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Pharmaceuticals for Poststroke and Brain Injury Rehabilitation

ABSTRACT


Key Words: Brain Injury, Stroke, Pharmacologic Therapy, Rehabilitation

In the June and July issues, we introduced the first half of a four-issue special series of the American Journal of Physical Medicine & Rehabilitation, focused on innovative, physiologic treatments for stroke and traumatic brain injury. These disorders are leading causes of adult disability in the United States today, accounting for tremendous personal, social, and financial costs for survivors, caregivers, and society. In the June issue, Hillis has provided an up-to-date review on how physiologic treatments may optimize poststroke aphasia recovery. Choi et al. and Buxbaum et al. have presented data in the July issue on treatment of poststroke spatial neglect.

In this issue, we consider pharmaceutical interventions. Minimal profit incentive to study patent-expired medications for cognition exists—thus, older, familiar medications with proven safety are not usually eligible for industry support, which is available to research newer, relatively unproven agents. The burden of developing a pharmaceutical treatment science for older medications, balancing patient safety with innovation, may have fallen on the resources of individual researchers and public and private grant funding. Clinicians wishing to provide best care for patients despite these limits have established the current practice standard for brain injury rehabilitation, including off-label use of stimulants, dopaminergic agents, cholinesterase inhibitors, and other agents with possible neurotropic or neuroprotective effects. Last year, Hokenson et al. reported that more than 30% of acute rehabilitation patients with poststroke spatial neglect received off-label dopaminergic, stimulant, and alerting medications.

In this issue, we present two papers on pharmaceuticals in neurorehabilitation. Barrett and Eslinger present a preliminary report suggesting that amantadine improved speech fluency in an inhomogenous group of brain-injured subjects, some of whom had linguistic problems, and some of whom may have had attentional or cognitive deficits. Barrett and Eslinger propose studying amantadine for abnormal speech output in acquired aphasia associated with perisylvian cortical injury. Martin et al. performed a meta-analysis of a series of "n = 1" trials of methylphenidate in minimally conscious patients and those in vegetative states following TBI. Surprisingly, they report no definite...
evidence of a methylphenidate treatment effect. Group studies with parallel designs may better address whether persistent improvement is associated with methylphenidate treatment of TBI, because single-subject designs with on-off periods are less sensitive to detect these changes.

REFERENCES
Amantadine for Adynamic Speech
Possible Benefit for Aphasia?

ABSTRACT

Objective: Dopaminergic agents may stimulate behavior and verbal expression after frontal lobe dysfunction. Although amantadine is used in neurorehabilitation of motivational disorders and head injury, it is not commonly prescribed to improve aphasia. This pilot study examined verbal fluency on and off amantadine for nonfluent speech.

Design: Four participants undergoing inpatient rehabilitation, meeting criteria for transcortical motor aphasia had stroke (2), stroke postaneurysm surgery (1), or brain tumor resection (1). We administered 100 mg of amantadine twice a day in an open-label, on–off protocol, with multiple assessments per on–off period.

Results: Off medication, subjects generated a mean 12.62 of words (abnormally few) on the Controlled Oral Word Association test. On medication, word generation significantly improved to 17.71 words (∗P < 0.04), although scores remained psychometrically in the abnormal range.

Conclusions: Further research on amantadine, specifically for nonfluent speech and nonfluent aphasia, including effects on functional communication and control conditions, may be warranted.

Key Words: Amantadine, Aphasia, Rehabilitation

Hypothesis-driven physiologic treatment of cognitive disorders according to cognitive neuropsychological models could be considered true translational rehabilitation. Physiologic treatment might be defined as somatic interventions to induce bodily changes directly, as contrasted with behavioral treatment, which consists of controlling learning experiences to induce neurophysiological change indirectly. Unfortunately, a process of scientific translational method is still developing for physiologic rehabilitation in the acquired speech and language disorder, aphasia.

Nonfluent aphasia occurs with poststroke brain injury when subjects have (1) abnormal spontaneous speech and communication ability, with a conversation partner making the major portion of the effort supporting verbal commu-
amantadine, one million stroke survivors with aphasia in the accompanying chronic neurological disorders, and to consciousness after traumatic brain injury (TBI). Other disorders primarily affecting attention (the ability to focus, remain vigilant, and ignore irrelevant stimuli) or conation (amotivational or apathetic states) may also produce a combination of communication disorder and nonfluent speech. We would suggest that although their problem is of a different origin, these patients are also significantly disabled.

Ideally, pharmacotherapy of aphasia might begin with an agent selected because its predicted mechanisms of action correspond with specific dysfunctional processing in brain-behavior systems, or because an agent is known to act on neurotransmitter–neuroanatomic networks critical to a dysfunctional processes. However, the theoretical basis for improvement with some currently proposed agents for pharmacotherapy of aphasia is not specific to dysfunctional cognitive mechanisms. Instead, agents are often used that may benefit brain function more generally (e.g., decrease poststroke diaschisis, induce a permissive state for plastic remodeling, or improve brain metabolic activity).

Both stimulants and dopamine agonists (e.g., bromocriptine) may stimulate behavior in brain-injured patients with frontal lobe syndromes (for a review, see DeMarchi et al.3). Dopamine agonists may also be helpful for aphasia. Amantadine, which has prodopaminergic and anticholinergic effects, has been in use for many years, has few side effects, and is safe5,6 and inexpensive.7 Its primary indications in medicine, neurology, and rehabilitation include use as an antiviral, for fatigue accompanying chronic neurological disorders, and to improve hyperkinetic and parkinsonian movement disorders. It is also widely used in neurologic rehabilitation for motivational disorders/minimally conscious state after traumatic brain injury (TBI).10,11,11a

In contrast, it is not common rehabilitative practice to prescribe amantadine for communication disorders or nonfluent aphasia. In many rehabilitative settings, in fact, standard care of communication disorders in acute or chronic stages does not combine pharmacologic and behavioral treatment.

The magnitude of the problem of acute and chronic poststroke aphasia mandates wider action to improve its disability. There are an estimated one million stroke survivors with aphasia in the United States alone; thus, a low-risk agent with even minor likelihood to benefit communication might have a significant impact on decreasing the individual and national burden of communication disorder, in lost work time for people with aphasia and their caregivers, dollars spent on care, and reduced quality of life.

Specific information about a possible effect of amantadine on nonfluent aphasia is not easily obtained. To locate recent studies on the use of amantadine in aphasia rehabilitation, we performed a Medline search of published literature (1966 to present) and a Psychlit search of literature (1872 to present) using the terms aphasia, rehabilitation, and amantadine, which identified no articles on either database. Searching aphasia and amantadine identified via Medline one Japanese language article on improvement of perseverative speech in three patients with 200 mg of amantadine daily.14 We then combined the search terms amantadine and verbal behavior to search both databases, but, again, no therapeutic articles were identified. Medline identified a case report of amantadine-induced vocal myoclonus.15

We examined selected existing studies on the effects of amantadine on attention and cognitive function, to determine whether improvement in verbal fluency in patients meeting diagnostic criteria for aphasia was reported. Schneider et al.16 report that 300 mg/day of amantadine administered orally to traumatic brain-injured patients, given in a placebo-controlled fashion to assess improvement in attention and higher cognitive skills, and reduction of agitation, did not have significant effects. Naming and verbal fluency were examined in this negative study, but these two measures were collapsed into a composite cognitive variable, and so medication effect is difficult to determine. In a case study reporting benefits of amantadine treatment in a patient with posthypoxic encephalopathy and transcortical sensory aphasia, Arciniegas et al.17 include a summary statement that verbal fluency improved on amantadine, declined when it was tapered, and improved again when amantadine was reinstated. However, the patient’s fluency and how it was evaluated were not specified. We were, thus, unable to find specific reporting of improved language output or verbal fluency with accompanying documentation.

One of us (A.M.B.) previously attended on an acute inpatient neurorehabilitation service. Established standard evaluation of patients with brain injury by the resident physician staff included assessing frontal lobe function and testing speech and language, including verbal fluency. A standard treatment administered to patients identified on screening as having frontal lobe dysfunction of the amotivational type, including isolated nonfluent
speech, was 100 mg of amantadine administered orally twice daily. To address the lack of specific reports of amantadine benefit in nonfluent aphasia, we retrospectively examined data collected on patients admitted for inpatient neurorehabilitation under A.M.B.’s care, to identify any patients meeting criteria for nonfluent aphasia who were treated with amantadine between July 1999 and February 2001. On our unit, amantadine administered for the treatment of frontal lobe symptoms was given in a nonblinded protocol of multiple on–off sessions 2–6 days in length, to assist with determining, on an individual patient basis, whether to continue the medication at discharge. Our goal in examining this initial case series information collected on a clinical care unit was to learn whether there was evidence supporting further controlled research on amantadine in nonfluent aphasia.

Although amantadine has a longer half-life than do most clinically used stimulants, the clinical on–off regimen over multiple on–off cycles and multiple testing sessions used on the inpatient neurorehabilitation unit was based on that used for administration of stimulants for attention-deficit disorder. We suggest that it may still be appropriate to the study of amantadine for treatment of aphasia. On the basis of previous literature supporting the use of dopaminergic agents for nonfluent aphasia,18,19 amantadine’s cognitive effects on cognition can be postulated to be transient.

SUBJECTS

We identified four records of consecutive patients admitted to the neurological rehabilitation service at the Penn State Rehabilitation Center in the year 2000 (mean 51.75 yrs of age, range 37–66 yrs; mean 10.75 yrs of education, range 8–12 yrs) who met criteria for the diagnosis of nonfluent speech and were treated with amantadine for frontal lobe dysfunction of the amotivational type. To meet our clinical criteria for this diagnosis, subjects had to demonstrate (1) abnormal spontaneous speech and communication ability, with the conversation partner making the major portion of the effort supporting verbal communication, and (2) nonfluent spontaneous speech (fewer than 50 words per minute generated in response to an open-ended question such as “How did you come to the hospital?”). All subjects who were identified (see below) also exhibited (3) relatively spared comprehension of single words and simple commands, and (4) relatively spared repetition of single words and short phrases (e.g., no ifs, ands, or buts), consistent with a possible diagnosis of transcortical motor aphasia.

In the acute rehabilitation hospital where the study was performed, clinical assessment with an instrument permitting aphasia subtyping was not standard. Because the treating attending physician (A.M.B.) felt that syndromic subtyping of speech and language disorders was necessary to plan theoretically based treatment, resident physicians were trained to perform a bedside assessment of spontaneous speech, naming, comprehension, repetition, reading, and writing on every patient (per Albert et al.20 and the Florida Mental Status Examination21), repeated and confirmed in its essential parts by the attending physician. It should be noted that when the combination of nonfluent speech, relatively spared repetition, and comprehension were noted on assessment, we did not rigorously distinguish whether nonfluent speech was primarily a result of language abnormality or whether it was related to a primary attentional disturbance or abnormal conative function. It is possible that the subjects in this study suffered from the latter two disorders.

The subjects were all diagnosed as having a frontal lobe disorder of the primary amotivational type as part of a structured neurocognitive assessment carried out by the therapy and resident physician teams, confirmed in its essential parts by the attending physician (A.M.B.) and based on the Florida Mental Status Exam.21 Amotivational frontal lobe dysfunction was defined as a disinclination to interact or behave that produced impairment on specific tasks and functional disability. Frontal lobe function was assessed by observing spontaneous interactive behaviors and speech, body kinesis, and activities of daily living. Our clinical criteria for the diagnosis of amotivational frontal lobe dysfunction required that subjects also have evidence of cooccurring motor response disinhibition, planning and organizational deficits, and/or deficits of abstract thinking. Although we cannot guarantee that speech therapy was completely identically administered, the same clinician treated all four patients in the study, and all patients were treated for 1 hr, 5 days/wk. This treatment situation was similar for occupational and physical therapy (although several OT/PT clinicians rotated depending on the day of treatment for these specialties). Subjects received treatment with amantadine for frontal lobe disorder as part of our inpatient rehabilitation unit’s established clinical rehabilitation practice.

METHODS

Normal renal function as measured by screening blood urea nitrogen/creatinine was confirmed for all subjects before starting amantadine. We administered 100 mg of amantadine orally twice a day (6 a.m. and 6 p.m.) to all subjects in an on–off multiple-assessment protocol without blinding. On the first day, subjects received 100 mg of amantadine orally (6 a.m.), with the dosage increased to
oral 100-mg doses twice a day thereafter; they were assessed between 2 and 6 days after starting amantadine. Patient 1 received four assessments, one per on-off session, with an ABAB (off-on-off-on) design. Patients 2–4 received multiple assessments per off-on session, in an ABAB protocol for patients 2 (total of six assessments) and 3 (eight assessments), and in an ABA (off-on-off) protocol for patient 4 (ten assessments), who was discharged before the last “on” session could be completed. “Off” periods commenced with 1 day during which subjects received a single, oral, 100-mg dose of amantadine (6 a.m.). Drug-washout periods lasting a mean of 4.25 days (range 3–6 days) were used.

We examined for evidence of a possible treatment effect on verbal fluency by recording the results of bedside testing with the Controlled Oral Word Association Test. Subjects were asked to generate words beginning with the letters F, A, and S in 1 min, respectively, and the score was the total number of allowable words generated (no derivatives, proper names, or repeated words were permitted). A priori, we hypothesized that performance on medication would improve compared with off-medication performance. Therefore, we compared mean performance on and off medication using a one-tailed, paired-sample Student’s t test.

An observed group effect may reflect improvement of similar magnitude in individual patients treated, or it may sum disparate effects in different patients. Disparate treatment effects are of obvious clinical concern, because some patients may not benefit from a treatment, or they may experience adverse effects. We anticipated that not enough trials per patient would be available to detect individual effects with sensitivity. However, to assess for robust disparate individual effects in a preliminary fashion, we performed two-tailed, paired-sample t tests for each subject, comparing mean performance on and off medication, with the understanding that a failure to obtain significance for these comparisons might be attributable to limited power.

RESULTS

Amantadine is reported to be associated with the following side effects in more than 5% of people taking the medication: nausea, dizziness (lightheadedness), and insomnia. In 1–5% of patients, livedo reticularis, depression, irritability, hallucinations, confusion, anxiety, dry mouth, constipation, ataxia, peripheral edema, delirium, orthostatic hypotension, headache, somnolence, nervousness, dream abnormality, agitation, dry nose, diarrhea, and fatigue may occur. The anticholinergic-like effects of amantadine may lead to delirium or attention/memory dysfunction. No side effects were reported in the patients studied during the time they took amantadine, or at any time during their hospitalization.

Off medication, participants generated a mean of 12.62 words (range, 1.5–19.5) on the Controlled Oral Word Association Test (below the first-percentile criterion for a hypothetical subject with 8 yrs of education). On medication, group mean words generated increased (mean word generation, 17.71 words; range, 3.5–28 words; t = 3.38, P = 0.043, two tailed). Results for each subject are presented in Table 1.

When results were examined individually with paired-samples, two-tailed t tests, mean words generated on amantadine significantly exceeded mean words generated off amantadine for only one subject (subject 1; see Table 1). However, all subjects generated more mean words on than they did off medication.

DISCUSSION

This study was designed to examine preliminary data generated from clinical treatment of patients with frontal lobe syndromes with amantadine, to determine whether there is feasible rationale for further study of the drug, specifically as an agent for nonfluent aphasia. The participants in this retrospective analysis all had nonfluent speech and were diagnosed clinically as meeting criteria for diagnosis of transcortical motor aphasia (type 2).

Among rehabilitation professionals, transcortical motor aphasia may not be regarded as the aphasia type most requiring treatment. However, impaired fluency, and impaired language production in general, may be a more relevant target for rehabilitation than other symptoms of aphasia. Fluency may be impaired because of grammatical or phonetic–articulatory deficit, as occurs in classical aphasia syndromes associated with left cortical injury. However, some patients are able to generate utterances that are, from a grammatical and articulatory standpoint, well formed, but that do not initiate or elaborate verbal messages (Raymer, 2003). Although this may be an uncommon form of aphasia in people with left-hemisphere ischemic injury, in our experience, it occurs commonly in neurological rehabilitation, and the underlying causes in neurorehabilitation patients may be diverse. Patients with nonfluent speech, but relatively spared comprehension and repetition, may have a primary disorder of language, or they primarily may have impaired attention or conation. These three disorders are supported by different brain-behavior systems and are impaired by theoretically distinct mechanisms. As in the current patient group, subjects with nonfluent speech may even demonstrate primary cortical pathology in the right hemisphere. In this setting, transcortical mo-
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<td>Right ACoA aneurysm complicated by vasospasm, right MCA, and right putamenal stroke</td>
<td>Left omissions on cancellation; amnesia with confabulation</td>
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<td>18.67/25.33 (35.7% imp.); ( P = 0.017 ), two tailed</td>
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<td>2</td>
<td>66-yr-old man; 11 yrs; 5 off/5 on</td>
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<td>10.80/14.00 (29.6% imp.); ( P = 0.325 ), NS</td>
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<tr>
<td>3</td>
<td>43-yr-old man; 12 yrs; 2 off/2 on</td>
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<td>Abnormal emotional expression, leftward line bisection, (ipsilateral neglect), and left-arm motor neglect</td>
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</tr>
<tr>
<td>4</td>
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<td>Right neglect dyslexia and perseverative speech</td>
<td>CT: large left-basal-ganglia hemorrhage (volume not specified); B12 = 17 after 2 wks of oral supplementation, IM supplemented 1 wk before beginning amantadine; RHP (es. mild)</td>
<td>1.5/3.5 (133% imp.); ( P = 0.201 ), NS</td>
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ACA, anterior cerebral artery; MCA, middle cerebral artery; ACoA, anterior communicating artery; RHP, right hemiparesis; LHP, left hemiparesis; COWA, Controlled Oral Word Association Test; CT, computed tomography; MRI, magnetic resonance imaging; imp., improvement; B12, vitamin B12 level; IM, intramuscular.
transcortical motor aphasia, amantadine treatment might augment communication recovery still further.

If transcortical motor aphasia type 2 is a subset of adynamic frontal lobe disorders, it may not be surprising that our retrospective examination of verbal fluency on and off amantadine suggests that amantadine is of potential benefit. In previous reports, adynamic behavior in frontal lobe disorders seemed to improve on amantadine. In other patient groups not specifically identified as having transcortical motor aphasia, amantadine treatment has been associated with improvement on the Controlled Oral Word Association task.

Although these findings are preliminary, we feel that they may be of pragmatic importance. Pharmacological treatments for aphasia are not yet standard in the assessment and care of aphasia. If amantadine, an inexpensive and safe drug that is easy to administer, improves verbal output even in only a subset of people with communication disorders, it may decrease the cost of care, improve functional outcomes, and positively affect patients’ and families’ lives. Although it is possible that only subjects with adynamic transcortical motor aphasia may benefit from amantadine treatment, this could be formally investigated in studies including subjects with other acute or chronic nonfluent aphasia syndromes.

Our study has significant limitations. Although verbal fluency improved on amantadine, fluency was still uniformly below the normal range. Although it is possible that incremental improvement in fluency improved function, we do not have any evidence that this occurred. Unfortunately, we did not specifically assess whether spontaneous word generation to an open question, or effort of communication, improved; these also would be expected to improve communicative function. We did not comeasure motor function to examine whether a general improvement in kinesis might underlie improved speech in our small group of subjects. The length of treatment needed for optimal results, additional functional and neuropsychological measures to be used to assess improvement, and timing of amantadine administration all need to be elucidated if the agent is to be recommended for clinical use; a larger, prospective patient study may help to address these issues. This retrospective chart review study included data collected in a clinical, rather than a research, setting. As a result, the treatment criteria for prescription of amantadine may not have been as rigorously defined as would be appropriate in a research setting. Also, the subjects included may have had different clinical characteristics and may have been more variable from each other than would be expected in prospective clinical research—some patients included in this report (patients 2 and 4) would be expected to improve for reasons unrelated to amantadine administration (recovery from surgery, B12 supplementation). However, spontaneous improvement does not account fully for the observed on–off medication differences. Lastly, the protocol for amantadine administration varied between subjects; this can occur in a clinical setting, but it might not be appropriate for a prospective study design. The half-life of amantadine (range, 10–30 hrs) limits our ability to state that a therapeutic level was achieved during “on” periods, and that adequate washout occurred when the medication was discontinued for “off” assessments. However, because we observed a significant on–off difference despite this confound, the beneficial effect associated with amantadine administration might be even larger than that we observed.

Amantadine may be particularly feasible for use in rehabilitation, because clinicians are familiar with its use in the setting of brain injury, although for different indications. This medication is widely prescribed for patients with traumatic brain injury, amotivational syndromes, and minimally conscious state, and most rehabilitation professionals are experienced with its use. It is likely that clinicians would be willing to prescribe amantadine for aphasia, were they informed of possible patient benefit. At present, it is not specifically identified among reviewed agents for treatment of aphasia (e.g., Greener et al. or Klein and Albert), and it is unlikely that subjects with aphasia or nonfluent speech who have a normal level of consciousness, and who do not have a history of head injury, receive it.

Amantadine’s properties are not unequivocally useful to augment rehabilitation, however. It may have anticholinergic or anticholinergic-like effects on attention, thinking, and memory (e.g., Postma and Van Tilburg), and it is unlikely that subjects with aphasia or nonfluent speech who have a normal level of consciousness, and who do not have a history of head injury, receive it.

The results of this preliminary inquiry support the feasibility of wider study of amantadine for treatment of nonfluent aphasia symptoms. We propose that investigators should plan further studies of this agent. It may be appropriate for future studies to include subjects with nonfluent speech.
and linguistic, attentional, and conative abnormalities, as we did in this study, including sufficient subjects numbers in each category to permit secondary subgroup analysis. We would argue that such a mixed subject group may be appropriate to study because patients with abnormal speech output may be underrepresented in the current research that is focused on measuring language improvement. Linguistic abnormalities associated with motor speech processing, such as syntactic dysfunction, are not quantified on some standard instruments such as the NIH stroke scale.34 Thus, researchers may systematically underrepresent subjects with nonfluent speech in therapeutic studies.

We urge future rehabilitation researchers to work hard to consider all of the cognitive and functional abnormalities associated with nonfluent speech in studies of aphasia therapies. We would advocate including a range of functional outcome measures, systematic impairment assessment (measures expected to improve vs. those not expected to improve; measures expected to be sensitive to changes of the magnitude observed), and appropriately blinded assessment. Qualitative observations on and off medication, and family/caregiver assessment, may also be an important part of future research. Traditional impairment measures are more sensitive to changes in performance than the functional outcome measures that are currently used. Thus, for future studies, functional outcome measures specific to disorders causing nonfluent speech may need to be developed.

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The Effects of Methylphenidate on Command Following and Yes/No Communication in Persons with Severe Disorders of Consciousness
A Meta-Analysis of n-of-1 Studies

ABSTRACT


Objective: To determine the effects of methylphenidate (MPH) on command following and yes/no communication in brain injured patients with severe disorders of consciousness (DOC).

Design: A meta-analysis of a series of single-subject repeated crossover trials, using doses ranging from 7.5 to 25 mg (median dose: 10 mg), generally given twice a day. A Wilcoxon signed ranks test was performed, comparing mean responsiveness and accuracy by drug condition. Drug effect sizes were calculated for the full group and for participant subgroups of interest.

Results: No significant effect of MPH was seen on either responsiveness or on accuracy in the whole group. None of the patient subgroups examined showed a substantial drug effect size.

Conclusions: This study did not identify a clinically meaningful effect of MPH in the doses used on responsiveness or accuracy in standardized command-following protocols in the overall study group of patients with severe DOC, or in any subgroup that was assessed. Because MPH has been shown to have some positive effects in higher-level patients with TBI, more research is needed to define the types of individuals with TBI who do and do not benefit from this drug, and/or the dose that provides optimal benefit.

Key Words: Brain Injuries, Vegetative State, Minimally Conscious State, Methylphenidate, n-of-1 Studies
Severe brain injury can result from both traumatic and nontraumatic causes. Both forms of acquired brain injury (ABI) frequently result in loss of consciousness. Some individuals quickly move from unconsciousness to performing some level of purposeful behavior, whereas others continue to display severe disorders of consciousness (DOC) for prolonged periods, and even permanently. Coma is the initial state of an individual after a severe brain injury and involves unarousability with the absence of sleep–wake cycles and a general loss of ability to interact with the surrounding environment. Coma typically involves diffuse bilateral hemispheric or brainstem pathology. Individuals who remain unconscious typically evolve into the vegetative state (VS) within 2–4 wks. Whereas the VS reflects the spontaneous recovery of brainstem-controlled bodily functions such as respiration, sleep–wake cycles, and cardiovascular function, patients in the VS, like those in coma, fail to show evidence of conscious interaction with the environment. In contrast, a minimally conscious state (MCS) is distinguished by basic cortically mediated behaviors, such as visual tracking, and movements that occur meaningfully in response to stimulation. Giacino et al. define the MCS (formerly referred to as the minimally responsive state) as a condition of severely altered consciousness in which minimal but definite behavioral evidence of self- or environmental awareness is demonstrated. One of the criteria for diagnosing MCS is the demonstration that commands are followed in a reproducible fashion.

For individuals who remain in the VS or MCS for prolonged periods, improved treatments to enhance recovery and functional abilities are a crucial priority. Whereas the topic of pharmacologic treatment aimed at improving cognitive function in ABI is still in the early stages of research and understanding, most treatments that have been used for this aim are designed to either facilitate or inhibit acetylcholine, norepinephrine, dopamine, serotonin, or GABA. Treatment with these agents after ABI is typically based on sparse empirical support. Most literature is based on case studies and group studies with small sample sizes, and clinicians are often forced to rely on theoretical assumptions from animal literature and other patient groups, and on clinical experience. Despite these limitations, there is evidence that the medical manipulation of neurotransmitters in ABI can have beneficial effects on cognition, including memory, initiation, attention, and executive function. There is, however, very little research that establishes the efficacy of pharmacological intervention on arousal and responding in patients with prolonged DOCs, and the research that has been conducted has been limited to case studies or group studies that lack rigorous control for spontaneous recovery. Thus, this study—a meta-analysis of controlled, single-subject designs—was performed to assess, in a more rigorous fashion, the effects of one such widely used psychoactive agent—methylphenidate (MPH)—on function among patients with prolonged DOCs after ABI.

THE CONTEXT OF THE RESEARCH

The present study involves a meta-analysis of a series of single-subject studies conducted within the responsiveness program (RP) at MossRehab Hospital in Philadelphia. The RP is a specialized assessment program for individuals thought to be in the VS or MCS after brain injury; it relies on the methods of single-subject experimental design to assess sensory, motor, and cognitive function of such individuals and to evaluate their recovery over time and their response to treatments, including psychopharmacologic treatments. The RP was initially developed under a demonstration project grant from the National Institute on Disability and Rehabilitation Research (J.W., principal investigator), from 1992 to 1995. On completion of the demonstration project, the RP was launched as an ongoing clinical specialty program. The general structure of this program, and its use to assess vision and visual attention, as well as command following and yes/no communication, have been described previously. In addition to the work to assess cognitive function, the RP also focused on identifying and treating any medical problems (e.g., hydrocephalus, occult seizures, chronic infection) that might be limiting recovery, and withdrawing any sedating medications (e.g., antispasmodic medications, sedating anticonvulsants) and replacing them, when necessary, with alternatives that were less sedating.

Candidates for admission were reviewed on the basis of referral clinical records and/or reports from nurse liaisons who assessed the patients in person. Patients who were believed to be either vegetative or minimally conscious on the basis of reports of no clear and consistent evidence of conscious responding were admitted to the program and evaluated during their first 2–3 days by a transdisciplinary rehabilitation team, to identify clinically important questions and behaviors that might be under volitional control. In some patients, the initial questions centered around command following, whereas in others they centered around issues of arousal and sensory processing, which needed to be addressed before command following could be meaningfully evaluated.

When command following was the outcome of interest, an individually tailored assessment protocol was designed on the basis of candidate behav-
tions that seemed promising. Command following was defined as the patient’s ability to follow simple statements involving the candidate behavior such as “kick your leg.” When patients seemed to have two different movements under volitional control, establishing yes/no communication was generally the clinical priority. In such instances, candidate behaviors representing yes or no were requested, such as “show me yes (no)” or “touch the yes (no) card.” When patients were successful in demonstrating yes and no signals, these signals were typically incorporated into yes/no communication protocols, in which the patient was asked to demonstrate the appropriate signal in response to short factual questions that required, with equal frequency, a correct response of yes or no. Administration instructions such as patient positioning, delivery of the command or question, time allowed for responding, number of trials administered, and operational definitions of commands, questions, and responses were all standardized and discussed with the treatment team. Order of trial administration was randomized for every assessment session. The protocol was administered across multiple treatment sessions throughout the day, and responses were rated by two observers independently on a proportion of trials to ensure interrater reliability.

Performance was evaluated in two different ways, depending on whether the patient had only one or more than one candidate response potentially under volitional control, as previously described.\textsuperscript{1,4} In cases where only one potential response was identified, the frequency of this response was compared under three command conditions: instructions to perform the movement, instructions to “hold still,” and a silent observation interval of identical length. In cases where two candidate movements were identified, the frequency of the two target responses was compared when the command was to “perform response A” vs. “perform response B.” When these responses were linked to questions, performance was assessed by comparing the frequency of the two target responses when the question required a “yes” answer vs. when it required a “no” answer. All of these assessments evaluated two related issues: responsiveness and accuracy. Responsiveness was defined as the frequency of responses (number of responses divided by the number of trials, regardless of accuracy). Accuracy in the single-response protocols was defined by the nonparametric signal-detection measure, A’.\textsuperscript{20} Accuracy in the dual-response protocols (command and biographical questions) was defined as percent correct on trials where responses occurred. The specific formulas for responsiveness and accuracy in the two types of protocols are shown in Table 1.

In many cases, once baseline performance was assessed, the protocol was continued while a psychoactive drug was initiated, to determine whether the drug improved either responsiveness or accuracy. The drug chosen was frequently MPH, initially because of its safety, ease of assessment, and established (albeit off-label) use in TBI, and, later, because of research suggesting its usefulness in

<table>
<thead>
<tr>
<th>TABLE 1 Computation of responsiveness and accuracy scores</th>
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<tbody>
<tr>
<td><strong>Single-Response Command Protocols</strong></td>
</tr>
<tr>
<td><strong>Responsiveness</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Accuracy</strong></td>
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<td></td>
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</tbody>
</table>

Optimal responsiveness in the single-response command protocols = 0.5 (i.e., 100% responses to command and 0% responses to contrasting condition; possible range, 0–1.0). Optimal responsiveness in the dual-response command and biographical protocols = 1.0 (i.e., 100% responses to both commands). Optimal accuracy in the single-response command protocol = A’ of 1.0 (with 0.5 being chance performance) and 1.0 in the dual-response command and biographical protocols (with 0.5 being chance performance).
higher-level (i.e., not in VS/MCS) TBI patients.\textsuperscript{13,14} Although the mechanisms of MPH are not fully known, it is a psychostimulant thought to affect brainstem and cortical mechanisms responsible for arousal and attention by blocking the reuptake of norepinephrine and dopamine, thus increasing their availability.\textsuperscript{21} Peak plasma concentrations occur 1–3 hrs after an oral dose, with a plasma half-life of 1.5–2.5 hrs.\textsuperscript{21} It acts quickly and has a short half-life; thus, it is ideal for single-subject designs because it can be administered and withdrawn quickly and repeatedly.

