiatry of the U.S.S.R. Academy of Medical Sciences, he coordinated research in biological psychiatry throughout the Soviet Union. In 1977 his dedication to the proper use of psychiatric science led him to resign his appointment and immigrate to the United States to protest abuses perpetrated by members of his profession under a leadership that had been co-opted by the demands of a totalitarian government. As he rebuilt his scientific career at NIH, he never faltered in his allegiance to the highly principled and ethi-
Dr. John S. March, M.D., Professor of Psychiatry and Chief of Child and Adolescent Psychiatry at Duke University Medical Center's Department of Psychiatry and Behavioral Sciences. He also holds faculty appointments at the Duke Clinical Research Institute and in the Department of Psychology: Social and Health Sciences. Dr. March received a bachelor's degree from the University of California at Riverside and a master's of science degree in molecular biology from the University of California at Berkeley. He obtained an M.D.-M.P.H. (epidemiology) degree from the UCLA School of Medicine and later completed a residency in family practice at that institution. Following several years as a family practitioner in rural Montana, Dr. March trained in general psychiatry and child and adolescent psychiatry in the Department of Psychiatry at the University of Wisconsin, Madison. Among his current research projects are psychosocial interventions, the Child Anxiety Management Study, and the Treatment of Adolescent Depression Study, and he is also working to establish a practical clinical trials network in pediatric psychiatry, the Child and Adolescent Psychiatry Trials Network. Dr. March has extensive experience in conducting phase III and IV clinical trials in pediatric psychopharmacology and in consulting to industry in the design and implementation of trials. He has been a member of the American Academy of Child and Adolescent Psychiatry Workgroup on Research, the Tourette's Syndrome Medical Advisory Board, and the Depression/Bipolar Support Alliance Scientific Advisory Board. In addition to published and ongoing research, Dr. March has been active in teaching and training in the treatment of child and adolescent mental disorders locally, nationwide, and internationally.

The American Psychiatric Institute for Research and Education (APIRE)/Kempf Fund Award for Research Development in Psychobiological Psychiatry was presented to the following mentor and mentee: John H. Krystal, M.D. (mentor), Robert L. McNeil, Jr., Professor of Clinical Pharmacology and Deputy Chairman for Research for the Department of Psychiatry, Yale University School of Medicine; and Daniel H. Mathalon, M.D. (mentee), who received his bachelor of arts degree in psychology from the University of California, Berkeley, where he graduated summa cum laude. He received his doctoral degree in clinical psychology from Indiana University and his medical degree from Stanford University. Dr. Mathalon has worked under the mentorship of Dr. John Krystal in expanding research on the use of pharmacological probes with functional magnetic resonance imaging, using pharmacological probes to better understand the neurotransmitter systems that subserve the cognitive functions impaired in schizophrenia.

Donald Gair, M.D., Professor Emeritus at Boston University School of Medicine and former director of services in public mental hospitals for nearly 35 years, received the Agnes Purcell McGavin Award for Distinguished Career Achievement in Child and Adolescent Psychiatry. This award, established in 1964, is given to honor psychiatrists who have done or are currently doing outstanding work related to the preventive aspects of the emotional disorders of childhood.

The Agnes Purcell McGavin Award for Prevention was presented to Charles Casat, M.D., Child Psychiatry Fellow at the New York State Psychiatric Institute and former Director of Research at the Behavioral Health Center, Charlotte, N.C. The Agnes Purcell McGavin Award was established in 1964 in memory of Agnes Purcell McGavin, M.D., an APA Fellow, to honor a psychiatrist who has done and is currently doing outstanding work related to the preventive aspects of the emotional disorders of childhood, through framing concepts, developing proofs, or creating applications.

