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Risk of venous thromboembolism due to antipsychotic drug therapy

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Abstract

An increasing number of reports suggest a link between venous thromboembolism (VTE) and the use of antipsychotics. To better understand this association the available body of evidence has been critically scrutinised. Relevant articles were identified in the databases Scopus and PubMed. Several observational studies using different methodologies show an increased risk of VTE in psychiatric patients. This elevated risk seems to be related to the use of antipsychotic medication and in particular to the use of clozapine and low-potency first-generation drugs. Many studies investigating the association have, however, methodological limitations. The biological mechanisms involved in the pathogenesis of this possible adverse reaction are largely unknown but several hypotheses have been suggested such as drug-induced sedation, obesity, increased levels of antiphospholipid antibodies, enhanced platelet aggregation, hyperhomocysteinemia and hyperprolactinemia. The association may also be related to underlying risk factors present in psychotic patients. Physicians need to be aware of this possible adverse drug reaction. Although supporting evidence has not been published they should consider discontinuing or switching the antipsychotic treatment in patients experiencing VTE. In addition, although data is lacking, the threshold for considering prophylactic antithrombotic treatment should be low when risk situations for VTE arise, such as immobilisation, surgery and so on.

1. Introduction

Venous thromboembolism (VTE) is a disorder affecting ~ 1 in 1,000 – 2,000 adults annually and having the potential to cause significant morbidity and mortality [1,2]. It may be complicated by both pulmonary embolism and the postphlebotic syndrome, which is a cluster of symptoms from the leg such as pain, tiredness, oedema and skin discoloration [1].

Known risk factors include inherited coagulation abnormalities, pregnancy, surgery, malignancies and medications such as oral contraceptives and hormone replacement therapy [1-4]. Venous thromboembolism has also been associated with psychiatric disorders and medications used for such disorders. In several early studies published between 1953 and 1984, VTE was reported in patients with psychiatric disorders using antipsychotic medications [5]. However, the suspected adverse reaction was never generally acknowledged and the association sank into oblivion. Yet, in the late 1990s the relationship was rediscovered in a study on mortality in clozapine users [6], where an increased mortality rate in pulmonary embolism was noted in current users of clozapine compared to past users. In the year 2000 a case series of VTE in clozapine users was published [7], and later the same year a large nested case-control study [8] reported a sevenfold increased risk of VTE in patients currently treated with first-generation antipsychotics relative to non-users. After the turn of the millennium several further studies [9-19], case series [20-23] and case reports [24-47] suggesting an increased risk of VTE in patients using antipsychotics have been published. The association has previously been summarised by us [5] as well as by others [24,33,48,49]. The aim of this article is to critically review the available data on the risk for VTE in users of antipsychotics.

2. Methods

The Scopus and PubMed databases were searched for articles on the subject of antipsychotic medication and VTE. In Scopus, the title, abstract and keywords were searched for one of the following terms: ‘embolism’, ‘thrombosis’ and ‘thromboembolism’ in combination with one of the terms ‘antipsychotic agents’, ‘antipsychotic agent’, ‘neuroleptic agent’, ‘neuroleptic agents’, ‘antipsychotic drug’, ‘antipsychotic drugs’ or any one of 70 individual antipsychotic compounds (Appendix). In the Medline search the Medical Subject Heading (MeSH) terms ‘embolism and thrombosis’, ‘antipsychotic agents’ and ‘schizophrenia’ were exploded and used. Moreover, the reference lists in previously published reviews and original research articles were scrutinised to identify publications not covered by the original database searches.

3. Venous thromboembolism and its risk factors

Venous thromboembolism is a multicausal disease [1-4]. In two-thirds of all first-time deep vein thrombosis one or several risk factors are identified [1,4]. Venous thromboembolism is caused by the presence of one or a combination of components of the Virchow’s triad; vein wall injury, venous stasis and a hypercoagulable state [1-4]. Actually all presently known risk factors are considered to be involved in at least one of these mechanisms. These risk factors may also be categorised into three main groups: inherited risk factors, acquired risk factors and risk factors with a mixed origin. The main established risk factors are listed in Table 1.