Group studies with higher-level TBI patients have shown that MPH improves speed of information processing, on-task behavior, and caregiver ratings of attentiveness.\textsuperscript{11–14} No similar studies have been done with patients in the VS and MCS, but case reports and single-subject experiments suggest that MPH may improve responsiveness and/or accuracy, at least in some instances.\textsuperscript{18,22}

The decision to conduct a MPH trial was made on an individual basis by the treatment team. In many instances, the drug was administered in pseudorandom multiple crossover (ABAB... \textsuperscript{)} design, with data collectors blind to the administration schedule. In each case, data analysis was fed back to the treatment team in an individualized fashion, to guide treatment decisions. Although these individual assessments sometimes showed no apparent drug effect and, on other occasions, suggested drug efficacy, the results often were equivocal because of the great variability in performance from day to day and the limitations posed by short lengths of stay on the possible duration of the assessments.

The intent of this study is to group the individual evaluations discussed above to obtain a clearer understanding of the effects of MPH in this population. Although individual assessments have suggested that MPH can improve responsiveness and accuracy in some instances, group analyses have greater statistical power, and they may help to generalize the results of MPH effects to the larger population of VS and MCS patients. They also may allow assessment of differential efficacy of MPH in VS vs. MCS and on responsiveness vs. accuracy.

**METHODS**

**Participants**

Participants for this retrospective meta-analysis were selected from the larger database of prospectively studied RP patients on the basis of the following criteria: they were participants in either a single- or dual-response command or biographical question protocol; during the assessment, they received MPH in a repeated crossover trial of symmetrical design (e.g., A/B/A, A/B/A/B/A... or B/A/B, B/A/B/A/B... , where A = no treatment and B = MPH, to balance the impact of spontaneous recovery across drug conditions); they had some recorded response in at least one of the two conditions; and there was no change in any other psychoactive medications during the period chosen for analysis. This resulted in the selection of 17 patients who received dual-response command protocols, and five patients who received single-response command protocols. The original data for these cases were collected between November 1996 and October 2002. The longest segment of data that met the above criteria was chosen for analysis, but it was sometimes less than the full interval of the protocol, because of the need to eliminate unbalanced data or data confounded by other drug changes. Characteristics of the participants reported in this study are listed in Table 2. The RP protocols were reviewed by the governing institutional review board, but they were deemed not to constitute research because, although they used experimental methods, they were conducted on

<table>
<thead>
<tr>
<th>TABLE 2 Characteristics of study participants</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
</tr>
<tr>
<td><strong>Cause of Injury</strong></td>
</tr>
<tr>
<td><strong>Age</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Time between injury and rehabilitation admission</strong></td>
</tr>
<tr>
<td><strong>MPH dose</strong></td>
</tr>
</tbody>
</table>

* One participant was admitted >2 yrs after injury, but exact timing is not known. All statistics, other than range, are calculated without this individual.

** Milligrams given at each dose. All but three participants received this dose twice per day. One received it once per day but had data collected only in the 2–3 hrs after that dose. One received this dose three times per day, with the last dose given after data collection was complete.
treatments in routine use, for the purpose of guiding individual treatment decisions. This meta-analysis was given exempt approval for publication because it relied on retrospective data.

Data Analysis

Depending on the protocol (single or dual response), a mean responsiveness and a mean accuracy score were obtained (according to the formulas in Table 1) for each participant, each day. This was done to provide an equal weighting by day, because there was variability in the number of daily data-collection sessions. A pair of responsiveness and accuracy scores (separately reflecting performance on and off MPH) were calculated for each participant by taking a mean of the daily scores across all days in a given drug condition. A Wilcoxon signed ranks test was then performed on the full dataset of dual-response command protocols, comparing mean responsiveness and accuracy by drug condition for subjects in each protocol. Within-subject drug effect sizes were also calculated (mean of individual differences by drug condition/SD of individual differences by drug condition).23

We also calculated effect sizes on participant subgroups of interest among the dual-response command protocols, but we did not conduct a Wilcoxon signed ranks test because of the reduced sample sizes. We had considered the possibility that MPH might be more effective in augmenting responses in MCS patients than in creating the ability to respond among VS patients. Therefore, we eliminated the lowest-level participants (mean accuracy score <0.6 on and off MPH; remaining n = 18) to assess drug effects specifically on patients who were definitely in the MCS. We also eliminated participants with nontraumatic causes of brain injury, to assess the effects of MPH specifically on those with traumatic brain injuries (remaining n = 19), who are known to have a better prognosis for recovery than those with nontraumatic injuries.24 Because of the overall negative results of the study (see Results section), we conducted additional subgroup analyses intended to eliminate possible confounders that might have masked a significant drug effect. Specifically, we eliminated the highest-level participants for response rate (mean response rate >0.85 on and off MPH; remaining n = 10) and accuracy (mean accuracy rate >0.85 on and off MPH; remaining n = 16) to avoid ceiling effects (i.e., performance off MPH, which was sufficiently good to make it difficult to observe further drug-related improvements). Finally, we correlated responsiveness and accuracy on MPH with those same measures off MPH to assess the reliability of these scores across drug conditions (i.e., to ensure that these measures are relatively stable attributes of subjects, rather than measures that are highly contaminated by random noise and that, therefore, might not have been sensitive to drug effects).

RESULTS

Of the participants, some patients received more than one usable protocol, in which case these were treated as separate data points, resulting in a final analysis of seven single-response command protocols and 23 dual-response command protocols.

There was no significant drug effect on responsiveness or accuracy scores in the full set of dual-response command protocols, and the effect sizes were small (see Table 3). Responsiveness and accuracy scores for the two drug conditions in the dual-response command protocols were significantly correlated with each other (responsiveness score: r = 0.88, P < 0.001; accuracy score: r = 0.72, P < 0.001), suggesting stability in a given patient’s responsiveness and accuracy across drug conditions. Effect sizes calculated on the MCS subgroup, and on subgroups that did not display ceiling effects, as discussed above, were similarly very small, as shown in Table 3, with the exception of one effect size in the medium range.

MPH was associated with small to medium effect sizes in a negative direction in the single-response command protocols with respect to both responsiveness and accuracy, either when calculated using the “hold still” or the “observe” condition as a reference (see Table 3).

The distribution of difference scores on and off MPH, for both responsiveness and accuracy in the dual-response command protocols, are shown in Figures 1 and 2, demonstrating that they are centered around zero and seem unimodal in nature.

DISCUSSION

The results of this study fail to support a clinically meaningful effect of MPH on either rate of responding or accuracy of responding in command-following protocols among patients with prolonged and severe DOCs. In view of studies suggesting the benefits of MPH in other samples,11–14,25 however, it is important to consider the possible limitations in the study design. One is the relatively small sample and limited statistical power. However, the effect sizes computed suggest that if MPH has clinical effects on responding in this population, they must be very small (indeed, negative in the single-response command protocols), and it would, therefore, require a very large study to detect them with certainty. It is also possible that our measures of responsiveness and accuracy were unreliable, and that the “noise” they contained interfered with the measurement of a drug-related “signal.” However, the moderate to high correlations between responsiveness scores
and accuracy scores across drug conditions suggest that these measures have sufficient stability to support a drug effect analysis. Another possibility is that MPH had carryover effects that obscured differences between on- and off-drug performance. We collapsed data together from each subject’s on-MPH and off-MPH days, respectively, into two representative data points. If MPH effects tended to carry over into the off-drug performance scores, this might reduce our sensitivity. However, our other work with MPH has successfully used similar repeated crossover designs without finding evidence of carryover effects. Moreover, we plotted the data for several subjects on a day-by-day basis, and although considerable performance variability was seen both within and between drug conditions, there was no sign of carryover effects.

We considered the possibility that MCS patients might respond to the drug but that VS pa-

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**TABLE 3: Responsiveness and accuracy scores (mean [SD]) for dual- and single-response command protocols**

<table>
<thead>
<tr>
<th>Responsiveness</th>
<th>Accuracy</th>
<th>P Value</th>
<th>On MPH</th>
<th>Off MPH</th>
<th>Effect Size</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dual-response full data (n = 23)</td>
<td>0.81 (0.23)</td>
<td>0.79 (0.22)</td>
<td>0.18</td>
<td>0.22</td>
<td>0.32</td>
<td>0.18</td>
</tr>
<tr>
<td>Dual-response (excluding Ss with ceiling) (n = 20)</td>
<td>0.60 (0.20)</td>
<td>0.60 (0.20)</td>
<td>0.45</td>
<td>0.45</td>
<td>0.27</td>
<td>0.27</td>
</tr>
<tr>
<td>Dual-response with near-chance accuracy (n = 18)</td>
<td>0.83 (0.25)</td>
<td>0.75 (0.25)</td>
<td>0.15</td>
<td>0.25</td>
<td>0.17</td>
<td>0.17</td>
</tr>
<tr>
<td>Single-response protocol “hold still” (n = 7)</td>
<td>0.36 (0.13)</td>
<td>0.32 (0.15)</td>
<td>0.37</td>
<td>0.37</td>
<td>0.37</td>
<td>0.37</td>
</tr>
<tr>
<td>Single-response protocol “observe” (n = 7)</td>
<td>0.32 (0.15)</td>
<td>0.32 (0.15)</td>
<td>0.37</td>
<td>0.37</td>
<td>0.37</td>
<td>0.37</td>
</tr>
</tbody>
</table>

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**FIGURE 1** Figure 1 shows the distribution of drug-impact scores (proportion of trials with responses on MPH — proportion of trials with responses off MPH) on responsiveness for the full sample of dual-response command and biographical question protocol participants. A drug-impact score of 0 indicates equal response rates in both drug conditions, whereas positive values indicate greater responsiveness on MPH. Each dot represents the value for an individual subject.

**FIGURE 2** Figure 2 shows the distribution of drug-impact scores (proportion of correct trials on MPH — proportion of correct trials off MPH) on accuracy for the full sample of dual-response command and biographical question protocol participants. A drug-impact score of 0 indicates equal accuracy levels in both drug conditions, whereas positive values indicate greater accuracy on MPH. Each dot represents the value for an individual subject.
tients may not. To test this possibility, we removed patients that were performing at accuracy levels near chance and recalculated the effect sizes. This did not substantively alter the calculated effect sizes. Similarly, the elimination of patients who were performing close to ceiling, in which case a drug effect might be difficult to detect, did not alter the effect sizes. The one medium effect size, favoring MPH, occurred when patients with near-ceiling levels of accuracy were eliminated. However, rather than this effect size appearing in accuracy—as it should have if ceiling performance were obscuring the drug effect—it appeared in responsiveness, suggesting that it was likely a spurious finding. We also considered the possibility that TBI patients may respond to the drug, whereas non-TBI patients may not. However, after removing patients with a non-traumatic cause, effect sizes remained small. (Numbers of nontraumatically injured patients were too small to analyze as a subgroup.)

We also considered whether there might be subgroups of patients within the larger sample who were “drug responders” and other patients who were not. Although a rigorous search for subgroups is difficult with samples of this size, a review of the distributions of drug effect scores demonstrated unimodal distributions centered around zero, providing no hint of such subgroups for response rate. There were two subjects involved in dual-response command protocols that showed a large improvement in accuracy scores on MPH. However, further investigation revealed that these subjects were performing far below chance (chance performance = 0.5) off MPH, rather than performing substantially above chance on MPH (off-MPH accuracy rates of 0.33 and 0.36, and on-MPH accuracy rates of 0.67 and 0.72), suggesting that they were statistical outliers rather than true drug responders. When these two outliers are removed, the accuracy distribution seems symmetrical and centered around an effect of zero.

Perhaps the greatest limitation of this study is that although each assessment protocol was conducted prospectively, the meta-analysis was based on a retrospective selection of cases without confounding factors. This was undoubtedly a biased sample in that participants whose lengths of stay were very short or who had other psychoactive drugs added or removed during their MPH trial were eliminated from analysis. Moreover, the responses assessed and commands given varied across subjects, and there was no standardization of MPH dose. However, we have no reason to suspect that these criteria were specifically biased against participants with the greatest drug responses to MPH, and the intent in prescribing MPH is to improve a central arousal and information-processing function, not to target a specific motor behavior. Thus, although we cannot rule out the possibility that some patients may have had clinically meaningful drug responses, nothing in the analyses we have conducted in this study would motivate a more extensive search for MPH effects in ABI patients with severe DOCs. The median dose of MPH used was 10 mg (range, 7.5–25), generally given twice a day. It is possible that the small, nonsignificant effect sizes seen here reflect underdosing. Future studies will need to weigh the benefits of studying higher doses of MPH vs. studying other classes of medications.

The results of this analysis were surprising to the authors in view of their research on MPH in higher-level patients with brain injury, and in view of the impression derived from a number of the individual single-subject assessments, that particular patients seemed to increase either their responsiveness or their accuracy in response to this medication. These impressions may have arisen from unbalanced individual designs (e.g., A/B/A/B, rather than A/B/A or A/B/A/B/A), which still may have slightly confounded spontaneous recovery with MPH administration compared with the subset of data used for the analyses reported here. The impression of efficacy may have also arisen from internal “reporting bias,” in which cases that seemed to show drug responses were remembered and discussed more than those that did not, whereas in reality, both types may have come from the same overall distribution of results—an effect of zero plus/minus substantial variability. This underscores two dilemmas inherent in single-subject investigations. First, such investigations may not provide definitive results—even on the individual case—in the context of confounding, extreme variability, or limitations in the volume of data. Second, even if the results of each single-subject investigation are to be trusted, the process of deriving generalized conclusions is fraught with error unless an unbiased and structured group analysis is compiled.

CONCLUSIONS

We have conducted a meta-analysis on a series of single-subject studies of the effects of MPH on command following in patients with ABI resulting in severe and prolonged DOCs. On the basis of this analysis, we did not detect a clinically meaningful effect of MPH, with the doses used, on responsiveness or accuracy in standardized command-following protocols in the overall group, or in any subgroup that was assessed. Because MPH has been shown to have some positive effects in higher-level patients with TBI, more research is needed to define the types of individuals who do and do not benefit from this drug. Moreover, this study reveals some of the limitations associated with attempts at...
rigorous single-subject experimental designs, at least within the constraints of an inpatient rehabilitation stay. This, in turn, highlights the importance of further group research, involving parallel-group designs, to guide definitive assessment of the impact of larger doses of MPH or other psychoactive drugs in this population.

ACKNOWLEDGMENTS

We would like to thank Charles O’Malley for data collection for the meta-analysis, and Dr. Andrea Laborde and Ms. Patricia Grieb-Neff for participation in the data analysis. We would also like to thank Drs. Andrea Laborde, Jeanne Pelensky, Nathaniel Mayer, Madeline DiPasquale, Eileen Fitzpatrick-DeSalme, and Christianne Stern, and Ms. Monica Vaccaro for their participation in the single-subject analyses that form the basis of this research. Finally, we thank the many Drexel University Coop students and rehabilitation clinicians who implemented the single-subject analyses, and the patients and their caregivers for their participation.

REFERENCES

Falling in Parkinson Disease
Identifying and Prioritizing Risk Factors in Recurrent Fallers

ABSTRACT


Objectives: To identify falling risk factors in a study population of recurrent fallers compared with nonfallers who have Parkinson disease, and to prioritize falling risk factors in this patient population to target them for modification.

Design: Twenty-three recurrent fallers and 25 nonfallers who have Parkinson disease were recruited, and they participated in a comprehensive assessment probing for the presence of falling risk factors. To identify falling risk factors, a group comparative design was used to compare recurrent fallers and nonfallers across an array of variables. To prioritize those risk factors, modeling using recursive partitioning was performed, entering into the model falling, risk factors identified in this and other studies that were considered potentially modifiable.

Results: A specific profile of variables distinguished recurrent fallers who have Parkinson disease in our study population: higher disease severity, higher level of motor impairment, higher level of disability, impaired leg agility or lower-limb coordination, impaired ability to arise from a chair or compromised proximal lower-limb motor control, impaired ambulation, impaired motor planning of the hands and feet, impaired dynamic balance as measured by ability to walk in tandem, and fear of falling. Recursive partitioning prioritized three risk factors: impaired ambulation, impaired lower-limb motor planning, and orthostasis.

Conclusions: In this study, an idiosyncratic falling risk factor profile was demonstrated among our subjects who have Parkinson disease. Three variables were prioritized for potential modification: impaired ambulation, impaired lower-limb motor planning, and orthostasis.

Key Words: Parkinson Disease, Falling, Risk Factors, Movement Disorders, Aging, Neurodegenerative Diseases
Parkinson disease is a common aging-related neurodegenerative disease. Its prevalence in the United States is 20 per 100,000. Its cardinal clinical signs include tremor, rigidity, bradykinesia, and gait and postural disturbances. Falling among those who have Parkinson disease is common: up to 70% of people who have Parkinson disease are reported to fall yearly, and 13% are reported to fall once weekly. Falling risk factors in Parkinson disease have been identified in several studies (Table 1). These include risk factors that already were recognized as such among the elderly (e.g., orthostasis, polypharmacy, and dementia) and those that were idiosyncratically associated with those who have Parkinson disease (e.g., freezing of gait and undesired effects of dopaminergic medications). Among these risk factors, several may be considered modifiable; however, intervention trials aimed toward reducing risk factors and events in those who have Parkinson disease have not yet been performed.

Therapeutic trials evaluating multidimensional risk-factor modification to prevent falling are thought to be appropriate in high-risk, disease-specific groups, such as those who have Parkinson disease. Such trials, as have been executed by Tinetti and colleagues in the United States, and directed toward the community-based elderly without specific regard to diagnoses, can serve as a model for applying a similar therapeutic approach in disease-specific populations who are at high risk for falling. Before these types of intervention trials can be initiated for those who have Parkinson disease, further objectives need to be achieved, including identification of those falling risk factors that are potentially modifiable by specifically linked interventions that are clinically rational, evidence-based, and relevant to those who have Parkinson disease; and prioritization of those falling risk factors that should be targeted for modification, given that multiple risk factors have been articulated. As summarized in Table 1, multiple falling risk factors in Parkinson disease have been defined, yet there has been no explicit discussion in the literature as to which should be targeted for modification during therapeutic trials. Within this literature, several studies have prioritized risk factors that are strongly associated with or predictive of falling, including higher disease severity, longer disease duration, a higher level of disability, the predominance of bradykinesia, impaired proximal lower-limb motor control, impaired lower-limb coordination, impaired posture, loss of arm swing during walking, and impaired cognition. This study intends to contribute to supporting these objectives by (1) identifying falling risk factors in a population of subjects who have idiopathic Parkinson disease, and (2) prioritizing risk factors that should be targeted for modification. We hypothesize that (1) the falling risk factors that are identified in our subjects who have Parkinson disease will be congruent with those that have already been defined in the literature, and that (2) identified risk factors can be prioritized in an effort to target them for modification.

**METHODS**

This study was approved by the committee on human subjects participation of the Philadelphia Veterans Affairs Medical Center (PVAMC). Informed consent was obtained for all participating subjects.

### Table 1: Falling risk factors in Parkinson disease

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Inclusion Criteria</th>
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<tbody>
<tr>
<td>Older age</td>
<td>3,14</td>
</tr>
<tr>
<td>Longer disease duration</td>
<td>3-5,14</td>
</tr>
<tr>
<td><em>Higher disease severity</em></td>
<td>3-6,8,11</td>
</tr>
<tr>
<td>Orthostasis</td>
<td>4,10</td>
</tr>
<tr>
<td>Peripheral sensory disturbances</td>
<td>6</td>
</tr>
<tr>
<td>Daily use of alcohol</td>
<td>4</td>
</tr>
<tr>
<td>Affective disturbances such as depression, anxiety, and <em>fear of falling</em></td>
<td>5,8,11</td>
</tr>
<tr>
<td>Parkinson disease–specific clinical signs: rigidity, bradykinesia, freezing</td>
<td>4,6,12</td>
</tr>
<tr>
<td>Polypharmacy (use of more than three medications), especially the use of</td>
<td>8</td>
</tr>
<tr>
<td>dopaminergic medications</td>
<td>7</td>
</tr>
<tr>
<td>*Gait disturbances</td>
<td>3-8,11</td>
</tr>
<tr>
<td>Postural and *balance disturbances</td>
<td>3-5,8,11</td>
</tr>
<tr>
<td>Impaired hand and *foot agility or coordination</td>
<td>3</td>
</tr>
<tr>
<td>*Inability to rise from a chair or weak proximal leg motor control</td>
<td>3,11</td>
</tr>
<tr>
<td>Decreased arm swing</td>
<td>5</td>
</tr>
<tr>
<td>Dementia</td>
<td>5,14</td>
</tr>
<tr>
<td>*Higher level of disability</td>
<td>3,4,8,11</td>
</tr>
</tbody>
</table>

* Indicates congruency of falling risk factors among recurrent fallers in this study and subjects identified as fallers in studies cited.
Participants

During a 4-mo period of time, we recruited a convenience sample of 48 competent, community-dwelling male subjects who had idiopathic Parkinson disease and who were referred for outpatient physiatry consultation at the Parkinson's Disease Research, Education and Clinical Center (PADRECC) of the PVAMC. This PADRECC is one of six regional referral centers within the Department of Veterans Affairs that specializes in movement disorders. Among these 48 subjects, 23 were categorized as “recurrent fallers,” having reported more than one fall within the year before recruitment, and 25 were categorized as “nonfallers,” having reported no more than one fall within the year before recruitment. These group assignments were rationalized by several observations: the work of Tinetti and colleagues15,20 and Dunn and colleagues21 that has associated recurrent falling, as defined here, with the presence of cumulative risk factors in the elderly, including the presence of several chronic conditions, and with escalating risks of disability and mortality. Although these observations do not dismiss the occurrence of one fall during a specific period of time as unimportant in their study populations, the occurrence of one fall can sometimes be explained by a chance occurrence or associated with an acute, time-limited illness and/or the presence of an “extrinsic” environmental barrier, whereas recurrent falls are more often associated with “intrinsic” chronic conditions. Moreover, intrinsic falling risk factors have been considered more important than extrinsic/environmental risk factors when considering falling in Parkinson disease.22 Thus, these group assignments seemed appropriate in this study, because the experience of having Parkinson disease entails the accumulation of falling risk factors over time, and recurrent falling is common.2– 6 In this study, a fall was defined as a nonsyncopal, involuntary positional change from bipedal support to no or partial support by the feet, accompanied by contact with the ground. Falling events associated circumstantially with acute neurological events resulting in new-onset weakness, seizures, excessive alcohol exposure, and overwhelming external forces were not included. Falling events were distinguished from near-falls and stumbles when contact with the ground did not occur.23–26

Inclusionary criteria included idiopathic Parkinson disease as determined by the subjects' PADRECC neurologists and confirmed by medical record review; being ambulatory with or without an assistive device such as a cane or walker and confirmed on examination on the day of assessment; and being competent in one’s own medical decision making associated with having a Mini-Mental Status Examination (MMSE)27 score >24, indicating that dementia was not likely present and confirmed on examination on the day of assessment and by medical record review. Exclusionary criteria included Parkinson-plus syndromes; being nonambulatory; having an MMSE score ≤24 and/or clinical behaviors consistent with a dementia as confirmed on examination and by neuropsychological examination documented in the medical record at previous PADRECC outpatient visits; and having an already recognized affective or other psychiatric disorder(s) confirmed by medical record review and psychiatric examination performed at previous PADRECC visits. Subjects who had dementia and recognized psychiatric disorders were excluded at the recommendation of the committee on human subjects participation at the PVAMC, because it was thought that the presence of these entities would preclude informed consent without proxy. Moreover, the presence of dementia and psychiatric disturbances were considered potential confounders of valid participation in the physical examination (see below), which required some degree of procedural training to execute successfully. All subjects were interviewed and examined while on their dopaminergic medications. Table 2 summarizes data describing

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Group comparisons of recurrent fallers and nonfallers with Parkinson disease (mean [SD])</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recurrent Fallers</td>
</tr>
<tr>
<td>n</td>
<td>23</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>73.96 (8.33)</td>
</tr>
<tr>
<td>Education, yrs</td>
<td>14.39 (4.15)</td>
</tr>
<tr>
<td>Duration, mos since symptoms/signs onset</td>
<td>135.68 (135.07)</td>
</tr>
<tr>
<td>Duration, mos since diagnosis</td>
<td>106.91 (87.73)</td>
</tr>
<tr>
<td>Disease severity (modified Hoehn and Yahr stage/5)</td>
<td>2.80 (0.70)</td>
</tr>
<tr>
<td>Global functional status, Schwab and England ADL score (%)</td>
<td>73.06 (17.25)</td>
</tr>
<tr>
<td>Global cognitive status (MMSE Score/30)</td>
<td>25.83 (2.61)</td>
</tr>
</tbody>
</table>

SD, standard deviation; n, sample size; ADL, Activities of Daily Living; MMSE, Mini-Mental Status Examination.
the recurrent fallers and nonfallers who were recruited.

Procedures

Data collection during this study occurred using subject interviews, medical record reviews, and physical examinations. All data were collected on the same day during a several-hour outpatient visit that involved assessments by several PADRECC clinical care providers (Bunting-Perry, Martine, Duda, Stern) and research staff (Dennison, Robinson). The presence of specific risk factors to be probed was determined on the basis of a review of the relevant literature of falling risk factors among community-based elderly and those who have Parkinson disease, and on the basis of our own pilot data collection during an earlier study, which served to streamline relevant falling risk factors for this study. The subjects recruited for this study were a distinct population from those subjects recruited for this earlier pilot study.

During the subject interviews performed by the research staff, the following variables and falling risk factors was probed: age (years); education (years); disease duration (months since symptoms/signs onset, and months since diagnosis); history of falling during the past year (more than one fall/no more than one fall) to determine group assignment as a recurrent faller or nonfaller); participation in regular exercise (no/yes); participation in outside housework such as gardening and taking out the trash (no/yes); an experience of rapid “on–off” phenomena (rapid motor fluctuations) associated with the use of dopaminergic medications (yes/no); and fear of falling (yes/no). These interviews limited the recording of medical history factors to those that could indicate the integrity of the sensory systems that potentially influence motor control and balance: peripheral neuropathy (yes/no) and impaired vision (yes/no). Subjects’ ages, levels of education, disease duration, and medical history factors were verified by medical record review of clinical notes generated by the PADRECC staff from either the concurrent or previous outpatient visits. The group assignments were verified by a spouse, another family member, or a caregiver who attended the outpatient assessments, and by the PADRECC clinical staff’s blinded scoring of item 13 (falling) of the Unified Parkinson’s Disease Rating Scale on the same day.

As the basis for the medical record review for this study, the PADRECC clinical care providers at the PVAMC had used several measurement tools during their routine clinical interviews and examinations that encompassed part of the permanent clinical database, including the Unified Parkinson’s Disease Rating Scale, an internationally recognized and commonly applied tool comprising 42 (35 ordinal and 7 categorical) measurement items that probes Parkinson disease–specific impairment and disability/activity participation, the modified Heohn and Yahr stage as a measure of disease severity, the Schwab and England Activities of Daily Living scale as a measure of disease-specific functional status, the Mini-Mental Status Examination, a well-recognized cognitive screening tool; and the clock drawing test, a tool that probes visuoperception. These data were collected by the PADRECC neurologists (Duda, Stern) and advanced practice nurses (Bunting-Perry, Martine) who specialize in movement disorders, at every outpatient clinic visit, including on the day of subjects’ participation in this study. The PADRECC staff who were trained to use these well-known measurement tools were blinded to the group assignments of the recruited subjects when using these tools.

When organizing data generated from the Unified Parkinson’s Disease Rating Scale, falling risk factors were observed both as singular items and as cumulative items from which composite or summary scores were calculated. Selected items of the Unified Parkinson’s Disease Rating Scale were defined and/or reorganized as measures of disease impairment (clinical symptoms and signs) and disability/activity participation (integrative functional performance) according to the World Health Organization’s definitions of these concepts. Composite measures of disease impairment included the motor examination score of the Unified Parkinson’s Disease Rating Scale (items 18–31), an impairment subscale score (items 14, 16, 17, 19, 20, 21, 22, 28, 30, and 31); the dyskinesia subscale score (items 32–34), and the rapid motor fluctuations subscale score (items 36–39). These latter two subscale scores served to streamline falling risk factors included those that encompassed the composite impairment, disability and mobility subscales, as well as depression (item 3), sleep disturbance (item 41—yes/no), and symptomatic orthostasis (item 42—yes/no). Interrater reliability when using singular items that comprise the Unified Parkinson’s Disease Rating Scale has been reported as variable among the items, but satisfactory with significant correlation coefficients across almost all items, particularly when used.
by clinicians who specialize in movement disorders, as done in this study.  

The physical examination that probed for falling risk factors was performed collaboratively by the research staff (Dennison, Robinson), a fourth-year medical student and a physiatrist who specializes in neurological diseases. All study subjects were able to participate in the physical examination without the use of assistive devices and without adverse events. Systolic and diastolic blood pressure and heart rate in the sitting and standing positions were measured as probes of orthostasis, defined as a >20 mm Hg decrease in systolic blood pressure, a >10 mm Hg decrease in diastolic blood pressure, or a >10 beats/min increase in heart rate during the positional change from sitting to standing. Other factors observed during the physical examination included probes of fine motor control and motor planning, proximal lower-limb strength and muscle endurance, balance, and walking speed under single- and dual-task conditions.

Measures of fine motor control included observing finger tapping (clumsy/not clumsy during finger tapping for 10 secs), and foot tapping (clumsy/not clumsy during foot tapping for 10 secs). The decision making to operationalize these variables as dichotomous considered that these study subjects had a movement disorder, and thus their range of performances would likely be widely variable. What seemed more relevant in this study when considering falling risks was not their tapping rates but, rather, the quality of their performances within a prescribed time period at a self-selected tapping speed to support optimal performances.

Measures of motor planning included observing motor planning of the hands (unable/able to complete a three-step repetitive sequence for five consecutive repetitions) and motor planning of the feet (unable/able to complete a three-step repetitive; syncopated foot-tapping sequence for five consecutive repetitions). The decision making to operationalize these variables as dichotomous similarly included that observing the quality of their performances seems more relevant to falling risks, and that self-selected sequential movement rates would support optimal performances. Moreover, this approach allowed us to observe more fundamental cognitive functions that support motor planning as a complex cognitive operation—specifically, the subjects’ ability to be trained procedurally to perform these motor tasks during practice sessions, and their attentional functions (working memory and sustained attention) necessary to execute and repeat these motor tasks.

