Venous Thromboembolism Among Elderly Patients Treated With Atypical and Conventional Antipsychotic Agents

Rosa Liperoti, MD, MPH; Claudio Pedone, MD, PhD, MPH; Kate L. Lapane, PhD; Vincent Mor, PhD; Roberto Bernabei, MD; Giovanni Gambassi, MD

Background: Some antipsychotic agents have been indicated as a possible risk factor for venous thromboembolism (VTE) in adult patients with psychiatric disorders. The aim of this study was to estimate the effect of atypical and conventional antipsychotic agents on the risk of hospitalization for VTE among elderly patients.

Methods: We conducted a retrospective cohort study on nursing home residents in 5 states. We used data from the Minimum Data Set to identify 19,940 new users of antipsychotic agents and 112,078 nonusers. Hospitalization with VTE as primary discharge diagnosis was determined during a 6-month follow-up period using Medicare inpatient claims. Cox proportional hazards models provided estimates of effect adjusted for confounders.

Results: The rate of hospitalization for VTE was 0.91 per 100 person-years. Venous thrombosis accounted for 77.6% of events and 22.4% were pulmonary embolisms. Relative to nonusers, the rate of hospitalization for VTE was increased for users of atypical antipsychotic agents, including risperidone (adjusted hazard ratio [HR], 1.98; 95% confidence interval [CI], 1.40-2.78), olanzapine (adjusted HR, 1.87; 95% CI, 1.06-3.27), and clozapine and quetiapine fumarate (adjusted HR, 2.68; 95% CI, 1.15-6.28). No increased rate was associated with phenothiazines (adjusted HR, 1.03; 95% CI, 0.60-1.77) or other conventional agents (adjusted HR, 0.98; 95% CI, 0.52-1.87).

Conclusions: Atypical antipsychotic agents appear to increase the risk of VTE. However, these events are rare, and in clinical practice the absolute risk should be weighed against the effectiveness of these medications in the elderly population.

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A possible association between venous thromboembolism (VTE) and the use of antipsychotic agents was first suggested in the 1950s after the introduction of phenothiazines. Since then, several case studies have supported the notion of an increased risk of VTE with conventional antipsychotic agents. Recently, Zornberg and Jick documented a 7-fold increase in lethal pulmonary embolism was found. More recently, 3 cases of VTE have been reported among elderly patients treated with olanzapine and 1 case in a young man with a psychotic disorder. Finally, a possible association between risperidone and massive pulmonary thromboembolism has been suggested from a review of autopsy records in a Japanese population.

Despite these suggestions, clear evidence of a possible thromboembolic effect of antipsychotic agents is lacking. Most studies have been conducted on small samples with inadequate control for confounders. Moreover, elderly patients, who are among the most common recipients of antipsychotic medications, have been systematically excluded from research in this field. A single study among adults 65 years and older compared the effect of antipsychotic agents on the risk of VTE rela-
tive to that of thyroid replacement therapy and found only a slightly increased risk with butyrophenones. We conducted a retrospective cohort study to estimate the effect of atypical and conventional antipsychotic agents on the risk of hospitalization for VTE among elderly patients living in nursing homes in 5 states.

**METHODS**

**DATA SOURCE**

We used the Systematic Assessment of Geriatric Drug Use via Epidemiology (SAGE) database, which contains data from the Minimum Data Set (MDS). The MDS is a standardized, clinically based instrument that collects information on each resident's demographic, functional, medical, psychological, and cognitive status. Each Medicare- or Medicaid-certified nursing home conducts an MDS assessment of all residents on admission and quarterly thereafter. Since 1998, the Centers for Medicare and Medicaid Services has maintained a centralized repository of all MDS data, and these data are used for administrative and research purposes. The SAGE database links MDS data to the Medicare inpatient claim files (part A), which contain information on residents' hospitalizations. The Medicare inpatient claim file provides the admission diagnosis and up to 10 discharge diagnoses for each hospitalization, recorded by the International Classification of Diseases, Ninth Revision (ICD-9) codes.

**STUDY POPULATION**

Data collected in the nursing homes of 5 states (Kansas, Maine, Mississippi, Ohio, and South Dakota) between January 1, 1998, and December 31, 1999, were used in this study. Eligible candidates were residents 65 years or older. Residents with a diagnosis of schizophrenia were excluded from the study population because they might have presented noticeable differences in their cardiovascular risk profile compared with the general nursing home population.18