4. Venous thromboembolism and first-generation antipsychotics

Shortly after the discovery of the antipsychotic properties of chlorpromazine in the early 1950s, cases of fatal pulmonary embolism during treatment with antipsychotics were reported in the medical literature [50-52]. Subsequently, several case reports, case series and more systematic studies were published describing VTE in users of first-generation antipsychotics [5]. Although these studies are inconclusive as they lack detailed information about possible confounders and often do not have a control group, they suggest an increased risk of VTE in

users of first-generation antipsychotics. Since 1997 several studies investigating the association between antipsychotics and VTE have been published [6-19]. The current best evidence for the risk of VTE among users of antipsychotics in general is summarised in Table 2.

A large nested case-control study [8] using data from the General Practice Research Database in the UK reported a relative risk of VTE of 7.1 for patients currently treated with antipsychotics compared to non-use. The study subjects were aged < 60. In this study low-potency drugs such as chlorpromazine and thioridazine were more strongly associated with VTE than high-potency antipsychotic drugs such as haloperidol, although there were wide and overlapping confidence intervals. The risk of thrombosis was highest during the first 3 months of treatment. Users of antipsychotics were similar to non-users with respect to known risk factors, a finding that was expected since the study only included subjects with confirmed first-time 'idiopathic' VTE without any medical conditions potentially related to VTE. In this study neither the use of antidepressants nor the specific psychiatric diagnoses were associated with an increased risk for VTE.

In a New Zealand nationwide case-control study [9] the association between fatal pulmonary embolism and the use of antipsychotics or antidepressants was studied. A 10-fold increase in risk of VTE was observed in current users of antipsychotic drugs compared to non-users. In agreement with the study by Zornberg and Jick [8] low-potency antipsychotics seemed to carry the highest risk. Thioridazine was the drug most often involved. In contrast to the findings of Zornberg and Jick [8] an increased risk was also noted for current use of antidepressants.

In a recent nested case-control study [10] current users of antipsychotic drugs had a twofold increased risk of VTE compared with non-users, while former users of antipsychotic drugs had a non-significant elevated risk of VTE compared with non-users. Although a wide range of confounding factors was controlled for in the analyses, some uncontrolled factors such as smoking, diet, obesity and schizophrenic behaviour may have affected the results. As it was not possible to fully differentiate the risk for VTE between current and former user of antipsychotics, it was concluded that the increased risk found in users of antipsychotics can be explained by several factors such as the medication itself, lifestyle factors, the underlying disease or residual confounding.

In a retrospective study [11], antipsychotic drug use was investigated in subjects aged 18 – 60 years who had been hospitalised for VTE and in a control group of subjects with arterial hypertension at the same hospital. In total, 266 subjects with VTE and 274 subjects with hypertension were identified. Use of antipsychotic drugs was moderately more frequent (odds ratio 2.8) in the patients with VTE compared to the control subjects. In another hospital-based case-control study [12], designed to evaluate interactions between acquired and inherited risk factors of VTE, 677 cases hospitalised with VTE with no major acquired risk factor for VTE, and 677 controls matched for gender and age were compared. Drug exposure was defined in this study as current use of drugs at admission. Use of antipsychotics was associated with a 3.5-fold increased risk of VTE. No association was found between use of antidepressants and the risk of VTE.

In a forensic autopsy series [13] of 1,125 cases of sudden unexpected death a logistic regression analysis was performed to explore whether age, gender, body mass index and antipsychotic drug use were associated with fatal pulmonary embolism. Among all cases, 28

subjects died from pulmonary embolism, and 8 of these had taken antipsychotic drugs. The authors estimated that users of antipsychotics had a 10-fold increased risk for fatal pulmonary embolism. In another medicolegal autopsy series persons aged 18 – 65 years at the time of death, in whom pulmonary embolism was the cause of death were identified [14]. In these subjects use of antipsychotics was based on the presence of an antipsychotic drug in post-mortem blood analyses. Users of low-potency first- and second-generation antipsychotics had a 2.4- and 6.9-fold increased risk for fatal pulmonary embolism, respectively. None of the 26 subjects in whom high-potency first-generation drugs were detected had pulmonary embolism as the cause of death.

On the other hand, a retrospective cohort study on senior residents in Ontario, Canada [15], failed to show an increase in the rate of hospitalisation for VTE among users of antipsychotic drugs compared to users of thyroid hormones. However, a subgroup analysis showed a modest increased risk of VTE among users of haloperidol. In another retrospective cohort study on nursing home residents [16], the rate of hospitalisation for VTE was not increased in users of phenothiazines or other first-generation agents relative to non-users of antipsychotics. In contrast, the rate of hospitalization for VTE was increased for users of second-generation antipsychotics. The fact that these two studies were confined to patients aged ≥ 65 may have influenced the results.

