Antipsychotics and Venous Thromboembolism Risk: A Meta-Analysis

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Key words
- antipsychotics
- venous thromboembolism
- risk factor
- meta-analysis

Abstract

Background: Antipsychotics have been inconclusively implicated in susceptibility to venous thromboembolism (VTE).

Objectives and Methods: The aim of this study was to investigate the association between antipsychotic drugs and VTE risk by a meta-analysis. PubMed and EmBASE databases were searched for publications through to 10 October 2010. Statistical analysis was performed using Revman 4.2 and Stata 10.0 software.

Results: 7 case-control studies involving 31 095 cases and 143 472 controls were analyzed. The results indicate that antipsychotic exposure confers a 139% increased risk of VTE (odds ratio [OR]=2.39, 95% confidence interval [CI]:1.71–3.35). Pooled estimates by drug type showed that use of low-potency antipsychotics (OR=2.91, 95% CI 1.80–4.71) is the most important risk factor for VTE, followed by atypical (OR=2.20, 95% CI 1.22–3.96), conventional (OR=1.72, 95% CI 1.31–2.24) and high-potency drugs (OR=1.58, 95% CI 1.50–1.67).

Conclusions: This meta-analysis suggests that antipsychotics are a risk factor for VTE. Additional studies in large cohorts are required to validate our findings. Future analyses should study potential effect modifications by different doses and durations of antipsychotic exposure in different populations.

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Introduction

Venous thromboembolism (VTE), a phenomenon including deep venous thrombosis (DVT) and pulmonary embolism (PE), is a common cause of morbidity and mortality. Zamagni's investigation showed that VTE is a disease with a high prevalence in elderly people, affecting >5% of the population >65 years of age [1]. O'Connor et al. found that the incidence of VTE was 0.22% in 33 311 deliveries [2]. Cancer is a well-recognised risk factor for venous VTE. It has been shown that 5–10% of all cancer patients will develop VTE during the course of the disease [3]. Liperoti and his colleagues found that the rate of hospitalization for VTE was 0.91 per 100 person-years [4]. Wakefield's investigation showed the annual incidence of VTE is approximately 900 000 cases, resulting in about 300 000 deaths per year [5]. Up to 25% of affected patients die within one week, mainly following PE [6], and almost 33% of the survivors experience long-term effects [7]. VTE places a high and unacceptable burden on healthcare resources, up to US $ 1.5 billion annually in the United States of America [8]. VTE is a preventable disease, so identifying risk factors is a crucial step towards lowering the incidence; and, indeed, many have been confirmed, including advanced age, obesity, orthopedic surgery, active cancer, pregnancy, immobility, and heart failure [9–11]. However, there are still many risk factors which remain to be identified.

Antipsychotic drugs are widely used in medicine and psychiatry. Since their introduction, interest in associated side effect profiles has grown. Of these, the most thoroughly described are increased mortality and strokes in antipsychotic users, findings that have led to FDA warnings in the U.S.A. Attention has also focused on VTE, a potentially fatal adverse drug reaction, particularly since the introduction of phenothiazines in the 1950s [4]. Recently, increasing numbers of studies have shown that antipsychotic drugs are associated with an increased risk of VTE, and that the degree of risk depends on the type and potency of the agents used [12, 13]. However, some contradictory results regarding this association have been reported [14].

Therefore, the aim of this meta-analysis was to systematically and quantitatively analyze, according to type and potency of the agents used, all published studies performed to date that assess the association between VTE and antipsychotic drug exposure.

Materials and Methods

Search strategy and study selection

PubMed and EmBASE were searched to identify suitable studies done prior to 10 October 2010, and no starting date limit was applied. The search terms were 'antipsychotics', 'antipsychotic drug', 'VTE', 'venous thromboembolism', 'PE', 'pulmonary embolism', 'DVT', and 'deep venous thrombosis.' Articles were also identified by use of the 'related articles' function in PubMed. References of identified articles were searched manually. Although no language restrictions were imposed initially, for the full text review and final analysis only English language articles were included. Conference abstracts to journal editors were excluded because of the limited data they contain. The following inclusion criteria were applied: (i) studies evaluated antipsychotic use and VTE risk, (ii) design was case-control, and (iii) details of antipsychotic use in cases and controls were available for estimating an odds ratio (OR) with a 95% confidence interval (CI). Publications which may have been based on the same study data (e.g., same authors, institutions, and period of study) were discussed by 2 of the authors of this paper, and only the best-quality study was selected for inclusion.

Data extraction and quality assessment

2 reviewers independently checked all potentially relevant studies and reached consensus on all aspects. When disagreement occurred, a third author assessed the article. The following data were collected from each study: first author, year of publication, definition of cases, source of control, total number of cases and controls, and antipsychotic use in cases and controls.