Measures of proximal lower-limb strength and repetitive endurance included observing the ability to complete five consecutive sit-to-stand maneuvers in an unsupported manner with the hands folded on the chest. 

Balance measures included the Romberg test, observing the abilities incrementally to hold side-by-side stance, semitandem stance, and tandem stance, each for 10 secs; observing the ability to walk in tandem for up to 10 feet; and the functional reach test, forward and backward, measured in inches. Walking speeds were measured under a single-task and two dual-task conditions, using the timed up-and-go test.

Data Analyses

Data on 63 variables were collected for all subjects, and each variable was identified as one of three types of measures: (1) continuous, (2) ordinal, or (3) categorical. These variables are summarized in Table 3 according to their category of risk factor (demographic, disease-specific, medical history, impairment, disability, psychological, cognitive, motor control, balance, and gait) and type of measure.

To explore the first hypothesis, between-group comparisons of recurrent fallers and nonfallers were performed using SPSS version 12. The mean values of the continuous and ordinal variables were compared using the nonparametric Mann–Whitney U test. Categorical variables were compared using the $\chi^2$ test. Given multiple comparisons, a more conservative $P$ value of $P \leq 0.01$ determined significance during these group comparisons. Once those variables that distinguished recurrent fallers during the group comparisons were identified, they were compared qualitatively with those that existed in the literature (Table 1) and categorized as potentially modifiable or not. Potentially modifiable risk factors excluded those variables that were demographic, such as age, and those that were composite in their description of disease-specific characteristics, such as severity, duration, and associated impairment and disability. Some of these composite variables could potentially be modifiable with interventions, but only indirectly, and not by those that could be linked to them specifically as treatments. Potentially modifiable variables included more specific aspects of Parkinson disease that may be subjected to specifically linked cognitive/behavioral interventions that were either clinically rational, based on clinical experience, or evidenced based.

To explore the second hypothesis, a nonparametric modeling strategy, recursive partitioning, was performed using SPSS version 12. Recursive partitioning (also known as classification and regression tree analyses, or CART) used observational data to classify the study subjects into multiple and sequential subclasses, with the goal of increasing the likelihood of identifying a “true diagnosis” within each subclass (defined in this study as a recurrent faller who has Parkinson disease). It was a stepwise process, beginning with the dichot-
TABLE 3 Variables that were included during group comparisons of recurrent fallers and nonfallers who have Parkinson disease

<table>
<thead>
<tr>
<th>Risk factors: variable (type)</th>
<th>Demographic factors: age (years—continuous); education (years—continuous)</th>
<th>Disease-specific factors: duration (months since symptoms/signs onset, and months since diagnosis—continuous); severity (modified Hoehn and Yahr stage—ordinal)</th>
<th>Medical history factors: history of peripheral neuropathy (yes/no—categorical); history of impaired vision that cannot be corrected (yes/no—categorical)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impairment factors: motor examination score (UPDRS items 18 to 31—ordinal); impairment subscale score (UPDRS items 14 [freezing], 16 [tremor], 17 [sensory symptoms], 19 [facial expression], 20 [resting tremor], 21 [action tremor], 22 [rigidity], 28 [posture], 30 [postural stability], 31 [bradykinesia]—ordinal); dyskinesia subscale score (UPDRS items 32 to 34—ordinal); motor fluctuation subscale score (UPDRS items 36 to 39—ordinal); experience of on-off phenomena (yes/no—categorical); sleep disturbances (yes/no [UPDRS item 41]—ordinal); symptomatic orthostasis (yes/no [UPDRS item 42]—ordinal); orthostasis (increase in heart rate with positional change [beats/min], decrease in systolic and diastolic blood pressures [mm Hg]—continuous)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disability factors: Schwab and England ADL scale score (%—ordinal)*; ADL score (UPDRS items 5 to 17—ordinal); disability subscale score (UPDRS items 5 [speech], 7 [swallowing], 8 [handwriting], 10 [dressing], 11 [hygiene], 12 [turning in bed], 15 [walking], 18 [speech], 27 [arising from chair], 29 [gait]—ordinal); mobility subscale score (UPDRS items 12 [turning in bed], 15 [walking], 26 [leg agility], 27 [arising from chair], 28 [posture], 29 [gait], 30 [postural stability]—ordinal); regular exercise participation (no/yes—categorical); outside housework participation (no/yes—ordinal)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychological factors: depression (UPDRS item 3—ordinal); fear of falling (yes/no—ordinal)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive factors: MMSE score—ordinal*; overlapping pentagrams from the MMSE (unable/able—categorical); clock drawing test—ordinal*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor control/balance/gait factors: fine motor control of the hands (clumsy/not clumsy—categorical); motor planning of the feet (unable/able—categorical); fine motor control of the feet (clumsy/not clumsy—categorical); motor planning of the hands (unable/able—categorical); proximal leg strength/muscle endurance—ordinal; Romberg—ordinal; side-by-side/semitandem/tandem stance—ordinal; tandem walking—ordinal; functional reach forward and backward (inches—continuous)*; gait speed (timed get up and go); single- and dual-task conditions (seconds—continuous)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Higher score indicates a higher level of impairment/disability or worse performance, except where indicated by asterisk.

UPDRS, Unified Parkinson’s Disease Rating Scale; ADL, Activities of Daily Living; MMSE, Mini-Mental Status Examination.

omization of all of the selected variables to be entered into the model (here, the potentially modifiable risk factors that significantly distinguished recurrent fallers), including continuous and ordinal variables. Once the selected independent variables were rationally dichotomized, the study population was subjected to a stepwise splitting process in which they were compared and statistically assessed according to these variables, using an initial set of $\chi^2$ tests. The resultant $P$ values were then ranked, with the smallest (i.e., most statistically significant) $P$ value indicating the risk factor that best discriminated the true diagnosis (recurrent fallers) within this study population. This served as the first splitting or branch point in the “tree” model. Subsequent sets of $\chi^2$ tests were then performed, comparing the remaining variables among the subjects not yet classified as recurrent fallers. This stepwise splitting process was repeated until a stopping rule was applied, either until all subjects had been classified according to a specific risk factor or set of risk factors, or until further partitioning could not refine the classification scheme as determined by a $P$ value $\leq 0.01$ during repeated and sequential sets of $\chi^2$ tests. A resulting decision tree illustrated the stepwise process. The result of recursive partitioning was represented by a receiver-operated characteristic curve. The area under this curve was calculated to indicate a relative specificity/sensitivity trade-off: an area under the curve of $\geq 0.80$ was considered to have reasonably strong associations among the variables entered into the model and the “true diagnosis.”

**RESULTS**

No significant group differences were observed between recurrent fallers and nonfallers when observing mean age, mean education, mean disease duration, mean disease-specific functional status, and mean global cognitive status. Recurrent fallers demonstrated a significantly higher disease severity than did nonfallers ($P \leq 0.007$). These results are summarized in Table 2.

Other variables that significantly distinguished recurrent fallers from nonfallers during the group comparisons are summarized in Table 4. These include several composite measures: recurrent fallers demonstrated a significantly higher level of motor impairment as measured by the Unified Parkinson’s Disease Rating Scale motor examination score ($P < 0.002$) and higher level of disease-specific disability as measured by the Unified Parkinson’s Disease Rating Scale Activities of Daily
### TABLE 4 Risk factors that significantly distinguished recurrent fallers and nonfallers during group comparisons (mean value [SD] for ordinal and interval variables, and number of patients for categorical variables)

<table>
<thead>
<tr>
<th>Risk Factors (Composite)</th>
<th>Recurrent Fallers (n = 23)</th>
<th>Nonfallers (n = 25)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-specific: disease severity</td>
<td>2.80 (0.70)</td>
<td>2.38 (0.56)</td>
<td>0.007</td>
</tr>
<tr>
<td>Impairment: UPDRS motor examination score</td>
<td>38.52 (16.20)</td>
<td>25.79 (12.70)</td>
<td>0.002</td>
</tr>
<tr>
<td>Disability: UPDRS ADL score</td>
<td>18.71 (7.47)</td>
<td>12.46 (6.30)</td>
<td>0.005</td>
</tr>
<tr>
<td>Disability subscale score from UPDRS</td>
<td>17.96 (7.27)</td>
<td>11.30 (5.52)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mobility subscale score from UPDRS</td>
<td>14.21 (6.01)</td>
<td>7.82 (4.46)</td>
<td>0.001</td>
</tr>
<tr>
<td>Individual UPDRS items that comprised the above subscales and that may be modifiable risk factors:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking (item 15)</td>
<td>1.83 (0.80)</td>
<td>0.88 (0.78)</td>
<td>0.001</td>
</tr>
<tr>
<td>Leg agility (item 26)</td>
<td>3.54 (2.10)</td>
<td>1.92 (2.00)</td>
<td>0.005</td>
</tr>
<tr>
<td>Arise from chair (item 27)</td>
<td>1.76 (1.23)</td>
<td>0.80 (0.76)</td>
<td>0.003</td>
</tr>
<tr>
<td>Gait (item 29)</td>
<td>1.91 (0.73)</td>
<td>1.10 (0.61)</td>
<td>0.001</td>
</tr>
<tr>
<td>Psychological risk factor that may be modifiable:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fear of falling (yes/no)</td>
<td>13/10</td>
<td>4/21</td>
<td>0.003</td>
</tr>
<tr>
<td>Motor control/balance/gait risk factors that may be modifiable:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor planning—bilateral hands (unable/able)</td>
<td>17/6</td>
<td>9/14</td>
<td>0.008</td>
</tr>
<tr>
<td>Motor planning—bilateral feet (unable/able)</td>
<td>10/13</td>
<td>2/23</td>
<td>0.005</td>
</tr>
<tr>
<td>Tandem walking</td>
<td>2.00 (1.00)</td>
<td>1.16 (1.03)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

UPDRS, Unified Parkinson’s Disease Rating Scale; ADL, Activities of Daily Living.

Living score ($P < 0.005$), the disability subscale score ($P < 0.001$), and the mobility subscale score ($P < 0.001$). These also include individual items from the Unified Parkinson’s Disease Rating Scale: recurrent fallers demonstrated significantly more impaired leg agility or coordination as measured by item 26 ($P < 0.005$), more impaired proximal lower-limb motor control, observed during arising from a chair, as measured by item 27 ($P < 0.003$), and more impaired ambulation, as measured by items 15 ($P < 0.001$) and 29 ($P < 0.001$). Several of the individual risk factors that significantly distinguished recurrent fallers were observed during the physical examination, including impaired motor planning of the hands ($P < 0.008$) and feet ($P < 0.005$), and impaired dynamic balance, as measured by tandem walking ($P < 0.006$). Finally, a self-report of fear of falling ($P < 0.003$) also distinguished recurrent fallers in our study population.

On the basis of the findings in this study and those risk factors reported in the literature (Table 1), we selected 12 variables that idiosyncratically were associated with falling in Parkinson disease and that were viewed clinically as potentially modifiable, to be entered into the model. These variables and their dichotomization schemes are listed in Table 5. Unless already a categorical variable, each of the variables was dichotomized using the measures from this study. Seven variables were selected to be entered into the model because they significantly distinguished recurrent fallers in this study. Five variables (freezing, impaired posture, postural instability, dyskinesias, orthostasis) that did not significantly distinguish fallers in this study were selected to be entered into the model because they have been strongly represented in the literature as idiosyncratic falling risk factors in Parkinson disease (Table 1). The stepwise splitting process was initiated with an initial set of $\chi^2$ analyses of these dichotomized variables, allowing us to rank the variables according to how they would best distinguish a recurrent faller in our study population, with the variable having the lowest $P$ value being ranked highest, and thus generated from the model as the initial variable. The initial set of comparisons revealed that impaired ambulation ($P < 0.001$) was ranked highest; thus, it emerged from the model as the initial variable. From this initial set of comparisons, it was realized that 17 recurrent fallers and 4 nonfallers had impaired ambulation; thus, these 21 subjects were excluded from subsequent analyses. The stepwise splitting process was continued with a second set of $\chi^2$ analyses using the remaining variables and those 27 subjects who had unimpaired ambulation. This second set of comparisons indicated that the most significant variable that identified recurrent fallers was impaired lower-limb motor planning ($P < 0.006$), and three recurrent fallers and one nonfaller had impaired lower-limb motor planning, excluding four more subjects from subsequent analyses. The third set of $\chi^2$ analyses were then applied to those remaining 23 subjects who had both unimpaired ambulation and normal lower-limb motor planning. This set of comparisons demonstrated that symptomatic orthostasis ($P <
0.008) most significantly identified recurrent fallers among these 23 subjects, with only one recurrent fal1er and no nonfallers having symptomatic orthostasis. A fourth set of \( \chi^2 \) analyses, using the remaining nine variables and the remaining 22 subjects, demonstrated no significant differences as defined by a \( P \) value \( \leq 0.01 \); thus, the stopping rule was applied. This stepwise approach using recursive partitioning is illustrated in Figure 1. The resultant receiver-operated characteristic curve that

### TABLE 5 Potentially modifiable falling risk factors in Parkinson disease included in the recursive partitioning model

<table>
<thead>
<tr>
<th>Factor</th>
<th>Dichotimization Scheme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leg agility or lower-limb coordination (UPDRS item 26)</td>
<td>0 = normal heel tapping/1 (mild slowing), 2 (moderate slowing with occasional arrests), 3 (severe slowing with initial hesitation and frequent arrests), 4 (barely perform) = impaired heel tapping)</td>
</tr>
<tr>
<td>Arising from chair or proximal lower-limb motor control (UPDRS item 27)</td>
<td>0 = able to perform sit to stand with arms folded across chest/1 (slow or needs more than one attempt to stand without using arms), 2 (uses arms to stand), 3 (falls backward and required more than one attempt to stand), 4 (cannot arise without assistance) = unable to perform sit to stand)</td>
</tr>
<tr>
<td>Ambulation (UPDRS item 29)</td>
<td>0 = normal/1 (walks slowly with shuffle), 2 (walks with difficulty without assistance or with festination), 3 (severely disturbed and requiring assistance), 4 = impaired (nonambulatory even with assistance) = impaired)</td>
</tr>
<tr>
<td>Tandem walking (0 = can achieve &gt;10 feet/1 = can achieve between 3 and 9 feet, 2 = can achieve up to 3 feet, 3 = cannot perform without assistance, 4 = unable to perform even with assistance = cannot achieve)</td>
<td></td>
</tr>
<tr>
<td>Motor planning of the hands (able/unable) — already a categorical variable</td>
<td></td>
</tr>
<tr>
<td>Motor planning of the feet (able/unable) — already a categorical variable</td>
<td></td>
</tr>
<tr>
<td>Fear of falling according to self-report (no/yes) — already a categorical variable</td>
<td></td>
</tr>
</tbody>
</table>

Three factors selected from the literature that did distinguish fallers and their dichotimization scheme:

- Freezing of gait (UPDRS item 14) 0 = none/1 (rarely), 2 (occasionally), 3 (frequently, with occasional falls), 4 (frequently, with frequent falls) = present)
- Posture (UPDRS item 28) 0 = normal/1 (slightly stooped), 2 (moderately stooped), 3 (severely stooped with kyphosis), 4 (marked flexion) = impaired)
- Postural stability (UPDRS 30) 0 = normal response to shoulder pull/1 (retropulses but recovers unaided after shoulder pull), 2 (no postural responses and would fall if not caught by examiner), 3 (very unstable, tending to lose balance spontaneously), 4 (unable to stand without assistance) = impaired)
- Dyskinesia (UPDRS items 32 to 34) 0 = absent/1 on these items cumulatively = present)
- Symptomatic orthostasis [UPDRS item 42 (yes/no)] — already categorical

UPDRS, Unified Parkinson’s Disease Rating Scale.
was generated from recursive partitioning is depicted in Figure 2. When the area under the curve was calculated, the specificity–sensitivity trade-off was 0.85, indicating that the model demonstrated plausible associations among three variables and recurrent fallers in this study population. Thus, on the basis of those risk factors that distinguished recurrent fallers in this study and from those carefully selected from the literature, three variables can be prioritized for potential modification: impaired ambulation, impaired lower-limb motor planning, and orthostasis.

DISCUSSION
This study demonstrates that an idiosyncratic falling risk factor profile distinguished a group of recurrent fallers who have Parkinson disease (Table 4). The falling risk factors realized in this study represent some but not all of the risk factors reported in the literature. However, none of these other studies have demonstrated completely congruent findings. Thus, it may have been unrealistic to expect complete congruency in this study, as inferred by hypothesis 1. The lack of complete congruency among these studies can likely be explained by several issues, including different approaches to subject recruitment, different definitions for group assignment as fallers and nonfallers, and different selection of falling risk factors to be measured. For example, this study cross-sectionally recruited male subjects who were referred to a regional, hospital-based specialty program for subspecialty physiatry consultation; it made group assignments on the basis of confirmed retrospective experience of the subjects as recurrent fallers; and it excluded subjects if they had an already recognized dementia and affective disorder. In contrast, Ashburn and colleagues cross-sectionally recruited male and female subjects from community-based general practitioners’ offices and did not exclude those who had dementia and psychiatric illnesses; however, these investigators made group assignments on the basis of the subjects’ retrospective experience of having at least one fall. Other studies, such as those performed by Wood and colleagues and by Gray and Hildebrand, prospectively defined fallers on the basis of reporting at least one event, recruiting their subjects at comparable hospital-based specialty programs. Other reasons that could contribute to the lack of complete congruency between our observations of falling risk factors and those of other studies include the fact that several risk factors reported in the literature specifically were not probed in this study, such as daily use of alcohol, use of polypharmacy, and decreased arm swing. Our previously performed pilot study did not inform us that medical history factors, including regular alcohol use and pattern of medication use, would be useful to pursue when attempting to streamline risk factors to probe in this study. Thus, except for probing for

![ROC Curve](image)

FIGURE 2 Receiver-operated characteristic (ROC) curve generated from recursive partitioning.
Visual and peripheral sensory impairments, medical history factors were not included, and medication use was not observed here. Moreover, we chose to probe other aspects of the physical examination that may idiosyncratically be associated with falling in Parkinson disease and not previously observed in the literature, such as motor planning during distal-limb motor tasks. Finally, we chose to make specific qualitative observations of our subjects’ gait patterns in this study, except as observed by Uniform Parkinson’s Disease Rating Scale items 15 and 29. We chose to measure walking speed during a functional walking task under single- and dual-task conditions; thus, the presence/lack of arm swing was not observed. Yet, taken as a whole, these studies qualitatively have demonstrated a relatively high degree of congruency among them: among the 23 variables defined as falling risk factors in Parkinson disease and listed in Table 1, 15 of these have been identified by at least two studies. Table 1 also indicates those falling risk factors in Parkinson disease that were congruent between this study and other studies, appreciating the different methodological approaches among these studies.

Identifying falling risk factors in this and other studies can be considered the initial step for applying our and other investigators’ findings to be clinically useful within a therapeutic model that proposes risk factor modification to reduce falling. One therapeutic model that has been considered successful is multidimensional falling risk factor modification when directed toward targeted populations. One example of applying this model in this country has been executed by Tinetti and colleagues. These investigators have taken the approach of defining specific falling risk factors among the elderly from their own work and from the literature as potentially modifiable, and then linking these falling risk factors with specific treatment interventions that are clinically rational and variably evidence based to reduce falling risks and events. Such studies represent a treatment model that is rational for application within disease-specific populations who are at high risk for falling. To operationalize this treatment model for those who have Parkinson disease, prioritizing the multiple falling risk factors that have been identified can be viewed as essential to focus the selection of risk factors to be targeted for modification. Among the 12 falling risk factors that were considered modifiable by specifically linked treatment interventions and entered into the model to prioritize those that should be targeted during future intervention trials, three risk factors were identified in this study: impaired ambulation, impaired lower-limb motor planning, and orthostasis. Other studies have applied different strategies to cross-sectionally prioritize and/or longitudinally predict falling risk factors in study populations with Parkinson disease. Koller and colleagues used factor analysis to cluster their identified falling risk factors into groups of variables that were associated with falling. One cluster of variables was significantly associated with falling; it included the presence of bilateral disease, higher disease severity, high level of disability, bradykinesia, impaired proximal lower-limb motor control, impaired lower-limb fine motor control, impaired posture, and impaired cognition. Bloem and colleagues used logistic regression, entering their falling risk factors simultaneously: disease severity was the sole variable that was predictive of recurrent falls in their subjects who had Parkinson disease. Wood and colleagues used backward stepwise logistic regression as their modeling strategy, and several of their variables emerged as independent predictors of falling, including longer disease duration, loss of unilateral or bilateral arm swing, and dementia. Taken along with the findings of our study, these studies have prioritized several potentially modifiable risk factors, including impaired ambulation, impaired lower-limb motor planning, fine motor control and proximal motor control, orthostasis, impaired posture, and reduced arm swing.

A unique finding of this study was that lower-limb motor planning was both identified and prioritized as a falling risk factor in Parkinson disease. We were not aware that motor planning was observed explicitly in related studies in the literature. Motor planning has been reported as an important component of postural control in Parkinson disease when observing anticipation of movement; thus, it presented as a variable that usually has been embedded in more integrative measures, but it should be deconstructed from more complex motor sequences and measured in isolation, as performed in this study.

Several limitations of this study should be recognized, particularly those associated with its small sample size: (1) an increase in the potential for type 1 errors has occurred during the group comparisons, given that multiple comparisons were performed, and a more conservative P value of ≤0.01 was thus selected to determine significance in this study; (2) a decrease in the potential accuracy of risk factor prioritization using recursive partitioning as a modeling strategy was possible, given the relatively large number of variables that were entered into the model; recursive partitioning has been recognized as a powerful modeling approach, and more so when applied to large sample sizes, and recursive partitioning should be ideally applied to a comparable preliminary dataset before the definitive or validating analyses were performed which was not feasible in this study; and (3) among the variables that were prioritized in this study using recursive partitioning, impaired ambu-
lation was observed in almost half of the study sample, and is thus presented as the most important for potential modification during future intervention trials; impaired lower-limb motor planning and symptomatic orthostasis together were observed in only five subjects, yet they emerged from the model as significant.

Other limitations include the fact that several variables may have deserved more refined observation using recognized ordinal measures, such as fear of falling, which was measured categorically on the basis of self-report. Finally, our findings were based on cross-sectional observation using retrospective self-reporting of falls to determine group assignment; prioritization of risk factors on the basis of prospective observation of falling would clearly be a more powerful approach.

CONCLUSIONS

An idiosyncratic profile of falling risk factors distinguished recurrent fallers and nonfallers with Parkinson disease in this study. This profile was partially congruent with those risk factors identified in the literature. When combined with selected risk factors from the literature that were considered potentially modifiable with specific interventions, this profile serves as the basis for prioritizing three risk factors that should be targeted during a future risk factor–modification trial: impaired ambulation, impaired motor planning of the lower limbs, and orthostasis. Our findings can contribute to planning future multidimensional risk factor–modification trials to reduce falling risks and events in those who have Parkinson disease.

REFERENCES

Efficacy of a Self-Management Program for Osteoporotic Subjects

ABSTRACT


Objective: This study is based on whether the self-management program choices For Better Bone Health is effective to promote behavioral strategies for improving bone health, life quality, pain perception, physical function, and balance in osteoporotic subjects.

Design: In this single-blind, randomized controlled study, a total of 50 sedentary women with postmenopausal and idiopathic osteoporosis were selected from the outpatients of Atatürk Balneotherapy and Rehabilitation Center according to their physical activity level and T scores of dual-energy x-ray absorptiometry as the inclusion criteria. Fifty sedentary women with BMD T scores of $\leq -2.5$ or lower were randomized into two groups (self-management group: group 1; and control group: group 2) and enrolled in a 6-mo study. Participants attended self-management class once a week for 5 wks. Evaluations were done at baseline, at the end of the fifth week, and at the sixth month. Pain-intensity evaluation by Visual Analogue Scale (VAS), life-quality assessments by SF-36, balance testing by Sensitized Romberg Test (SRT), and functional assessment by Timed Sit to Stand test (TSS) and a simple questionnaire were the outcome measures.

Results: When the groups were compared by change scores and percentages of change, improvements observed in pain intensity by VAS ($P < 0.001$), SF-36 Physical Function ($P < 0.001$), SF-36 Physical Role Limitations ($P < 0.001$), SF-36 Social Function ($P < 0.001$), SF-36 Mental Health ($P < 0.001$), SF-36 Vitality ($P < 0.01$), SF-36 Pain ($P < 0.001$), SF-36 General Health Perceptions ($P < 0.05$), SF-36 Emotional Role Limitations ($P < 0.01$), SRT eyes open ($P < 0.001$), SRT eyes closed ($P < 0.001$), and TSS ($P < 0.001$) were determined to be superior in group 1 at the end of the sixth month. Seventy-four percent of patients in group 1 engaged in regular physical activities, and 92% of them declared that they understood the purpose and benefits of medications and dietary calcium intake. Fifty-seven percent of them formed personal plans for preventing traumas, whereas 8% of the subjects in group 2 experienced new falls but no fractures.

Conclusion: It is determined that the self-management class led to improvements in functional, balance, and life-quality outcomes and to reductions in pain perception.

Key Words: Balance, Function, Life Quality, Osteoporosis, Self-Management
Osteoporosis is called the “silent thief” because it steals bone without immediate consequence or attention, and it results in low bone mass and the structural deterioration of bone, ultimately leading to fragility fractures. Postmenopausal women are among those at greatest risk of osteoporosis, but anyone of either gender or any race can develop this disease. In 2010, it is estimated that there will be 32 million postmenopausal women in the United States, and by the end of this decade, some 5–10 million women will be diagnosed as having osteoporosis by clinical observations. Fractures of the spine and hip are known to be the major determinants affecting quality of life in elderly people. In addition, the annual expenditure of osteoporotic fractures is substantial and will increase with the age of the population.

In the last decade, medications such as antiresorptive (bisphosphonates, calcitonin, raloxifen) and anabolic (parathormone, growth hormone) agents have been developed to prevent and treat those people at risk of developing or who already have osteoporosis. However, there is no cure for this disease yet, and effective disease management for osteoporosis requires the individual to be willing to accept responsibility for adhering to recommendations in areas such as medication, exercise, and diet. Avoiding potentially harmful behaviors such as smoking, drinking, or inactivity is necessary. Patient education alone is not enough to change health behaviors, but if the person decides to take control of the illness, behavioral improvements can occur; this is called self-management. Self-management has been used successfully in chronic disease management and can lead to improvements in psychological outcomes and behavioral changes, and reductions in symptom severity.

Originally based on Bandura’s social learning theory and self-efficacy model, self-management programs have been designed for a variety of chronic illnesses including asthma, epilepsy, diabetes, fibromyalgia, and arthritis. On the other hand, in a 12-mo study of self-management training, people with chronic illness such as depression, diabetes, osteoporosis, and polio were seen to have long-term changes in self-efficacy, use of self-management behaviors, fatigue, and depressed mood. The self-management program for osteoporosis, choices For Better Bone Health, helps to educate people about the disease and to promote behavioral strategies for maximizing bone health. This program has been designed to help people control their osteoporosis, and it addresses three essential tasks: physical, psychological, and social management. People who face the challenges of osteoporosis and learn to manage the different aspects of this disease would have improved quality of life in the long run.

Self-management programs also offer the opportunity for patients to collaborate with health care providers in optimizing their care and would provide a context in which patients could support each other. Also, these social support can increase compliance and adherence to therapy, and increased compliance is associated with better clinical outcomes, increased hospitalization, higher quality of life, and higher overall health costs.

With these guidelines in mind, we intended to test the self-management model for postmenopausal and idiopathic osteoporotic subjects by means of functional ability, Sensitized Romberg Test, and life-quality assessments.

**MATERIALS AND METHODS**

**Subjects**

In this randomized, controlled, longitudinal study, the efficacy of the self-management program for osteoporosis, choices For Better Bone Health, was investigated in sedentary women with postmenopausal and idiopathic osteoporosis. Approval from the Uludag University ethical committee was obtained for the study. Fifty sedentary women with postmenopausal and idiopathic osteoporosis were selected from the outpatients of Atatürk Balneotherapy and Rehabilitation Center according to their physical activity level and T scores of dual-energy x-ray absorptiometry (DEXA) as the inclusion criteria. Inclusion criteria were to have postmenopausal or idiopathic osteoporosis (DEXA T scores less than −2.5) and to be sedentary according to the physical activity scale. Exclusion criteria were having secondary osteoporosis, having rheumatologic disorders with systemic involvement, having chronic infectious diseases (tuberculosis, etc.) or malignancy, or having severe joint disorders or severe cardiac/pulmonary insufficiency that would not allow daily activities and low-intensity physical exercise.

All subjects who met the study criteria were informed of the nature of the study, and each patient’s written consent was obtained. The term sedentary was functionally defined as <1.5 km of walking or <4 hrs of standing per day; activity questionnaires were used to confirm that all subjects were sedentary before enrollment in the protocol. Fifty sedentary women with BMD T scores of −2.5 or lower were randomized into two groups (self-management group: group 1; and control group: group 2) and enrolled in the 6-mo training study. Simple randomization was done using a computer-generated table of random numbers. Physical examinations and routine laboratory analysis (hemogram, erythrocyte sedimentation rate,
C-reactive protein, thyroid function tests, serum and 24-hr urine calcium, phosphate, glucose, serum levels of urea, creatinine, alkaline phosphatase, transaminases) were performed to ensure that no preexisting condition such as chronic inflammatory disease, malignancy, or infection would confound results. Blood and urine samples were collected between 8:00 and 10:00 a.m. after a 12-hr fast. Thoracic, lumbar, and pelvic radiographs of the subjects were examined to define previous fragility fractures. All subjects were already taking antosteoporotic medication, and their medications were kept stable for the duration.

Masking

In this single-blind study, an independent researcher gave the questionnaires and did the outcome measurements.

