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Venous thromboembolism following initiation of atypical antipsychotics in two geriatric patients

Thomas J. Maestri, PharmD[1]; Jessica Koenig, MD[2]; Christine Masuda, MD[3]; Tawny L. Smith, PharmD, BCPP[4]; Erica C. Garcia-Pittman, MD[5]

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Abstract

Background: Although not formally highlighted as a risk factor in current practice guidelines, several observational studies have reported a possible association between antipsychotic use and development of venous thromboembolism (VTE). However, it is unclear to what extent the risk is elevated.

Case Report: Described are 2 cases of VTE following recent initiation of second-generation antipsychotics in elderly patients. Ms A was a 65-year-old woman with newly diagnosed bipolar I disorder who was hospitalized for acute mania and psychosis. She was treated with risperidone along with traditional mood stabilizers and developed a pulmonary embolism shortly after treatment initiation. Ms B was a 77-year-old woman with newly diagnosed bipolar I disorder who was hospitalized for depression and psychosis. She was treated with quetiapine and electroconvulsive therapy and developed a pulmonary embolism and deep vein thrombosis within 2 months of starting treatment. Risk assessment tools were not able to definitively predict the VTEs that developed in our patients.

Conclusion: The association between antipsychotic medication and VTE has shown the highest risk with atypical antipsychotics, high dosages, and initiation within the past 3 months. Risk assessment tools may assist in assessing the risk of VTE in patients on antipsychotic therapy, although patients who are deemed by these tools to have minimal risk can still develop a VTE. Discussing VTE risk with patients when considering antipsychotic usage may help clinicians and patients safely determine the most appropriate treatment for their psychiatric illnesses while mitigating potential adverse effects.

Keywords: antipsychotics, antipsychotic, venous thromboembolism, VTE, risk, geriatric

[1] (Corresponding author) Clinical Assistant Professor, Xavier University of Louisiana College of Pharmacy, New Orleans, Louisiana, thom.maestri@gmail.com, ORCID: http://orcid.org/0000-0002-1332-3023; [2] Psychiatry PGY-4, The University of Texas at Austin Dell Medical School, Austin, Texas, ORCID: http://orcid.org/0000-0002-9562-0047; [3] Psychiatry PGY-3, The University of Texas at Austin Dell Medical School, Austin, Texas, ORCID: http://orcid.org/0000-0002-4083-9623; [4] Assistant Professor, Psychiatry Residency Program, The University of Texas at Austin Dell Medical School at Seton Family of Hospitals, Austin, Texas, ORCID: http://orcid.org/0000-0002-7512-4919; [5] Assistant Professor, Psychiatry Residency Program, The University of Texas at Austin Dell Medical School at Seton Family of Hospitals, Austin, Texas, ORCID: http://orcid.org/0000-0002-6835-1910

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Background

Venous thromboembolism (VTE), which includes deep venous thrombosis (DVT) and pulmonary embolism (PE), is a potentially life-threatening condition occurring in up to 900 000 Americans each year.[1] Advancing age and immobility, as well as various disease states and medications, have been linked with an elevated risk of VTE.[2]

Although antipsychotics are not an identified risk factor for VTE in the current CHEST guidelines,[1] reports linking antipsychotics with VTE date back to the late 1950s.[3] Early reports described a possible association between

low-potency antipsychotics and VTE. Soon after clozapine became available, reports emerged linking it to new-onset VTE. These findings included a potential 5-fold increase in mortality secondary to development of PE in patients prescribed clozapine.[4,5] More recent literature[6-9] has also found an association between other second-generation antipsychotics and elevated risk for VTE (Table).

Case Report

We report 2 cases of new-onset VTE after initiation of either risperidone or quetiapine therapies in ambulatory geriatric female patients with an overall low degree of risk other than age.