The Isaac Ray Award was presented to Thomas Grisso, Ph.D., Professor of Psychiatry, Director of Psychology, and Coordinator of the Law-Psychiatry Program at the University of Massachusetts Medical School. His research contributions include concepts and methods for legal competency assessment, reported in the book Evaluating Competencies: Forensic Assessments and Instruments, with Randy K. Otto, Randy Borum, and Jennifer Moye (1986; second edition, 2003); research on developmental capacities and juveniles' legal competence, described in Youth on Trial, co-edited with Robert G. Schwartz (2000); empirical guidance to improve policy and practice in the juvenile justice system's identification of mental disorders in youths, presented in Mental Health Screening and Assessment in Juvenile Justice, co-edited with G. Vincent and D. Seagrave (2005); and work on the provision of necessary interventions, reported in Double Jeopardy: Adolescent Offenders with Mental Disorders (2004). Dr. Grisso has been Executive Director of the American Board of Professional Psychology (Forensic), past president of the American
The **Jack Weinberg Memorial Award for Geriatric Psychiatry** was presented to Kenneth M. Sakauye, M.D., Professor of Clinical Psychiatry at the Louisiana State University Medical Center and Director of the Geriatric Psychiatry Program. This award honors a psychiatrist who has demonstrated special leadership or who has done outstanding work in clinical practice, training, or research in geriatric psychiatry anywhere in the world.

Dr. Riba then introduced Trisha Meili, known to the world as “the Central Park Jogger,” who revealed her amazing story of survival and recovery in her best-selling memoir *I Am the Central Park Jogger: A Story of Hope and Possibility*. The book is not a story of an attack but, rather, one of healing. Ms. Meili then presented the William C. Menninger Memorial Convocation Lecture.

Dr. Riba congratulated all the recipients and adjourned the Convocation at 6:30 p.m.

**Other Awards**

The **Administrative Psychiatry Award** was presented to Gabriel Koz, M.D., Professor of Clinical Psychiatry, Eastern Virginia Medical School, and Medical Director, Eastern State Hospital. This award was established in 1983 to honor an APA member who is a nationally recognized clinician executive, whose effectiveness as an administrator of major mental health programs has expanded the body of knowledge of management in the mental health services delivery system, and whose effectiveness has made it possible to function as a role model for other psychiatrists.

The **APA Award for Research in Psychiatry** will be presented at the 2005 Institute on Psychiatric Services to Dilip Jeste, M.D., Estelle and Edgar Levi Chair in Aging, Director of Sam and Rose Stein Institute for Research on Aging, and Distinguished Professor of Psychiatry and Neurosciences at the University of California, San Diego, and the VA San Diego Healthcare System; and to Herbert Y. Meltzer, M.D., Bixler/Mays/Johnson Professor of Psychiatry and Pharmacology and Director of the Division of Psychopharmacology at the Vanderbilt University School of Medicine, Chairman of the International Psychopharmacology Algorithm Project, and Director of the Schizophrenia Program of Centerstone Mental Health System. This award, formerly the Foundations’ Fund Prize for Research in Psychiatry, is the highest award for research given by APA. The award covers the full spectrum of psychiatric research.

The **APA/AstraZeneca Young Minds in Psychiatry International Awards** program was established in 2002 to recognize and promote promising work from four young physicians working in psychiatry in areas related to bipolar illness and schizophrenia. This year’s recipients were Raymond Y. Cho, M.D., Assistant Professor of Psychiatry and Director of the STEP (Services for the Treatment of Early Psychosis) clinic, Western Psychiatric Clinic and Institute, University of Pittsburgh; Jose M. Goikolea, M.D., psychiatrist at the Bipolar Disorders Program of the Hospital Clinic, Barcelona, Spain; Stefan Leucht, M.D., Assistant Professor (“Privatdozent”), Technischen Universität München, Munich; Etheldreda Nakimuli-Mpungu, M.D., postgraduate student of psychiatry at Makerere University; and Alexander B. Niculescu III, M.D., Assistant Professor of Psychiatry and Neuroscience at Indiana University School of Medicine.

The **APA/Merck & Co., Inc., Early Academic Career Research Award** was established in 2003 to help support the research of a junior faculty member with an interest in mood or anxiety disorders. This year’s recipients were Eduardo D. Leonardo, M.D., Research Fellow at the New York State Psychiatric Institute and the Department of Psychiatry, Columbia University; and Scott C. Matthews, M.D., research fellow at the University of California, San Diego.