The Self-Management Program: Choices for Better Bone Health

This program included five interactive sessions of 50 mins. Sessions were performed on Mondays at 2:00 p.m. for 5 wks. Subjects were encouraged to join the class by telephone calls, and entertaining coffee times were organized at the end of each session for the opportunity to meet each other and talk. In session 1, It’s Never Too Late, it is emphasized that osteoporosis is an inevitable part of aging and that getting enough calcium (1000 mg/day) and vitamin D (600–800 IU/day) is an important first step in making bones healthier. Getting enough (20 min/day) sunlight is another way of vitamin D synthesis. In session 2, There Is More You Can Do, it is emphasized that osteoporotic patients can take osteoporosis medicine as recommended by their health-care professionals. In session 3, Taking Charge, the key learning was that “osteoporosis can cause negative feelings and thoughts and can lead to changes in your social roles,” and the subjects were taught how to manage chronic pain and discomfort. Referrals to appropriate providers can improve a patient’s physical and emotional well-being. Physician specialists can help the patient manage comorbid conditions. Pain management is accomplished with physical therapy (heat, transdermal neurostimulation), thoracolumbar bracing, and medications. In session 4, Living Safe and Sound, the subjects are told about living safely and reducing their risk of falls by exercising and changing environment. Activities such as brisk walking, simple one-legged stance exercises, and Tai Chi, which promote coordination and balance even in frail persons, should be encouraged to prevent falls and their consequences (i.e., fractures). Wearing hip protectors may be advised to prevent hip fractures. Exercises that strengthen trunk extensor muscles are also important for preventing worsening of deformities. Aerobic, weight-bearing, and aquatic exercises are also advised to increase muscle mass and to strengthen bone. Subjects watched the exercise video and were given copies at the end of the session. In session 5, Putting It All Together, it is emphasized that the subjects’ bodies change with osteoporosis, and they are taught how to develop a personal plan for better bone health.

The self-management group (n = 25) was specifically instructed not to participate in any exercise class or organized activity outside of the study’s self-management class. The 25 control subjects were instructed to maintain their sedentary lifestyle for the duration of the study, and their compliance to the instructions was checked weekly by phone. Evaluations were done at baseline, at the end of the self-management class (fifth week), and at the sixth month. Pain-intensity evaluation by Visual Analogue Scale (VAS), life-quality assessments by Short Form-36 (SF-36), balance testing by Sensitized Romberg Test (SRT), and functional assessment by Timed Sit to Stand (TSS) were the outcome measures. At the end of the class, subjects were asked to answer a simple questionnaire about positive or negative changes in their lives.

Physical Activity Scale

The level of physical activity was determined by a graded questionnaire that varied from sedentary to heavy vocational and avocational activity levels. Physical activity was categorized as related to housework, job, and sports. These categories were each rated on a scale ranging from 0 to 6, and the total score used in the analysis was defined as the sum of the three components. Walking less than 1.5 km/day or standing less than 4 hrs/day constitutes the term sedentary, and it is categorized as 0–1 according to the scale.

DEXA

Axial (lumbar 1–4 and femur neck) bone mineral density (BMD) measurements were done at baseline by DEXA (Hologic) in Uludag University radiology department.

VAS

Daytime pain intensity is measured by a linear scale from 0 to 10.

SRT

This balance test is used to determine how long the patient is able to stand steady with feet approximated (the toes of one foot touching the heel of the foot in front of it), eyes open and then closed. The average length is recorded in seconds.
TSS

The subject is asked to stand up from a sitting position and then sit down again 10 times as quickly as possible, without using a support or shoes (seconds).\textsuperscript{18}

Quality of Life

SF-36 comprises 36 items selected from a larger pool of items used in the Medical Outcomes Study. The SF-36 assesses eight health concepts by using multi-item scales: physical functioning (SF-36PF) (10 items), role limitations caused by physical health problems (SF-36PRL) (four items), role limitations caused by emotional problems (SF-36ERL) (three items), social functioning (SF-36SF) (two items), mental health (SF-36MH) (five items), vitality (SF-36 vitality) (four items), pain (SF-36P) (two items), and general health perceptions (SF-36GHP) (five items). An additional single item assesses changes in perceived health. The first four concepts are physical component scores, and the last four concepts are mental component scores. The scores are between 0 and 100 (the higher the score, the better the health quality).\textsuperscript{24}

Simple Questionnaire

Our questionnaire consisted of four main items: a) understanding the purpose and benefits of medications, b) joining regular physical activities, c) making personal plans for better bone health, and d) new falls. The subjects were asked to answer the questions and write the answers on a paper.

Evaluations were done at baseline, at the fifth week, and at the sixth month.

Statistical Analysis

The groups were compared using the Kruskal–Wallis test to determine whether any differences existed among the initial mean values of the groups for age, BMI (kg/m\textsuperscript{2}), BMD (g/cm\textsuperscript{2}), pain intensity (VAS), SF-36, TSS, or SRT (Table 1). Because of the abnormal distribution of the raw scores and the small sample sizes, the Wilcoxon rank-sum test was used to determine the changes between baseline and follow-up in each group (Table 2). The Mann–Whitney U test was used to compare the groups by change scores and percent change (Table 3). The level of significance for all tests was \( P < 0.05 \).

RESULTS

The mean age for the subjects who met the study criteria was 66 ± 12 yrs. At baseline evaluation, group 1 (\( n = 25 \)) and group 2 (\( n = 25 \)) were not significantly different for patient characteristics and clinical measurements (Table 1). Six subjects in group 1 and five subjects in group 2 had dorsolumbar compression fractures on their radiograms, and one subject in group 2 had a history of Colles fracture from 2 yrs before (Table 1). The subjects’ compliance to the instructions about changes in lifestyle was checked by phone and was found to be good in the control group. Three subjects in group 1 and two subjects in group 2 were lost to follow-up.

Evaluation of intragroup comparisons revealed statistically significant improvements in pain intensity by VAS (\( P < 0.001 \)), SF-36PF (\( P < 0.001 \), \( P < 0.001 \)), SF-36PRL (\( P < 0.01 \), \( P < 0.01 \)), SF-36SF (\( P < 0.05 \), \( P < 0.01 \)), SF-36MH (\( P < 0.001 \), \( P < 0.001 \)), SF-36 vitality (\( P < 0.001 \), \( P < 0.001 \)), SF-36P (\( P < 0.01 \), \( P < 0.001 \)), SF-36ERL (\( P < 0.01 \), \( P < 0.01 \)), SRT eyes open (\( P < 0.001 \), \( P < 0.001 \)), SRT eyes closed (\( P < 0.001 \), \( P < 0.001 \)), and TSS (\( P < 0.001 \), \( P < 0.001 \)) in group 1 at the fifth week and sixth month, respectively. In group 2, there were significant decreases in SF-36P

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|}
\hline
 & Self-Management Group & Control Group \\
 & (\( n = 25 \)) & (\( n = 25 \)) \\
\hline
Age, yrs & 64 ± 8 & 67 ± 11 \\
BMI, kg/m\textsuperscript{2} & 24 ± 5 & 26 ± 7 \\
BMD (lumbar total) T score & −3.9 ± 1.4 & −3.7 ± 1.1 \\
BMD (femur total) T score & −3.1 ± 0.6 & 2.9 ± 0.5 \\
Pain (VAS) & 4.8 ± 2.4 & 3.5 ± 2.7 \\
Number of subjects with osteoporotic fracture & 8 & 7 \\
SF-36MH & 61.6 ± 17.1 & 60.8 ± 21.8 \\
SF-36PF & 59.1 ± 26.1 & 64.3 ± 23.4 \\
SRT eyes open, secs & 91 ± 69 & 85 ± 75 \\
SRT eyes closed, secs & 14 ± 13 & 15 ± 14 \\
TSS, secs & 30 ± 8 & 28 ± 8 \\
\hline
\end{tabular}
\caption{Baseline values of the variables and patient characteristics in each group}
\end{table}

\textsuperscript{25}BMI, body mass index; BMD, bone mineral density; VAS, Visual Analogue Scale; SF-36MH, Short Form Health Survey Mental Health; SF-36PF, Short Form Health Survey Physical Function; SRT, Sensitized Romberg Test; TSS, Timed Sit to Stand.
<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Changes from baseline at the fifth week and at the sixth month in the self-management group (G1) and control group (G2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Evaluation (a)</td>
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<tr>
<td></td>
<td>Mean</td>
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<tr>
<td>Pain (VAS)</td>
<td></td>
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<tr>
<td>G1</td>
<td>4.8</td>
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<tr>
<td>G2</td>
<td>3.5</td>
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<tr>
<td>SF-36PF</td>
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<tr>
<td>G1</td>
<td>59.1</td>
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<tr>
<td>G2</td>
<td>64.3</td>
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<tr>
<td>SF-36PRL</td>
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<tr>
<td>G1</td>
<td>55.6</td>
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<tr>
<td>G2</td>
<td>63.1</td>
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<tr>
<td>SF-36SF</td>
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<tr>
<td>G1</td>
<td>86.4</td>
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<tr>
<td>G2</td>
<td>85.4</td>
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<tr>
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<td>61.6</td>
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<tr>
<td>G2</td>
<td>60.8</td>
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<tr>
<td>SF-36 vitality</td>
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<td>G1</td>
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<td>G2</td>
<td>41.7</td>
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<tr>
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<td>57.3</td>
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<tr>
<td>SF-36GHP</td>
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<td>G1</td>
<td>60.7</td>
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<tr>
<td>G2</td>
<td>58.2</td>
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<tr>
<td>SF-36ERL</td>
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</tr>
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<td>G1</td>
<td>60.6</td>
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<tr>
<td>G2</td>
<td>46.3</td>
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<tr>
<td>SRT eyes open, secs</td>
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<td>G1</td>
<td>91.1</td>
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<tr>
<td>G2</td>
<td>85.4</td>
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<td>SRT eyes closed, secs</td>
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<td>G1</td>
<td>30.1</td>
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<tr>
<td>G2</td>
<td>28.2</td>
</tr>
</tbody>
</table>

VAS, Visual Analogue Scale; SF-36PF, Short Form Health Survey Physical Functioning; SF-36PRL, Short Form Health Survey Physical Role Limitations; SF-36SF, Short Form Health Survey Social Functioning; SF-36MH, Short Form Health Survey Mental Health; SF-36 vitality, Short Form Health Survey Vitality; SF-36P, Short Form Health Survey Pain; SF-36GHP, Short Form Health Survey General Health Perceptions; SF-36ERL, Short Form Health Survey Emotional Role Limitations; SRT, Sensitized Romberg Test; TSS, Timed Sit to Stand.
**DISCUSSION**

This study was designed to assess the impact of a self-management program in osteoporosis; the goal was to motivate patients to adhere to health behaviors that would maintain or improve their long-term health status by means of regular exercise, dietary modifications, and preventive strategies. The present data demonstrate that a 6-mo course of the self-management program, *choices For Better Bone Health*, motivated patients and increased predictors of compliance with long-term health behaviors that improve bone health. Seventy-four percent of patients in the intervention group engaged in regular physical activities such as balance and weight-bearing exercises two or three times a week, and 92% of them declared that they understood the purpose and benefits of medications and dietary calcium intake. Fifty-seven percent of them formed personal plans and strategies for preventing traumas, whereas 8% of the subjects in the control group experienced new falls (outside home). As the primary outcomes, balance, life-quality assessments, pain, and functional status in the intervention group improved during the study (5 wks) and were still improving at the sixth month.

Self-management programs emphasize the central role of the patient in managing his or her own illness. These programs focus on helping patients with medical management, maintaining social roles, and managing negative emotions such as fear and depression that frequently accompany the limitations imposed by chronic illness. Though there are no randomized controlled studies existing in the literature demonstrating the effects of *choices For Better Bone Health* in osteoporotic people, few studies have evaluated the impact of specific patient education on compliance and per-

(P < 0.05 at the sixth month) and SF-36PRL (P < 0.05 at the fifth week, P < 0.01 at the sixth month) scores, whereas there was an increase in pain intensity by VAS (P < 0.05 at the fifth week and P < 0.01 at the sixth month) according to baseline (Table 2).

When the groups were compared with each other by change scores and percent changes, improvements observed in pain intensity by VAS (P < 0.001), SF-36PF (P < 0.001), SF-36PRL (P < 0.001), SF-36SF (P < 0.001), SF-36MH (P < 0.001), SF-36 vitality (P < 0.01), SF-36P (P < 0.001), SF-36GHP (P < 0.05), SF-36ERL (P < 0.01), SRT eyes open (P < 0.001), SRT eyes closed (P < 0.001), and TSS (P < 0.001) were determined to be superior in group 1 at the end of the sixth month (Table 3).

Our questionnaire put forth that 74% of patients in the intervention group (group 1) engaged in regular physical activities such as balance and weight-bearing exercises two or three times a week, and 92% of them declared that they understood the purpose and benefits of medications and dietary calcium intake. Fifty-seven percent of them formed personal plans and strategies for preventing traumas. New falls or fractures did not occur in the intervention group for the study duration. There were no life or behavioral changes in the control group. In any case, 30% of them declared that they understood the benefits of the medications for osteoporosis, and 8% of them experienced new falls (outside home) but no fractures.

**TABLE 3** Comparison of the change scores and percent changes for each variable in group 1 (self-management) and group 2 (control) at the sixth month

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (mean ± SD)</th>
<th>Group 2 (mean ± SD)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain (VAS)</td>
<td>-3.4 ± 2.3</td>
<td>1.6 ± 2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SF-36PF</td>
<td>24.7 ± 20.8</td>
<td>-0.8 ± 7.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SF-36PRL</td>
<td>44.3 ± 44.1</td>
<td>-23.9 ± 51.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SF-36SF</td>
<td>13.5 ± 10.3</td>
<td>-1.2 ± 9.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SF-36MH</td>
<td>17.4 ± 13.5</td>
<td>0.7 ± 4.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SF-36 vitality</td>
<td>22.0 ± 19.0</td>
<td>5.2 ± 12.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SF-36P</td>
<td>23.2 ± 20.3</td>
<td>-6.9 ± 15.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SF-36GHP</td>
<td>9.3 ± 7.0</td>
<td>-3.8 ± 20.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>SF-36ERL</td>
<td>39.3 ± 25.6</td>
<td>-1.4 ± 38.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SRT eyes open (%)</td>
<td>137.9 ± 28.9</td>
<td>3.7 ± 1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SRT eyes closed (%)</td>
<td>200 ± 63.1</td>
<td>-32.6 ± 12.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TSS, secs (%)</td>
<td>-29.9 ± 11.3</td>
<td>7.8 ± 2.3</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

VAS, Visual Analogue Scale; SF-36PF, Short Form Health Survey Physical Functioning; SF-36PRL, Short Form Health Survey Physical Role Limitations; SF-36SF, Short Form Health Survey Social Functioning; SF-36MH, Short Form Health Survey Mental Health; SF-36 vitality, Short Form Health Survey Vitality; SF-36P, Short Form Health Survey Pain; SF-36GHP, Short Form Health Survey General Health Perceptions; SF-36ERL, Short Form Health Survey Emotional Role Limitations; SRT, Sensitized Romberg Test; TSS, Timed Sit to Stand.
sistence with osteoporosis medication and preventive strategies. Knowledge and health-related behaviors such as calcium intake and exercise are shown to increase by osteoporosis education initiatives during the short- to medium term in the osteoporotic population. A 2-yr randomized controlled trial designed to assess whether bone mineral density feedback and two different educational interventions (osteoporosis information leaflet or group-based behavioral education on osteoporosis knowledge and self-efficacy in 470 premenopausal women) showed that the educational interventions and bone density feedback increased osteoporosis knowledge but not self-efficacy. Premenopausal women with children or who worked full time decreased osteoporosis self-efficacy, suggesting that this group should be a specific target for future preventive interventional strategies. Another trial showed that both bone mineral density feedback and small-group education delivered to mothers are effective at inducing maternally reported osteoporosis preventive behavior change in their children, as are increasing calcium intake and physical activity. In addition, with the public health education model including both population-based and individual interventions, behavioral changes were reported in the prevention of falls and physical activity patterns among elderly people. Inactivity and deterioration of neuromuscular function cause loss of coordination, increased postural sway, and slow walking, all of which contribute to falls in the elderly. Our present data demonstrate the benefits of the self-management strategy: improvements in balance, function, pain, behavioral changes, and relatively low fall frequency compared with the control group. Consequently, exercise recommendations as part of the behavioral approach are thought to be the major determinant in these improvements and positive changes. Literature review confirms that exercise may reduce the rate of falls in the elderly, particularly when regimens comprise balance exercises. Two studies report the effect of Tai Chi on the frequency of falls in men and women ages 70 and older. The study that compared the efficacy of Tai Chi practiced for 15 wks and computerized stretching to improve musculotendinous extension are accompanied by pain attenuation. It is also reported that regular aerobic exercise can decrease peripheric muscle resistance and increase alpha wave activity in the central nervous system; this is a central relaxation sign. On the other hand, aerobic exercise can directly effect neurohumoral systems, and, in this way, central β-endorphins promote pain thresholds and decrease pain perception. These data suggest that different exercise approaches must be taken within the self-management process, determined according to the goals of the therapy.

Several limitations to this study design should also be noted. These include the small number of subjects and the short study duration. Because clinically relevant changes in behavioral approaches may be achieved only after longer periods of time, 6 mos may be considered a relatively short study period. Another limitation is the lack of generalizability of the study population. Because the subjects were selected from the outpatient department, they may not reflect the whole postmenopausal or idiopathic osteoporotic patient population outside.

In conclusion, the present data highlight the need for behavioral strategies in osteoporosis-treatment programs and demonstrate the positive impact of the self-management program, choices For Better Bone Health, on patient behaviors, pain perception, balance, functional status, and life-quality assessments in osteoporotic people. These results should stimulate further research with longer follow-up periods and larger patient groups.

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ABSTRACT


Objective: Using auditory and visual stimuli including facial affective stimuli, we analyzed the P300 components of event-related potentials (ERPs) in patients after traumatic brain injury (TBI) to assess their cognitive characteristics.

Design: Twenty TBI patients and 32 age-matched control subjects were recruited. Using conventional oddball paradigms, visual ERPs were recorded using images of crying and smiling babies as visual stimuli. Auditory ERPs were obtained using 2-kHz tones as stimuli without affective stimuli. The peak amplitude and latency for P300, and the latency for N200, were recorded.

Results: In visual ERPs, the P300 amplitudes were significantly smaller in patients than in controls for the crying baby, but the amplitudes were similar between groups for the smiling baby. Controls showed smaller P300 amplitudes for the smiling baby than for the crying baby, but patients showed no difference. In patients, the P300 latency for both smiling and crying babies was longer than in the controls. Patients’ auditory ERPs showed smaller P300 amplitudes but similar P300 latencies compared with controls. The N200 latency in patients was significantly longer than in controls only for the crying baby.

Conclusions: Visual ERPs are a potentially useful marker for evaluating cognitive dysfunction in patients after TBI.

Key Words: Traumatic Brain Injury, Event-Related Potentials, Visual and Auditory Stimuli, Facial Affect
Event-related potentials (ERPs) have been investigated as a biological marker of information processing by the human central nervous system. As pointed out by Polich, adherence to standard paradigms, such as the oddball paradigm, is necessary for meaningful comparisons between studies, because differences in stimulus presentation alter ERP components. ERP amplitudes vary widely, depending on the complexity of the task and the arousal and emotional states of subjects. Many studies of emotional influences have been reported, and the significant effects of viewing facial expressions on ERPs are known.

Measurement of the amplitudes of ERPs in patients after brain injury has been suggested as a useful complementary analysis to neuropsychological assessment. Several ERP studies in patients with cognitive dysfunction after brain injury have been reported, but some characteristics remain unknown. Muller et al. report that patients who had sustained traumatic brain injury (TBI) showed a significantly longer latency for the auditory P300 than did healthy subjects. A visual oddball paradigm showed a smaller P300 amplitude and prolonged P300 latency in patients after TBI. These authors suggest that the abnormalities reflect cognitive impairment in the patients. Sangal et al. report that head injury patients with mild cognitive complaints but no abnormal neurological findings or psychiatric disorders had prolonged P300 latencies in response to visual but not auditory stimuli. Furthermore, Werner and Vanderzant also report a normal auditory P300 in most patients with mild closed-head injury.

On the other hand, P300 of such patients showed both a longer latency and reduced amplitude in visual and auditory oddball paradigms. The results indicate that processing of visual and auditory stimuli, including perception and discrimination of stimulus features, and evaluation and categorization of stimuli, might be impaired after TBI. Clarification of the significance of ERP-modality differences such as visual vs. auditory stimuli may be important for the accurate evaluation of patients after TBI.

Some patients with TBI have been shown to manifest a significant deficit in the ability to correctly identify emotions associated with facial expressions. Such patients show a distinctive emotional inappropriate nature, to which an impaired ability to identify facial expressions might contribute. Up to now, few studies have compared the effects of facial affective recognition on ERPs between controls and patients with TBI. These patterns of facial expression effects might shed light on the mechanism of cognitive impairment in TBI.

We have reported previously that neutral stimuli caused ERPs similar to those caused by negative affective stimuli such as anger or crying. The present study was conducted to characterize cognitive dysfunction in patients after TBI, according to ERPs obtained with neutral auditory or affective visual stimuli, particularly concerning the effects of facial expressions on ERPs in patients compared with control subjects.

**SUBJECTS AND METHODS**

**Subjects**

The subjects included 20 patients who had sustained TBI (35.1 ± 11.8; 14 men and 6 women), who ranged in age from 20 to 55 yrs (mean, 33.3 ± 11.8), and 32 healthy volunteers (16 men and 16 women), who ranged in age from 20 to 54 yrs (mean, 33.5 ± 9.5). No significant age differences were noted between these groups. All subjects were right-handed and had no historical evidence of psychiatric illness. All patients were free from focal neurological or physical deficits such as motor palsies and speech disturbance (Table 1). No subjects had any history of alcoholism or drug abuse. No patients or control subjects had visual disabilities, and all subjects could recognize the images presented on photographs used for visual ERP analysis. Written informed consent was obtained from all subjects before the study.

**Electroencephalographic Recording**

Each subject sat in a sound-attenuated, electrically shielded room and was asked to relax with their eyes open. Subjects were requested to try not to blink during the test. ERPs were recorded from

**TABLE 1** Characteristics of patients (n = 20)

<table>
<thead>
<tr>
<th>Age, yrs (range)</th>
<th>35.1 ± 11.8 (20–55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male:female (n)</td>
<td>14:6</td>
</tr>
<tr>
<td>Time to event-related potential from injury, mos</td>
<td>25.68 ± 8.87</td>
</tr>
<tr>
<td>Mechanism</td>
<td></td>
</tr>
<tr>
<td>Traffic</td>
<td>13</td>
</tr>
<tr>
<td>Fall</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
</tr>
<tr>
<td>Intracranial diagnosis*</td>
<td></td>
</tr>
<tr>
<td>Diffuse brain injury</td>
<td>16</td>
</tr>
<tr>
<td>Evacuated mass lesion</td>
<td>4</td>
</tr>
<tr>
<td>Post-resuscitation GCS</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>11.85 ± 2.80</td>
</tr>
<tr>
<td>13–15</td>
<td>12</td>
</tr>
<tr>
<td>9–12</td>
<td>6</td>
</tr>
<tr>
<td>≤8</td>
<td>2</td>
</tr>
<tr>
<td>GOS</td>
<td></td>
</tr>
<tr>
<td>Good recovery</td>
<td>18</td>
</tr>
<tr>
<td>Moderate disability</td>
<td>2</td>
</tr>
</tbody>
</table>

* TCDB computed tomography classification for intracranial diagnosis.
GCS, Glasgow coma scale; GOS, Glasgow outcome scale (6 mos after injury).
Ag/AgCl electrodes at Fz, Cz, Pz, Oz, T3, and T4 positions, as designated by the international 10–20 system, with reference electrodes at the mastoids. A forehead electrode served as the ground. The electroencephalographic signal was amplified and processed with filters that passed a band from 0.5 to 50 Hz and was then recorded conventionally (Neurofax, Nihon-Kohden; Tokyo, Japan) for examination of the continuous electroencephalographic. The impedances was maintained below 5 kΩ. An averaged waveform was obtained from 20 artifact-free epochs associated with individual target stimuli for each type of tone or image during one block of stimulus presentation, as proposed by Polich. One block was presented to each subject as the first session. Vertical electrooculogram was recorded from electrodes positioned above the left eye. Trials exceeding 50 μV in amplitude were automatically excluded from the averaging process. The sampling rate was 256 Hz. The P300 latency was estimated from the peak amplitude beginning at stimulus initiation. Sampling was initiated 100 msecs before stimulus onset and continued for 1 sec. The averaged value before the stimulus was used as the baseline value.

In auditory ERPs, tone frequencies of target stimuli were 2000 Hz (probability of presentation, 20%), and those of no target stimuli were 1000 Hz (probability, 80%) without affective stimuli. All subjects were asked to maintain their gaze within a circle on a 1.5-m square panel, positioned 1 m away at eye level. Both stimulus types were presented at an appropriate intensity (sound presentation at 70 dB). Tone duration was 100 msecs, with a 10-msec rise time. Tones were presented in a random sequence at a mean rate of 1700 msecs. The P300 latency was estimated from the latency of the largest positive peak occurring between 250 and 500 msecs. The P300 amplitude was calculated from the baseline to the peak of the largest positive waveform between 300 and 600 msecs.

The N200 latency was determined as the latency of the largest negative peak between 200 and 300 msecs.

**Protocol for Recording ERPs and Evaluating Facial Expression**

ERP recording sessions took place from 2:00 to 4:00 p.m. Auditory ERPs were recorded first, in about 30 mins. Then, visual ERPs were obtained in about 1 hr. For visual ERPs, sessions included the presentation of two photographs (smiling or crying) during double-task performance to maintain attention and arousal (counting and pressing a button on seeing target stimuli). After completing a session, subjects were asked to look closely at each of the two target stimuli presented (smiling or crying) to evaluate the affect associated with the facial expression. All healthy controls and patients responded as expected with respect to expression in the two photographs: smiling was associated with pleasure, whereas crying was associated with sadness.

**Statistical Analysis**

ERP data were examined using two-way analysis of variance (ANOVA; groups × electrodes: Fz, Cz, and Pz) in auditory ERPs for the main group effects, and for each emotion (crying or smiling) in visual ERPs for the main group effects. In visual ERPs, three-way ANOVA (groups × face types × electrodes) was also done. G–G epsilon was used to measure the extent to which the correlation of the observations violated the validity of the P values. The uncorrected differences were used in reporting the ANOVA outcomes.

Next, if an interaction was obtained, one-way ANOVA was performed (between controls and patients) to assess the main group effect for each electrode site including Oz, T3, and T4. Tukey–Kramer analysis, carried out post hoc, was used to test for significant differences. A probability of <5% was considered significant. Pearson's correlation coefficient was used to identify significant relationships between the duration of illness or symptom scores and measures of ERPs. A level of P < 0.05 was accepted as significant. Values are presented in the text as means ± standard deviation.

**RESULTS**

**Auditory ERPs**

**P300 Peak Amplitude**

Significant main effects for groups were seen using two-way ANOVA (F2191 = 20.20, P < 0.0001; Fig. 1B, upper panel) The peak amplitude was larger for controls than that for patients (P <
There was no interaction between groups and recording sites. The peak amplitude for controls was larger than for patients at Fz ($F = 11.8, P < 0.01$), Cz ($F = 5.93, P < 0.05$), and Pz ($F = 4.35, P < 0.05$). The peak amplitude for controls was significantly larger than for patients at T3 ($F = 11.26, P < 0.01$) and T4 ($F = 6.08, P < 0.05$).

### P300 Latency

Significant main effects for groups were not seen using two-way ANOVA (Fig. 1B, lower panel). There was no interaction between groups and recording sites. The latency for controls was similar to that for patients. No significant difference for latency was observed between controls and patients at Oz, T3, and T4 recording sites.

### N200 Peak Amplitude

Significant main effects for group were not seen using two-way ANOVA. There was no interaction between groups and recording sites. The peak amplitude for controls was similar to that for patients in all recording sites.

### N200 Latency

Significant main effects for group were not seen using two-way ANOVA. There was no interaction between groups and recording sites. The latency for controls was similar to that for patients in all recording sites.

### Reaction Time

Controls (374.3 ± 94.3 msecs) had significantly shorter reaction times than patients (542.7 ± 175.3; $F_{1191} = 33.03, P < 0.0001$). There was no significant correlation between the reaction time and P300 and N200 amplitude and latency, respectively.

### Accuracy of Counting and Tone Assessment

Both counting and button-pressing accuracy exceeded 90% for all subjects. No significant difference was evident between controls and patients.

### Visual ERPs

#### P300 Peak Amplitude

Significant main effects for group were seen using three-way ANOVA ($F_{2382} = 9.46, P < 0.01$; Figs. 2 and 3). The peak amplitude for controls was larger than that for patients. The peak amplitude for the crying stimulus was larger than that for the smiling stimulus. A significant interaction was observed between groups and face type ($P < 0.01$). Significant main effects for group were seen using two-way ANOVA for the crying stimulus ($F_{2191} = 16.39, P < 0.0001$) and for the smiling stimulus ($F_{2191} = 0.04, P = 0.831$). The peak amplitude for the crying baby was larger for controls than for patients. There was no interaction between groups and recording sites. The peak amplitude for patients was significantly smaller than for controls at Oz ($F = 6.22, P < 0.05$) and T3 ($F = 12.60, P < 0.001$). In healthy controls, the amplitude while viewing the crying baby was signifi-
...cantly larger than while viewing the smiling baby \( (F_{1269} = 48.53, P < 0.0001) \). Significant differences were obtained from all recording sites (Fz: \( F = 10.25, P < 0.001 \); Cz: \( F = 17.22, P < 0.0001 \); Pz: \( F = 22.03, P < 0.0001 \)). However, in patients, the amplitude while viewing the crying baby was similar to that observed while viewing the smiling baby.

**P300 Latency**

Significant main effects for group were seen using three-way ANOVA \( (F_{2382} = 104.6, P < 0.0001; \text{Fig. } 4) \). The latency for controls was shorter than that for patients. Significant main effects for group were seen using two-way ANOVA for the crying stimulus \( (F_{2191} = 86.68, P < 0.0001) \) and for the smiling stimulus \( (F_{2191} = 30.03, P < 0.0001) \). The latency when viewing the crying baby was shorter for controls than for patients. There was no interaction between groups and recording sites. The latency for patients was significantly longer than for controls at Fz \( (F = 27.95, P < 0.0001) \), Cz \( (F = 31.81, P < 0.0001) \), and Pz \( (F = 27.58, P < 0.0001) \) for the crying stimulus and at

![FIGURE 2](image-url)

*FIGURE 2* Grand-averaged waveforms (A) and mean amplitude of visual P300 (B) when viewing the crying baby. ◊, controls; ●, patients. Significant difference was observed between patients and controls. Bars indicate the standard error (SE).

![FIGURE 3](image-url)

*FIGURE 3* Grand-averaged waveforms (A) and mean amplitude of visual P300 (B) when viewing the smiling baby. ◊, controls; ●, patients. No significant differences were observed between patients and controls. Bars indicate the standard error (SE).
Fz \( (F = 5.88, P < 0.01) \), Cz \( (F = 13.01, P < 0.001) \), and Pz \( (F = 13.26, P < 0.001) \) for the smiling stimulus. The peak amplitude for controls was significantly larger than for patients at Oz \( (F = 17.33, P < 0.0001) \), T3 \( (F = 14.90, P < 0.0001) \), and T4 \( (F = 12.75, P < 0.0001) \) for the crying stimulus. The peak amplitude for controls was significantly larger than for patients at Oz \( (F = 14.6, P < 0.0001) \), T3 \( (F = 8.7, P < 0.01) \), and T4 \( (F = 10.19, P < 0.001) \) for the smiling stimulus.