Case 1

Ms A was a 65-year-old white woman (162 cm, 76 kg, and body mass index [BMI] of 29 kg/m^2) with no past medical history, positive family history of bipolar disorder, and past psychiatric history positive only for depression. She presented for voluntary psychiatric hospitalization with severe symptoms of mania and psychosis. While hospitalized, she required multiple medication adjustments due to a lack of initial response until she was ultimately stabilized on a combination of lithium carbonate 900 mg at bedtime, divalproex sodium 500 mg twice a day, risperidone 4 mg at bedtime, and lorazepam 2 mg at bedtime. Despite her multiple medications, she was never overly sedated and remained ambulatory throughout her stay. Also of note, her platelet counts were stable around $200 \times 10^3/\mu L$ (reference range, $150 \times 10^3/\mu L$ to $450 \times 10^3/\mu L$) throughout her stay.

Four weeks after her initial presentation to the hospital she began outpatient treatment, at which time her complete blood count and comprehensive metabolic panel were within normal limits and vitals were stable, although lorazepam 2 mg and risperidone 4 mg were discontinued because of concerns for delirium. Family monitored her closely throughout this period and reported no periods of prolonged immobility or other physical complaints. On week 5, Ms A complained of 2 to 3 days of new-onset shortness of breath. The following week (week 6), she reported shortness of breath with additional complaints of fatigue on exertion. She was assessed by her primary care provider for further workup of these symptoms.

Ms A was admitted to a local medical hospital on week 7 after laboratory testing revealed elevated D-dimer levels. She was later found to have bilateral diffuse pulmonary emboli on computed tomography scan. The patient continued to deny chest pain, pleurisy, or other cardiovascular complaints throughout this time. The patient was fully mobile leading up to the event, apart from a 3-hour airplane flight in the days prior to her psychiatric hospitalization. A lower extremity ultrasound was also performed, without evidence of DVT. Ms A had a thorough evaluation for hereditary clotting disorders and cancer following the acute PEs to rule out additional medical causes, all of which were negative. Additionally, she denied use of hormonal therapy, treatment for any oncologic disease, or use of tobacco products, and denied personal or family history of clotting disorders.

Ms A was started on rivaroxaban and maintained mood stability with lithium monotherapy without requiring a retrial of antipsychotic therapy. Of note, Ms A continued anticoagulant therapy for 6 months after the VTE, although 4 months after discontinuation she had a repeat PE. Her only additional risk factor at this time was a previous VTE. She was then restarted on anticoagulant therapy indefinitely.

Case 2

Ms B was a 77-year-old white woman (51.48 kg, 167.6 cm, and BMI of 18.3 kg/m^2) with a past medical history of hyponatremia and hypertension treated with valsartan. She presented involuntarily for psychiatric hospitalization for severe depression symptoms with suicidality. Prior to her hospitalization, she denied substance use, and she had failed outpatient trials of mirtazapine and clonazepam. Following admission, Ms B initiated treatment with olanzapine (titrated to 10 mg daily) and escitalopram 5 mg daily. Soon after admission, her diagnosis was updated to bipolar I disorder and escitalopram was discontinued. She also failed to have significant improvement on olanzapine, which was discontinued after 9 days of treatment.

Following the above medication trials, Ms B began a trial of electroconvulsive therapy (ECT) plus quetiapine (immediate release) 100 mg daily to target her severe depressive symptoms. She responded to ECT after 5 to 6 unilateral treatments and was discharged after 4 weeks with continued ECT and quetiapine therapy. Her quetiapine was further increased to 300 mg daily per her outpatient provider.

Within 1 month of quetiapine initiation, Ms B presented for medical evaluation with acute complaints of shortness of breath, palpitations, and swollen feet lasting for 2 days. In the emergency department, she was found to have a small PE in the right lung and 3 DVTs in her right lower extremity. Additional studies included 2 abnormal electrocardiograms and a negative nuclear stress test. Cardiology consultation attributed the above abnormalities to her acute PE. She had no family history of clotting disorders and no history of recent immobilization,

TABLE: Summary of literature on the association between venous thromboembolism (VTE) and antipsychotic use