In an autopsy series of 27 deaths in which pulmonary embolism was regarded as the sole cause of death, 10 occurred in psychiatric patients [18]. Although the presence of selective factors leading to an increased autopsy rate in psychiatric patients cannot be excluded, the referral rate of such patients to autopsy was reported to be on average only 5 – 10%. Of 10 psychiatric patients with fatal pulmonary embolism, 5 used an unspecified antipsychotic medication. In the same article, the authors reanalysed data from a case-control study on patients with VTE (the Leiden Thrombophilia Study), and found that 4 patients used unspecified antipsychotic drugs in the VTE group as compared to none in the control group [17].

Finally, in a case-control study [53] on cardiovascular mortality in women between 16 and 39 years of age, a 17-fold increase in the risk of myocardial infarction and an ~ 3 -fold increased risk of VTE were coincidentally observed in current users of psychotropic drugs such as antipsychotics, antidepressants, lithium and anxiolytics, compared to non-users. However, this study provides limited information as it was not designed to investigate the relations between cardiovascular disease and the use of the specific subgroups of psychotropic drugs.

5. Venous thromboembolism and second-generation antipsychotics

There is an inconsistency between studies on whether there is an increased risk with first-generation antipsychotics only, second-generation psychotics only or both (Table 2). Liperoti et al. [16] reported a 2-fold increase in VTE in elderly users of second-generation antipsychotics but no such increase in elderly users of first-generation antipsychotics, whereas Lacut et al. [12] reported a 4.1-fold increase in users of first-generation antipsychotics and a 2.7-fold non-significant increase in users of second-generation antipsychotics. In a Swedish autopsy study [14] both first- and second-generation antipsychotics were significantly associated with fatal pulmonary embolism. In a Danish case-control study [10] a 2-fold increased risk of VTE in patients currently being prescribed antipsychotics compared with non-users was observed. Although the risk of VTE was highest in users of second-generation antipsychotics in that study [10] all categories of current users of antipsychotics had increased risks compared with non-users. Due to the size of the study it was not possible to investigate

the risk for VTE for individual compounds. Main studies on the risk for venous thromboembolism in users of the individual second-generation antipsychotics are presented in Table 3.

In a study of the WHO international database of adverse drug reactions, a total of 754 suspected cases of VTE related to treatment with antipsychotics were identified [18]. Using a data mining technique applied on the database a robust association was found between VTE and second-generation antipsychotics, but not for high- or low-potency first-generation antipsychotics. The individual second-generation antipsychotics having a disproportionately high number of VTE reports in the database were clozapine, olanzapine and sertindole.

The link between clozapine and VTE has been investigated in several studies [6,16,18,19] and case series [7,21,22] and in several case reports [5,24-33]. In a US record linkage study [6] mortality rates of various causes of death in 67,072 current and former clozapine users was investigated. Current clozapine users had a fivefold increase in the mortality rate for pulmonary embolism compared with past clozapine users. Moreover, pulmonary embolism was found to be the second most frequent cause of death among current clozapine users, after death due to external causes such as suicide and accidents. In a retrospective US cohort study on nursing home residents described in detail earlier [16], the rate of hospitalisation for VTE was increased in users of the second-generation antipsychotic agents olanzapine, risperidone and either clozapine or quetiapine.

Among 561 clozapine-treated patients, 4 sudden deaths (0.7%) were observed between 1991 and 1997 at an Israeli psychiatric hospital [19]. The only autopsy performed in these 4 cases showed a pulmonary embolism. The Swedish pharmacovigilance system had reports of 6 cases of pulmonary embolism and 6 of venous thrombosis during clozapine treatment between 1989 and 2000 [7]. In 8 of these 12 cases the VTE event occurred within the first 3 months of clozapine treatment. The reaction was fatal in 5 cases. Likewise, the US FDA received 99 reports of VTE during treatment with clozapine between 1990 and 1999 [20]. However, objective evidence of VTE was only documented in 39 of these cases. Of the 63 cases of fatal pulmonary embolism the diagnosis was confirmed by autopsy in only 32 cases. Within a systematic surveillance programme of severe adverse drug reactions in 35 psychiatric hospitals in Germany and Switzerland, 5 episodes of VTE (0.038%) were identified in 4 of 13,081 clozapine-treated inpatients [21]. Within the same system 17 cases of VTE (0.029%) were found among 59,637 inpatients treated with other antipsychotics, and 8 cases of VTE (0.026%) were noted among 30,282 psychiatric inpatients not treated with antipsychotics. The differences between the groups did not, however, reach statistical significance.

