

Graylands Hospital Drug Bulletin

Venous Thromboembolism and Antipsychotics

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Associations between Venous Thromboembolism and Antipsychotic Use

Venous thromboembolism (VTE) has been associated with psychiatric disorders as well as with medications used for these disorders since 1953, but the suspected association was never generally acknowledged until clozapine was associated with increased rates of VTE in the 1990s.¹ This increased risk of VTE may be associated with the use of antipsychotics, especially low potency drugs such as chlorpromazine and thioridazine.^{2,3}

The adverse effect profile of second-generation antipsychotics (SGAs) differs from first generation antipsychotics (FGAs), particularly in the risk of metabolic effects such as obesity, dyslipidaemia, and diabetes. Although FGAs have been associated with VTE, it is relatively recently that the association with SGAs has been reported and studied.^{3,5-7,8}

Among SGAs, clozapine has consistently been associated with VTE, but evidence from large observational studies⁹ has suggested that other atypical antipsychotics carry a similar risk, especially among new users and elderly patients. It may be that the underlying psychiatric disorders themselves have some association with VTE and it is the combined risk that leads to higher rates of VTE with antipsychotics.³

Known precipitants for VTE include acquired risk factors such as pregnancy, surgery or active malignancy; and inherited risk factors such as antithrombin, protein S, protein C deficiencies, factor V Leiden mutation, and G20210A variation of the prothrombin gene. Among acquired risk factors, smoking, some medications such as the oral contraceptive pill

and hormone replacement therapy are also reported to be risk factors for VTE.^{12,4} Table 1 lists acquired causes of thromboembolism.⁴

Evidence

An analysis of the World Health Organisation Adverse Drug Reaction(WHO ADR) database showed that VTE was reported more often in combination with SGAs and particularly with the individual drugs clozapine, olanzapine, sertindole and zuclopenthixol.^{5,13} Clozapine accounted for half the reports of antipsychotic associated VTE in the database.⁵ The increased risk has been estimated at between 2.5- and 13-fold based on small-scale studies.¹⁴

An association with risperidone has been reported in one study¹⁵ but that population was significantly older than the younger population generally using SGAs.

A nested case-control study, based on the primary care clinical records of 115 000 people in the UK, found a 32% increased risk of venous thromboembolism for individuals prescribed antipsychotic drugs in the previous 24 months.¹⁴ The increase in risk was 56% for individuals with any antipsychotic use in the past three months, and 97% for those who had newly started on an antipsychotic in the past three months. The absolute risks, however, were low, with an excess of four extra cases of venous thromboembolism per 10 000 patients treated over one year in patients of all ages, and 10 per 10000 in patients aged 65 and over. In this study, the risk was higher for individuals taking SGAs than for those taking FGAs.¹⁴

Psychiatric patients may be at additional risk for Deep Vein Thrombosis (DVT) because of trauma (when they are being subdued or restrained), drug-induced obesity, depressive

illnesses and psychoses with catatonic states,¹⁶

However, the EDITH study¹² showed a strong relationship between DVT and antipsychotics. In this study, several elements implied a causal relationship.

The study showed a strong relationship, which was independent of age, gender, body mass index, major acquired risk factors (surgery, plaster cast immobilization, active malignancy, pregnancy and delivery) and of two major inherited risk factors (factor V Leiden and prothrombin G20210A gene variation).

The results of the prospective case–control study, including only patients with unprovoked objectively proven VTE, are in line with results of previous studies that used different designs.⁸

The highest risks were for quetiapine (nearly fourfold increased risk) and for low potency antipsychotics rather than high potency ones. New users of antipsychotics seemed at greater risk than continuing users, and the effect was not seen in those who stopped taking the drug. In addition, the risk of VTE was higher when antipsychotics were injected. These findings indicate that VTE is directly linked to the use of an antipsychotic, and that the risk of VTE increases early after starting the drug.³ Similar conclusions were found in a 2015 review which found a strong odds ratio (3.21) in current new users of antipsychotics, while individuals with more than 30 days duration of treatment had no increased risk.¹⁷

Mechanism

Although the exact biological mechanism to explain the possible association between antipsychotic drugs and VTE is unknown, several plausible biological mechanisms have been suggested:^{1, 3, 6, 18}

- reduction of the patient's movements due to sedation, causing increased blood stasis,

- increased risk of obesity from clozapine and olanzapine,
- increased levels of anti-phospholipid antibodies (aPL) associated with chlorpromazine or clozapine,
- an indirect pathway via hyperprolactinemia,¹²
- antipsychotics that have an affinity with 5HT2 receptors blockade serotonin receptors, which in turn might provoke enhanced aggregation of platelets.¹⁹

It has been suggested that the lack of mobility associated with sedating effects as well as weight gain associated with olanzapine treatment can induce predisposing conditions for VTE. The strong affinity of olanzapine for 5-HT2A receptors increasing coagulability or the olanzapine-induced increase in serum anticardiolipin antibodies may be other explanations.^{16, 19}

Because VTE has been observed to occur early and during treatment of short duration and the risk of VTE appears to be higher when antipsychotics are injected,¹⁸ changes in platelet function, plasma coagulation, or fibrinolysis seem more likely to be responsible for the increase in thrombotic events. Metabolic changes due to antipsychotics would take long periods of time to have an effect.¹⁸

It has also been suggested that diagnoses of schizophrenia or bipolar affective disorder themselves, as well as hospitalisation or stress-induced increases in sympathetic activation and catecholamine blood levels, are also thrombogenic factors¹⁶. It has been shown that unmedicated patients with acute psychosis have an increased level of blood markers of the pathological activation of blood clotting and fibrinolysis, as well as activation of thrombocytes when compared with matched healthy volunteers.¹⁶