The **APIRE/GlaxoSmithKline Young Faculty Award for Research Development in Biological Psychiatry** was presented to Karl Deisseroth, M.D., Ph.D., Assistant Professor of Biochemical Sciences at Stanford University; and Daniel Saal, M.D., Ph.D., Assistant Professor of Psychiatry and Behavioral Sciences at the Emory University School of Medicine. This fellowship, formerly the APIRE/GlaxoSmithKline Junior Faculty Fellowship for Research Development in Biological Psychiatry, was established in 1995 to support the research of a junior faculty member in the biology and psychopharmacology of mood disorders and/or anxiety disorders.

The **APIRE/Lilly Psychiatric Research Fellowship** was established in 1988 to provide support for the career development of a postgraduate medical trainee who has shown exceptional promise in psychiatric research. This year’s recipient was Joshua L. Roffman, M.D., a fourth-year resident at the Massachusetts General Hospital/McLean Hospital adult psychiatry training program and chief resident of the Massachusetts General Hospital consultation-liaison service. He completed undergraduate training at Amherst College, where he earned a summa cum laude degree in neuroscience. During medical school at the University of Maryland, Dr. Roffman participated in the Research Scholars Program, sponsored by Howard Hughes Medical Institute and NIH, where he worked in the laboratory of Dr. Daniel Weinberger.

The **APIRE/Wyeth M.D./Ph.D. Psychiatric Research Fellowship** was presented to Arie Kaffman, M.D., Ph.D., a fourth-year resident at Yale University, who is currently studying whether some of the behavioral sequelae of post-
natale maternal care are mediated by the ability to regulate neurogenesis during development and/or in the adult animal. This award was established in 1996 to support the work of a postgraduate psychiatry trainee who has shown exceptional promise in psychiatric research.

The Assembly Profile of Courage Award was established in November 1996 to formally recognize an APA member who has accepted a risk to his or her professional and personal status by taking an ethical stand against intimidating pressure for the good of patient care and in keeping with APA Principles of Medical Ethics. This year’s award recipient was Richard A. Kaye, M.D., a psychiatrist in private practice in Virginia.

The Simon Bolivar Award, which is given to honor a prominent Hispanic statesman or spokesperson and is designed to sensitize the APA membership to the problems and goals of Hispanics, will be awarded at the 2005 Institute on Psychiatric Services to Nora D. Volkow, M.D., Director of the National Institute on Drug Abuse.

The Solomon Carter Fuller Award will be presented at the 2005 Institute on Psychiatric Services to Nancy Boyd-Franklin, Ph.D., an African American psychologist and a Professor at Rutgers University in the Graduate School of Applied and Professional Psychology. She is also an internationally recognized lecturer and author. This award honors a black citizen who has pioneered in an area that has significantly benefited the quality of life for black people.

The Carol Davis Ethics Award was established by the Board of Trustees in 2003 to honor a former APA employee, Carol Davis, for her 30 years of service to APA and the Ethics Committee. This award is intended to promote the educational role of the ethics process. This year’s recipients were David Wahl, M.D., APA Distinguished Fellow, who has served on the APA Ethics Committee for nearly 10 years; Claire Zilber, M.D., Distinguished Fellow and Editor of the Colorado Psychiatric Society Newsletter during 1992–1998 and again since 2002; and Charles V. Giannasio, M.D., member of the Pennsylvania Psychiatric Society’s Ethics Committee.

The Alexander Gralnick, M.D., Award for Research in Schizophrenia was established in 1966 to honor an individual who has contributed to research into the discovery and/or treatment of the earliest signs of schizophrenia, emphasizing psychosocial aspects of the disease process. The award will be given at the 2005 Institute on Psychiatric Services to Anthony F. Lehman, M.D., Professor and Chair of the Department of Psychiatry at the University of Maryland School of Medicine.

The Manfred S. Guttmacher Award, given to honor outstanding contributions to the literature of forensic psychiatry, was given to Robert I. Simon, M.D., Clinical Professor of Psychiatry and Director of the Program in Psychiatry and Law at Georgetown University School of Medicine.