There is limited published information regarding the possible association between other second-generation antipsychotics and VTE. In US nursing home residents a 1.9- and a 2.0-fold increase in the rate of hospitalisation for VTE was reported for olanzapine and risperidone, respectively [16]. A possible association between VTE and olanzapine has also been suggested in a limited number of case series [22,23] and case reports [34-41]. In one case series [22] three elderly subjects (an 89-year-old male, a 78-year-old male and an 83-year-old female) developed first time VTE within the first 6 weeks of olanzapine treatment. In the female subject other VTE risk factors such as a malignant disease and treatment with tamoxifen were present. However, the close relationship between the VTE event and the olanzapine treatment suggests that this drug might have been involved in the aetiology of the reaction.

In another small case series [23] VTE was reported during olanzapine treatment in 4 patients aged 37 – 54 years. Of these, 3 were males. In 3 subjects the VTE event occurred within the first 6 months of olanzapine treatment. The subjects had a variety of clinical and laboratory risk factors. A case of pulmonary embolism was reported in a 28-year-old male 10 weeks after starting treatment with olanzapine due to a psychotic disorder [35]. Except for overweight, no risk factors for VTE were described. A case of pulmonary embolism was reported in another 28-year-old male 3 months after starting treatment with olanzapine due to a suspected bipolar disease [40]. Except for weight lifting, an exercise possibly associated with deep vein thrombosis [54], he had no known risk factors. In another case report massive pulmonary embolism was reported in 25-year-old man with no identified risk factors for VTE, but who had been treated with olanzapine for 3 weeks [35]. Subsequently, the patient also developed pulmonary embolism on two further occasions during treatment with risperidone (3 and 19 weeks after the commencement of treatment, respectively). In a retrospective investigation of 47 patients with acute pulmonary embolism transferred to a Japanese emergency centre [42], 7 subjects used antipsychotic medication. Of these, 2 patients had used risperidone for 40 and 6 days, respectively. The remaining 5 had used first-generation antipsychotics. In another report venous thrombosis were described in 2 men (aged 71 and 72 years) during treatment with a combination of zotepine and paroxetine [26]. With the exception of high age no risk factors for VTE were identified in these cases.

6. Risks associated with psychiatric disorders

6.1 The underlying disorder

Venous thromboembolism has also been associated with underlying psychiatric disorder. Early observational studies and autopsy studies suggest a relatively high incidence of pulmonary embolism among patients with schizophrenia and related disorders [5]. However, in these studies no or limited information on drug treatments was given.

In a more recent report [55], 22 cases of pulmonary embolism in patients with the catatonic syndrome were presented, suggesting that certain subtypes of schizophrenia may carry an increased risk of VTE. Among the 22 patients, 5 received treatment with a phenothiazine, 1 did not and in the other cases there was no information about the antipsychotic treatment. Among 172 women admitted to a US hospital, 2 of 4 women with the catatonic type of schizophrenia developed VTE compared with none of the remaining 168 women [56]. In another report [57], fatal VTE after acute psychotic exacerbation was described in 5 women with schizophrenia and without any co-morbidity. No information on drug treatment was presented. In a case report [58] a 43-year-old woman who developed VTE during depressive stupor was described. She was treated with antipsychotics including chlorpromazine and trifluoperazine. The authors considered that immobility, dehydration and possibly faecal impaction were predisposing factors and secondary to the psychiatric stupor. No other risk factors for VTE were recognised.

6.2 Physical restraint

Venous thromboembolism has been reported in association with physical restraint. In one report two such cases are described [59]. In the first case fatal bilateral pulmonary embolism was noted in a 37-year-old man being restrained for 8 days. During the same period he was treated with olanzapine, haloperidol, sodium valproate and benztropine. The other case concerned a 70-year-old woman who died from pulmonary embolism after being restrained for 2 days. She received treatment with several drugs including olanzapine. In another report [60] two further cases are described. In the first case a 29-year-old man with chronic paranoid

schizophrenia and obesity was restrained due to agitation. He also received treatment with perphenazine and levomepromazine. After 3 days he developed chest pain and after another 4 days a diagnosis of venous thrombosis and pulmonary embolism was confirmed. No predisposing factors were identified. In the second case a 59-year-old man with bipolar disorder died suddenly a few hours after being restrained for 38 h. He was treated with haloperidol and clonazepam. Autopsy revealed a massive pulmonary embolism and thrombosis in the femoral veins in addition to a recent myocardial infarction. No other risk factors were identified.