Table 1. Acquired Causes of Thromboembolism^{4,7}

Condition	Comments
Autoimmune disorders	Antiphospholipid syndrome, lupus anticoagulant
Atherosclerosis	Increases risk of arterial thrombi Higher risk in patients with pre-existing stenosis When atherosclerotic plaques rupture, they release tissue factor into the blood, activate coagulation, initiate local platelet adhesion and aggregation, and cause thrombosis
Cancer (promyelocytic leukemia; lung, breast, prostate, pancreas, stomach, and colon tumors)	May activate coagulation by secreting a factor X-activating protease, by expressing tissue factor on exposed membrane surfaces, or both
Heparin-induced thrombocytopenia	Associated with platelet aggregation and increased risk of thrombosis
Hyperhomocysteinaemia	Possible cause due to folate, vitamin B12, or vitamin B6 deficiency
Infection, if severe (e.g. sepsis)	Increases risk of venous thrombosis Increases expression of tissue factor by monocytes and macrophages
Inflammatory disorders	Crohn's disease, ulcerative colitis and infections increase inflammatory mediators, monocyte procoagulants and C4 binding protein, thereby decreasing free protein S. These conditions may contribute to a prothrombotic state.
Myeloproliferative disorders	Abnormal platelets and increased viscosity
Pregnancy	Decreased levels of natural anticoagulants such as total and free protein S, or antithrombin. Increased levels of procoagulant proteins such as FVIII, von Willebrand factor and fibrinogen. Decreased rate of blood flow, increasing the risk of stasis.
Nephrotic Syndrome	Nephrosis leads to an increase in inflammatory mediators and a decrease of free protein S due to an increase of C4 binding protein. Additionally, urinary loss of antithrombin and proteins C and S are increased resulting in acquired deficiencies. Moreover, thrombocytosis and increased platelet aggregability may occur. All of these associated changes may contribute to thromboembolism in nephrosis.
Oral contraceptives that contain oestrogen	Low risk with low-dose regimens More frequent in patients who have a genetic abnormality that predisposes to venous thromboembolism and in women who smoke
Smoking	Smoking is a risk factor for VTE with a dose-response relationship ^{10,11}
Stasis	Due to surgery, orthopaedic or paralytic immobilisation, heart failure, pregnancy or obesity
Tissue injury	Due to trauma or surgery

Use of several psychotropic drugs, e.g. chlorpromazine or clozapine, is associated with an increased blood level of aPL, which are thrombogenic. On the other hand, aPL can be primarily increased in schizophrenic patients. Canoso et al.²⁰ determined antinuclear antibodies (ANA), aPL, rheumatoid factor (RF), and immunoglobulin (Ig) M levels in 184 male chronic psychiatric patients on long-term therapy with neuroleptics, and in 35 age matched normal

male controls. The prevalence of one or more of these autoantibodies was 70% in the neuroleptic-treated patients and 9% in the normal controls. The risk of VTE significantly increases if several causative factors are present at the same time. In this case, the individual odds ratios are not simply added, but multiplied by each other.²¹

This could occur, for example, by the increased concentrations of adrenaline seen

during psychotic excitation increasing blood coagulation risk.¹⁸

Which Drug is Best?

Virtually all the SGAs have been suggested to increase the risk of thromboembolism.²²

Some drugs like sertindole only have case reports supporting the link.²²

There are many reports regarding clozapine and it is generally regarded as having the worst effect on the risk of thromboembolism.⁶

The one recent study to offer evidence for a relationship between DVT and risperidone³ was in an older (> 65) population. Most of the other references cited here seem to include risperidone as being at risk as a matter of course without offering evidence.

Of the other long-acting injections available, olanzapine and zuclopenthixol have been more strongly implicated than risperidone. Only one paper implicated risperidone directly but this was a case report.¹⁹ Based on the current level of knowledge, it is reasonable to regard risperidone as being relatively safer than the alternative long-acting injections.

Should we monitor for VTE?

It is not completely clear whether the increased risk for thrombosis in psychiatric patients is medication-related or not. Dissenting voices point out that patients with schizophrenia have low levels of physical activity, a risk factor that was generally ignored.²³ Patients with dementia prescribed antipsychotics may also be more at risk of thrombosis for various non-pharmacological reasons.

The effect of antipsychotics on the risk remains small. Estimates put it between 4 and 10 extra cases of thrombosis for 10000 patients prescribed antipsychotics.^{3, 23} This low level of risk should not be a major consideration when deciding whether they should be used.²³ However, one study showed

schizophrenia or schizoaffective disorder were diagnosed in only four out of 13 patients with VTE, while all of them were treated with an antipsychotic drug.²¹

Although VTE is treatable, it has a three month mortality rate of 15-18%.³ The rarity of such adverse events does not justify antithrombotic prophylaxis for patients on antipsychotics without other medical conditions for which such preventive treatment is indicated.¹⁸

In a 2015 editorial,²⁴ Patel goes further and makes the point that although, in all patients, prophylaxis reduces the incidence of non-fatal venous thromboembolism, there is no strong evidence that mortality is reduced. There is even less evidence to support prophylaxis in mental healthcare.

In a Nutshell


- Antipsychotics are a risk factor for venous thromboembolism.
- The mechanism of increased risk remains uncertain.
- Prescribers should bear in mind the risk of thromboembolism with antipsychotics but it should not be a major consideration of whether to prescribe antipsychotics or not
- Patients should be informed that that VTE is a rare adverse effect, and should seek prompt medical advice should symptoms develop.
- The risk is small enough that routine prophylaxis against thromboembolism is not recommended.

This Drug Bulletin was written by Darren Schwartz and was reviewed by the Graylands Pharmacy Department

Comments are welcome at the email address: DrugInformation.Graylands@health.wa.gov.au

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