The Jacob K. Javits Public Service Award, established in 1986 in memory of Senator Jacob K. Javits (R–N.Y.) and conferred annually to a public servant who has made a significant contribution to the cause of the mentally ill, was awarded to the Honorable Eliot Spitzer, Attorney General of the State of New York. Mr. Spitzer has initiated policies to make New York a national leader in investor protection, environmental stewardship, labor rights, personal privacy, public safety, and criminal law enforcement. On legal matters related to mental health care, Mr. Spitzer has strongly sought disclosure of clinical trials data needed to evaluate research results involving children.

Established in 1999 to honor an individual who has made a substantial contribution to advancing the biopsychosocial model of psychiatry, the Judd Marmor Award was awarded to Thomas R. Insel, M.D., Director of the National Institute of Mental Health (NIMH) in Bethesda, Md. He was former W.E. Timmie Professor of Psychiatry and Behavioral Sciences and Director of the Center for Behavioral Neuroscience at Emory University in Atlanta. In his research, Dr. Insel has used molecular, cellular, and pharmacological approaches to explore the neurobiology of complex social behaviors, including maternal behavior, formation of pair bonds, and aggression, and to examine the role of the neuropeptides oxytocin and vasopressin in these behaviors. Dr. Insel serves on the editorial boards of Critical Reviews in Neurobiology, Psychoneuroendocrinology, and Biological Psychiatry.

The Frank J. Menolascino Award for Psychiatric Services for Persons With Mental Retardation/Developmental Disabilities was established in 1997 to recognize an APA member who has made significant contributions to psychiatric services for persons with mental retardation, by means of direct clinical services and/or dissemination of knowledge in this field through teaching or research. This award was presented to Nancy N. Cain, M.D., Clinical Associate Professor of Psychiatry at the University of Rochester School of Medicine and Dentistry. She has been the Director of Psychiatric Services for Individuals with Mental Retardation and Developmental Disabilities since 1985. She has published articles in peer-reviewed journals, coauthored book chapters, and given numerous local, national, and international presentations on these topics.

The Adolf Meyer Award honors outstanding investigators and will be awarded at the 2005 Institute on Psychiatric Services to Jimmie C. Holland, M.D., Wayne Chapman Chair in Psychiatric Oncology at Memorial Sloan-Kettering Cancer Center; Professor of Psychiatry at Weill Medical College, Cornell University; founding President of both the International Psycho-Oncology Society (1984) and the American Psycho-Oncology Society (1986); and Fellow and past President of the Academy of Psychosomatic Medicine. She was also editor of the first textbook of psycho-oncology in 1989 and co-editor of the journal Psycho-Oncology.

The Award for Patient Advocacy was established in 1989 to recognize a public figure respected for personal accomplishments and beliefs who has promoted the improvement of services for people coping with mental disorders and substance abuse and who has fought stigma by speak-
ing out about experiences with mental illness and psychiatric treatment. This award will be presented later in the year to Representative Patrick J. Kennedy (D-R.I.), currently serving his sixth term as the representative from the 1st Congressional district. Kennedy has placed improvement of the nation’s mental health at the top of his legislative agenda. Working with Senator Pete Domenici (R-N.Mex.) and others, he has led the fight to pass mental health parity in the House of Representatives, ending discrimination in health insurance. He has introduced legislation to help states respond to the psychological effects of terrorism, to address crisis shortages of children’s mental health providers, and to keep families with severely mentally ill children from being broken up.

The Oskar Pfister Award was established in 1983 in memory of Oskar Pfister, an ordained minister who studied and used psychoanalytic principles in his work. The award is given to honor outstanding contributions in the field of psychiatry and religion and was awarded to Armand M. Nicholi, Jr., M.D., Associate Clinical Professor of Psychiatry at both Harvard Medical School and Massachusetts General Hospital. He is a diplomat of the American Board of Psychiatry and Neurology and an APA Distinguished Life Fellow.

The Kun-Po Soo Award was presented posthumously to K. Patrick Okura, Ph.D., Director of the Okura Mental Health Foundation. This award is given to recognize significant contributions to understanding the impact and import of Asian cultural heritage in areas relevant to psychiatry, to encourage scholarship and research in culture-specific mental health issues and treatment needs of Asian populations, and to stimulate scientific exchange on transcultural issues.