In another case report [61] a 46-year-old man with schizophrenia and obesity who died suddenly after being restrained for 6 days is described. He also received treatment with diazepam, risperidone, zuclopenthixol and biperiden. He was also dehydrated. Autopsy revealed venous thromboses in both lower extremities, and a pulmonary embolism. Moreover, a 27-year-old male with physical agitation developed bilateral venous thrombosis after being restrained for a total of 13 days [62]. The patient also received treatment with zuclopenthixol, haloperidol, chlorprothixene and various benzodiazepines. In all the cases described in this section, it was not possible to exclude that treatment with antipsychotics might have contributed to the VTE event, in addition to the physical restraint.

7. Biological mechanisms

The biological mechanisms explaining the relationship between antipsychotic drugs and VTE are unknown but the pathogenesis is most likely multifactorial. Accordingly, a growing number of hypotheses have been postulated. All conditions associated with immobilisation can cause venous stasis and blood pooling in the lower extremities, and thereby increase the risk of VTE [1,3]. Psychotic patients might be immobilised due to sedation, which is a frequent adverse effect of many antipsychotic drugs, particularly clozapine [63] and low-potency first-generation drugs [64]. Such drug-induced sedation may also predispose patients to a sedentary lifestyle, which can increase venous stasis as well. Interestingly, the association between VTE and antipsychotics has been best documented for clozapine and low-potency first-generation drugs.

Obesity, an independent risk factor for VTE, can also increase immobility and is associated with decreased fibrinolytic activity [3]. In addition, obesity is linked to congestive heart failure [65] and myocardial infarction [66], both of which increase the risk for VTE [4]. Obesity is frequent in patients with schizophrenia [67], and antipsychotic drugs, in particular clozapine and olanzapine, can induce significant body weight gain [68]. Nevertheless, in previous studies demonstrating an association between antipsychotics and VTE [8-10,12,13,16], the increased risk of VTE has remained after controlling for body weight/body mass index.

Raised levels of antiphospholipid antibodies (APLs) including lupus anticoagulants and anticardiolipin antibodies are established risk factors of VTE, and have been observed in patients treated with first-generation antipsychotics [69-77] and clozapine [78,79]. However, elevated titres have also been found in large proportions of unmedicated psychotic patients [73,80,81]. Nevertheless, clozapine serum levels were associated with increased APL levels in patients with schizophrenia [79]. Still, increased APL levels induced by antipsychotics seldom seem to be associated with VTE [74,75], although a few cases have been reported [76,78,82].

In early studies enhanced platelet aggregation has been reported in patients treated with first-generation antipsychotics [5]. In a recent in vitro study using blood samples from 57 healthy

volunteers, clozapine but not olanzapine, risperidone or haloperidol increased platelet adhesion and aggregation [83]. In another in vitro study no direct effect of risperidone could be detected on human platelet function or plasma coagulation [84]. The fact that the suggested increase of platelet aggregation induced by antipsychotics has never been associated with clinical cases of VTE is consistent with the lower impact of platelet function in the formation of VTE as compared to the formation of an arterial thrombosis.

Hyperhomocysteinemia has been associated with an increased risk of VTE [85], and increased homocysteine levels have been observed in patients with schizophrenia [86,87]. However, this effect might be related to the psychiatric disorder itself, with factors such as poor diet, cigarette smoking and high coffee and tea consumption, rather than to the use of antipsychotics [88,89].

Hyperprolactinemia has recently been suggested as a plausible underlying mechanism for VTE in users of antipsychotics [90]. Prolactin has been reported as a potent platelet aggregation co-activator [91,92] and hyperprolactinemia is a well-known adverse reaction of antipsychotics [90,92]. Moreover, increased plasma levels of prolactin correlated with activation of platelets in users of antipsychotic in one study [90]. On the other hand clozapine, the drug most often associated with VTE, is considered a prolactin-sparing agent [93], and again, increased platelet aggregation would be expected to cause arterial rather than venous thromboses.