**EXPOSURE ASSESSMENT**

Nursing home staff recorded the name, dose, frequency, route of administration, and national drug code for up to 18 medications administered to the resident in the 7 days before the assessment. Exposed residents were “new” users of antipsychotic agents. To select them, we initially identified residents for whom antipsychotic drug use was reported at any MDS assessment during the study period (n=50,405). Then, we selected the first assessment in which residents reported any antipsychotic drug use (index assessment). Residents were considered new users if the MDS assessment documented no antipsychotic drug use (index assessment). Residents were censored at their time of death to adjust for the competing risk. We calculated person-time as number of days from the date of the index assessment to hospitalization for VTE, death, or end of follow-up. Because structural factors of facilities may affect the rates and pattern of hospitalization,19 we stratified the analysis by facility and calculated pooled estimates to minimize this potential confounding effect. To rule out departures from the proportionality assumption for each model, we examined the log-log survival function. From these models, we derived crude and adjusted estimates of effect and corresponding 95% confidence intervals (CIs). Finally, to rule out the confounding effect of major risk and protective factors for VTE, we conducted a

**STATISTICAL ANALYSIS**

We used methods described by Kaplan and colleagues to estimate event-free survival curves and compared these curves using Mantel-Haenszel tests. The effect of antipsychotic agents on the risk of hospitalization for VTE was evaluated using Cox proportional hazards models, with users of no antipsychotic agents as the reference category. Residents were censored at their time of death to adjust for the competing risk. We calculated person-time as number of days from the date of the index assessment to hospitalization for VTE, death, or end of follow-up. Because structural factors of facilities may affect the rates and pattern of hospitalization,20 we stratified the analysis by facility and calculated pooled estimates to minimize this potential confounding effect. To rule out departures from the proportionality assumption for each model, we examined the log-log survival function. From these models, we derived crude and adjusted estimates of effect and corresponding 95% confidence intervals (CIs). Finally, to rule out the confounding effect of major risk and protective factors for VTE, we conducted a

**OUTCOME ASSESSMENT**

Based on previous reports,5,6 the thromboembolic effect of antipsychotic agents may be manifest within 3 months of the initiation of therapy. We defined the length of follow-up to be 6 months. The outcome of this study was defined as any hospitalizations for VTE that occurred during that time. We identified all hospitalizations in which the primary discharge diagnosis was one of the following: deep venous thrombosis (ICD-9 code 453.8), femoral vein thrombosis (ICD-9 code 451.11), popliteal vein thrombosis (ICD-9 code 451.19), iliac vein thrombosis (ICD-9 code 451.81), deep vessels of lower extremity thrombophlebitis (ICD-9 code 451.1), and pulmonary embolism and infarction (ICD-9 code 415.1). We used the first hospitalization for VTE among persons with multiple events (n=29).

**POTENTIAL CONFOUNDERS**

Risk and protective factors for VTE, including body mass index, indicators of functional and cognitive status, history of deep venous thrombosis, history of hip fracture, chronic obstructive pulmonary disease, cancer, and use of anticoagulants, aspirin or antplatelets, and estrogens, were considered potential confounders in this study. We also identified as confounders those variables that altered the estimate of effect by more than 10% after being included in the multivariate model. These variables included age, sex, dementia, depression, peripheral vascular disease, cerebrovascular disease, heart failure, and diabetes mellitus.

To evaluate functional status, we used the activities of daily living scale (ADL), a 7-item, 5-level score based on the resident’s performance in 7 areas: dressing, eating, toileting, bathing, locomotion, transferring, and incontinence.20 We classified the degree of dependence as mild (ADL score 0-1), moderate (ADL score 2-3), or severe (ADL score 4-5). The Cognitive Performance Scale (CPS) was used to measure cognitive status.20 The CPS is a validated scale embedded in the MDS with scores that range from 0 (intact cognition) to 6 (severe dementia). The CPS has a good correlation with the Mini-Mental State Examination.20 We categorized cognitive impairment as follows: minimal (CPS score 0-1), moderate (CPS score 2-3), and severe (CPS score 4-6).
subgroup analysis that restricted the sample to those residents without a history of deep venous thrombosis, without a history of hip fracture, without cancer, and being treated with neither anticoagulant agents nor estrogens (n=88 441). Similarly, based on the hypothesis that severe cognitive impairment (CPS score 4-6) may limit mobility, therefore representing a risk factor for VTE, we conducted a second subgroup analysis on a restricted sample of residents with minimal or moderate cognitive impairment (n=98 370). Statistical analysis was performed using SAS statistical software, version 8 (SAS Institute Inc, Cary, NC).

**RESULTS**

The sociodemographic characteristics, indicators of functional and cognitive status, and comorbid conditions of antipsychotic users and nonusers are given in Table 1.

Users were younger and more cognitively impaired than nonusers. No major differences were evident between the 2 groups with respect to all other variables considered. Only neuropsychiatric conditions were more prevalent among users of antipsychotics, with noticeable differences in the case of Alzheimer disease (23.0% vs 13.6%), dementia other than Alzheimer disease (49.8% vs 30.8%), and depression (44.7% vs 29.8%). Consistently, no differences occurred in concomitant medication use between the 2 groups except that users of antipsychotic agents were more likely to use antidepressants (45.3% vs 30.7% among nonusers) (Table 2).

