

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

Section Editor: Craig M. Kessler, MD

Association Between Antipsychotic Drugs, Antidepressant Drugs, and Venous Thromboembolism

Karine Lacut, MD, PhD
Associate Professor
Department of Internal Medicine
and Chest Diseases
Cavale Blanche Hospital
Brest University
Brest, France

H&O What have previous studies suggested to us about the association between antipsychotic drugs, antidepressant drugs, and venous thromboembolism (VTE)?

KL The relation between antipsychotic drugs and venous thromboembolism (VTE) was first suggested in the 1950s, a few years after the introduction of phenothiazines. Since then, there were several reports that suggested a possible association between conventional antipsychotic drugs and VTE. However, these early studies had several methodological limitations (eg, lack of control groups and information about potential cofounders) and the evidence for a true link between these medications and VTE had not been established. More recently, studies with better methodologies reopened the debate, but results remain discrepant (Table 1).¹⁻⁵

In a case-control study from a database of 29,952 recipients of antipsychotic drugs, Zornberg and Jick found that exposure to conventional antipsychotic agents was associated with an increased risk of VTE, compared with patients who did not receive antipsychotic drugs (adjusted odds ratio [OR]=7.1; 95% confidential interval [CI] 2.3–21.9); subjects were under 60 years of age.¹ A French case-control study including 677 cases and their matched controls supported a significant association between antipsychotic drugs and VTE with an estimated risk of 3.5 (95% CI, 2.0–6.2).²

In contrast, in a large population-based cohort study, Ray and colleagues failed to confirm such association in patients aged 65 years or older, except for a slightly increased risk among users of butyrophenones.³ Another cohort study conducted among 19,940 new users of antipsychotic agents and 112,078 non-users found that the rate of hospitalization for VTE was significantly increased for users of atypical antipsychotic agents (ie, clozapine, risperidone, and olanzapine) when compared with non-users, but found no increase in recipients of phenothiazines and other conventional agents.⁴

Fewer data are available concerning antidepressant drug use and the risk of VTE. A case-control study of fatal pulmonary embolism (PE) found an increased risk for current users of antidepressants (adjusted OR=4.9; 95% CI, 1.1–22.5) when compared with non-users.⁵ Recently, exposure to tricyclic antidepressants was associated with a small increased risk of idiopathic VTE compared with non-use (OR=1.4; 95% CI, 1.1–1.8) in a nested case-control study, whereas no increased risk was found among users of selective serotonin reuptake inhibitors or other antidepressant drugs.⁶ When evaluating individual drugs in this study, investigators found that amitriptyline conferred an increased risk of thromboembolism (OR=1.7; 95% CI, 1.2–2.4) that increased with dose (>25 mg/day). No other individual antidepressant drug was associated with an increased risk of VTE in this study. No association was found between antidepressant

Table 1. Principal Studies Evaluating the Association Between Antipsychotic Drugs and the Risk of Venous Thromboembolism

Reference	Years	Age (years)	Design	Population	Events	Results
Zornberg and Jick	1990–1998	<60	Nested case-control	29,952 antipsychotic users	First event of idiopathic VTE	OR: 7.1 (95% CI, 2.3–22.0)
Parkin et al	1990–1998	15–59	Case-control	75 cases and 300 controls matched on age and gender	Fatal PE	OR 9.7 (95% CI, 2.3–40.9)
Ray et al	1994–2000	>65	Retrospective cohort	22,514 antipsychotic users and 33,033 controls	DVT and PE	HR: 1.13 (95% CI, 0.97–1.32)
Liperoti et al	1998–1999	>65	Retrospective cohort	19,940 new users of antipsychotic and 112,078 non-users	Hospitalization for VTE	HR for conventional antipsychotics: 1.02 (95% CI, 0.52–1.87) HR for atypical antipsychotics: 2.01 (95% CI, 1.50–2.70)
Lacut et al	2000–2004	≥18	Case-control	677 cases and 677 controls matched on age and gender	Idiopathic VTE	OR=3.5 (95% CI, 2.0–6.2)

CI=confidential interval; DVT=deep venous thrombosis; HR=hazard ratio; PE=pulmonary embolism; OR=odds ratio; VTE=venous thromboembolism.

drugs and VTE in the Canadian cohort of adults aged 65 years and older³ and in the French case-control study.²

H&O Does patient age make a difference in the association of antipsychotic drugs and/or antidepressant drugs and VTE?