8. Summary and conclusions

Since the advent of antipsychotic agents in the early 1950s VTE has repeatedly been reported in users of these drugs. However, in the past decade a clearer relationship has been established. The association is mainly based on observational studies. Although the studies showing an association have several methodological shortcomings, they suggest that the observed higher risk of venous thrombosis in psychiatric patients is related to the use of antipsychotic medications and in particular to clozapine and low-potency first-generation drugs. The risk has been reported to be highest during the first 3 months of treatment. Moreover, a growing number of case reports have linked VTE with other antipsychotics as well. Clozapine is noticeably the drug most often implicated in these reports, but olanzapine is also subject to several reports.

There are no biological mechanisms fully explaining the increased risk of VTE associated with antipsychotic drugs. Several possible pathogenetic factors have been proposed, such as antipsychotic-induced sedation, obesity, increased levels of antiphospholipid antibodies, enhanced platelet aggregation, hyperhomocysteinemia and hyperprolactinemia. The association might also be an expression of other underlying risk factors present in psychotic patients. More experimental and clinical studies are needed to further explain these hypotheses.

Although supporting data are lacking, the threshold for considering prophylactic antithrombotic treatment should be low when risk situations for venous thromboembolism arise. Malý et al. have presented an algorithm for the prevention of VTE in hospitalised patients treated with antipsychotics [48]. Although this algorithm has not been validated and should therefore be used with caution, it may be a helpful tool to determine individual preventative clinical measures based on risk level for VTE.

9. Expert opinion

- An increased risk of VTE in patients with mental disorders • treated with antipsychotic drugs has been reported in several observational studies using different methodologies. Although these studies often have shortcomings in design and reporting, the overall picture clearly supports an elevated risk for VTE in users of antipsychotic drugs.
- This increased risk particularly seems to be related to the use • of clozapine and low-potency first-generation antipsychotics. Limited data support an increased risk, but it is possibly smaller for VTE in users of olanzapine, risperidone and high-potency first-generation antipsychotics. With the exception of a few case reports suggesting an association no data is available for other second-generation antipsychotics.
- The fact that psychotic disorders and physical restraint also • have been associated with VTE makes it difficult to distinguish the actual contribution of the underlying disease from the antipsychotic medication on the aetiology of VTE.
- Although several possible alternatives have been proposed • the biological mechanisms explaining the increased risk of VTE in users of antipsychotics are still unknown.
- Physicians should take into account drug-specific as well as • patient-specific risk factors for VTE when choosing an antipsychotic drug for a patient.
- Patients with other risk factors for VTE should be informed • of this possible adverse effect when antipsychotics are prescribed. The information should include recognition of early symptoms of venous thrombosis and pulmonary embolism, and the importance of seeking medical care immediately.
- There is no data on the possible use of anticoagulants such as • low molecular weight heparins for primary prophylaxis in patients on antipsychotics. However, it should be considered in special risk situations, such as in patients on low-potency first-generation antipsychotics or clozapine in whom physical restraint is used for longer periods or repeatedly.
- The threshold for commencing prophylactic treatment with • low molecular weight heparins should be low in other situations where there is a temporarily increased risk for VTE (such as surgery, fractures, etc.).
- A manifest venous thrombosis or pulmonary embolism • should be treated in accordance with current VTE guidelines. After the diagnosis has been made suspension of the antipsychotic treatment or switching to an antipsychotic not associated with VTE should be strongly considered.
- The association between VTE and antipsychotic medication needs to be further studied, with an emphasis on quantifying the risk for individual antipsychotic drugs and elucidating the underlying mechanisms.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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Table 1. Risk factors for venous thrombosis [1-4].

Inherited factors	Acquired factors		Mixed/unknown factors
Antithrombin deficiency Dysfibrinogenemia Factor II (prothrombin) G2021A mutation Factor V Leiden mutation High levels of coagulations factors Protein C deficiency Protein S deficiency	<i>Diseases</i> Acute medical illness such as acute myocardial infarction Antiphospholipid antibody syndrome Behcet's syndrome Cancer Congestive heart failure Dyslipoproteinemia Fractures of pelvis, hip or long bones Inflammatory bowel disease Myeloproliferative disorders Nephrotic syndrome Obesity Paralytic stroke Paroxysmal nocturnal haemoglobinuria Polycythemia Spinal cord injury Varicose veins	<i>Interventions</i> Central venous access Immobilisation Major surgery Drugs Antiestrogens (tamoxifen and others) Antipsychotics Chemotherapy Heparin-induced thrombocytopenia Hormone replacement therapy Oral contraceptives Thalidomide Others Advanced age Pregnancy/recent postpartum state Previous VTE	Activated protein C resistance in the absence of factor V Leiden mutation Congenital venous malformation High levels of coagulation factors VII, VIII, IX, XI Hyperfibrinogenemia Hyperhomocysteinemia Lupus anticoagulants

Table 2. A summary of recent studies on the risk for venous thromboembolism in users of antipsychotic drugs in general.