Among antipsychotic users, 40% were receiving risperidone, 14% were receiving olanzapine, and nearly 18% were receiving haloperidol. Residents taking multiple antipsychotic agents (4%) were treated with a combination of 2 antipsychotic medications, mostly risperidone and either haloperidol or thioridazine or olanzapine and haloperidol. Among atypical agents, risperidone accounted for nearly 70% of prescriptions, whereas among conventional antipsychotic agents, haloperidol was the most commonly used medication (nearly 40% of prescriptions) followed by thioridazine. Daily doses for antipsychotic agents were in accordance with recommendations for use in elderly people. The mode of the daily dose was 1 mg for risperidone, 5 mg for olanzapine, 20 mg for thioridazine hydrochloride, and 1 mg for haloperidol.

We identified 539 hospitalizations for VTE; the rate of hospitalization for VTE was 0.91 per 100 person-years. Venous thrombosis accounted for 77.6% and pulmonary embolism for 22.4% of all VTE hospitalizations. The median follow-up time was 180 days for both antipsychotic users and nonusers. The Figure shows the event-free survival curve by antipsychotic use. Survival curves for the 2 groups differed at the Mantel-Haenszel test (P=.02). The occurrence of VTE hospitalizations started early (30-60 days) and was distributed throughout the entire follow-up time.

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After adjusting for all potential confounders, the rate of hospitalization for VTE was increased for users of atypical antipsychotic agents, including risperidone (adjusted hazard ratio [HR], 1.98; 95% CI, 1.40-2.78), olanzapine (adjusted HR, 1.87; 95% CI, 1.06-3.27), and clozapine and quetiapine (adjusted HR, 2.68; 95% CI, 1.15-6.28) (Table 3). No increased rate of hospitalization for VTE was associated with phenothiazines (adjusted HR, 1.03; 95% CI, 0.60-1.77) or other conventional medications (adjusted HR, 0.98; 95% CI, 0.52-1.87). Residents who were receiving more than 1 antipsychotic agent were hospitalized for VTE at a rate much greater than nonusers (adjusted HR, 4.80; 95% CI, 2.28-10.10). When we restricted the study sample to residents without major risk and protective factors for VTE and to residents with minimal or moderate cognitive impairment, estimates of effect did not change remarkably, although they appeared less precise because of the reduced size of samples (Table 4).

The findings of our study document that atypical antipsychotic agents, including risperidone, olanzapine, clozapine, and quetiapine, increase the likelihood of deep venous thrombosis or pulmonary embolism among elderly patients. An association between atypical antipsychotic agents and VTE has been previously suggested for clozapine among young adults with psychiatric disorders.8-11 More recently, an increased risk of VTE was suspected for olanzapine or risperidone.12-14 A single study15 among elderly patients under an insurance plan in Ontario found no excess risk of VTE associated with atypical antipsychotic agents compared with thyroid replacement therapy.

In the current study, we found that no increased risk of VTE was associated with the use of phenothiazines or other conventional agents. The results for phenothiazines are apparently in contrast with previous reports.5,6 However, residents in the current study were receiving phenothiazines at doses substantially lower than those previously associated with the occurrence of thromboembolic events.1-6

The mechanisms by which antipsychotic medications may contribute to VTE remain to be established conclusively. Although conventional agents have been associated with enhanced aggregation of platelets,22 atypical antipsychotic agents have not been tested systematically. Recent in vitro data coming from the maker of risperidone do not support a direct effect of risperidone on human platelet function, plasma coagulation, and fibrinolysis.23 However, atypical agents possess a high affinity for the serotonin receptor type 2A, and serotonin-induced platelet aggregation may be affected.24 Evidence also exists that lupus anticoagulant and antiphospholipid antibody levels may be raised in patients taking conventional antipsychotic agents25 and clozapine.26 Venous stasis can be exacerbated by excessive sedation.10 Moreover, a recent meta-analysis27 has suggested a nearly 3-fold increased risk of peripheral edema associated with risperidone. Metabolic abnormalities (dyslipidemia, increased plasma levels of leptin and glucose, hyperhomocysteinemia) observed among users of atypical antipsychotic agents,28 and known to be associated with decreased fibrinolytic activity,29 are unlikely to be etiologic factors in the early thromboembolic occurrence.