In healthy controls, there were main group effects \( (F_{1269} = 9.78, P < 0.01) \), and the latency while viewing the crying baby was significantly shorter than while viewing the smiling baby. The latency was significantly shorter for the crying baby than for the smiling baby at Fz \( (F = 4.49, P < 0.05) \) and Cz \( (F = 4.45, P < 0.05) \). However, in patients, the latency while viewing the crying baby was similar to that observed while viewing the smiling baby.

**N200 Peak Amplitude**

Significant main effects for group were not seen using three-way ANOVA for visual stimuli. Significant main effects for group were not seen using two-way ANOVA for both stimuli. There was no interaction between groups and recording sites. The amplitude of patients was similar to that of controls at all recording sites.

In healthy controls, a significant main effect for the N200 amplitude was observed \( (F_{1269} = 7.86, P < 0.01) \). The amplitude while viewing the crying baby was significantly smaller than while viewing the smiling baby. However, in patients, the amplitude for the crying baby was similar to that for the smiling baby.

**N200 Latency**

Significant main effects for group were seen using three-way ANOVA for the visual stimulus \( (F_{1382} = 9.20, P < 0.01) \). The latency was significantly longer for patients than for controls. Significant main effects for group were seen using two-way ANOVA for only the crying stimulus \( (F_{1269} = 15.36, P < 0.0001) \). The latency was significantly longer for patients than for controls. There was no interaction between groups and recording sites.

The latency of patients was significantly longer than that of controls at Fz \( (F = 6.18, P < 0.05) \), Cz \( (F = 4.54, P < 0.05) \), and Pz \( (F = 4.98, P < 0.05) \). The latency for controls was significantly shorter than for patients at T3 \( (F = 4.90, P < 0.05) \) and T4 \( (F = 6.88, P < 0.01) \) for the crying stimulus.

There was no significant difference in the N200 latency between the two stimuli, both in controls and in patients.

**Reaction Time**

The reaction time for controls was 472.2 ± 88.2 msecs for the crying baby and 485.1 ± 98.2 msecs for the smiling baby. The reaction time for patients was 603.8 ± 178.5 msecs for the crying baby and 578.5 ± 123.6 msecs for the smiling baby.

Significant main effects for group were seen using two-way ANOVA \( (F_{1166} = 34.61, P < 0.001) \). The reaction time was significantly longer for patients than for controls \( (P < 0.0001) \) for both stimuli. There was a significant correlation between the reaction time and P300 latency \( (r = 0.402, P < 0.01) \) in controls and patients \( (r = 0.514, P < 0.01) \) only for the smiling baby.


**Accuracy of Counting and Tone Assessment**

Both counting and button-pressing accuracy exceeded 90% for all subjects. A significant difference was not evident between controls and patients.

**Relationship Between Glasgow Coma Scale or Duration from TBI, and P300 Measures**

No significant relationship was observed between Glasgow coma scale (level of consciousness disturbance when hospitalized) and the duration from the TBI and P300 or N200 measures (amplitude and latency, respectively).

**DISCUSSION**

The present findings clearly show prolongation of the visual P300 latency in patients after TBI, whereas the auditory P300 latency was not prolonged compared with age-matched control subjects. The present findings also show that the P300 amplitude in patients after TBI is affected by exposure to emotionally charged images and differed from the P300 amplitude in controls.

TBI patients have been reported to show deficiencies in cognitive function, reflected by P300 and reaction time. In the early stages of ERP research in patients with TBI, only auditory ERPs were evaluated for correspondence to patient characteristics. As ERP evaluation continued to develop, Lew et al. reported that TBI patients had significantly longer P300 latencies in response to both auditory or visual stimuli, and they concluded that TBI patients demonstrated impaired performance both electrophysiologically and behaviorally.

Duncan et al. report that auditory P300 latency was prolonged but that visual P300 latency was not, suggesting that the processing of auditory stimuli may be impaired after head trauma, whereas visual sensory processing may be spared. The same report notes that auditory P300 abnormalities correlated strongly with the duration of unconsciousness, concluding that the processing of auditory stimuli, including perception and discrimination of stimulus features and evaluation and categorization of stimuli, may be impaired after head trauma.

In disagreement with respect to modality, Werner and Vanderzant report a normal amplitude and latency of auditory P300 in most patients with mild closed-head injury, with P300 abnormalities being apparent only for visual stimuli.

Considering all reports, the P300 latency seems to be a better index for evaluating patients after TBI than the P300 amplitude. In the present study, auditory P300 latency for patients was not prolonged beyond that seen in healthy controls, but visual P300 latency was prolonged significantly. Morita et al. report that P300 latency when viewing a neutral face was similar to that when viewing smiling, angry, and crying faces at Fz, Pz, and Cz. This indicates that P300 latency caused by auditory modality without emotionally laden stimuli was essentially similar to P300 latency with facial affective stimuli. However, ERPs using visual modality without emotionally laden stimuli are needed. Our present TBI subjects were outpatients who were studied during the recovery period (over 10 mos after brain injury: 25.68 ± 8.87 mos) and who lacked neurological deficits, consistent with mild TBI.

One should note that auditory ERPs have been reported to be prolonged in severe TBI and in the short term. Although the auditory system is more likely to be injured by TBI rather than the visual system, visual sensory processing may be more complex and involve a higher order of function. Therefore, the speed of allocation of attention resources, reflected by visual P300 latency, may be more likely to be affected than auditory latency in mild-TBI patients.

Polich suggests that the P300 amplitude might be a good indicator for determining the effect of attention resource diversion and allocation time (evaluation time) in both healthy subjects and patients with cognitive disorders. In the present study, the P300 amplitude for visual stimuli in controls was larger than in patients when viewing the crying baby, but no difference was apparent when viewing the smiling baby.

Assuming that the magnitude of the P300 amplitude reflects the emotional impact of the observed facial expression, attention resources devoted to evoking the visual P300 seem to be diverted by exposure to external stimuli. Psychologically, sadness stimuli and anger stimuli have been reported to divert more attention resources than pleasure. Thus, patients recovering from TBI may show particular impairment of attention resource allocation when exposed to negative stimuli. Recently, Lew et al. have suggested that patients’ ability to recognize facial affective stimuli was impaired after brain damage. This disability may disturb interpersonal relationships, because it interferes with the interpretation of cues that require specific responses according to social conventions. TBI patients have shown significantly impaired electrophysiological and behavioral functions while attempting to detect affective facial cues.

One explanation is that the attention level may increase while viewing a crying baby but decrease while viewing a smiling face, because subjects are expected to be more attentive to anger or sadness than pleasure, as reported previously. In contrast to the crying and angry faces, the smiling face is a...
positive stimulus\textsuperscript{6} that caused less alteration of visual P300 characteristics than did the pictures with negative emotional content.

These properties resulted in a significant difference in the visually induced P300 amplitude. When TBI patients viewed the smiling baby, their P300 amplitude was not reduced from that in control subjects, whereas the patients’ P300 latency was significantly prolonged compared with controls. In other words, bigger changes in P300 abnormalities were observed by the negative stimulus rather than the positive stimulus.

Further study is needed to clarify the emotional effects on the auditory ERPs using an affective stimulus. N200 latency prolongation in patients has been reported previously\textsuperscript{23,25} in the present study, the N200 latency was prolonged only for the crying baby. These results indicate that the N200 latency under negative affective stimuli may be useful, and task discrimination may be more difficult in patients than in controls.

The push-button reaction time was significantly prolonged, both in the auditory and the visual tasks. A significant correlation between the reaction time and P300 latency was observed in the visual task, both in the controls and the patients. These results indicate that the reaction time may also be a useful marker for evaluating patients.

There was no significant correlation between Glasgow coma scale or the duration from TBI, and the p300 or the n200 measures.

Further study is needed to assess patients during the acute and subacute phases, and among severe-TBI patients.

Finally, the present results indicate that the stimulus-recognition process, reflected by P300 characteristics, is particularly impaired when stimuli involve negative emotion (crying baby). Thus, TBI may impair more complex facial recognition. Therefore, improvement of a patient’s social skills might benefit from an increased focus on rehabilitation training in emotion perception.

Our present technique, in terms of the emotionally charged visual ERPs, seems useful for evaluating subtle problems with facial affective perception and expression. Hereafter, results have to be compared serially across some period to evaluate progress in recovery from TBI.\textsuperscript{26,27} Additional studies could determine how meaningful this assessment method is for patients’ psychosocial functioning in the community.

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**BOOK REVIEW**

The Mutilated Hand


*The Mutilated Hand* is a comprehensive textbook covering essentially all aspects of the management of mutilating injuries of the arm and hand. The book is designed to be a definitive resource and reference textbook for hand surgeons, surgical residents, plastic surgery fellows, and orthopedic hand-surgery fellows. Rehabilitation professionals including PM&R physicians, hand therapists, prosthetists, and orthotists will also find this textbook to be a valuable resource.

The text is detailed and comprehensive in nature. It is organized into 12 sections and 42 chapters. The editors have selected well-known and respected individuals to author chapters for the text. Most chapters have two or three contributors. Overall, the text is very well written, readable, and well organized. The textbook begins with a historical perspective and an overview and classification of mutilating injuries. Subsequent chapters provide in-depth descriptions and management strategies for various arm- and hand-mutilating injuries. The text ends with sections on postoperative management and limb allotransplantation. Although each chapter can stand alone, the text overall flows well from chapter to chapter, and the editors seem to have minimized redundancy.

Outstanding features of this text include the introductory sections to each chapter, the marvelous color photographs, and the summary tables. The color photographs are included in each chapter and help to illustrate the devastating nature of mutilating injuries to the arm and hand. The case studies included in many of the chapters are also enlightening. The chapters on psychological aspects, rehabilitation management, pain management, and prosthetics are particularly well suited for rehabilitation professionals.

Overall, this text is rated as excellent. The text seems unique in its comprehensive coverage of mutilating injuries to the arm and hand. Although primarily designed for surgeons, the text will also be a very good reference book for PM&R physicians, therapists, prosthetists, and orthotists who deal with mutilating injuries of the arm and hand.

Rating: ★★★★★

Joseph B. Webster, MD
Salt Lake City, Utah
Impact of Patient’s Weight on Stroke Rehabilitation Results

ABSTRACT

Objective: To evaluate the influence of patient’s weight on rehabilitation results after first stroke.

Design: Retrospective, comparative study. The sample comprised 84 males and females, first-time stroke patients, who had been hospitalized in the department of rehabilitation at the Hartzfeld Geriatric Hospital, Gedera, Israel for a full 3 mos and who, on admission, had scored between 40 and 60 on the total Functional Improvement Measure (FIM) test. We evaluated the difference in total FIM improvement between normal-weight, overweight, and obese patients.

Results: The relative improvement of FIM score was significantly higher in normal-weight patients than in overweight patients, and improvement in overweight patients was significantly higher than in obese ones. We also found a statistically significant negative correlation \(r = -0.27, P = 0.014\) between relative improvement of FIM score and body mass index (BMI) in the total sample.

Conclusions: Our study revealed that during the first 12 wks, rehabilitation is statistically significantly less effective in overweight and, particularly, in obese patients (evaluated by BMI). We also found a statistically significant negative association between the individual’s BMI and relative improvement of the FIM score, representing the functional status of the stroke patient.

Key Words: BMI, CVA, Stroke, Rehabilitation, FIM Test
Stroke is one of the most common causes of death and a major cause of chronic disability. With its high incidence and high mortality rates, a large proportion of survivors are left with significant residual physical, cognitive, and psychological impairment. Many stroke survivors continue to live with residual physical impairment (i.e., reduced mobility, poor balance, and muscle weakness), leading to physical inactivity and a sedentary lifestyle. A significant financial and emotional burden is brought to bear on the patient, his family, and society in general.

Feigin et al.’s review study of 2003 demonstrates that an increase in life expectancy initiated an increasing incidence of stroke. Conversely, stroke mortality rate has been declining, translating into a larger number of chronic stroke survivors.

Several factors such as age, sex, and urinary incontinence were studied as possible predictors of quality poststroke rehabilitation. Meijer et al., in a systematic review, conclude that there is insufficient evidence concerning possible predictors in the subacute stage of stroke to make an evidence-based prediction of future residence. In 2004, Meijer et al. found that marital status and social support proved to be important factors in predicting discharge destination of stroke patients.

Our clinical experience in a rehabilitation department (Gedera, Israel; B.R.) and in an outpatient physical therapy clinic (L.K.) has demonstrated that overweight patients achieve less satisfactory results in their functional rehabilitation after stroke. Overweight is a well-known risk factor for stroke; however, we did not find any publication dealing with the influence of overweight on poststroke rehabilitation outcome. We hypothesized that overweight patients would show less improvement in their functional status after 12 mos of rehabilitation than would patients of normal weight.

The aim of the present study was to evaluate the association between the patient’s weight (measured by body mass index [BMI]) and rehabilitation functional outcome (measured by the Functional Improvement Measure [FIM]) after a first stroke.

**METHODS**

**Sample**

The study sample comprised 100 participants who had been hospitalized at the department of rehabilitation at Hartzfeld Geriatric Hospital, Israel between December 2002 and May 2003. Criteria for inclusion included having suffered a first stroke, having been hospitalized in the department for a full 3 mos (the usual period of rehabilitation), and having scored 40–60 on the total FIM measure on admission. In Israel, an FIM score between 40 and 60 for stroke patients is a commonly accepted criterion for a patient’s transfer to a rehabilitation department and for commencement of rehabilitation. Exclusion criteria were falls during hospitalization, recurrent stroke during hospitalization, discharge before completing the full rehabilitation period, or death.

**Study Design**

A retrospective study using data collected from medical records of a rehabilitation department in a geriatric hospital.

**Studied Traits**

Eighty-four patients met the criteria. Data collected included age, sex, weight, and height on admission, and total FIM scores for three different time periods: day of admission (FIM0), 6 wks later (FIM6), and 12 wks after commencement of rehabilitation (FIM12; usually toward the end of hospitalization period). Weight and height were measured by a nutritionist. FIM measurement was performed by ward nurses highly experienced in FIM evaluation.

The FIM instrument was developed by a joint Task Force of the American Congress of Rehabilitation Medicine and the American Academy of Physical Medicine and Rehabilitation. It has been used widely in rehabilitation facilities in the United States and internationally. The FIM instrument evaluates the patient’s neurological functioning and may be used for assessing outcomes of rehabilitation. The FIM instrument, adopted by geriatric physicians, was developed to resolve the lack of uniform measurement and data on disability and rehabilitation outcomes. A meta-analysis of 11 studies showed a median interrater reliability for the total FIM score of 0.95, a median test–pretest reliability of 0.95, and an equivalence reliability of 0.92.

BMI is calculated by dividing weight by height squared. The index of weight/height squared was first described by Adolphe Quetelet in the 19th century as an index of weight adjusted for height. Ancel Keys reinvented it in the 1950s, labeling it body mass index. BMI has been found to be consistently associated with an increased risk of cardiovascular disease, type 2 diabetes, and stroke.

The study was approved by the ethics committee (Helsinki) of Hartzfeld Geriatric Hospital, Gedera, Israel.

**Statistical Analysis**

Statistical analyses were performed using SPSS and the Microsoft Excel program. The de-
Descriptive statistics of all studied variables were separately calculated for three groups: (1) normal-weight patients (BMI ≤ 24.9), (2) overweight (25 < BMI < 29.9), and (3) obese patients (BMI ≥ 30).

To compare the mean values of FIM score between males and females, the one-way ANOVA was used. To compare mean values of total FIM score at each time point and rehabilitation FIM score (RI-FIM) between the studied groups, we built whiskers plots; the bivariate correlation was used to evaluate the association between relative improvement in RI-FIM and BMI. The relative improvement in FIM score was calculated as follows: \[
\text{RI-FIM} = \left(\frac{\text{FIM}_{12} - \text{FIM}_0}{\text{FIM}_0}\right) 
\]

**RESULTS**

Table 1 illustrates the descriptive statistics of the studied sample. The studied groups were similar in size (31 patients in the normal-weight group, 35 in the overweight group, and 18 in the obese group) and age of participants (70.16 ± 3.07, 70.46 ± 3.44, and 71.17 ± 2.96, respectively). Mean BMI was 22.14 ± 2.25 in the normal-weight group, 27.42 ± 1.38 in the overweight group, and 32.49 ± 1.92 in the obese group.

Comparison results of the mean values of FIM score between males and females in the total sample and in normal, overweight, and obese groups showed no significant sex differences in the three FIM measurements (FIM<sub>0</sub>; \(P = 0.52−0.70\); FIM<sub>6</sub>; \(P = 0.45−0.72\); FIM<sub>12</sub>; \(P = 0.16−0.77\); RI-FIM; \(P = 0.15−0.98\); Table 2). Therefore, all further computations were performed on mixed groups, comprising males and females.

Figure 1 illustrates the comparison results of the three FIM scores (upper graph) and the RI-FIM (lower graph) between studied groups of patients according to weight. There was no statistically significant difference in total FIM score between the normal-weight group and overweight group on day of admission. The obese patients showed statistically significantly lower mean values of FIM score than did the overweight group. After 6 wks of rehabilitation, no significant difference was found between the first two groups. However, the third group showed statistically significantly lower mean values in total FIM score than did the overweight group. The difference between those two groups became more prominent, and the group difference between normal-weight individuals and the obese group became greater, but it still was not statistically significant. After 12 wks of rehabilitation, almost no difference was found between groups of normal-weight and overweight patients, however significant difference was found between those two groups and group of obese patients. On the day of admission, if the difference in the mean FIM score was approximately 1.5 between normal-weight and obese patients, the FIM score increased to about 8 points 12 wks after commencing rehabilitation.

RI-FIM score showed a statistically significant difference between patients with normal weight and the other groups. The relative improvement was (mean ± SE) 29.98 ± 2.77 in the normal-weight group, 20.15 ± 2.61 in the overweight patients, and 18.53 ± 6.64 in the obese patients.

A statistically significant negative correlation \((r = −0.27, P = 0.014)\) between relative improve-

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normal-Weight Group (BMI ≤ 24.9)</th>
<th>Overweight Group (25 &lt; BMI &lt; 29.9)</th>
<th>Obese Group (BMI ≥ 30)</th>
<th>Total Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>31</td>
<td>35</td>
<td>18</td>
<td>84</td>
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<tr>
<td>Female sex</td>
<td>17</td>
<td>19</td>
<td>14</td>
<td>50</td>
</tr>
<tr>
<td>Age, yrs (SD)</td>
<td>70.16 (3.07)</td>
<td>70.46 (3.44)</td>
<td>71.17 (2.96)</td>
<td>70.50 (3.19)</td>
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<tr>
<td>BMI, kg/m&lt;sup&gt;2&lt;/sup&gt; (SD)</td>
<td>22.14 (2.25)</td>
<td>27.42 (1.38)</td>
<td>32.49 (1.92)</td>
<td>26.56 (4.31)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Total Sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean RI-FIM ± SE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>30.58 ± 5.14</td>
<td>19.34 ± 2.87</td>
<td>28.59 ± 7.58</td>
</tr>
<tr>
<td>Females</td>
<td>29.48 ± 4.66</td>
<td>20.83 ± 2.63</td>
<td>15.65 ± 4.05</td>
</tr>
<tr>
<td>ANOVA P value</td>
<td>0.88</td>
<td>0.70</td>
<td>0.15</td>
</tr>
</tbody>
</table>
ment of FIM score and BMI in the total sample was also found (Fig. 2). However, sex and age showed no significant correlation of FIM score improvement within the 12 wks.

DISCUSSION

There is a lack of information regarding the predictive factors used to determine the functional ability of a patient after stroke. Our study demonstrates that the first 12 wks of rehabilitation were statistically significantly less effective in overweight and, especially, in obese patients (evaluated by BMI). We also found a statistically significant negative association between an individual's BMI and relative improvement of the total FIM score, representing the functional status of the stroke patient.
Overweight increases stroke risk in general, particularly ischemic stroke.20 In a meta-analysis of prospective studies that included 76,000 participants,21 BMI >27 was found to be an independent risk factor for cardiovascular diseases and stroke. A reduction of BMI <24 can prevent the incidence of stroke by 15% in males and 24% in females. Our study shows that obese patients begin their rehabilitation with a lower total FIM score than do those of normal weight or overweight. In addition, functional improvement was much slower in the overweight patients, particularly in the obese.

Several hypotheses can be used to explain our findings. Firstly, lower FIM scores at the baseline of the obese patients may influence the rate of functional improvement. This hypothesis, however, cannot explain the difference in RI-FIM between normal-weight and overweight patients. Secondly, even healthy overweight and, especially, obese individuals have, on average, lower functional abilities than do individuals of normal weight. After stroke, these individuals probably have more difficulties than do those of normal weight in restoring their basic daily functions (measured by the FIM instrument), because of their excessive weight. Thirdly, rehabilitation personnel (nurses, physical, and occupational therapists) have more difficulty assisting an overweight patient. Overweight patients need additional support when trying to function independently (i.e., transferring, walking, going up and down stairs, etc.). Logistic difficulties to provide additional support can also influence the outcome of rehabilitation. Therefore, our study provides additional support for weight reduction in individuals at risk. Additional research is needed to evaluate whether weight-reduction programs during rehabilitation might improve the rehabilitation results.

Our short period of follow-up is a major limitation of our study. A longer follow-up would enable us to observe the influence of overweight on poststroke rehabilitation outcome at least 1 yr later. Another limitation is the relatively small sample size. A larger sample would enable us to distinguish between underweight and overweight patients, and to evaluate the results of rehabilitation in individuals with morbid obesity. Additional studies are needed to investigate the association between weight and rehabilitation outcome in patients after recurrent stroke or in patients with other health problems that require long-term rehabilitation.

CONCLUSION

Our study provides the clinician with an additional parameter that must be taken into account when predicting rehabilitation outcome for stroke patients. Further investigations are needed to evaluate whether weight-management programs during rehabilitation can improve rehabilitation outcome in addition to decreasing general risk factors for stroke.

ACKNOWLEDGMENTS

This study was performed in partial fulfillment of the master degree requirements of Biana Rodrigues, Diana Gurvich, Ziva Israelov, and Elina Spivak. We wish to thank Mrs. Phyllis Curchak Kornsapan for her editorial assistance.

REFERENCES


Associated Reaction and Spasticity Among Patients with Stroke

ABSTRACT


Objectives: The objectives were to investigate the relationship between associated reaction (AR) and clinical spasticity in the paretic arm.

Design: The participants were ten patients with hemiparetic stroke, mean age of 65.2 yrs, and duration of stroke of 13.3 mos. The AR of the hemiparetic arm was analyzed with surface EMG, and AR ratio was calculated on the basis of comparison of the surface amplitude of the affected side to that of the nonaffected side. Simultaneously, we measured M-, H-, and T-wave amplitudes and calculated H/M and T/M in the paretic arm. The AR ratio, H/M, and T/M were compared with spasticity as assessed with the modified Ashworth scale (MAS). We repeated the same measurements after median nerve block to examine its effects on the parameters.

Results: The AR ratio correlated significantly with MAS ($P < 0.01$), whereas H/M and T/M did not. Median nerve block did not alter these relationships.

Conclusion: AR, which could be elicited easily in patients with spastic hemiparesis, correlated strongly with spasticity, both before and after the median nerve block. However, the so-called monosynaptic reflex (H- and T reflexes) did not correlate significantly with spasticity. These results indicate that AR and spasticity partially share common pathways.

Key Words: Modified Ashworth Scale, Polysynaptic Reflex, Hoffman Reflex, Median Nerve Block
Ass ociated reaction (AR) is unintentional movement induced by voluntary movement of the other side.\(^1\) For poststroke patients, increasing muscle tone and AR in the paretic arm sometimes disturb the activities of daily living. AR is thought to result from irradiation or overflow of neural excitation across the cortex or spinal cord during voluntary movement.\(^2\) AR has been assumed to be one of the manifestations of spasticity. It has been regarded as a part of the spastic syndrome, and it is believed to occur clinically only in the presence of spasticity.\(^3,4\) Both AR and spasticity are supposed to be related to hyperexcitability of spinal reflexes, which usually are assessed electrophysiologically with H- and T reflexes.

Spasticity has been assessed with the modified Ashworth scale (MAS), electrophysiological spinal reflexes (H reflex, T reflex, stretch reflex, reciprocal inhibition of H reflex), and other electromyographic parameters. In contrast, practical methods to assess AR are limited.\(^5\) The purpose of this study is to investigate the relationship of AR to spinal monosynaptic reflexes (H- and T reflexes) and MAS by the method of quantifying AR by obtaining integrated electromyography (EMG) ratio between the affected and unaffected homonymous muscles, measured with surface EMG during two motor tasks.

**METHODS**

**Participants**

We selected patients who were at least 3 mos poststroke and who were admitted to a 120-bed, nonacute-setting, general rehabilitation center. Patients with severe contractures that precluded the necessary clinical and electrophysiological examinations were excluded. The participants were ten patients (seven men and three women) with chronic hemiparetic stroke, with a mean age of 65.2 yrs (range, 42–84). The mean duration from stroke onset was 13.3 mos. Six patients had suffered from ischemic stroke and four patients from hemorrhagic stroke. No patient had received anti-spasticity medications. Clinical details of the ten patients are shown in Table 1. The study was approved by the institutional ethics committee, and the participants gave informed consent after being fully informed of the details of the experimental procedures.

**Assessment of Muscle Tone**

Muscle tone of the wrist and elbow flexors was assessed with the MAS,\(^6\) which is graded from 0 to 4 (0, 1, 1+, 2, 3, and 4). In our study, we regarded MAS 1+ as 2, 2 as 3, 3 as 4, and 4 as 5 in the our calculations.

**Assessment of AR**

Each patient was comfortably seated in a chair, with the affected arm on his or her knee. AR was induced by having the patient perform maximal hand gripping (task 1) and elbow flexion of the unaffected side (task 2). Task 1 was a 10-sec sustained maximal voluntary grip of the unaffected hand with the elbow extended. Task 2 was a 10-sec sustained maximal voluntary elbow flexion of the unaffected arm with 90-degree elbow flexion. Muscle activities were recorded with surface electrodes from bilateral biceps brachii (BB) and flexor carpi radialis (FCR) muscles. Before attaching the electrodes, the skin areas were rubbed with alcohol, and the skin resistance was kept below 5 kΩ. A Neuropack EMG machine (Nihon Kohden Co., Tokyo, Japan) was used to record and analyze EMG data. The band pass filter was set at 30 Hz to 2kHz. EMG data were transferred after the end of the measurement to a personal computer and were further processed by wave-analysis software (PowerLab Chart 5, AD instruments). All EMG signals were rectified and integrated,\(^5\) and peak integrated EMG (IEMG) values during tasks 1 and 2 were defined as IEMG\(_{\text{max}}\). In both tasks, we measured IEMG\(_{\text{max}}\) of bilateral FCR and BB, and AR

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Type</th>
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<th>Time Since Stroke, mos</th>
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<td>Hemorrhage</td>
<td>64</td>
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<tr>
<td>2</td>
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<tr>
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<td>8</td>
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<td>Hemorrhage</td>
<td>42</td>
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<td>9</td>
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<td>Male</td>
<td>Infarction</td>
<td>84</td>
<td>13</td>
<td>Right</td>
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</table>
ratios of FCR and BB were calculated as the ratios between IEMG\textsubscript{max} of the affected and the unaffected sides.

**H- and T Reflex**

H reflex was recorded from the affected FCR with surface electrodes. It was elicited by electrical stimulation of the median nerve at the antecubital fossa with a 1-msec square-wave constant current. The reflex responses were measured as the peak-to-peak amplitude of the H reflex. The size of the maximum motor response (M\textsubscript{max}) and H\textsubscript{max} were measured, and H/M ratio (H\textsubscript{max}/M\textsubscript{max}) was calculated in each patient.\(^7,8\)

T reflex was recorded from the affected BB with surface electrodes. A clinical hammer for tendon tapping was used to evoke tendon-jerk reflex in the BB. A piezoelectric device was embedded in the rubber of the contact plane to signal tapping impact. The examiner carefully tapped the BB tendon under the elbow crease to ensure that the amplitude of acceleration at the time of impact was consistent throughout the trials. Reflex response was measured as the peak-to-peak amplitude of the T reflex recorded by a bipolar disc electrode placed over the BB. A tendon tap for evoking tendon-jerk reflex in the BB was applied at about 2-sec intervals, and its amplitude was recorded 10 times.\(^7,9\)

M\textsubscript{max} also was elicited by electrical stimulation of the musculocutaneous nerve at the ERB’s point. The size of M\textsubscript{max} and average T reflex amplitudes (T\textsubscript{ave}) were measured, and the T/M ratio (T\textsubscript{ave}/M\textsubscript{max}) of each subject was calculated.

**Median Nerve Block**

To confirm the relationships of AR with spinal reflexes and MAS, we assessed these parameters before and after blocking the median nerve. The median nerve was blocked at the elbow with 5 ml of 1% lidocaine. The participant’s affected arm was supported in 45-degree abduction at the shoulder. The median nerve was blocked at the antecubital fossa with a stimulation needle, connected to an electrical nerve stimulator.\(^10\) When wrist flexion was observed with minimal electrical intensity, 5 ml of 1% lidocaine was injected through the stimulation needle. No reinjection was performed. No subject reported pain or sensory disturbances. Before and 10 mins after the median nerve block, we assessed MAS, AR ratio, H/M, and T/M.

**Statistical Analysis**

Correlations between MAS and AR ratio, H/M, and T/M were analyzed with Spearman’s rank-correlation test. The change of each parameter before and after the median nerve block was compared with Wilcoxon’s signed rank test. All statistical analyses were performed with SPSS for Windows version 12.0.

**RESULTS**

ARs in FCR and BB were recorded in all patients during tasks 1 and 2. Figure 1 shows an example of muscle activities during the two tasks.

**Relationships Between AR Ratio and MAS, H/M, and T/M**

The BB AR ratio correlated significantly with the MAS of the elbow flexors (r = 0.78, P < 0.01; Table 2). The FCR AR ratio also correlated significantly with the MAS of the wrist flexors (r = 0.72, P < 0.05). However, the ARs did not correlate significantly with the T/M and H/M ratios (r = 0.473 and 0.075; NS; Table 2), and the T/M and H/M ratios did not correlate significantly with the MAS of elbow flexors and wrist flexors (Table 2).