Study	Time period	Age (years)	Study design	Study subjects	Events	Number of cases	Results (95% CI)
Zornberg et al. [8]	1990 – 1998	< 60	Nested case-control study	42 Cases of VTE and 172 controls from a baseline population of 29,952 users of AP in the UK	VTE	14 Cases were using FGA; 7 LP and 7 HP 11 Controls were using FGA; 2 LP and 9 HP	AOR, FGA: 7.1 (2.3 – 22.0) AOR, LP FGA: 24.1 (3.3 – 172.7) AOR, HP FGA: 3.3 (0.8 – 13.2)
Parkin et al. [9]	1990 – 1998	15 – 59	Case-control study	75 Cases and 300 GP controls in New Zealand	Fatal PE	9 Cases were using AP; 7 LP FGA 3 Controls were using AP; 1 LP FGA	AOR, FGA: 9.7 (2.3 – 40.9) AOR, LP FGA: 29.3 (2.8 – 308.2)
Jönsson et al. [10]	1997 – 2005	All ages	Case-control study	5,999 cases and 59,990 controls in Denmark	VTE	221 Cases were using AP; 51 LP FGA, 116 HP FGA and 75 SGA 1,128 Controls were using AP; 224 LP FGA, 648 HP FGA and 315 SGA	AOR, AP 2.0 (1.7 – 2.3) AOR, LP FGA 2.1 (1.5 – 3.0) AOR, HP FGA 1.8 (1.5 – 2.3) AOR, SGA 2.5 (1.9 – 3.3)
Masopust et al. [11]	1996 – 2004	18 – 60	Case-control study	266 cases and 274 controls with hypertension in the Czech Republic	VTE	13 Cases and 5 controls were using AP	OR, AP: 2.8 (1.0 – 7.6)
Lacut et al. [12]	2000 – 2004	≥ 18	Case-control study	677 cases and 677 controls in France	VTE	56 Cases were using AP; 46 FGA and 10 SGA 19 Controls were using AP; 15 FGA and 4 SGA	OR, AP: 3.5 (2.0 – 6.2) OR, FGA: 4.1 (2.1 – 8.2) OR, SGA: 2.7 (0.7 – 10.0)
Hamanaka et	1998 –	NR	Retrospective	28 PE cases among 1,125	Fatal PE	Of 28 PE cases, 8 were	AOR, AP: 10.5 (4.0 –

al. [13]	2002		prevalence study with a control group	medico-legal autopsy cases in Japan		using AP and 26 of the controls were using AP	27.9)
Jönsson et al. [14]	1992 – 2005	18 – 65	Medicolegal autopsy series	279 PE cases among 14,439 medico-legal autopsy cases in Sweden	Fatal PE	Of the PE cases, 33 were using AP; 18 LP FGA, 15 used SGA Of 14,160 subjects without PE, 505 were using AP; 389 LP FGA, 107 SGA	AOR, LP FGA 2.4 (1.5 – 3.9) AOR, SGA 6.9 (3.9 – 12.1)
Ray et al. [15]	1994 – 2000	≥ 65	Retrospective cohort study	Individuals with 22,514 prescriptions of AP, 75,649 of AD or 33,033 of TH in Canada	VTE	Cases of VTE per 1,000 person-years of users: 19.2 for AP, 12.0 for TH and 14.3 for AD	AHR, AP: 1.1 (1.0 – 1.3) AHR, haloperidol: 1.4 (1.2 – 1.7)
Liperoti et al. [16]	1998 – 1999	≥ 65	Retrospective cohort study	19,940 new users of AP* and 112,078 non-users in the US	VTE	64 Cases of VTE in 11,613 users of SGA, 28 cases of VTE in 7 652 Users of FGA; < 11 cases of VTE in 675 users of more than one AP; 439 cases of VTE among 11,2078 non-users of AP	AHR, SGA: 2.0 (1.5 – 2.7) AHR, FGA: 1.0 (0.7 – 1.6) AHR, > 1 AP: 4.80 (2.3 – 10.1)

*Excluding nursing home residents with a diagnosis of schizophrenia.