KL Reasons for antipsychotic drug use are different according to age. Schizophrenia, for example, more often affects younger patients while dementia more often affects older patients. Because previous studies selected their populations in different age groups (<60 years in Zornberg and Jick study,¹ and ≥65 years in the 2 other studies^{3,4}), it is difficult to know if patient age can make a difference in the association between antipsychotic drugs and VTE. The negative results in the 2 cohort studies in older patients, and the positive results in younger patients in the nested case-control study with conventional antipsychotics tend to suggest a difference related to patient age. However, analyses stratified according to quartiles of age in the French case-control study revealed no heterogeneity of the association between antipsychotic drugs and VTE, suggesting that the potential risk of such association may be independent of age.²

With regards to antidepressant drugs, age was evaluated as a potential effect modifier of the association between amitriptyline and VTE in the study by Jick and Li.⁶ Among the different age groups (<40, 40–49, 50–59, and ≥60 years) the estimated risks of VTE remained unchanged.

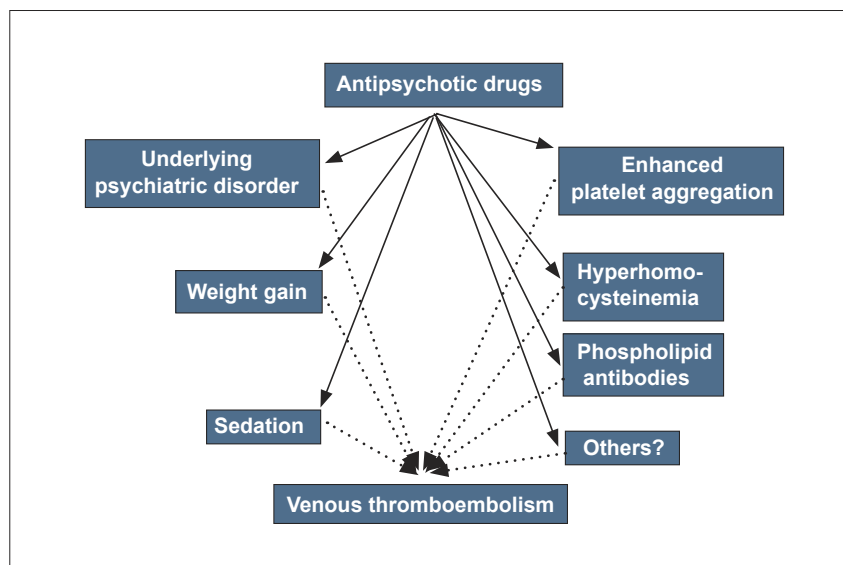
H&O What is the biological mechanism explaining these relationships?

KL Numerous underlying mechanisms have been proposed to explain the association between antipsychotic agents and VTE (Figure 1). Circulating antiphospholipid antibodies, including the immunoglobulin lupus anticoagulants and anticardiolipin antibodies, have been associated with an increased risk of thrombosis. Anticardiolipin antibody levels have frequently been reported to be raised in patients taking conventional antipsychotics and clozapine. However, these antibodies have also been found at increased levels in patients with psychiatric disorders who received no treatment. To date, no study has proven that the antibodies induced by antipsychotic drugs were linked with an increased risk of VTE.

An enhanced aggregation of platelets has also been suggested as a plausible mechanism involved in the venous thrombotic risk of antipsychotic drugs. Enhanced platelet aggregation induced by serotonin has been reported with various conventional antipsychotics. However, the suggested increase of platelet aggregation induced by antipsychotics has never been associated with clinical cases of VTE.

Hyperhomocysteinemia is another hypothetical biological mechanism. On one hand, hyperhomocysteinemia is known as a risk factor of VTE. On the other hand, this biological parameter has been reported to be associated with neurodegenerative diseases and psychiatric

Figure 1. Underlying mechanisms potentially involved in the association between antipsychotic drugs and venous thromboembolism.



disorders such as schizophrenia. Nevertheless, to date, there is no demonstration of an effect of antipsychotic drugs on homocysteinemia.