**FIGURE 1** The surface EMG of associated reaction (AR) in patient 5. A, Task 1 (maximal grip flexion). According to maximal grip flexion of the unaffected arm, AR was induced in the biceps brachii (BB) and flexor carpi radialis (FCR) of the affected arm. AR was more massive in the FCR than in the BB. B, Task 2 (maximal elbow flexion). According to maximal elbow flexion of the unaffected arm, AR was induced in the BB and FCR of the affected arm. AR was more massive in the BB than in the FCR.
Before and After the Median Nerve Block

Table 3 shows the changes of EMG parameters before and after the median nerve block. Wrist-flexion MAS decreased in all but one patient (subject 1) after the block \((P < 0.01)\). Unexpectedly, elbow MAS also decreased in half of the patients after the nerve block \((P < 0.05)\). FCR AR ratio decreased significantly in

### TABLE 2 Correlation coefficients \((r)\) among the clinical and electrophysiological parameters

<table>
<thead>
<tr>
<th></th>
<th>Spearman Rank-Correlation Test</th>
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<tr>
<td></td>
<td>Correlation Between MAS and AR Ratio, Monosynaptic Reflexes</td>
<td></td>
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<tr>
<td></td>
<td>MAS (Elbow Flexor)</td>
<td></td>
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<tr>
<td></td>
<td>(r)</td>
<td>(P)</td>
</tr>
<tr>
<td><strong>Before block</strong></td>
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<tr>
<td>AR ratio (BB)</td>
<td>0.776</td>
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</tr>
<tr>
<td>T/M</td>
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<td>NS</td>
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<tr>
<td><strong>After block</strong></td>
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<td>AR ratio (BB)</td>
<td>0.864</td>
<td>&lt;0.01</td>
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<tr>
<td>T/M</td>
<td>0.481</td>
<td>NS</td>
</tr>
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</table>

Correlation Between AR Ratio and Monosynaptic Reflexes

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<table>
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<tr>
<td></td>
<td>T/M</td>
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<tr>
<td>(r)</td>
<td>(P)</td>
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<tr>
<td><strong>Before block</strong></td>
<td>0.473</td>
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<tr>
<td><strong>After block</strong></td>
<td>0.527</td>
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</table>

AR, associated reaction; BB, biceps brachii; FCR, flexor carpi radialis; MAS, modified Ashworth scale; H/M, H waves/M waves; T/M, T waves/M waves; AR ratio (BB), BB:AR ratio; AR ratio (FCR), FCR:AR ratio.

### TABLE 3 The change of clinical and electrophysiological parameters with median nerve block

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<td></td>
<td>MAS (Elbow*)</td>
<td>Wrist**</td>
<td>AR ratio</td>
<td>T/M</td>
</tr>
<tr>
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<td>FCR**</td>
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</table>

BB, biceps brachii; FCR, Flexor carpi radialis; AR, associated reaction; MAS, modified Ashworth scale; H/M, H waves/M waves; T/M, T waves/M waves.

Wilcoxon \(t\) test: * \(P < 0.05\); ** \(P < 0.01\).
nine patients after the nerve block ($P < 0.01$). Five patients showed decreased T/M ratio, and eight patients showed reduced H/M ratio. The AR ratio correlated significantly with the MAS both before and after the nerve block (Table 2).

**DISCUSSION**

We examined the relationships between AR and spasticity with our originally developed method of quantifying AR. In all participants, AR could be elicited by maximum grip (task 1) and elbow flexion (task 2) of the unaffected side. The AR ratio correlated significantly with the MAS, but not with the H/M and T/M ratios.

Although neurophysiological assessment methods for AR have been increasingly reported in the literature during the last decade, there are few established methods for quantifying AR. Previous studies have tried to quantify AR by recording the changes of joint angle during maximum contraction of the unaffected arm or by measuring its amplitudes with surface EMG. However, the change of joint angle could be influenced by contractures. In addition, the amplitudes measured with surface EMG have variability depending on the interelectrode distance, the placement site of electrodes, or the individual muscle forces, and normalization procedures are mandatory. In this study, we calculated the IEMG ratio of the unaffected side to minimize individual differences.

H- and T reflexes have been widely regarded as representing the so-called monosynaptic reflexes. H reflex is influenced by α-motor neuron excitability, modulated by excitatory inputs from Ia-afferents. The T reflex is assumed to be responsive to fusimotor tone; when fusimotor fibers contract, muscle spindles become more sensitive to stretch. Because of their predominantly monosynaptic character, the H- and T reflexes are considered clinically as well as experimentally relevant in spasticity measurement. It is reported that the amplitudes of these reflexes are usually significantly increased on the affected side of spastic patients compared with the unaffected side, or compared with healthy people. Therefore, H/M ratio and T/M ratio are often used as sensitive measures of changes in motor neuronal excitability.

However, Milanov (1999) has shown that H/M ratio did not correlate with spasticity as assessed with the MAS. It also was reported that the correlation between the T reflex amplitude and muscle tone was not clear. Our study also demonstrates that H/M did not correlate with MAS. The correlations between T/M and MAS and T/M and AR were not significant, either. Burke points out that some mechanoreceptors in the skin and other muscles contribute to the tendon reflex and the motor spindle, so the tendon reflex is unlikely to be solely monosynaptic, because cutaneous and other mechanoreceptor afferents also have polysynaptic connections.

Generally, spasticity is defined as a velocity-dependent increase in muscle resistance against passive lengthening caused by a supraspinal disinhibition of both tonic and phasic stretch reflexes. Polysynaptic pathways might contribute to spasticity. The MAS measures hypertonia, whereas the H reflex and T reflex assess hyperreflexia. Our results suggest that AR might be related to hypertonia rather than hyperreflexia.

With regard to the relationship between AR and spasticity, some authors claim that they are significantly correlated with each other, whereas others have found no significant correlation. In our study, AR ratio correlated significantly with the MAS, and furthermore, this correlation persisted even after the median nerve block. These results suggest that there are common pathways for both AR and spasticity as assessed with the MAS, and treatment of spasticity could alleviate AR.

Our results suggest that the newly developed method of quantifying AR is clinically useful for the assessment of AR and spasticity. However, there are several problems inherent in quantifying spasticity with the MAS (i.e., the presence of muscle stiffness and contractures). These factors could interfere with the measurement of spasticity, and spasticity, in turn, promotes contracture formation. To minimize these effects, we selected patients with minimum contractures for our study. However, muscle stiffness gradually develops more or less after stroke, and it is practically difficult to evaluate spasticity alone while excluding the influence of muscle stiffness. In future studies, we need to analyze the influence of stiffness on the relationship between spasticity and AR.

To prove the usefulness of our new method of quantifying AR, we also need to study the longitudinal changes of the relationship between MAS and AR.

**REFERENCES**


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Prevalence of Depression Diagnoses and Use of Antidepressant Medications by Veterans with Spinal Cord Injury

ABSTRACT


Objectives: The objectives of this study were to examine the prevalence of depression diagnoses among veterans with spinal cord injuries and disabilities (SCI&D) for a 3-yr period, and to characterize patterns of antidepressant medication use in this population.

Design: This study was a retrospective analysis of clinical and administrative data. The sample consisted of 3678 veterans with SCI&D who had received any health care at a Department of Veterans Affairs facility between fiscal years 1999 and 2001, a depression diagnosis, and complete data. Logistic regression analysis was used to examine associations between patient characteristics, antidepressant types, and prescription patterns.

Results: Approximately 22% of veterans with SCI&D received a diagnosis of depression during at least one encounter with a healthcare provider. Of those diagnosed, 72% received antidepressant prescriptions. However, a large percentage (67%) did not continue antidepressant use for 6 mos. Patients started on a selective serotonin reuptake inhibitor were more likely to have at least 6 mos of continuous use than patients started on other, newer antidepressants.

Conclusions: Many veterans with SCI&D may not be receiving adequate treatment for depression. Veterans with SCI&D should be aggressively screened and treated for depression, and further research is necessary to determine which treatments for depression are most effective for persons with SCI&D.

Key Words: Depression, Antidepressants, Spinal Cord Injury, Veterans
Depression has a significant negative impact on the health and quality of life of persons with spinal cord injuries and disorders (SCI&D), resulting in impaired physical functioning, increased pain, and increased disability. As in the general population, depression also increases the risk of suicide for persons with SCI&D. The rate of suicide in a Danish study of persons with SCI&D was almost five times higher than expected in the general population. Among persons with SCI&D, the functional impairment attributable to depression is equal to or greater than the impairment found in other diseases. Furthermore, patients with SCI&D and persistent or delayed onset of depression during acute rehabilitation experienced less improvement in their pain ratings than did patients without depression.

Estimates of the prevalence of depression among persons with SCI&D vary widely, from 16 to 60%. This high variability may be attributable to differences in study samples, screening methods, and definitions of depression. Given the high rates of depression among persons with SCI&D, it is surprising how little we know about effective treatments. The lack of well-controlled clinical trials of antidepressant medications in this population is especially evident; most studies have focused on psychological treatment, and the available antidepressant studies have not included control groups. A 6-mo study of 43 persons with SCI&D has concluded that treatment with antidepressants and psychotherapy significantly reduced symptoms of depression. Clearly, there is a need for a better understanding of current practices in treating depression among persons with SCI&D and identifying best practices.

Although there is limited knowledge of the effectiveness of antidepressants for persons with SCI&D, there is extensive research concluding that antidepressants are efficacious in other populations. However, delivery of these treatments in real-world settings is highly variable, with one study showing that slightly more than half of persons with identified depression received treatment. Numerous factors have been shown to relate to receipt of antidepressant medication, including gender, age, and race and ethnicity. A number of studies also have had mixed results as to which patient characteristics and antidepressant types are associated with longer durations of continuous use. Six months of continuous treatment is important because this has been found to lower the risks of recurrence and relapse. Continuous treatment (≥6 mos) is used as a quality measure by the National Committee for Quality Assurance, consistent with Agency for Healthcare Research and Quality clinical practice guidelines for treating depression.

Few studies have examined the prevalence of depression among veterans with spinal cord injuries (SCI) receiving care through the Department of Veterans Affairs (VA), which is the largest integrated healthcare system in the world serving persons with SCI&D. To our knowledge, there have been no studies examining patterns of antidepressant use among persons with SCI&D. Persons with SCI&D receiving health care at VA facilities offer a unique opportunity for exploring questions related to treating depression in this population. This study included a population of more than 17,000 veterans with SCI&D who received VA health care. In addition to the advantages of having a large cohort, the VA also has extensive data about the use of health care and medication prescriptions, and researchers have found good to excellent agreement between chart reviews and VA administrative data for depression information. Previous research investigating depression among veterans with SCI has used relatively small samples located at individual VA hospitals, raising questions of generalizability. This study uses VA administrative data to examine the prevalence of diagnoses of depression and patterns of antidepressant treatment among veterans with SCI across the entire VA system of care.

The primary objectives of this study were to examine the prevalence of depression diagnoses among veterans with SCI&D for a 3-yr period, and to identify and characterize patterns of antidepressant medication use in this population. Secondary objectives were to explore associations between individual characteristics, antidepressant types, and receipt of 6 mos of continuous antidepressant care. Use of national VA clinical data allowed for the inclusion of a large, stable cohort of patients with extensive health, demographic, and SCI&D information.

**METHODS**

**Participants**

This was a retrospective observational study of national clinical data on veterans with SCI&D. The basis of the sample was a cohort developed from the VA Allocation Resource Center (ARC). The ARC maintains a cumulative list of veterans with SCI&D who have used VA healthcare services any time in approximately the past 10 yrs; inclusion in the list is based on having diagnostic codes for SCI&D, and use of SCI specialty services. The sample for these analyses included 17,656 veterans on the ARC list with any inpatient or outpatient use between fiscal years 1999 and 2001. Subjects were excluded if they had a diagnosis of multiple sclerosis. Analyses of depression diagnoses involved a total of 3678
veterans with SCI&D who had any depression diagnoses during the study period and who had complete data. Patterns of antidepressant use were examined among the 938 veterans with diagnoses of depression who had new antidepressant prescriptions during the study period. Approval was obtained from the institutional review board at Edward Hines VA Hospital.

Measures

Depression Diagnoses

To determine whether a veteran received a depression diagnosis, VA medical datasets were examined. These files include data for both inpatient and outpatient encounters. Diagnoses for each encounter or hospitalization were made by the healthcare provider. The International Classification of Diseases, version 9 (ICD-9) codes were used to identify diagnoses of major depression disorder, single episode; major depressive disorder, recurrent episode; brief depressive reaction; prolonged depressive reaction; neurotic depression; and depressive disorder, not elsewhere classified (NEC; 296.2x, 296.3x, 309.0, 309.1, 300.4, and 311).

Antidepressant Receipt

To determine whether a subject had a prescription for an antidepressant, outpatient medication data were obtained from the VA’s pharmacy benefits management group. Low doses of tricyclic antidepressants (TCAs) were excluded because they are often used for conditions other than depression, such as pain. An antidepressant prescription was defined as new if no other antidepressant prescriptions had been filled during the 6 mos before the date of the first antidepressant prescription in the study period. Patients with missing demographic information (n = 133) were excluded from analyses.

The final outcome measure was the continuous use of antidepressant medication for 6 mos. The numbers and types of prescriptions that subjects received were obtained from the VA pharmacy benefits management group outpatient medication data. For the purposes of this study, antidepressants were classified into drug categories according to their treatment mechanism. The Consortium for Spinal Cord Medicine clinical practice guideline for depression in SCI uses four classifications (Table 1): TCAs, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors, and second- or third-generation drugs that do not fit into the other categories. For this study, we excluded monoamine oxidase inhibitors because their use was extremely limited in this population. Patients who started with more than one type of drug (n = 113) were excluded, to facilitate comparisons between drug classes.

Continuous use was defined as at least 180 days of consecutively filled antidepressant prescriptions. To create this variable, the consecutive total days of prescriptions were summed: if the sum was at least 180 days, this variable had a value of 1; if it was less than 180 days, it had a value of 0. This number was adjusted for patients whose dose levels were augmented, to prevent double counting of their prescriptions.

Finally, for the veterans who received antidepressant medications, we calculated the mean number of prescriptions and types of prescriptions. For each antidepressant prescribed, we calculated how frequently it was prescribed as a percentage of total antidepressants, and what percentage of subjects received that particular medication.

Patient Characteristics

Demographic characteristics (age ≥65 yrs, race, and marital status) of the subjects were included as dichotomous variables in the models. Veterans with ages ≥65 yrs were coded with a 1 in the model; younger veterans were coded as 0. We dichotomized the age variable to facilitate comparisons with other studies that have examined use of antidepressants in the elderly population. Race and ethnicity were defined as a single dichotomous variable, with one group including veterans identified as white, and a reference group with all other veterans. Marital status was defined as a dichotomous variable, with a value of 1 if the veteran was married.

Health characteristics also were categorized for modeling purposes. The presence of common comorbidity was measured by a dichotomous variable, defined as the presence of either chronic renal disease, coronary heart disease, chronic pulmonary disease, or diabetes mellitus. To be coded as having any of these diseases, a subject had to have a corresponding ICD-9 code in either the outpatient or inpatient data during the study period. The definition for renal disease includes 581–583, 585, and 587; for coronary heart disease, values include 93, 393–398, 402–404, 410–417, 424, 425, 427–429, and 440; chronic pulmonary disease includes ICD-9 codes 490–519, chronic; and diabetes includes the 250 codes.

A variable to indicate the presence of secondary complications of SCI&D was also included. A dichotomous variable for indicating the presence of respiratory, kidney, and/or skin conditions as the major diagnostic category (grouping of diagnostic-related group) for an inpatient stay was created as a proxy for a subject having respiratory-, urinary tract–, or pressure ulcer–related hospitalizations during the previous year. These conditions are three of the most common complications for persons with SCI&D. Characteristics describing a
TABLE 1 Types of antidepressants prescribed

<table>
<thead>
<tr>
<th>Classification</th>
<th>Drug Name</th>
<th>Mechanism of Action</th>
<th>Percentage of Total Antidepressant Prescriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCA</td>
<td>Amitriptyline</td>
<td>Tertiary amine, norepinephrine and serotonin reuptake inhibitor</td>
<td>12.80</td>
</tr>
<tr>
<td></td>
<td>Doxepin</td>
<td>Tertiary amine, norepinephrine and serotonin reuptake inhibitor</td>
<td>2.51</td>
</tr>
<tr>
<td></td>
<td>Nortriptyline</td>
<td>Secondary amine, norepinephrine and serotonin reuptake inhibitor</td>
<td>2.40</td>
</tr>
<tr>
<td></td>
<td>Imipramine</td>
<td>Tertiary amine, norepinephrine and serotonin reuptake inhibitor</td>
<td>1.10</td>
</tr>
<tr>
<td></td>
<td>Desipramine</td>
<td>Secondary amine, norepinephrine and serotonin reuptake inhibitor</td>
<td>0.70</td>
</tr>
<tr>
<td></td>
<td>Protriptyline</td>
<td>Norepinephrine and serotonin reuptake inhibitor</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Trimipramine</td>
<td>Norepinephrine and serotonin reuptake inhibitor</td>
<td>0.02</td>
</tr>
<tr>
<td>SSRI</td>
<td>Sertraline</td>
<td>SSRI</td>
<td>22.36</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine</td>
<td>SSRI</td>
<td>11.66</td>
</tr>
<tr>
<td></td>
<td>Paroxetine</td>
<td>SSRI</td>
<td>9.42</td>
</tr>
<tr>
<td></td>
<td>Citalopram</td>
<td>SSRI</td>
<td>4.48</td>
</tr>
<tr>
<td></td>
<td>Fluvoxamine</td>
<td>SSRI</td>
<td>0.02</td>
</tr>
<tr>
<td>MAOIs</td>
<td>Phentolamine</td>
<td>MAOI</td>
<td>0.05</td>
</tr>
<tr>
<td>Second generation</td>
<td>Trazodone</td>
<td>Serotonin antagonist and reuptake inhibitor</td>
<td>17.34</td>
</tr>
<tr>
<td></td>
<td>Bupropion</td>
<td>Dopamine reuptake inhibitor and norepinephrine reuptake inhibitor</td>
<td>5.32</td>
</tr>
<tr>
<td></td>
<td>Amoxapine</td>
<td>Serotonin antagonist and inhibiter, norepinephrine reuptake inhibitor</td>
<td>0.01</td>
</tr>
<tr>
<td>Third generation</td>
<td>Venlafaxine</td>
<td>Selective norepinephrine inhibitor</td>
<td>4.36</td>
</tr>
<tr>
<td></td>
<td>Mirtazapine</td>
<td>Serotonin antagonist</td>
<td>2.19</td>
</tr>
<tr>
<td></td>
<td>Nefazadone</td>
<td>Serotonin antagonist and reuptake inhibitor</td>
<td>3.13</td>
</tr>
</tbody>
</table>

patient’s SCI were obtained from the VA Spinal Cord/Dysfunction Registry, and they include the level of injury (paraplegia vs. tetraplegia) and duration of injury in years.

The final health characteristics included in the model were related to depression diagnoses and mental health use. For recurrent major depression (296.3x), depressive reaction (309.x), neurotic depression diagnosis (300.4), and depression NEC (311), four dichotomous variables were created to indicate the receipt of the diagnosis during the study period. To capture use of mental health care, a variable was created to indicate the number of hospitalizations with any depression diagnoses listed in the previous year, and the number of depression-related outpatient visits. These variables were obtained from VA national clinical data.

Setting

Care for veterans with SCI&D is coordinated through 23 SCI&D centers, although some veterans receive care at VA facilities that do not have SCI centers. In addition to the individual characteristics that may influence the duration of antidepressant use, the site at which care is provided may also impact duration. Therefore, site of care was included as a variable in the analysis, coded as 1 if care was received at any of the SCI centers and as 0 if care was received in a VA facility without an SCI center.

Analyses

To examine the association between patient characteristics and receipt of an antidepressant prescription, a random-effects logistic regression...
model was estimated using the program STATA (Stata Corporation, College Station, TX). Variability between contexts (e.g., hospitals) and between individuals is taken into account in multilevel models, including random-effects models.\(^{21}\) Random-effects models estimate both the variation between individuals (veterans with SCI&D) and between contexts (VA center where the individual received care). By taking group membership into account, the random-effects model results in improved efficiency of results and more accurate estimates of standard errors.\(^{22}\) Of the 3811 patients who received depression diagnoses, 36\% were missing the level of injury data, and 45\% were missing the duration of injury. Because of the large amount of missing data, we did not include these variables in the predictive model, but we did examine the association between level of injury and antidepressant receipt, using analysis of variance.

To explore the association between the type of antidepressant initially prescribed and continuous use, we estimated a multivariate logistic regression model that included a random effect for the site of care. Because this was an observational study, the results could have been biased by selection effects; in other words, factors that influenced outcomes (e.g., continuous use of an antidepressant) also may have affected whether a person received a particular treatment (type of antidepressant). For example, if we found a relationship between the type of antidepressant prescribed and continuous use in a model that wasn’t adjusted for selection bias, it is possible that subjects on TCAs may have already tried several other antidepressants and, thus, may have been more likely to quit. To address this problem, we estimated the probability of being treated with a particular antidepressant (the propensity score), and the findings were examined within quintiles created from those scores. Rosenbaum and Rubin\(^{21}\) have demonstrated that assigning observations to quintiles on the basis of propensity scores eliminates 90\% of bias associated with selection effects.

RESULTS

Depression Diagnoses

Of the 17,656 veterans with SCI&D who used any VA health care between fiscal years 1999 and 2001, 3811 (22\%) had at least one inpatient or outpatient encounter with a depression diagnosis. Among the 3811 patients with depression encounters, 2227 (58\%) had only outpatient encounters, 805 (21\%) had both outpatient and inpatient encounters, and 779 (20\%) had only inpatient encounters. The mean number of inpatient hospitalizations with any depression diagnosis was 0.63, and the mean number of outpatient encounters with a depression diagnosis was 4.86. The majority of patients with depression diagnoses did not have any hospitalizations for depression (58\%); 29\% had one hospitalization, and 13\% had two or more admissions.

Depression NEC was the most common primary diagnosis for inpatient hospitalizations; approximately 27\% of all inpatient hospitalizations for depression had this diagnosis (Table 2). This was also the most frequent primary diagnosis (29\%) for outpatient encounters with depression.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Inpatient Encounters, % (n = 310)</th>
<th>Outpatient Encounters, % (n = 13,127)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression, not elsewhere classified</td>
<td>26.8</td>
<td>29.3</td>
</tr>
<tr>
<td>Neurotic depression</td>
<td>9.0</td>
<td>16.6</td>
</tr>
<tr>
<td>First episode, unspecified</td>
<td>10.0</td>
<td>11.9</td>
</tr>
<tr>
<td>First episode, mild</td>
<td>0.6</td>
<td>1.6</td>
</tr>
<tr>
<td>First episode, moderate</td>
<td>2.9</td>
<td>2.4</td>
</tr>
<tr>
<td>First episode, severe</td>
<td>4.2</td>
<td>0.8</td>
</tr>
<tr>
<td>First episode, severe with psychosis</td>
<td>2.9</td>
<td>0.6</td>
</tr>
<tr>
<td>First episode, partial remission</td>
<td>0.4</td>
<td>0.1</td>
</tr>
<tr>
<td>Recurring episode, unspecified</td>
<td>10.0</td>
<td>20.3</td>
</tr>
<tr>
<td>Recurring episode, mild</td>
<td>0.0</td>
<td>1.5</td>
</tr>
<tr>
<td>Recurring episode, moderate</td>
<td>7.1</td>
<td>4.6</td>
</tr>
<tr>
<td>Recurring episode, severe</td>
<td>4.9</td>
<td>1.6</td>
</tr>
<tr>
<td>Recurring episode, severe with psychosis</td>
<td>9.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Recurring episode, partial remission</td>
<td>0.0</td>
<td>0.7</td>
</tr>
<tr>
<td>Brief depressive reaction</td>
<td>10.0</td>
<td>5.9</td>
</tr>
<tr>
<td>Prolonged depressive reaction</td>
<td>1.9</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Other common diagnoses included neurotic depression and the major depression diagnoses. For outpatient encounters, depression NEC and neurotic depression also were the most common diagnoses listed.

**Receipt of Antidepressant**

A total of 3678 patients who had any inpatient or outpatient encounter with a depression diagnosis between 1999 and 2001 had complete data for analysis and were included in the model to examine receipt of an antidepressant. Characteristics of patients are presented in Table 3. Most (83%) had at least one diagnosis of recurring depression; 77% had a diagnosis of depression NEC, 22% had a neurotic depression diagnosis, and 15% had a depressive reaction diagnosis. Hospitalizations for secondary complications including either kidney, respiratory, or skin diseases were frequent (37%), and one half of the subjects had one of the selected comorbid conditions (i.e., chronic renal disease, diabetes, or coronary heart disease). Patients received care at 144 different sites. Approximately 72% of patients with depression diagnoses (n = 2655) received at least one prescription for an antidepressant during the study period. The results of the random-effects model to examine receipt of an antidepressant are presented in Table 4. Patient characteristics that were significantly associated with receiving an antidepressant prescription included being younger than 65 yrs, married, white, and having a diagnosis of recurring depression, depression NEC, or neurotic depression (P = 0.000). The intraclass correlation coefficient (rho) between hospitals was approximately 0.03, indicating a small but significant (P = 0.000) amount of variation between hospitals in prescription receipt. Differences between individuals, not hospital sites, accounted for most of the variance in antidepressant receipt. Because of the large amount of missing data, we did not include level of injury or duration in the predictive model; instead, we examined these characteristics using bivariate analyses. Neither level of injury nor duration of injury were significantly associated with receipt of antidepressant.

Patients who received an antidepressant prescription had a mean of almost 11 antidepressant prescriptions per patient during the study time, and these patients received an average of two different types of antidepressants during the study period. The most frequently prescribed antidepressant medications were the SSRIs (48%) (Table 1). The most frequent SSRI prescription was sertraline. Approximately 20% of the antidepressants prescribed were TCAs (primarily amitriptyline), and 32% were second- or third-generation drugs, the most frequent of which was trazodone. Fewer than 1% of the prescribed antidepressants were monoamine oxidase inhibitors. This group was dropped from additional analyses.

**Type of Antidepressant and Continuous Use**

During the study time period, 948 veterans with SCI&D and a diagnosis of depression received a new antidepressant treatment episode and had complete data for inclusion in the propensity score models. Almost three quarters (72%) of the subjects with a new antidepressant started treatment with an SSRI, 12% started with a TCA, and 16% started with a second- or third-generation drug. Of

### TABLE 3 Subject characteristics: veterans with spinal cord injuries and disabilities (SCI&D) and a depression diagnosis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Received Antidepressant Prescription (n = 2655)</th>
<th>No Antidepressant Prescription (n = 1023)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age,* yrs (mean [SD])</td>
<td>53.5 (12.8)</td>
<td>55.1 (14.7)</td>
</tr>
<tr>
<td>Age 65 yrs and over,* %</td>
<td>22.7</td>
<td>30.6</td>
</tr>
<tr>
<td>Male,* %</td>
<td>96.3</td>
<td>97.9</td>
</tr>
<tr>
<td>Married,* %</td>
<td>43.7</td>
<td>35.4</td>
</tr>
<tr>
<td>White,* %</td>
<td>78.4</td>
<td>72.0</td>
</tr>
<tr>
<td>Neurotic depression diagnosis,* %</td>
<td>24.7</td>
<td>15.0</td>
</tr>
<tr>
<td>Prolonged or brief grief reaction diagnosis,* %</td>
<td>13.8</td>
<td>19.0</td>
</tr>
<tr>
<td>Depression not elsewhere classified,* %</td>
<td>80.0</td>
<td>69.1</td>
</tr>
<tr>
<td>Recurring major depression, %</td>
<td>79.7</td>
<td>91.7</td>
</tr>
<tr>
<td>Has a comorbidity, %</td>
<td>49.5</td>
<td>46.0</td>
</tr>
<tr>
<td>Has hospitalization for SCI&amp;D complication (respiratory, skin, or kidney),** %</td>
<td>36.8</td>
<td>40.4</td>
</tr>
<tr>
<td>Received majority of care at SCI center,** %</td>
<td>41.9</td>
<td>46.1</td>
</tr>
</tbody>
</table>

* P < 0.01; ** P < 0.05.
the veterans with SCI&D who had a new episode of antidepressant treatment, approximately 33% had 6 mos of continuous use.

The results of the multilevel logistic regression model are presented in Table 5. Subjects were less likely to have 6 mos continuous use if they started treatment with a second- or third-generation drug than with an SSRI. In this model, subjects who started with TCAs also were less likely to have continuous use than those who started with an SSRI. There were no significant differences between subjects who started with a TCA and those initially treated with a second- or third-generation antidepressant. Patients were more likely to have at least 6 mos of continuous antidepressant use if they were married, white, or had switched and/or augmented their antidepressant medications. The intraclass coefficient for the facility at which the prescription was obtained was extremely close to zero, indicating that differences between individuals, and not differences between sites, accounted for the unexplained variance.