AD: Antidepressant drugs; AHR: Adjusted hazard ratio; AOR: Adjusted odds ratio; AP: Any antipsychotic drug; CI: Confidence interval; FGA: First-generation antipsychotic drugs; GP: General practitioner; HP: High potency; LP: Low potency; NR: Not reported; OR: Odds ratio; PE: Pulmonary embolism; SGA: Second-generation antipsychotic drugs; TH: Thyroid hormones; VTE: Venous thromboembolism

Table 3. A summary of studies on the risk for venous thromboembolism in users of the individual second-generation antipsychotics clozapine, olanzapine, risperidone, quetiapine and sertindol.

Study	Time period	Age (years)	Study design	Study subjects	Events	Number of Cases	Results (95% CI)
Walker et al. [6]	1991 – 1993	10 – 54	Record linkage study	67,072 Current and former users of clozapine in the US	Mortality, including PE	18 Cases of PE in current users of clozapine and 1 case of PE in former users	Rate ratio, current use of clozapine versus former use: 5.2 (0.7 – 38.6)
Hägg et al. [7]	1989 – 2000	18 – 60	Case series from a Swedish ADR database	Spontaneously reported cases of VTE	VTE	12 Cases of VTE during treatment with clozapine 3 Cases of VTE during treatment with all other antipsychotics	A conservative risk estimation was 1 case per 2,000 – 6,000 clozapine-treated patients
Liperoti et al. [16]	1998 – 1999	≥ 65	Retrospective cohort study	19,940 New users of antipsychotic drugs* and 112,078 non-users in the US	VTE	64 Cases of VTE in 11,613 users of SGA (43 cases in users of risperidone, 15 in users of olanzapine and < 11 in users of clozapine or quetiapine)	AHR, risperidone: 2.0 (1.4 – 2.8) AHR, olanzapine: 1.9 (1.1 – 3.3) AHR, clozapine/quetiapine: 2.7 (1.2 – 6.3)
Hägg et al. [18]	1975 – 2004	All ages	Data mining of the WHO ADR database	3.2 Million ADR case records worldwide	VTE	734 Cases of VTE during treatment with antipsychotics	Significantly more VTE events than expected reported for clozapine (n = 375), olanzapine (n = 91) and sertindole (n = 9)

*Excluding nursing home residents with a diagnosis of schizophrenia.

ADR: Adverse drug reaction; AHR: Adjusted hazard ratio; CI: Confidence interval; PE: Pulmonary embolism; SGA: Second-generation antipsychotic drugs; VTE: Venous thromboembolism; WHO, World Health Organisation.

Appendix: Scopus search

(TITLE-ABS-KEY(embolism OR thrombosis OR thromboembolism)) AND (((TITLE-ABS-KEY(9-hydroxy-risperidone OR acepromazine OR amperozide OR aripiprazole OR azaperone OR benperidol OR bromperidol OR butaclamol OR chlorpromazine OR chlorprothixene OR clopenthixol OR clozapine OR dapiprazole OR dicarbine OR dixyrazine OR droperidol) OR TITLE-ABS-KEY(etazolate OR fananserine OR fencamfamine OR fluanisone OR flupenthixol OR fluperlapine OR fluphenazine OR fluspirilene OR haloperidol OR isofloxythepin OR loxapine OR mesoridazine OR methiothepin))) OR ((TITLE-ABS-KEY(methotrimeprazine OR metylperon OR molindone OR monohydrochloride OR nemonapride OR olanzapine OR ondansetron OR penfluridol OR perazine OR perospirone OR perphenazine OR piflutixol OR pimozide OR pipamperone OR prochlorperazine OR promazine) OR TITLE-ABS-KEY(quetiapine OR raclopride OR remoxipride OR reserpine OR rimcazone OR risperidone OR ritanserin OR sertindole OR spiperone OR stepholidine OR sulforidazine OR sulpiride OR sultopride OR tetrahydropalmatine OR thioridazine OR thiothixene OR tiapride))) OR (TITLE-ABS-KEY(timiperone OR trifluoperazine OR trifluoperidol OR trifluopromazine OR zetidine OR ziprasidone OR zotepine)) OR (TITLE-ABS-KEY ('Antipsychotic Agents' OR 'Antipsychotic Agent' OR 'neuroleptic agent' OR 'neuroleptic agents' OR 'antipsychotic drug' OR 'antipsychotic drugs'))).