This study investigates a topic of high public health significance. In fact, behavioral disturbances and psychosis are increasingly recognized as significant mental health issues for older people. It has been shown that 15% of all residents in US nursing homes receive antipsychotic agents.30 Prescriptions are increasingly being written for atypical agents. At the time of this study, nearly 60% of users were receiving atypical agents,30 which is owing to their purported superior extrapyramidal side effect profile compared with conventional agents. Atypical antipsychotic agents have been approved by the US Food and Drug Administration for the treatment of schizophrenia only. Regardless, evidence exists that more than 70% of atypical prescriptions are for off-label indications, including depression and psychosis associated with dementia.31 Despite this widespread clinical acceptance, evidence supporting the efficacy and safety of atypical antipsychotic agents is still limited, especially among patients with dementia.32 Recently, other serious complications have been associated with the use of atypical antipsychotic agents, including an increased risk of cerebrovascular events and death, especially in persons with dementia and preexisting risk factors.33 This finding has led to restrictions in their use. In the current study, we documented an increased relative rate for an event that is rare and associated with an extremely low absolute risk. In clinical practice, physicians should judge, on an individual basis, whether or not the magnitude of this risk outweighs the benefits that can be expected from the use of antipsychotic agents. This seems especially true in the case of behavioral disturbances and psychotic symptoms of dementia, which can be distressing for patients and caregivers and are known to be associated with early institutionalization and increased morbidity and mortality.34
This study has some limitations. Thromboembolic events were selected on the basis of Medicare claims data; therefore, the potential for misclassification of the outcome exists. We documented an incidence of VTE of 0.91 per 100 person-years, which is somewhat lower than that observed in previous studies.35 Our study was restricted to events that could be confirmed by hospital diagnosis; thus, we have missed all events that resulted in a fatality before hospital referral and all events for which hospitalization was deemed unnecessary. Most antipsychotic prescriptions among patients with dementia are for atypical agents.30 Dementia, especially in the advanced stage, may predispose patients to immobility. Although findings were confirmed after excluding residents with severe cognitive decline from the sample, confounding by indication is possible. We have no information on whether the users were taking antipsychotic agents at the time of hospitalization, which introduces a potential for misclassification of the exposure. With respect to dosages, we observed low variability among drug regimens, and we were not able to investigate dose-response relationships. Finally, although we have taken due care to address numerous potential confounders, residual confounding is always possible.

In conclusion, our study documented that atypical antipsychotic agents may increase the risk of VTE among elderly patients. It seems advisable to be cautious when prescribing antipsychotic agents to elderly patients. However, the therapeutic choice should be individualized based on a careful evaluation of the benefits and risks of both classes of antipsychotic agents and patients’ risk profiles.

### Table 3. Effect of Antipsychotic Drug Use on the Risk of Hospitalization for Venous Thromboembolism

<table>
<thead>
<tr>
<th>Agent</th>
<th>No. of Events</th>
<th>Total Follow-up, Person-Years</th>
<th>Crude Incidence Rate per 100 Person-Years</th>
<th>Crude HR</th>
<th>Adjusted HR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical agents</td>
<td>64</td>
<td>5173</td>
<td>1.24</td>
<td>1.57</td>
<td>2.01 (1.50-2.70)</td>
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<tr>
<td>Risperidone</td>
<td>43</td>
<td>3451</td>
<td>1.25</td>
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<tr>
<td>Olanzapine</td>
<td>15</td>
<td>1279</td>
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<tr>
<td>Clozapine–quetiapine fumarate*</td>
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<td>Phenothiazines</td>
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<tr>
<td>Other</td>
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<td>0.91</td>
<td>0.98 (0.52-1.87)</td>
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<tr>
<td>&gt;1 Antipsychotic agent*</td>
<td>439</td>
<td>50,604</td>
<td>0.87</td>
<td>Referent</td>
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Nonusers

Abbreviations: CI, confidence interval; HR, hazard ratio.

*Number of events was less than 11; we are unable to report the actual number under our data use agreement with the Centers for Medicare and Medicaid Services.

†Adjusted for age, sex, body mass index, activities of daily living score, Cognitive Performance Scale score, history of deep venous thrombosis, history of hip fracture, chronic obstructive pulmonary disease, cancer, dementia, depression, peripheral vascular disease, cerebrovascular disease, heart failure, diabetes mellitus, and concomitant drug use, including anticoagulants, aspirin or antiplatelets, and estrogens.

### Table 4. Effect of Antipsychotic Drug Use on the Risk of Hospitalization for VTE Among Residents Without Major Risk and Protective Factors for VTE Among Residents With Minimal or Moderate Cognitive Impairment

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Nonusers

Abbreviations: CI, confidence interval; HR, hazard ratio.

*Main risk factors for VTE included history of deep venous thrombosis, history of hip fracture, cancer, use of anticoagulants, and use of estrogens. These HRs were adjusted for age, sex, body mass index, activities of daily living score, Cognitive Performance Scale score, chronic obstructive pulmonary disease, dementia, depression, peripheral vascular disease, cerebrovascular disease, heart failure, diabetes mellitus, and use of aspirin or antiplatelets.

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