The Jeanne Spurlock, M.D., Minority Fellowship Achievement Award was established in 1999 to recognize outstanding achievements of former fellows of the minority fellowship program and encourage continued involvement in the program. The award was presented to Robert T.M. Phillips, M.D., Ph.D., Medical Director of Forensic Consultation Associates, Inc. Dr. Phillips also serves as a psychiatric consultant to the Protective Intelligence Division of the U.S. Secret Service and has provided consultation to the National Center for State Courts, the U.S. Justice Department, NIMH, and the Center for Mental Health Services. Dr. Phillips is also a Distinguished Fellow of APA and served as Deputy Medical Director (1993–1998).

The Alexandra Symonds Award was presented to Kathryn J. Zerbe, M.D., Professor and Vice Chairperson for Psychotherapy in the Department of Psychiatry at Oregon Health and Sciences University. She also holds a joint appointment as Professor in the Department of Obstetrics and Gynecology and is Director of Behavioral Medicine in the Center for Women’s Health at Oregon Health and Sciences University. She has authored over 50 clinical papers and book chapters and written four books, including The Body Betrayed: Women, Eating Disorders, and Treatment and the forthcoming Integrated Treatment of Eating Disorders: Beyond the Body Betrayed (W.W. Norton). This award is given to recognize and honor women psychiatrists’ outstanding contributions and leadership in promoting women’s health and the advancement of women.

The George Tarjan Award was established in 1992 to recognize an individual who has made significant contributions to the enhancement of the integration of international medical graduates into American psychiatry. It was presented to Hagop S. Akiskal, M.D., an APA Distinguished Fellow and chairperson of the section on private practice of the World Psychiatric Association. He is also Professor of Psychiatry and Director of the International Mood Center, University of California, San Diego.

The Arnold L. van Ameringen Award in Psychiatric Rehabilitation was presented to J. Steven Lamberti, M.D., Associate Professor of Psychiatry at the University of Rochester Medical Center. The award was established in 1985 in memory of Arnold L. van Ameringen, friend of mental health and rehabilitation of the mentally ill. This award recognizes an institution, organization, or individual that has made an outstanding contribution to the field of psychiatric rehabilitation and care of the chronically mentally ill in the area of clinical service, education, advocacy, research, or a combination thereof.

The APA/NIMH Vestermark Psychiatry Educator Award, which recognizes an educator who has made outstanding contributions to undergraduate, graduate, or postgraduate education and career development in psychiatry, was given to Harold Alan Pincus, M.D., Professor and Executive Vice Chairman of the Department of Psychiatry at the University of Pittsburgh School of Medicine. He is also a Senior Scientist at RAND and directs the RAND—University of Pittsburgh Health Institute in Pittsburgh. Dr. Pincus directs the Robert Wood Johnson Foundation’s National Program on Depression in Primary Care: Linking Clinical and Systems Strategies. Previously he was a Deputy Medical Director of APA, the founding director of APA’s Office of Research, and Executive Director of APIRE.

The Psychiatric Services Achievement Awards were established in 1949 to recognize programs that have made a significant contribution to the field of mental health, that provide a model for other programs, and that have overcome limited staff or financial resources or other handicaps. The Gold Awards were given to Grove Street Adolescent Residence, the Bridge of Central Massachusetts, Worcester, Mass.; and Skyland Trail, Atlanta. The Silver Awards were given to TennCare Centers of Care for Children in State Custody, Tennessee; and Thresholds Grais Apartments, Chicago. The Bronze Awards were given to Youth and Family Centers, Dallas Independent School District, Dallas; and New York Service Program for Older People, New York.

The Assembly William Sorum Award was established in 1991 in memory of William Sorum, M.D., past Speaker of the Assembly. This award honors a Member-in-Training
and a district branch in each Area that have made the most notable progress in Member-in-Training activities, involvement, participation, or representation in APA. The award recipients were Area 2 and Mahmoud A. Mohamed, M.D.; and Area 7, Lee Hamilton, M.D., Steven Thielke, M.D., and the Nevada Psychiatric Association.