Additionally, 2 other mechanisms have been proposed:

1. Antipsychotic drug use could be associated with VTE by an indirect effect on weight. Obesity is associated with a significant increased risk of VTE in several studies, and antipsychotics are known to frequently induce a marked bodyweight gain. No study took into account the potential weight gain induced by the antipsychotic therapy in the association between antipsychotic drugs and VTE. However, in studies adjusting the results on body mass index, the association remained unchanged.
2. Significant sedation is a common adverse drug reaction of antipsychotic agents, particularly clozapine and low-potency conventional agents. The induced sedation may therefore increase the risk of VTE by increasing immobility and venous stasis. This hypothesis is supported by a stronger association between low-potency antipsychotic drugs and VTE (OR=24.1; 95% CI, 3.3–172.7) than between high potency drugs and VTE (OR=3.3; 95% CI, 0.8–13.2) in the nested case-control study.¹ However, although sedative effect is generally correlated with the dose used, no dose-effect was found in the same study.

Fewer hypotheses exist for the potential association between antidepressant drugs and VTE; chemical similitude between tricyclic drugs and phenothiazine is evoked.

H&O Is it possible that VTE is caused, not by the drugs, but by the underlying disease itself?

KL A few studies based on autopsy findings suggested that venous thrombotic events could be related to the underlying psychiatric disease. Catatonic schizophrenia, for example, is thought to carry an increased risk of pulmonary embolism. Nonetheless, all these studies have methodological limitations such as reporting no information or limited information on concomitant drugs, and therefore no conclusion can be drawn on a hypothetical link between psychiatric disorders and VTE. No psychiatric or medical condition was independently associated with VTE in the study by Zornberg and Jick (OR=1.2; 95 % CI, 0.2–6.4 for schizophrenia and other psychoses; OR=1.2; 95 % CI, 0.5–3.1 for affective and anxiety disorders).¹

H&O In your opinion, do antipsychotic drugs and/or antidepressant drugs represent a risk factor for VTE?

KL Many arguments exist to consider antipsychotic drug exposure as a risk factor for VTE. However, only data from heterogeneous observational studies are available, and the causality is not well established. Antidepressant drugs results are less convincing.

The following advice could be given for clinical practice: Firstly, because the beneficial effect of antipsychotic drugs has been clearly demonstrated in some psychiatric disorders, the potentially unfavorable effect

of antipsychotic drugs on VTE should not discourage doctors from using these drugs. To date, insufficient data exist to consider previous or current VTE as a contraindication of antipsychotic drug use. However, particular attention should be paid to patients with previous thrombotic events and/or other major risk factors of VTE. This is not synonymous to the use of systematic medical thromboprophylaxis. Clear recommendations exist for thromboprophylaxis in surgical and medical units, but no such information is currently available in psychiatric settings.

Secondly, before and during treatment, patients should be questioned and examined for signs of VTE. Symptoms such as chest pain or dyspnea that is easily attributed to an anxiety manifestation deserve serious attention and diagnostic tests.

H&O What should be done to further elucidate this issue?

KL Many questions are still unresolved. New studies should aim to determine the predisposing factors of VTE associated with antipsychotic drugs and to identify the

patients at higher risk of VTE when using these drugs. Information about the incidence of VTE in psychiatric units is needed. Randomized clinical trials similar to those conducted in medical or surgical units are necessary to evaluate the potential efficacy of thromboprophylaxis in psychiatric hospitalized patients. Clinical and fundamental studies are also needed to further explore the potential biological underlying mechanisms involved in the association between antipsychotic drugs and VTE.

References

1. Zornberg G, Jick H. Antipsychotic drug use and risk of first time idiopathic venous thromboembolism: a case-control study. *Lancet*. 2000;356:1219-1223.
2. Lacut K, Le Gal G, Couturaud F, Cornily G, Leroyer C, Mottier D, Oger E. Association between antipsychotic drugs, antidepressant drugs and venous thromboembolism: results from the EDITH case-control study. *Fundam Clin Pharmacol*. 2007;21:643-650.
3. Ray JG, Mamdani MM, Yeo EL. Antipsychotic and antidepressant drug use in the elderly and the risk of venous thromboembolism. *Thromb Haemost*. 2002;88:205-209.
4. Liperoti R, Pedone C, Lapane KL, Mor V, Bernabei R, Gambassi G. Venous thromboembolism among elderly patients treated with atypical and conventional antipsychotic agents. *Arch Intern Med*. 2005;165: 2677-2682.
5. Parkin L, Skegg DC, Herbison GP, Paul C. Psychotic drugs and fatal pulmonary embolism. *Pharmacoepidemiol Drug Saf*. 2003;12:647-652.
6. Jick SS, Li L. Antidepressant drug use and risk of venous thromboembolism. *Pharmacotherapy*. 2008;28:144-150.