Source, y	Population	Results/Conclusions
Parker et al,[6] 2010	Nested case-control of 25 523 patients with VTE matched to control in the UK QResearch database	Antipsychotic exposure increased the risk of VTE (OR, 1.32; 95% CI, 1.23-1.42), with an increase of 4-10 cases per 10 000 patients. Highest risk: • Patients initiating therapy in past 3 mo (OR, 1.97; 95% CI, 1.66-2.33) • Atypical agents (OR, 1.73; 95% CI, 1.37-2.17) • High dose (OR, 2.59; 95% CI, 1.27-5.29) • Quetiapine (OR, 2.81; 95% CI, 1.75-4.50) This study suggests that antipsychotics are a risk factor for VTE, although the overall risk is low.
Liperoti et al,[7] 2005	Retrospective cohort of 19 940 US nursing home patients ages ≥65 y treated with antipsychotic therapy for medical indications	Total incidence of VTE was 0.91 per 100 person-y in the antipsychotic group versus 0.87 per 100 person-y in nonusers. Atypical agents were found to increase the risk of VTE (OR, 2.43; 95% CI, 1.69-3.49), although conventional agents did not affect the risk (OR, 1.00; 95% CI, 0.57-1.78). Risperidone displayed the highest risk of individual agents (OR, 2.54; 95% CI, 1.69-3.82). This study displayed an increased association of VTE with antipsychotics, although it was an overall lower increase in the risk compared with other studies. This could be attributable to lower average doses used in this study. Risperidone was the highest risk in this study, although there were few patients assessed in the individual agent groups.
Barbui et al,[8] 2014	17 Observational studies reporting	Antipsychotic exposure was associated with a significant increase in risk of developing VTE (OR, 1.54; 95% CI, 1.28-1.86; 11 studies).
	VTE and PE outcomes in patients on antipsychotic therapy	Although there was a high degree of heterogeneity as well as an indiscriminate increase based on individual characteristics of antipsychotics, antipsychotic exposure elucidated an approximately 50% increase in the risk of VTE in this study. The risk similarly applies to first- and second-generation antipsychotics.
Chapelle et al,[9] 2012	Meta-analysis of 7 case-control studies and 2 cohort studies reporting VTE outcomes on antipsychotic therapy	Antipsychotic exposure increased the risk of VTE (OR, 1.84; 95% CI, 1.39-2.44), and the risk was greatest within the first 3 mo (OR, 1.85; 95% CI, 1.37-2.50). Despite a high degree of heterogeneity between studies, there was a weak but significant association found in antipsychotic therapy and VTE. Further studies are needed to fully elucidate the risk.

CI = confidence interval; OR = odds ratio; PE = pulmonary embolism.

smoking, or cancer treatment, but she did have a short estrogen and testosterone trial a month before admission to the psychiatric hospital, as well as scheduled ECT treatments.

Rivaroxaban was initiated and during the next 4 months quetiapine and ECT were slowly tapered and discontinued. Ms B transitioned to lithium for mood stabilization, and it was titrated to a therapeutic level. Rivaroxaban was discontinued, and Ms B achieved complete remission of her depressive episode after 6 months since her initial presentation to the hospital. Of note, she did have 1 episode of vaginal bleeding lasting 2 weeks following rivaroxaban initiation, which spontaneously resolved.

Discussion

To date, literature assessing the risk of VTE in the use of antipsychotics has not been definitive, and it has been retrospective and observational in nature. Each study

assesses the risk in a slightly different manner, and results have been heterogeneous. Overall, current data indicate that atypical antipsychotic agents may possess the highest risk among antipsychotics, although the individual agents displaying the highest risk have been variable between studies. Both quetiapine[6] and risperidone[7] have been implicated, congruent with our patient cases.

The underlying mechanism of this risk has yet to be determined; however, several mechanisms have been proposed, including increased platelet aggregation, anti–phospholipid antibody production, and homocysteine levels, as well as the side effects of sedation and metabolic disturbances that are associated with antipsychotic use.[10-12] It is likely that several mechanisms influence the risk for each individual agent. Other additional factors identified in the literature[6-8,13] include antipsychotic therapy initiated within the past 3 months and high-dose antipsychotic therapy. Both of our patients developed VTEs within 5 weeks of antipsychotic initiation.