The Assembly Warren Williams Speaker's Awards were established in 1984 and are administered by the APA Area councils to recognize outstanding recent or current activity/contributions in the field of psychiatry and mental health. The recipients of the awards were William R. McFarlane, M.D., in Area 1; Norman A. Clemens, M.D., in Area 4; and Jeremy A. Lazarus, M.D., in Area 7.

The Bruno Lima Awards were established in 1995 in memory of Bruno Lima, M.D., one of the original members of the APA Task Force on Psychiatric Dimensions of Disaster. This award recognizes outstanding contributions of district branch members to the care and understanding of the victims of disasters. The 2005 winners of this award were Margaret E. Tompsett, M.D., for her ongoing dedication and direct service in disaster preparedness, education, and training; Ira Brenner, M.D., for his commitment to the cooperation of public organizations in disaster response; Victor Fornari, M.D., for his direct involvement with disaster mental health response efforts over the past 14 years; Allan Rabin, M.D., for his efforts in disaster work and mitigation of potential disaster since residency; and Elspeth C. Ritchie, M.D., for her contributions to the treatment of disaster victims and her role as a combat stress control unit psychiatrist supporting American soldiers in Somalia.

The Nancy C.A. Roeske Certificate of Recognition for Excellence in Medical Student Education is awarded to APA members who have made outstanding and sustaining contributions to medical education, in both salaried and volunteer positions. The winners have demonstrated significant contributions to the advancement of medical student education, including lectures, small group teaching, supervision, and course design. Certificates were awarded to 13 volunteer faculty and 29 salaried faculty.

Scientific Sessions

The scientific program began on Monday, May 23, but continuing medical education (CME) courses and industry-supported symposia began on Saturday, May 21.

The program consisted of 22 discussion groups, 113 symposia, 45 industry-supported symposia, 733 New Research presentations, 164 Young Investigator presentations, one debate, 105 papers presented in 35 scientific and clinical report sessions, 184 workshops (including 51 APA component presentations and 127 issue workshops), 98 CME courses, 11 forums, four medical updates, three Review of Psychiatry sessions, one Advances in Psychotherapy session, three Focus Live sessions, four clinical case conferences, two two-part continuous clinical case conferences, three “Research Consultation With...” sessions, and 12 master educator clinical consultation sessions.

There were 22 lectures presented. On Sunday, May 22, Robert I. Simon, M.D., gave the Manfred S. Guttmacher Award Lecture.


On Tuesday, May 24, the following lectures were given: Distinguished Psychiatrist Lecture, Robert Freedman, M.D.; Kun-Po Soo Award Lecture, discussion of K. Patrick Okura, Ph.D. (deceased), by John Luo, M.D., and Russell F. Lim, M.D.; Judd Marmor Award Lecture, Thomas R. Insel, M.D.; Frontiers of Science Lecture, Daniel Weinberger, M.D.; outside lecture, Robert P. Charron, Esq.; and APA/NIMH Vestermark Psychiatry Educator Award Lecture, Harold Alan Pincus, M.D.

On Wednesday, May 25, the following lectures were given: Oskar Pfister Award Lecture, Armando A. Nicholi, Jr., M.D.; Frontiers of Science Lecture, Nancy Frasure-Smith, Ph.D.; Distinguished Psychiatrist Lecture, Stuart C. Yudofsky, M.D., and Randolph M. Nesse, M.D.; and International Psychiatrist Lecture, Gerald E.M. Ellis, Russell, M.D.

On Thursday, May 26, the following lectures were presented: Distinguished Psychiatrist Lecture, Laura W. Roberts; and Frontiers of Science Lecture, Margaret A. Pericak-Vance, M.D.

Meeting of the Board of Trustees

The Board of Trustees met in regular session on Sunday, May 22.

Meetings of the Assembly

The Assembly met from Thursday, May 19, through Monday, May 23.

NADA L. STOTLAND, M.D.
Secretary, American Psychiatric Association