### Table 4: Characteristics associated with receipt of antidepressant

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 65 yrs and over</td>
<td>0.60</td>
<td>0.50–0.72</td>
<td>0.000</td>
</tr>
<tr>
<td>Male</td>
<td>0.66</td>
<td>0.40–1.09</td>
<td>0.106</td>
</tr>
<tr>
<td>Married</td>
<td>1.50</td>
<td>1.28–1.77</td>
<td>0.000</td>
</tr>
<tr>
<td>White</td>
<td>1.50</td>
<td>1.25–1.80</td>
<td>0.000</td>
</tr>
<tr>
<td>Neurotic depression diagnosis</td>
<td>2.36</td>
<td>1.90–2.94</td>
<td>0.000</td>
</tr>
<tr>
<td>Prolonged or brief grief reaction diagnosis</td>
<td>0.98</td>
<td>0.78–1.23</td>
<td>0.885</td>
</tr>
<tr>
<td>Depression not elsewhere classified</td>
<td>2.70</td>
<td>2.21–3.29</td>
<td>0.000</td>
</tr>
<tr>
<td>Recurring major depression</td>
<td>0.28</td>
<td>0.21–0.36</td>
<td>0.000</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>1.14</td>
<td>0.97–1.34</td>
<td>0.104</td>
</tr>
<tr>
<td>Had hospitalization for SCI&amp;D complication (respiratory, skin, or kidney)</td>
<td>0.94</td>
<td>0.80–1.10</td>
<td>0.432</td>
</tr>
<tr>
<td>Received majority of treatment at SCI center</td>
<td>0.92</td>
<td>0.75–1.14</td>
<td>0.463</td>
</tr>
<tr>
<td>Intraclass correlation for hospital (rho)</td>
<td>0.03</td>
<td>0.01–0.06</td>
<td>0.000</td>
</tr>
</tbody>
</table>

### Table 5: Association between initial type of antidepressant and continuous use

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial tricyclic antidepressant prescription</td>
<td>0.61</td>
<td>0.38–0.98</td>
<td>0.039</td>
</tr>
<tr>
<td>Initial second-/third-generation antidepressant prescription</td>
<td>0.62</td>
<td>0.41–0.94</td>
<td>0.023</td>
</tr>
<tr>
<td>Age</td>
<td>1.00</td>
<td>0.99–1.02</td>
<td>0.451</td>
</tr>
<tr>
<td>Married</td>
<td>1.50</td>
<td>1.12–2.02</td>
<td>0.007</td>
</tr>
<tr>
<td>White</td>
<td>1.82</td>
<td>1.27–2.62</td>
<td>0.001</td>
</tr>
<tr>
<td>Depression not elsewhere classified diagnosis during previous year</td>
<td>1.20</td>
<td>0.88–1.65</td>
<td>0.256</td>
</tr>
<tr>
<td>Recurring major depression during previous year</td>
<td>1.44</td>
<td>0.86–2.40</td>
<td>0.164</td>
</tr>
<tr>
<td>No. of depression outpatient encounters during previous year</td>
<td>0.98</td>
<td>0.92–1.05</td>
<td>0.620</td>
</tr>
<tr>
<td>No. of depression hospitalizations during previous year</td>
<td>0.83</td>
<td>0.59–1.18</td>
<td>0.309</td>
</tr>
<tr>
<td>Comorbidity during previous year</td>
<td>0.97</td>
<td>0.70–1.34</td>
<td>0.711</td>
</tr>
<tr>
<td>Hospitalization for SCI&amp;D complication (respiratory, skin, or kidney) during previous year</td>
<td>0.58</td>
<td>0.39–0.86</td>
<td>0.007</td>
</tr>
<tr>
<td>Switched/augmented antidepressant</td>
<td>2.15</td>
<td>1.46–3.15</td>
<td>0.000</td>
</tr>
<tr>
<td>Received initial prescription at VA SCI center</td>
<td>1.33</td>
<td>0.97–1.83</td>
<td>0.074</td>
</tr>
<tr>
<td>Intraclass correlation for hospital (rho)</td>
<td>0.02</td>
<td>0.97–1.83</td>
<td>0.182</td>
</tr>
</tbody>
</table>
To address possible problems with selection bias, the odds ratios for having continuous use were estimated within propensity quintiles. To create the propensity scores, logistic regression models comparing each pair of drugs (i.e., SSRIs and TCAs, SSRIs and second- or third-generation antidepressants, TCAs and second- or third-generation drugs) were created, and then the subjects were sorted into quintiles according to their predicted likelihood of receiving one type of antidepressant vs. another. In the comparisons of continuous use between users of TCAs and SSRIs, having an initial prescription for a TCA was no longer associated with decreased odds of having continuous treatment. In the model comparing SSRIs and second- or third-generation drugs, however, subjects who had started with SSRIs were more likely to have 6 mos of continuous use for the highest quintile compared with veterans who had started with second- or third-generation drugs. The results of propensity score analyses suggest that selection bias may have influenced this result, which, starting with a TCA, was significantly associated with decreased odds of continuous use. However, selection bias did not account for the differences between subjects who started an SSRI vs. those who started a second- or third-generation antidepressant.

**DISCUSSION**

**Depression Diagnoses**

Because this study examined patient data retrospectively, the percentage of subjects who had a diagnosis of depression is not readily comparable with the results of studies that have prospectively examined depression prevalence in persons with SCI&D. However, the result that approximately 22% of patients had at least one inpatient or outpatient encounter with a depression diagnosis is similar to previous prevalence estimates for depression that have ranged from 16 to 60%.4–6 Moreover, the findings are consistent with past research suggesting that rates of depression among persons with SCI are approximately twice the rates found among the general population.23 That being said, the 22% prevalence for depression during 3 yrs is probably an underestimate of the number of veterans with SCI&D who have depression, because the estimate is based on diagnostic codes entered in administrative databases. For example, patients may not receive diagnostic codes if depression is attributed to an adjustment reaction.24 Also, antidepressants may be prescribed for somatic symptoms often associated with depression, without recording a diagnosis, because of the stigma patients may associate with depression diagnoses.24

The distribution of diagnoses is interesting because of the large number of depression diagnoses that are coded as *not specific*. The extensive use of the *depression NEC* code may suggest depression that is relatively minor, or it may reflect unique depression issues encountered by veterans with SCI&D. Also, a large number of diagnoses were unspecified. Further, the frequency of visits and hospitalizations related to the antiquated diagnosis of neurotic depression was surprising, given the questionable validity of this diagnosis and its exclusion from the DSM-III-R (the latest DSM version in use at time of study) or the ICD-10.25

**Receipt of Antidepressant Medication**

The majority (72%) of veterans with SCI&D and a depression diagnosis received prescriptions for antidepressants. Receipt of antidepressant medication was not related to gender, other health conditions, or whether care had been received at an SCI center. Older veterans in this sample were less likely to receive antidepressant medication—a finding consistent with previous research.9 This study also found that nonwhite veterans were less likely to receive antidepressant medication, which also is consistent with previous studies.26 These differences may be a result of differing patient attitudes about treatment. Previous research has found that African American patients may be more likely than others to prefer psychological treatments over antidepressant medications.26

A diagnosis of neurotic depression has been associated with treatment in previous studies.27 However, neurotic depression, a diagnostic category present in DSM version II, has been left out in subsequent versions and replaced with other diagnostic categories, including major depressive disorder and dysthymic disorder.25 Yet, it continued to be used in this population. A patient with a diagnosis of depression NEC was more likely to receive antidepressants than a subject without this depression diagnosis, whereas a patient with a recurring diagnosis of depression was less likely to have received an antidepressant prescription. This result was surprising because we would expect that patients with a recurring diagnosis would receive more treatment than those with unspecified or unrecognized diagnoses (e.g., neurotic depression).19 One possible explanation for this finding is that a diagnosis of recurrent depression in the absence of a current treatment may reflect the presence of a depressive disorder viewed as intractable by clinicians and/or patients. On the other hand, these cases may be treated using psychotherapy or other nonpharmacological therapy. Further research to determine which depression diagnoses are associated with more severe depression symptoms would provide insight about why patients with certain diagnoses were more likely to receive antidepressants vs. other or possibly no treatment.
Marital status was the final significant predictor of receipt of an antidepressant medication. A meta-analysis of studies focusing on social support and adherence to medical treatment found that married subjects were 1.27 times more likely to adhere than unmarried subjects. Several mechanisms related to social support might influence treatment adherence, including stress, behavior, and physiologic mechanisms.

Subjects who did receive antidepressants were most likely to receive an SSRI. There was, however, a large amount of variability in the types of drugs prescribed. It seems that many veterans received more than one type of medication, either over time or when one antidepressant was augmented with the use of an additional antidepressant. Although the guidelines issued by the Consortium for Spinal Cord Medicine advise caution regarding the use of TCAs in this population because of the side effects, a substantial percentage of veterans had prescriptions of these medications at doses that were higher than those typically prescribed for pain management. Although we assumed that TCAs were used in these situations for depression rather than pain, without a thorough medical record review, we could not determine medication indication.

Continuous Use

Certain results suggest ways that providers could potentially increase the number of veterans receiving treatment for depression, as recommended in the guidelines. First, patients who were initially prescribed SSRIs were more likely to have continuous use than those who started on second- or third-generation drugs. This association was still significant in the propensity score models, which are designed to address selection bias. Prescribing an SSRI instead of a second- or third-generation drug may increase the probability that a patient will remain on antidepressants for at least 6 mos, thus decreasing the risk of relapse. Some research has demonstrated elevated rates of aversive side effects among second- or third-generation drugs compared with SSRIs. For example, compared with SSRIs, venlafaxine is associated more often with nausea, and buproprion is associated more often with headache and dizziness in the general population.

Switching and/or augmenting an existing antidepressant medication with a different antidepressant are additional strategies that were related to increased duration/continuity of use. Although significant in this work, previous research has shown mixed results in this area. The need to switch or augment a drug could indicate that the initial treatment was not effective, potentially increasing the likelihood that a person would discontinue medication use. However, our data suggest that switching or augmenting antidepressant use was associated with a higher likelihood of continuous use and, perhaps, closer monitoring of treatment effects by providers.

We found that being married was related to more continuous use of antidepressant medications; this finding is consistent with the general literature on how social relationships influence adherence to medical treatment. However, some research has shown that marriage relates to poorer adherence to medical regimens. The discrepancy between the present results and that of Streja and colleagues might be explained by the nature of the variable in question. Marital status is a fair reflection of only the presence of others; it does not necessarily relate to the quality of relationships, which is a better predictor of adherence. Although marital status has an average positive influence on adherence, a wide range of effects that are attributable to the quality of relationships and other moderating factors might account for these discrepant findings. Finally, hospitalization for an SCI&D complication during the previous year was also associated with decreased odds of continuous use. This could be the result of patients using inpatient pharmacy services for ongoing antidepressant use (data that were not available for our analyses), or it may have occurred because patients’ illnesses interfered with adherence, or because antidepressant use was contraindicated with other medical treatments some patients received. Another possible explanation might be that the seriousness or complexity of other illnesses may have interfered with depression treatment.

There are several limitations to this study. The analyses were based on electronic medical record data, which are subject to coding errors. However, a previous study comparing national VA clinical and chart data found good agreement for depression diagnosis. Second, we did not examine data on other treatment strategies that could have been used instead of or in addition to medication, such as psychotherapy, nor did we have access to information about their use of health care outside of the VA. Third, veterans may have received antidepressants to treat conditions other than depression, such as anxiety or smoking cessation, although every veteran in this study had been diagnosed with depression. Nonetheless, this large database provides a great deal of information about current practices for the pharmacological treatment of depression in SCI&D.

CONCLUSIONS

Identifying and describing the prevalence and pharmacological treatment of depression among veterans with SCI&D is the first step toward identifying and implementing effective screening and
treatment strategies for this population. This study has characterized patterns of depression diagnosis and treatment among veterans with SCI&D. Results point to elevated rates of depression diagnoses compared with the general population, and to some patterns of antidepressant prescribing that are inconsistent with guidelines-based care. Future research should explore explanations for patterns of care that depart from clinical practice guidelines, and use of other strategies for treatment of depression in this population.

REFERENCES

2. Hays RD, Wells KB, Sherbourne CD, Rogers W, Spritzer K: Functioning and well-being outcomes of patients with depression compared with chronic general medical illnesses. Arch Gen Psychiatry 2005;52:11–9
Noninvasive Ventilatory Assistance During Exercise for Patients with Kyphoscoliosis
A Pilot Study

ABSTRACT


The goal was to determine whether noninvasive ventilatory assistance (NIV) could facilitate exercise performance and benefit physiologic parameters for eight hypercapnic kyphoscoliosis patients using a cycloergometer for 6-min periods at a constant power (20 W). The exercise protocols were performed in random order while breathing unaided (spontaneous breathing test or SBT) and also while receiving NIV (NIV test or NIVT). The NIV was pressure support (15 cm H2O) plus positive end expiratory pressure (PEEP) (4 cm H2O) via a nasal mask. Of the compared parameters, heart rate was not significantly different, but acidosis (pH = 7.32 ± 0.04 vs. 7.36 ± 0.04), hypoxia (PaO2 = 61.5 ± 15.9 vs. 69.5 ± 15.7 mm Hg), and hypercapnia (PaCO2 = 54.3 ± 7.6 vs. 47.1 ± 7.1 mm Hg) were significantly greater for the SBT than for the NIVT (P < 0.05). The hypercapnia and hypoxia for the NIVT were not significantly greater than preexercise resting levels. Dyspnea and perceived effort were significantly greater for the SBT (P < 0.05). In conclusion, NIV can improve clinical and physiologic response to exercise.

Key Words: Noninvasive Mechanical Ventilation, Kyphoscoliosis, Scoliosis, Exercise Test, Nasal Ventilation, Pressure Support Ventilation, Exercise Noninvasive Ventilation
With decreased chest wall compliance and diaphragm function, patients with severe kyphoscoliosis have increased work of breathing with decreased tidal volumes (Vt) and increased respiratory rates (RR). This results in alveolar hypoventilation with increased dead space ventilation.1 Exercise can exacerbate hypoventilation and dyspnea.1

Typically, patients with hypoxia from any cause receive supplemental oxygen during sleep or exercise. Whereas oxygen therapy exacerbates hypoventilation, NIV during sleep alleviates hypercapnia, inspiratory muscle work, and hypoxia,2 can decrease daytime PaCO2 and increase PaO2, and can result in clinical and functional improvement.3

At rest, oxyhemoglobin saturation (SpO2) and carbon dioxide levels can often be normalized (SpO2 >94%) by volitionally increasing tidal volumes. However, because this is fatiguing for hypercapnic patients, especially during exercise, NIV can be provided through simple mouthpieces, nasally, or through oronasal interfaces using lightweight, portable ventilators with internal batteries. Such ventilators can be as portable as liquid oxygen–delivery systems.

NIV has been reported to enable severe chronic obstructive pulmonary disease (COPD) patients to improve exercise capacity by reducing muscle effort and improving breathing pattern.4,5 The only publication on exercising kyphoscoliosis patients reported that NIV, applied via a mouthpiece to a group of patients with severe scoliosis, did not benefit speed of ambulation on a treadmill.6 However, the authors suggested that the lack of benefit might have been attributable to difficulties adapting to NIV. Because seven of our eight patients were already using NIV on a daily basis, and because we planned to use oronasal interfaces instead of mouthpieces, we anticipated less difficulty. Consequently, the aim of this study was to determine whether NIV via oronasal interfaces could facilitate exercise performance for kyphoscoliosis patients by improving breathing pattern, physiologic condition, dyspnea, and decreasing dead space ventilation.

**MATERIALS AND METHODS**

**Patients**

Eight of the 18 patients managed in our outpatient unit met the inclusion criteria, which were having kyphoscoliosis, signing an informed consent that had been approved by the hospital ethics committee, having a Cobb angle greater than 90 degrees or forced vital capacity (FVC) less than 50% of normal,6 having a PaO2 greater than 60 mm Hg at rest, and having transportation to our facility. A PaO2 greater than 60 mm Hg was mandated by the ethics committee because our protocol did not permit oxygen supplementation. The cause of kyphoscoliosis was idiopathic (6), traumatic (1), and postpolio (1).

The exclusion criteria were other cardiopulmonary pathology, hereditary neuromuscular disease, inability to pedal, lack of transportation, and clinical instability during the 4 wks before the study. Those excluded were for refusal to participate (1), lack of transportation (2), comorbidity with COPD (2), recent abdominal surgery (1), history of thoracoplasty (1), idiopathic unilateral diaphragm paralysis (1), primary cardiac insufficiency (1), and ischemic cardiomyopathy (1). No patients received beta-blocker therapy.

Seven patients had been using home nocturnal NIV delivered by volumetric ventilators for 87 ± 24 mos, to relieve symptomatic chronic hypoventilation. The remaining patient had symptomatic hypoxemia and hypercapnia at rest and was being introduced to NIV.

**Experimental Protocol**

**Preexercise Assessment at Rest**

Spirometry was performed (Masterlab; E. Jaeger Company, Friedberg, Germany) using a mouthpiece and a nose clip. FVC, FEV1, and FEV1/FVC were recorded in accordance with European Respiratory Society guidelines and suggested normal
Maximum inspiratory pressure (PImax) and maximum expiratory pressure (PEmax) at the mouth were measured (Sibelmed 163; Siebel Inc., Barcelona, Spain) with the cheeks held. PImax was performed at close to residual volume, and PEmax was performed at close to maximum inspiratory capacity; the pressures sustained for 1 sec were recorded. Three measurements with <5% variability were taken, and the highest value was used for the data analysis. All measurements were done while the patients were seated. Arterial blood gas samples were obtained from radial artery puncture (Radiometer ABL 500; Radiometer Inc., Copenhagen, Denmark). The patients’ demographic profile, pulmonary function, and Cobb angles are summarized in Table 1.

### Exercise Testing Procedures

The ergometric protocol was carried out in a pulmonary function laboratory. A cycloergometer (ER 800; E. Jaeger Company, Friedberg, Germany) with an electronic brake was used. The patients were monitored (SpO2 and HR) by pulse oximeter (OXimeter; Radiometer, Copenhagen, Denmark). After 3 mins of sitting quietly on a cycloergometer, the subjects pedaled at about 60 revolutions/min for 6 mins at 20 W. The physiologic response was similar to that of walking slowly on a flat surface. Two tests were undertaken on separate days and in random order: one with the patients breathing unaided, and the other using NIV. The subjects received NIV via an oronasal interface (Softfit; Tyco Puritan-Bennett Inc., Pleasanton, CA) connected to an ONYX Plus (Nelcor Puritan-Bennett, Pleasanton, CA) ventilator with in-line exhalation valve on pressure support of 15 cm H2O and positive end-expiratory pressure of 4 cm H2O. Ventilation parameters (tidal volume, respiratory rate, and minute ventilation) were measured continuously by pneumotachograph (Meteor monitor; CardioPulmonary Technologies, Inc; Pewaukee, WI) connected to the ventilator circuit when the patient was using NIV, and connected to the nasal interface when the patient was breathing spontaneously. The mean of the results taken from the last five respiratory cycles was analyzed. The SpO2 was noted at the end of every exercise minute.

Each test was concluded after 6 mins of pedaling or when SpO2 decreased below 85%, if the patient was unable to maintain the pedaling rate, or if he or she simply stopped, in which case the reason for the interruption was recorded. Immediately on conclusion of each test, the HR, RR, VE, V/FVC% were recorded, and arterial blood gas samples were drawn from radial artery puncture. Then the degree of dyspnea was assessed by Visual Analog Scale (VAS) and degree of perceived effort by the modified Borg scale (MBS).

### Statistical Analysis

SPSS 11.5 for Windows (Chicago, IL) was used. Descriptive data are presented as mean ± SD (SD). Differences between paired groups of data were evaluated using the paired t test if the sample came from a normal distribution (Shapiro–Wilks) and with the Wilcoxon test if it did not. The Bonferroni step-down adjustment for multiple comparisons within each outcome was used, and differences were considered significant if the P value was <0.05.

### RESULTS

Six patients completed both 6-min tests, but one patient discontinued the SBT after 30 secs and the NIVT at the third minute because of dyspnea, and data were not recorded for him. Another patient also discontinued the SBT because of dyspnea at 90 secs but was able to complete the NIVT. Table 2 compares heart rate, ventilatory parameters, and blood gas values at rest with those just after the SBT and NIVT (n = 7) and also the patients’ dyspnea and effort data (n = 8). Unlike the SBT, PaCO2 decreased by comparison with resting values for three patients performing the NIVT. The SpO2 measured at the end of each minute of both exercise tests is demonstrated in Table 3.

### DISCUSSION

This study demonstrates that light exercise for kyphoscoliosis patients necessitates considerable effort and exacerbates alveolar hypoventilation, hypoxemia, and respiratory and metabolic acidosis, and that these factors can be relieved and exercise can be better tolerated by using NIV. Previous work of other authors has pointed out that exercise oxygen consumption (VO2) for kyphoscoliosis patients increases by approximately 40% above resting levels. This effect is exacerbated during...
exercise. At 20 W, VO₂ for these patients is similar to that of normals at 40 W. The high energy needed for breathing when there is decreased thoracic-pulmonary compliance results in poor exercise tolerance and favors a sedentary lifestyle. This contributes to physical deconditioning that further limits the muscular response to exercise.

Our data demonstrate that RR increases significantly during exercise while breathing with or without assistance, but it increases significantly more so without NIV (P = 0.03). There was also significantly less acidosis, hypoxia, hypercapnia, dyspnea, and effort when exercising using NIV (P < 0.05). Likewise, the significantly improved exercise

### TABLE 2 Exercise outcomes with and without noninvasive mechanical ventilation

<table>
<thead>
<tr>
<th></th>
<th>Resting</th>
<th>SBT</th>
<th>NIVT</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, b/m</td>
<td>90 ± 11</td>
<td>119 ± 18</td>
<td>111 ± 16</td>
<td>0.004*</td>
</tr>
<tr>
<td>RR, b/m</td>
<td>21.4 ± 4.3</td>
<td>36.9 ± 10.4</td>
<td>32 ± 11.2</td>
<td>0.018*</td>
</tr>
<tr>
<td>Vt, ml</td>
<td>432 ± 121</td>
<td>458 ± 220</td>
<td>587 ± 200</td>
<td>0.490*</td>
</tr>
<tr>
<td>VE, liters</td>
<td>9.1 ± 2.85</td>
<td>15.2 ± 5.9</td>
<td>17.6 ± 4.3</td>
<td>0.034*</td>
</tr>
<tr>
<td>Vt/FVC %</td>
<td>0.45 ± 0.19</td>
<td>0.40 ± 0.16</td>
<td>0.56 ± 0.13</td>
<td>0.930*</td>
</tr>
<tr>
<td>VAS</td>
<td>1.37 ± 1.1</td>
<td>5.53 ± 2.5</td>
<td>4.02 ± 2.5</td>
<td>0.006*</td>
</tr>
<tr>
<td>MBS</td>
<td>ND</td>
<td>5.88 ± 2.8</td>
<td>4.13 ± 1.72</td>
<td>0.041†</td>
</tr>
<tr>
<td>pH</td>
<td>7.40 ± 0.03</td>
<td>7.32 ± 0.04</td>
<td>7.36 ± 0.04</td>
<td>0.018*</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>46.3 ± 7.2</td>
<td>54.3 ± 7.6</td>
<td>47.1 ± 7.1</td>
<td>0.010*</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>72.8 ± 8.9</td>
<td>61.5 ± 15.9</td>
<td>69.5 ± 15.7</td>
<td>0.072*</td>
</tr>
<tr>
<td>HCO₃, mmol/liter</td>
<td>26.2 ± 1.8</td>
<td>24.9 ± 2.7</td>
<td>24.7 ± 1.9</td>
<td>0.026*</td>
</tr>
</tbody>
</table>

HR, heart rate; RR, respiratory rate; Vt, tidal volume; VE, minute ventilation; Vt/FVC, tidal volume/forced vital capacity ratio; VAS, visual analog scale for dyspnea; MBS, modified Borg scale for effort; HCO₃, bicarbonate. n = 7 for all measurements, except for VAS and MBS (n = 8).

Resting = at rest, before starting the exercise test; SBT = after the exercise test, breathing unaided; NIVT = after the exercise test, using noninvasive ventilation. Comparing the results at rest and after the SBT; comparing the results at rest and after the NIVT; comparing the results of the SBT and the NIVT.

### TABLE 3 Percentage of oxyhemoglobin saturation after every minute of exercise

<table>
<thead>
<tr>
<th></th>
<th>Resting</th>
<th>1 m</th>
<th>2 m</th>
<th>3 m</th>
<th>4 m</th>
<th>5 m</th>
<th>6 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>95.3 ± 1.2</td>
<td>92.3 ± 2.0</td>
<td>89.8 ± 3.2</td>
<td>90.2 ± 3.5</td>
<td>89.8 ± 4.0</td>
<td>89.5 ± 4.2</td>
<td>89.2 ± 4.3</td>
</tr>
<tr>
<td>Median</td>
<td>95.5</td>
<td>92.5</td>
<td>89.0</td>
<td>89.5</td>
<td>89.5</td>
<td>89.5</td>
<td>88.5</td>
</tr>
<tr>
<td>NIVT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>97.2 ± 1.7</td>
<td>95.7 ± 1.9</td>
<td>93.2 ± 3.1</td>
<td>93.5 ± 2.9</td>
<td>92.7 ± 3.7</td>
<td>92.2 ± 4.0</td>
<td>92.9 ± 2.4</td>
</tr>
<tr>
<td>Median</td>
<td>97.5</td>
<td>96.0</td>
<td>93.5</td>
<td>93.5</td>
<td>93.0</td>
<td>92.5</td>
<td>92.0</td>
</tr>
<tr>
<td>P</td>
<td>0.038</td>
<td>0.028</td>
<td>0.045</td>
<td>0.028</td>
<td>0.157</td>
<td>0.221</td>
<td>0.038</td>
</tr>
</tbody>
</table>

SBT, Exercise test with unaided breathing; NIVT, exercise test using noninvasive ventilation.
tolerance and performance permitted one patient who could not complete the SBT to complete the NIVT.

The authors of the single study that did not demonstrate benefit from using NIV for exercise reported having difficulty with patient–ventilator synchrony and ventilator triggering because of the patients’ high breathing rates. Dyssynchrony would lead to failure to decrease the work of breathing and result in breathlessness and NIV failure. They also noted problems related to CO2 rebreathing and did not use oronasal interfaces. Indeed, people performing intensive exercise breathe both through the mouth and the nose. Obliging patients with limited respiratory reserve to breathe via one orifice would limit their ability to augment alveolar ventilation for exercise. We find that once each breath is sufficiently augmented using assist/control mode ventilation at high delivered volumes and pressures, breathing rate spontaneously slows, and synchrony is facilitated. Using an expiratory valve in the ventilator circuit also decreased CO2 rebreathing.

NIV was reported to reduce RR and increase VT during exercise for patients with COPD and those with restrictive pulmonary pathology associated with sequelae of pulmonary tuberculosis. In that study, there was an improvement in exercise tolerance using nasal NIV delivered via a volumetric ventilator along with significantly better pH and PaCO2. The authors stressed the importance of good patient–ventilator synchrony and of decreasing respiratory muscle effort.

Our small number of subjects and large number of variables for analysis are study limitations. However, even using the Bonferroni step-down adjustment for multiple comparisons within each outcome yielded significant differences. Further, the level of pressure support we chose in this pilot study was relatively low. Higher inspiratory and lower expiratory pressures would provide greater tidal volumes and might further improve outcomes, because ventilatory assistance is a function of bilevel positive airway pressure span or the extent of delivered volume/pressure support.

It is conventional to administer oxygen to kyphoscoliosis patients rather than to use NIV or increase NIV settings for NIV users. This is true even though oxygen therapy exacerbates hypercapnia, whereas NIV has been demonstrated to improve the prognosis for kyphoscoliosis patients and others with respiratory muscle dysfunction by comparison with oxygen therapy. Indeed, NIV alone has been shown to be effective in normalizing CO2 and PaO2 levels as well as pulmonary artery pressures, without concomitant oxygen therapy for kyphoscoliosis patients. Because the issue is hypoventilation and not primary lung/airway disease or lack of diffusion capacity, and because some of the new portable ventilators are so light and portable, patients with access to assisted ventilation may now maintain more normal SpO2 and CO2 levels by using NIV when exercising. Indeed, we already have reported patients with severe lung disease dependent on continuous NIV with no ventilator-free breathing ability, who walk and perform all activities of daily living receiving NIV via mouthpieces while pulling a trolley that holds their ventilators, or by using a walker with a ventilator tray. Thus, the full therapeutic potential of NIV for exercise has yet to be explored.

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**BOOK REVIEW**

**Thieme Atlas of Anatomy, General Anatomy and Musculoskeletal System**


This 541-page atlas is intended as both a text to demonstrate anatomic concepts to beginning students and as a reference for practicing professionals. It includes 1694 illustrations and 100 tables. It is divided into a general anatomy section, followed by a systematic presentation of trunk-wall, upper-limb, and lower-limb anatomy. After a brief review of human ontogeny and surface anatomy, the atlas focuses on musculoskeletal anatomy, and then it progressively adds neurovascular anatomy in context. Detailed drawings present bony anatomy, including joint surfaces from multiple perspectives, and clinical and radiographic correlations. Equally clear drawings of muscular anatomy are presented along with schematic diagrams of muscular attachment. Accompanying text outlines the origin, insertion, action, and innervation of each muscle. Additional diagrams and text describe kinematics and selected clinical correlations. Skeletal anatomy in particular is presented in a way that allows conceptualization of the three-dimensional structure, which should be particularly helpful in preparation for therapeutic injections.

The main strength of this atlas is the detail and clarity of the anatomic drawings. Although not a substitute for a complete anatomy text because of its narrow focus, it is an excellent atlas of the peripheral neurologic and musculoskeletal systems and a potentially valuable tool for both learning and teaching.

**Rating:** ★★★★

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Current Evidence and Clinical Applications of Therapeutic Knee Braces

ABSTRACT

Braces are commonly used for the management of musculoskeletal injuries. With improvements in design and application, the knee brace has gained recognition by many as a treatment and prevention modality. However, there exist many different categories of knee braces, leading to confusion among many end users. The theoretical basis of the mechanism of action of the unloader, prophylactic, patellofemoral, and functional knee braces are explained in this review. This article also provides an update on the various knee braces in terms of the clinical efficacy and appropriate prescription recommendations.

Key Words: Knee Brace, Unloader, Prophylactic, Patellofemoral, Functional

The knee is one of the more common sites for injuries. The wide and varied methods of treatment and prevention of knee injuries include the use of knee braces. The general purpose of the knee brace is to support, align, or immobilize the knee. Its role extends to prevention or correction of deformity, thus improving function and possibly slowing disease progression. The knee brace has gained recognition by many as a treatment and prevention modality with improvements in design and application. Particularly in the sporting context, the use of knee braces by high-profile athletes has heightened awareness. Knee braces are divided into several categories: (i) the unloader knee brace (used in osteoarthritis [OA] of the knee to provide pain relief and improve function), (ii) the prophylactic knee brace (used to protect the healthy knee from injuries during athletic activities), (iii) the patellofemoral knee brace (used for anterior knee pain), and (iv) the functional knee brace (used to provide stability for the unstable knee in ligament injury, such as a torn anterior cruciate ligament [ACL] or post-ACL reconstruction). Because there are many different categories of knee braces, confusion exists among players, coaches, parents, patients, and physicians regarding their use. The objectives of this paper are to review the various types of knee braces and their respective mechanisms of action, and to summarize the current evidence regarding their clinical efficacy.
More than 20 million people in the United States have OA. The disease's chronic course and high costs for intervention comprise a considerable societal burden. Trauma and other inflammatory conditions have been implicated in the pathogenesis of OA. In sports, the development of OA has been linked to injuries of the ACL, the posterior cruciate ligament (PCL), the meniscus, and the articular cartilage. OA involves destruction of hyaline cartilage attributable to repeated mechanical friction in any of the three articular compartments of the knee. The compartments are divided into the medial, lateral, and patellofemoral compartments. The medial compartment is usually first affected as greater compressive and rotational forces are transmitted through the medial compartment, where the medial femoral condyle is larger and longer than the lateral condyle. Medial-compartment OA is often associated with varus knee alignment, shifting the mechanical axis and load bearing more through the medial compartment, contributing to the progression of the disease. Given that alignment has an important role in the disease process, interventions are aimed at correcting alignment and, thus, reducing stress in the affected compartment. The purpose of the unloader knee brace is to “unload” the affected compartment by altering alignment.