The Naranjo algorithm rated both of the DVTs that developed in these cases as a possible adverse effect of initiating antipsychotic therapy. Both patients were ambulatory, with no history of VTE or other independent risk factors for VTE prior to initiating antipsychotic therapy. Also of note, although Ms A developed a second PE despite discontinuation of risperidone, prior VTE is considered an independent risk factor for future VTEs and can occur in 7% of patients within the first 6 months of the initial event.[1,15]

Because of the possible association reported in the literature, several VTE risk assessment tools that include antipsychotics as a risk factor have been published.[16,17] The first tool is the QThrombosis®-2014 risk calculator (ClinRisk Ltd, Leeds, UK), which has been validated to estimate the risk of VTE during the succeeding 5 years in patients, dependent on their individual risk factors.[17] The second is a tool used to assess the need for VTE prophylaxis in the hospitalized psychiatric patient.[16] This tool has not been validated because of a lack of clinical documentation, although it still may be helpful in assessing whether a patient is at high risk for developing a VTE in a psychiatric hospital.

At an age of 65 years and a BMI of 29 kg/m^2, Ms A was at low risk for developing a VTE, although her risk increased with the initiation of antipsychotic therapy. According to the QThrombosis® tool, her risk increased from 1.1% during 5 years to 1.9%.[17] Using the tool developed by Malý et al,[16] she would not have qualified for prophylaxis in the inpatient setting with these risk factors. Ms B had underlying risk factors as well, including estrogen replacement therapy and her age of 77 years, although, again, these are not independent risk factors. Also, ECT does carry a low risk for VTE. Fatal PE is reported in 0.002% of patients following ECT, although there has been very little documentation of nonfatal PE following ECT treatment.[18] Using the QThrombosis® tool, her 5-year risk of VTE went from 1.4% up to 2.3% with the addition of antipsychotic therapy. At the time that antipsychotic therapy was added in the inpatient setting, she still would not have qualified for prophylaxis according to the tool for hospitalized psychiatric patients.[16] It is important to note that because she stopped estrogen therapy prior to her psychiatric hospitalization, this risk factor could not be included for either of the risk assessment tools, despite being a potential contributory factor. A drawback of the current risk assessment tools is that they are only able to take a snapshot of patients' risks. The tools also do not account for the individual characteristics of the medications included in the assessment, such as dosing, timing, or type of antipsychotic. External validity is also a concern with these tools because they were studied in largely white populations of the United Kingdom[17] and Denmark.[16] Previous reports have indicated that African Americans have a higher risk of VTE, whereas Asian/Pacific Islanders have the lowest risk.[19]

Although the currently available risk assessment tools do have their limitations and are not certain methods for identifying which patients will develop a VTE, they can still be tailored to determine whether patients are at high risk for VTE. The QThrombosis® tool can be used in less than a minute in outpatient settings by psychiatrists and by pharmacists dispensing medications, in order to assess the risk of VTE in high-risk patients.[17] It is then up to the providers to work with the patients to take into account all of the risks and benefits of antipsychotic therapy and determine whether this is the optimal choice in treatment. The tool by Malý et al[16] is specific to the inpatient psychiatric setting, but it is more useful in determining which patients require VTE prophylaxis. When using this tool, providers should take into account the risks and benefits of antipsychotic use versus the risks and benefits of initiating VTE prophylaxis, which is associated with its own set of risks.

Despite the absolute risk of VTE being very low after initiation of antipsychotic therapy, both patients still developed a VTE. We were fortunate to be able to stabilize both patients on alternative mood stabilizers and successfully treat the VTEs with anticoagulation agents without having to resort to a retrial of antipsychotics. It is unclear what the risk would be of restarting or continuing the patients on antipsychotic therapy, although close monitoring and weighing of risk versus benefit should be performed if continuing with this therapy. Alternative treatments should be considered in the absence of

psychotic symptoms, especially in patients with risk factors for VTE.

Conclusion

Although the overall risk is small, antipsychotic use has appeared in previous literature to be associated with the development of VTE. At this time, vigilant monitoring and patient education are the most effective ways to minimize the risk of the development of VTE in patients on antipsychotic therapy. Risk assessment tools provide a quick and easy way of assisting providers in assessing a patient's risk of VTE, although they should not be the sole factor in determining whether antipsychotic therapy is warranted. Future studies should be performed to further quantify this association.

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