**Mechanism of Action of the Unloader Knee Brace**

The medial unloader knee brace was designed to apply a valgus moment about the knee for medial-compartment OA. Conversely, the lateral unloader allows for application of varus moments for lateral-compartment OA. The brace is made of hinge components, which create an angulation that induces a bending moment at the hinge. This produces a valgus or varus alignment greater than that of the lower-limb alignment. The hinge components are secured with a series of straps that produce a three-point-contact bending system. The valgus brace produces medially directed force to the lateral aspect of the knee joint and laterally directed forces to the medial aspects proximally and distally from the joint, as illustrated in Figure 1. There is, thus, a resultant valgus moment produced about the knee.

**Clinical Efficacy of the Unloader Knee Brace**

Most clinical research evaluating the efficacy of the unloader knee brace has been carried out on medial-compartment OA because of its higher prevalence. Many of the studies have measured effectiveness through the magnitude of improvements in pain, function, and quality of life. Hewett and coworkers have evaluated the effectiveness of valgus bracing on symptoms and functional gait patterns in patients with OA knees and found significant improvements in pain parameters but not in dynamic gait parameters. This prospective study, however, includes a broad range in baseline characteristics and demographics in a small cohort of subjects. It has attempted to use more objective measures to estimate improvement, but the only improvements noted in the study have been subjective in nature. The Cochrane library published a critical review of a study by Kirkley and colleagues, who report a prospective randomized control trial that compared valgus knee bracing vs. a neoprene sleeve vs. controls. The valgus brace (Generation II Orthotics, Richmond, British Columbia, Canada) used in this study was custom made with a valgus angulation of 4 degrees. Quality of life was measured with the Western Ontario and McMaster University Osteoarthritis Index and the McMaster–Toronto Arthritis Patient Preference Disability Questionnaire. Functional status was measured by performance on 6-min walking and 30-sec stair-climbing tests. The researchers found significant improvements in patients in the brace and sleeve groups compared with controls, as well as a significant difference between those in the brace and sleeve groups with regard to pain after functional tests. They conclude that valgus bracing was better than the use of a neoprene sleeve, which was better than no support with regard to improving...
ing pain, stiffness, and function. The authors were able to adequately overcome difficulties with randomization and, to a lesser extent, blinding. However, the evaluation period was 6 mos in the study; this is relatively short, considering that OA is a chronic condition. The long-term benefits of application of the unloader brace for OA still need to be assessed. The fact that the treatment groups had different baseline characteristics adds to the methodological problems of the study. On the basis of this study, the Cochrane recommendation concludes that “there was only limited evidence for the effectiveness of bracing in the treatment of medial-compartment knee OA.”

Because increased knee adduction moment during gait is associated with OA, biomechanical parameters are generally thought of as useful markers of objective efficacy. Linderfeld and coworkers have shown the effects of the custom unloader brace on gait by decreasing adduction moment about the knee. Mean adduction moment was 10% greater without the brace than with the brace. Improvements in pain and function resulted from decreased biomechanical knee loading through the medial compartment. This study nicely demonstrates the biomechanical improvements with brace use in reducing adduction moments. Matsumo and coworkers evaluated the effects of the Generation II OA brace (Generation II USA Inc., Bothell, WA) for 12 mos in patients with moderate to severe medial OA of the knee, in terms of pain relief and mechanical improvement. The researchers found significant improvements in the Japan Orthopedic Association’s knee scoring system (which evaluates pain on walking and stair climbing) and in isokinetic quadriceps strength. The authors theorize that the improvements may be attributable to increased knee stability through decreased center of gravity, increased quadriceps strength, and decreased femorotibial angle. However, the study had no control group for comparison, raising into question the strength of the findings. In a prospective cohort study, Pollo and coworkers quantify the valgus moment produced by custom Generation II valgus braces and reduction of medial-compartment loads, using three-dimensional gait analyses. Compartment loads were extrapolated using gait analysis and brace-moment data. Pollo and coworkers found that varus moment about the knee was reduced by an average of 13%, and medial-compartment load at the knee was reduced by an average of 11%.

**Effect of Proprioception**

Proprioception is the perception of limb position in space and involves sensory inputs from muscle, skin, and joint structures. The OA disease process has been associated with deficits in various aspects of neuromuscular function, including proprioception and other sensory–motor functions. Increased proprioception, as a neuromuscular component, may be the underlying mechanism for improvements with brace use. If so, one wonders whether a sleeve should suffice. In 2001, Birmingham and coworkers set out to investigate the mechanical effects of valgus-directed thrust of the Generation II unloader knee brace on proprioception and posture control in subjects with OA. In this study, proprioception was assessed with the subjects seated, using an isokinetic dynamometer to quantify the subjects’ ability to reproduce target knee-joint angles. Postural control was assessed with a force platform using single-leg standing balance on a stable surface and, subsequently, on foam, to quantify deviation from the center of pressure. Small improvements were seen in proprioception (0.7 degrees) but not in postural control. However, the quality of the study was compromised by the lack of a control group for comparison of effects.

**Recommendations for the Use of the Unloader Knee Brace**

There are situations in which patients with knee OA may be unsuitable for arthroplasty because of medical or other conditions that compromise the patient’s ability to withstand anesthesia or surgery. The medial unloader knee brace is designed to create a valgus moment about the knee to counteract the varus moments in knees with medial-compartment OA. The above-cited clinical studies have shown some improvements in pain symptoms and function with the use of the unloader brace. The biomechanical data from these studies demonstrate a reduction in adduction moments in varus knees with brace use. From the existing evidence, it seems that the unloader knee brace may provide reductions in pain when it is properly fitted in selected patients with OA of the knee.

**II) PROPHYLACTIC KNEE BRACES**

Prophylactic braces are designed to protect the knee from valgus stress injuries; they are generally used in sports with a high risk of collision, such as football. Because knee injuries frequently occur in football, and because the medial collateral ligament (MCL) is a frequently injured ligament, attention is focused on ways of decreasing its incidence. Players that seem most at risk are the offensive and defensive linemen, linebackers, and tight ends (who, additionally, are the most common users of the prophylactic brace).
Mechanism of Action of the Prophylactic Knee Brace

There are two basic constructs of the prophylactic knee brace: a single lateral upright with single-axis, dual-axis, or polycentric hinges, and braces with bilateral uprights and polycentric hinges. The design of the construct is intended to protect the MCL during valgus knee stresses and, secondarily, to support the cruciate ligaments during rotational stress. The sequence of a valgus injury begins with application of force to the lateral joint line, leading to immediate tension in the MCL, the ACL, and then the PCL with increasing valgus.

Clinical Efficacy of the Prophylactic Knee Brace

The prophylactic knee brace’s efficacy in preventing ligament injury with routine use has been of continued controversy. A few studies have supported the belief that prophylactic knee braces decrease the incidence and severity of MCL injuries with routine use. Biomechanical studies have shown that the prophylactic knee brace can add 20–30% greater resistance to a lateral blow to the knee (one that potentially could cause medial-joint-line opening). At West Point, Sitter and colleagues conducted a study of 1396 cadets to assess the prophylactic knee brace’s effectiveness in reducing the incidence and severity of knee injuries in football players. A significantly higher rate of injury was found in the control group (3.4 injuries per 1000 exposures) compared with the braced group (1.5 injuries per 1000 exposures). The study reveals that brace use was associated with a reduction in the number of MCL injuries, but not in the severity of injury. In a descriptive study of 987 Big Ten Conference football players, Albright and colleagues compare the injury rates in players of the same position and in the same playing conditions, with or without the use of prophylactic knee braces. A nonsignificant but consistent reduction in MCL injuries was found for braced players in every position and string during practice. Reduced injury rates also have been found for linemen and the linebacker/tight-end group during games, but not in the skilled position group. These two epidemiologic studies suggest a trend in the clinical effectiveness of the prophylactic knee brace.

Effect of the Prophylactic Knee Brace on Performance

The use of prophylactic knee braces has been associated with decrease in performance, especially in athletes involved in speed and agility. Important factors that contribute to this decrease in performance are the weight, restrictive straps, and fit of the brace. The effect of weight of the brace on athletic performance was shown by increased energy consumption measured by various parameters such as heart rate, oxygen consumption, and blood lactate levels. The restrictive straps were associated with increased intramuscular pressure, which was related to premature muscular fatigue from reduced blood flow to the muscles. The fit of the brace was an important factor, because migration and slipping of the brace during athletic activity affected speed and agility. Views on the effect of prophylactic-brace use on strength are conflicting. Houston and colleagues report a 12–30% reduction in maximal torque output during isokinetic knee extension in braced subjects. This reduction was more evident at higher angular velocities. Sforzo and coworkers found that peak torque performance was negatively influenced by brace wear in their cohort of female athletes, but not in their male athletes. On the other hand, Veldhuizen and colleagues did not find any significant drop in peak torque of knee flexion and extension.

Potential Adverse Effects of the Prophylactic Knee Brace

Other studies question the effectiveness of the brace and report its potentially adverse effects. Grace and coworkers studied the effects of using single- and double-hinged prophylactic knee braces compared with matched controls in 580 high school football players. The authors noticed that knee injuries were significantly more frequent in athletes who wore single-hinged braces than in matched controls. There was no significant difference in the number of knee injuries in athletes who wore double-hinged braces compared with their matched controls. Of note, significantly more injuries of the foot and ankle were reported in the athletes who wore braces. The National College Athletic Association study by Teitz and coworkers compared the effects of prophylactic-brace use on strength are conflicting. Houston and colleagues report a 12–30% reduction in maximal torque output during isokinetic knee extension in braced subjects. This reduction was more evident at higher angular velocities. Sforzo and coworkers found that peak torque performance was negatively influenced by brace wear in their cohort of female athletes, but not in their male athletes. On the other hand, Veldhuizen and colleagues did not find any significant drop in peak torque of knee flexion and extension.

Recommendations for Use of Prophylactic Knee Braces

The American Academy of Orthopaedic Surgery and the American Academy of Pediatrics conclude in their position statement that “prophylactic braces lack sufficient evidence of efficacy in reducing the incidence or severity of ligamentous knee injuries.” Furthermore, it has been shown that these braces may slow the athlete down and inhibit performance. Evidence on the efficacy of the pro-
Phylophotic brace has been conflicting, and therefore, routine use of the prophylactic knee brace is currently not recommended.

**III) PATELLOFEMORAL BRACES**

Patellofemoral pain syndrome is one of the most common disorders of the knee, and it affects athletes and non-athletes alike. Females experience anterior knee pain more often than males, with incidence rates of 10% in young female athletes and 7% in young male athletes. Patellofemoral pain accounts for 33% of all knee injuries in female athletes and 18% of all knee injuries in male athletes. Three main mechanisms have been identified for developing patellofemoral pain: articular cartilage damage from direct trauma, overuse repetitive microtrauma, and abnormal patellar tracking (which results in increased strain on the peri-patellar soft tissues and/or increased patellofemoral joint stress). The patellofemoral brace is designed to resist lateral displacement of the patella, and to maintain patellar alignment. It is usually made of elastic material such as neoprene, and it may include straps or buttresses that help to stabilize the patella.

**Mechanism of Action of the Patellofemoral Brace**

The mechanism of action by which the patellofemoral knee brace alleviates knee pain remains unclear; however, the theories of how it works are shown in Table 1.

The patellofemoral knee brace is said to improve pain by altering patellar alignment or tracking. Shellock and coworkers have examined the effects of the patellofemoral brace (OnTrack Patellofemoral Knee Brace System, OrthoRx, Inc, San Diego, CA) in influencing patella alignment using kinematic magnetic resonance imaging with the limb in open-chain active movement and against resistance. The majority of patients were found to have improved centralization of the patella or a decrease in patellar displacement after application of the brace. However, Muhle and coworkers using kinematic magnetic resonance imaging, analyzed patellar tracking patterns with open-chain knee movements with regard to patellar tilt angle, bisect offset, and lateral patellar displacement, and found no statistically significant differences with the patellar realignment brace (Genutrain P3, Bauerfeind USA, Kennesaw, GA).

Powers and colleagues have proposed that a change of patellofemoral position may be an alternate mechanism in which contact is shifted from sensitive to less irritated areas. The researchers made measurements using kinematic magnetic resonance imaging through a range of 0–45 degrees of open-chain knee flexion in subjects with lateral patella subluxation. They found that there were no significant changes in medial/lateral patellar displacement and medial/lateral patellar tilt. A small but significant change in depth of the trochlear groove was found, indicating a change in patellar position within the trochlea. Another study by Powers and colleagues examined the influence of patellofemoral brace (On-Track; Don Joy, Vista, CA) on patellar alignment and patellofemoral-joint-contact area. Patellofemoral mechanics were assessed using the more physiologic closed-chained knee exercises. The authors found that decreases in pain were associated with changes in the patellofemoral contact area, without sizable changes in patellar alignment, with the use of patellofemoral brace. Because stress is proportional to force and inversely proportional to the surface area it acts on, increases in patellofemoral contact area could serve to distribute forces over a greater surface area and, theoretically, decrease stress to the patellofemoral articular surface.

Still another proposed mechanism is through unloading of the knee-extensor mechanism. Earl and coworkers studied the effect of knee bracing (Protonics brace, Empi, St. Paul, MN) at moderate or high resistance during the lateral step-down exercise and found that there was less quadriceps activity in patients in the braced group compared with those in a control group. Aside from the above mechanisms, other proposed mechanisms have been suggested, such as through improvements of temperature, circulation, or proprioception. Recently, Powers and colleagues examined the effects of bracing in patients with patellofemoral pain with functional activities such as walking, stair ascent, and stair descent. An average decrease in pain of 56% was found with use of the On-Track Patellar Tracking brace (On-Track; Don Joy, Vista, CA). Peak stress during walking was significantly reduced, and this was associated with improvements in joint-contact area. This was not so for stair ascent and descent, where improvement in contact area was balanced with greater knee-extensor muscle moments and joint-reaction forces.

<table>
<thead>
<tr>
<th>TABLE 1 Proposed mechanisms of action of patellofemoral brace</th>
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<td>1. Improved patellar tracking</td>
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<td>2. Dissipated lateral patellar forces</td>
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<td>3. Increased patellofemoral contact area</td>
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<td>4. Changed patella positioning</td>
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<td>5. Unloads the extensor mechanism</td>
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<td>6. Increased temperature, neurosensory feedback, and circulation</td>
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<td>7. Psychological: improved confidence</td>
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Clinical Efficacy of the Patellofemoral Brace

Outcome in the treatment of patellofemoral pain syndrome using the patellofemoral brace (Special FX Knee Brace; Generation II Orthotics, Inc, Richmond, BC) was assessed recently by Lun and colleagues.48 Treatments in this prospective study were randomized into home exercise program alone, patellar bracing, home exercise program and patellar bracing, and home exercise program with knee sleeve. The clinical outcome of all treatment groups resulted in no significant differences in improvements in knee pain and function. This implies that patellar bracing can be used for patellofemoral pain syndrome but that it is not a superior treatment option compared with other strategies. Timm and coworkers49 randomly divided 100 subjects into control and braced groups to assess the effects of bracing on patellofemoral pain, position, and function. Significant improvements were found in patellofemoral congruence (using the merchant view on radiographs), in function (using the Kujala patellofemoral score), and in pain (using the visual analog scale). However, the merchant view is a static measure that may not reflect true physiologic conditions. In a prospective randomized study, Miller and colleagues50 investigated the efficacy of the Palumbo Dynamic Patellar Brace (DynOrthotics, Vienna, VA) in treating a homogeneous group of military subjects with anterior knee pain syndrome. Change of symptoms was compared with the control group. All the studies mentioned did not prove more effective than others; thus, further studies that directly compare the different models of the patellofemoral braces on the market are needed.

Recommendations for Use of the Patellofemoral Knee Brace

The effectiveness of the patellofemoral knee brace lacks consensus, because conflicts on the true mechanism of action remain. Multiple contributory factors such as patellofemoral biomechanics, temperature, proprioception, and neuromuscular factors may play a role in its effectiveness. Further research is, therefore, needed to elucidate the exact mechanism of action. There likely is a subgroup of patients with patellofemoral pain who are likely to benefit from the brace, such as those with obvious patellofemoral maltracking or subluxations. Future research in the efficacy of brace use on specific subgroups is needed. As technology continues to improve, it is possible that certain braces might prove more effective than others; thus, further studies that directly compare the different models of the patellofemoral braces on the market are needed.

(IV) FUNCTIONAL KNEE BRACE

The functional knee brace is designed to provide support for an unstable knee from ACL injury. It is commonly used to protect the ACL graft after ACL reconstructive surgery, and it also may be used for collateral ligament injury.52 The brace may be presized or custom fit, and it typically incorporates the use of double-hinged uprights with range-of-motion stops and straps with fitted shells or cuffs. The construct is intended to restore normal motion and kinematics in ACL-deficient knees by reducing anterior translation of the tibia in relation to the femur.

Mechanism of Action of the Functional Knee Brace

Beynnon and coworkers53 investigated the effect of functional bracing on the ACL by arthroscopic implantation of a transducer on the ligament to measure its strain behavior. Significant increase in ligament strain was detected in the unbraced knee when injury loads were applied to non–weight-bearing and weight-bearing knees. Bracing significantly reduced the strain values for anterior-directed loading and internal–external torque of the tibia. Similarly, Fleming and coworkers54 affirm that the brace reduced strain in anterior-posterior shear loading and in internal torque of the tibia. The authors further found that it did not reduce strain values when the knee was subjected to external torques or varus–valgus moments in non–weight-bearing and weight-bearing conditions.

Clinical Efficacy of the Functional Knee Brace in ACL-Deficient Knees and After ACL Reconstruction

Biomechanical studies by Wojtys and coworkers55 of ACL-deficient knees have shown decreased anterior tibia translation in braced knees under low loads, which was similar to daily activities. Beynnon and colleagues56 had concerns of anteroposte-
rior shear when compressive loads were applied. Significant reduction of anteroposterior laxity was found during non–weight bearing and weight bearing, but not in transition between the two. Recently, Swirtun and coworkers evaluated the effect of functional bracing on acute ACL injuries and found that most of their subjects who used the brace reported significant benefits, with 95% reporting improved knee stability. However, most of the clinical outcome scores used in this prospective randomized study were subjective measures.

Improvements in the surgical technique and accelerated rehabilitation programs have led to more predictable results in the treatment of ACL injuries. The need for postoperative functional bracing and for consensus involving the duration of the bracing in many rehabilitation protocols comes into question. Harilainen and colleagues have compared the effects of functional bracing after ACL reconstruction against nonbracing postoperatively. No significant difference in functional outcome, degree of stability, or isokinetic muscle torque was detected at 1 and 2 yrs postoperatively between the two groups. In a similar study, Risberg and coworkers found no significant differences in knee-joint laxity, range of motion, muscle strength, functional knee tests, or pain. Patients in the braced group had significantly increased thigh atrophy compared with those in the nonbraced group at 3 mos. However, patients in this group recorded significantly improved knee function with the Cincinnati knee score compared with those in the nonbraced group at the 3-mo follow-up. Muellner and coworkers evaluated the effects of functional bracing compared with bandaging after ACL reconstruction and found no differences between the two groups in terms of strength and stability. Free range of motion was achieved significantly earlier in the bandaged group. The sensorimotor performance of the knee after ACL reconstruction has been studied by Wu and coworkers, who found that bracing improved proprioception. The study involved comparison between the functional knee brace, placebo knee brace, and no brace after ACL reconstruction. Similar improvements in proprioception were found in the brace and placebo brace groups, suggesting that the apparent improvement was not attributable to the mechanical restraining action of the functional brace. Recently, in a study of young military servicemen, McDevitt and coworkers found no significant difference in clinical outcome in braced and unbraced groups after ACL reconstruction.

**Recommendations for Use of the Functional Knee Brace**

It has been shown that functional bracing may be effective in controlling anteroposterior translation in ACL-deficient knees under low loading conditions, but it may not be effective under high loading conditions that occur during athletic activities. The danger is when ACL-deficient patients are led to have a false sense of security by the use of the brace, especially when normal knee stability is not restored under higher loading conditions. Subjective improvements in knee stability and function are frequently reported, but objective evidence has yet to prove its effectiveness. The effectiveness of the functional brace in ACL-deficient knees depends heavily on appropriate rehabilitation programs. The decision to use functional knee braces after ACL reconstruction depends greatly on the surgical outcome in terms of stability and the patient's physiologic factors. Given the generally predictable results and high success rates of ACL reconstruction techniques, the evidence does not support the use of a functional knee brace after successful ACL reconstruction.

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Physiatrist Volunteerism in Specialty Societies and Organized Medicine

ABSTRACT


Key Words: Volunteerism, Professional, Associations, Quality of Care, Networking

Why should a physiatrist volunteer to join a professional organization, and what can one do to enhance his or her ability to rise to a leadership position? Professional associations are groups of people who share a common background in a particular career area. These organizations are typically nonprofit, cooperative, and voluntary, and they exist to serve their members in a variety of ways, such as by providing professional development activities, analyzing public policy, setting professional standards, sponsoring networking and social events, and providing career services. They also compile and disseminate information about the field, and they may lobby for legislation that is sympathetic to their particular cause.1 Physicians are members of a variety of communities—professional, social, local, regional, national, and global—and each physician bears a primary ethical and professional responsibility for the health of the community members they serve.2

Some professional medical associations operate with state-sanctioned authority, but this may be revoked and replaced with governmental controls if society becomes dissatisfied with their performance.2–4 The collegiality that these associations foster helps to establish common goals and encourages compliance with them. Self-regulation is the norm, as is the expectation that these associations will advise the public as experts in their domain. Medical associations have a primary role in strengthening the quality of healthcare services, but they also have an obligation to protect the interests of their individual members. These two roles can sometimes conflict with one another, and professional associations have not always managed such conflicts wisely, sometimes being perceived as subordinating the public’s interest to their own. This has contributed to a loss of trust in physicians.3 However, the control of the profession of medicine seems to be shifting from the profession to the state and to the corporate sector. Physicians must assume greater responsibility for their national medical associations. When associations fail to adequately represent them, then the societies, officers, or management must be replaced with ones who will do so effectively.

The extent to which professional medical associations should attempt to protect the economic interests of their members or represent their members in...
negotiations with government regulators, insurers, and other third parties is debatable, but some such activity may well be unavoidable. There is a fine line between a professional association and a trade union. However, associations should be aware of the danger of focusing too much attention on the economic concerns of their members at the expense of their many—and more important—public and professional responsibilities. To increase the likelihood that the legitimate concerns of the public will receive the attention they deserve, it is the author’s belief that all of our professional medical societies should have public members.

Professional associations should try to improve the performance of their physician members, foster professionalism, and provide mutual professional support for their colleagues. Associations should help to advance medical knowledge, and should be leaders in improving the quality of health care within their discipline.

Strong competition has developed over the issue of quality of medical care, a topic long monopolized by medical organizations through their control of education, training, and credentialing of physicians. Quality is now seen as a legitimate concern for purchasers, employees, managed care plans, provider organizations, politicians, and consumers, and it is the subject of serious measurement and reporting efforts under a variety of auspices. If physicians and their organizations do not take a proactive leadership position in the debates over high quality, cost-efficiency, and access to care, others will make the decisions for them.

Reasons Why You Should Play An Active Role in a Professional Medical Association

1. Access opportunities to meet and network with people in your field of interest. By attending meetings, volunteering, and collaborating with other members, you build a powerful network of professionals in your specialty that can serve as a source of potential mentors.

2. Have a built-in support group. You gain access to a group of professionals with a shared background and perspective that can provide you with valuable support, resources, and education.

3. Get up to speed in your field of interest. Professional associations provide many opportunities to learn about trends in your area of interest. Many medical associations sponsor conferences and workshops, publish newsletters, journals, and magazines, have articles on their Web sites, and host Web-based discussion groups that can provide information on new and emerging trends. These activities will provide you with valuable ideas and benchmarks for assessing and improving your own performance.

4. Find out about job and training opportunities. Professional associations share their job listings through their publications. Many have Web site access for members only for jobs and training openings.

5. Stand out in the crowd and show your commitment to your specialty. Many of your colleagues do not join or are unaware of the benefits of professional associations; by joining one, you show that you are motivated, committed, and genuinely interested in the specialty.

6. Strengthen your leadership, presentation, and communication skills. By volunteering to be on a committee, or by serving in a leadership position, you learn from seasoned professionals, and master the art of communicating in a less stressful environment with colleagues who are usually supportive and encouraging.

Some Keys to Successful Participation and Advancement Within Professional Organizations

Volunteer to serve on a committee(s). All organizations are looking for new energetic members who are willing to participate. Always be prepared, and carefully read the material before the committee meeting. Volunteer for committee projects, and be sure to deliver a quality product on time. Dependable committee members are appreciated and are often chosen for more responsible organizational duties, including the committee chair. Do not commit to too many committees, projects, or organizations. Concentrate on those organization(s) and committees that meet your personal interests, time constraints, and goals. Remember, if you fail to deliver or are ill prepared to participate, that unfavorable reputation may follow you for years in the future. A good initial approach is to listen carefully and to speak only when you can clarify or add to the issue.

To become an officer of the organization, you need to prove yourself through years of effective service within the committee and task-force structure. My advice is to develop a very specific agenda of what you desire to accomplish for the organization during your term as an officer. The reputation you develop as a goal-directed officer within a professional organization can “open doors” within organized medicine and into other associations that you may wish to enter.

One should consider participating in professional organizations beyond the more obvious ones such as the Association of Academic Physiatrists (AAP), American Academy of Physical Medicine and
Rehabilitation (AAPM&R), or the American Congress of Rehabilitation Medicine (ACRM). Some others are the Association of American Medical Colleges (AAMC), National Board of Medical Examiners (NBME), American Board of Medical Specialties (ABMS), Accreditation Council for Graduate Medical Education (ACGME), and the American Medical Association (AMA). These organizations are influential in forming overall healthcare policies that can benefit our patients and our specialty. These are the forums in which you can significantly contribute to the quality and efficiency of patient care. I encourage each of you to give back to your specialty and its patients.

REFERENCES


An Underestimated Culprit of Groin Pain: Acetabular Labrum Tear

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A 41-yr-old woman was seen for her complaint of right groin pain that had persisted for 1 yr. She felt hip pain as she changed leg positions, and the pain radiated toward her knee when she stood for a long time. She did not have low-back pain, numbness, or tingling in her right lower limb. Her medical history was otherwise noncontributory.

On physical examination, she had painful, limited range of motion during external rotation of her right hip joint. Neurological examination of the lower extremities was unremarkable. Radiologic evaluation of the hip joints was inconclusive. Thereafter, magnetic resonance imaging of the right hip was performed, and it was consistent with a partial tear of the anterior labrum with a perilabral cyst (Fig. 1). She was then given analgesics and a home-based exercise regimen for strengthening the hip muscles. On a control visit after 2 mos, she was found to have improved.

The clinical presentation of a labral tear of the acetabulum may be variable, and the diagnosis is often delayed; moreover, it has received little attention in the relevant literature. Patients usually suffer moderate to severe pain (86%), predominating in the groin region (92%), and the mean time from the onset of symptoms to diagnosis has been reported to be 21 mos.1 More importantly, these patients are seen by a mean of 3.3 healthcare providers before the definitive diagnosis, and even surgery on another anatomic site has been recommended in 17%.1 Magnetic resonance imaging seems to be the most accurate noninvasive method of depicting not only the labral tear but also concomitant pathologies—in our case, a paralabral cyst. We conclude that in patients with groin pain—with or without a history of trauma—hip labral pathologies should be considered, especially if dislocation of the hip, any sports injury, dysplastic hip, Legg–Calve–Perthes disease, or osteoarthritis are present.2

REFERENCES

MASSIVE PULMONARY EMBOLI AFTER LEGS MASSAGE

To the Editor: A 53-yr-old woman presented with progressively worsening shortness of breath for the past 1 wk. She denied chest pain, cough, or hemoptysis. Three weeks earlier, she had a vigorous manual massage of her calf muscles during a visit to a pedicure shop. The massage was prolonged (for more than 10 mins), and at the end it became so painful that she asked the pedicurist to stop massaging. The left-calf muscle soreness persisted for 2 wks, and was followed by shortness of breath. Medical history is consistent with depression, hypertension, and former heavy smoking. She is not taking estrogen treatment. Physical examination revealed blood pressure 148/79, heart rate 90 beats/min, and oxygen saturation 97%. Laboratory blood workup showed D-dimer elevated at 8.47 μg/ml (0–0.50 μg/ml), white blood cells 16,000/mm, hemoglobin 10.6 g/dl, and platelets 388000/mm. Chest x-rays were normal, and electrocardiogram showed only sinus tachycardia. Computed tomography showed filling defects in several pulmonary arteries supplying each of the lung lobes and in the bifurcation of the main pulmonary artery, consistent with extensive acute pulmonary emboli. Venous duplex of the left lower extremity showed an occlusive thrombus of the distal superficial femoral vein through the trifurcation vessels, including the entire popliteal vein, suggesting residual deep venous thrombosis. Blood tests for thrombophilia, including factor V Leiden, were negative. The patient was treated with heparin and coumadin, with resolution of symptoms. During anticoagulation, she developed vaginal blood spotting. Further workup and hysterectomy revealed stage I endometrial adenocarcinoma. She continued coumadin for 6 mos.

DISCUSSION

Massage is defined as the manipulation of soft body tissues with the aim of decreasing pain; it is generally considered a safe therapy for many musculoskeletal and rheumatologic conditions. Few case reports and case series of massage-related adverse events are mentioned in the literature.1 In many of these reports, the massages were done by laymen. Manipulation of extremities affected by deep vein thrombosis can dislodge a blood clot, leading to pulmonary embolism. In one case from the literature, a 72-yr-old woman developed a pulmonary embolus after her husband had performed vigorous massage of her leg, which was already affected by deep vein thrombophlebitis.2 In another report, massage (walking on the back) resulted in dislodgement of a thrombus in the aortobifemoral bypass graft to the kidney.3 In the present report, although the endometrial adenocarcinoma had increased the patient’s risk for thrombosis, the massage itself was at least partly responsible for the deep venous thrombosis of the leg, possibly through damage to the lining of the venous vessels. This is consistent with Virchow’s triad of thrombosis formation: venous stasis, vein damage, and/or activation of coagulation factors. Damage to the endothelial lining and lymphatic collectors had been demonstrated when the external pressure of a manual lymph massage reached 70–100 mm Hg for 10 mins.4 In summary, massage of the lower extremities done by nonprofessional persons, using forceful techniques, and for prolonged duration is not free of risks. Not only can it dislodge an already established blood clot, but, as in this case, it can also predispose an individual to venous thrombosis and subsequent pulmonary embolism. The incidence is very minimal, considering the popularity of massage therapy, but there is likely underreporting.

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REFERENCES