Statistical analysis

The strength of association between the antipsychotic used and VTE risk was measured by ORs at 95% CI. The statistical significance of the summary OR was determined by the Z-test. Heterogeneity was evaluated by a χ^2-based Q statistic and was considered statistically significant at P-value < 0.10. When the P-value was > 0.10, the pooled OR of each study was calculated by the fixed-effects model; otherwise, a random-effects model was used. The significance of the pooled OR was determined by the Z-test, and $P < 0.05$ was considered statistically significant. Sensitivity analysis was performed through sequentially excluded individual studies to assess the stability of the results. Begg's test and Egger's test were used to statistically assess publication bias. All statistical tests were performed using Revman 4.2 (The Cochrane Collaboration, www.cochrane.org) and Stata 10.0 (StataCorp, College Station, TX, USA, www.stata.com) software.

Results

Study inclusion and characteristics

Our search strategy recovered 61 studies. After reviewing the titles and abstracts, 48 were excluded for irrelevance to VTE risk and antipsychotic use. The remaining 13 articles were identified for full-text review [4, 12–23]. After the full-text review, 4 articles were excluded because they did not provide usable data [4, 19, 20, 22], and 2 more were excluded because they were not case-control studies (**Fig. 1**) [21, 23]. In total, 7 case-control studies [12–18] involving 31 095 VTE patients and 143 472 controls were available for analysis. The characteristics of each case-control study are listed in **Table 1** and **Table 2**.

Quantitative data synthesis

All studies: In all studies, 'exposure' was defined as current and recent antipsychotic use, and 'non-exposure' as none or

Table 1 Characteristics of the 7 case-control studies included in the meta-analysis.

First author	Year	Country	Case age (years)	Case number (n)		Control number (n)		Diagnosis of VTE
				Exposure	Non-Exposure	Exposure	Non-Exposure	
Zornberg [13]	2000	USA	44.2 ± 10.1	16	26	18	150	clear
Parkin [15]	2003	New Zealand	female 42.0; male 47.0	8	54	2	241	clear
Lacut [10]	2007	France	67.9 ± 17.0	56	621	19	658	clear
Jonsson [14]	2008	Sweden	54 (44–61)	38	241	530	13 630	clear
Jonsson [9]	2009	Denmark	unclear	140	3 331	775	33 833	clear
Kleijer [11]	2010	Netherlands	76 (60–104)	239	793	932	3 193	clear
Parker [12]	2010	UK	67 (53–77)	1 587	2 394	3 200	320 086 291	clear

Table 2 Distribution of different antipsychotics among patients and controls included in the meta-analysis*.

First Author	Year	Case number (n)					Control number (n)				
		C	A	L	H	Total	C	A	L	H	Total
Zornberg [13]	2000	-	-	7	7	42	-	-	2	9	168
Parkin [15]	2003	-	-	6	2	62	-	-	1	1	243
Lacut [10]	2007	46	10	-	-	677	15	4	-	-	677
Jonsson [14]	2008	23	15	22	1	279	423	107	389	34	14160
Jonsson [9]	2009	92	48	33	79	3471	580	195	146	484	34608
Kleijer [11]	2010	157	47	-	-	1032	603	229	-	-	4125
Parker [12]	2010	1817	221	162	1 875	25532	4 156	462	316	4 293	89491

*C: conventional antipsychotics; A: atypical antipsychotics; L: low-potency antipsychotics; H: high-potency antipsychotics

former use. As shown in **Fig. 2**, we analyzed heterogeneity for all 7 studies, and the χ^2 value was 83.35 with 6 degrees of freedom and $P<0.00001$ in a random-effects model. In addition, the I^2 value, another index of the test of heterogeneity, was 92.8% (**Fig. 2**). Therefore, we chose the random-effects model to synthesize the data. Overall, OR was 2.39 (95% CI = 1.71–3.35), and the overall-effect Z value was 5.10 ($P<0.00001$). The results suggest that, compared to controls, individuals who take antipsychotics have a 139% increased risk for VTE.

Different types of antipsychotics

ORs differ among types of antipsychotics used. As shown in **Fig. 3**, the risk was greater for individuals prescribed low- vs. high-potency drugs (OR 2.91 [1.80–4.71] and 1.58 [1.50–1.67], respectively). The risk was also greater for patients prescribed atypical vs. conventional antipsychotics (OR 2.20 [1.22–3.96] and 1.72 [1.31–2.24], respectively), as shown in **Fig. 4**.

Publication bias

Publication bias was assessed by Begg's funnel plot and Egger's test. The shape of the funnel plots seemed asymmetrical in the all-antipsychotics vs. controls comparison model, suggesting the existence of publication bias (**Fig. 5**). Next Egger's test was performed to provide statistical evidence of funnel plot asymmetry. The results indicate the existence of publication bias in the current meta-analysis (t = 3.14, $P=0.026$).

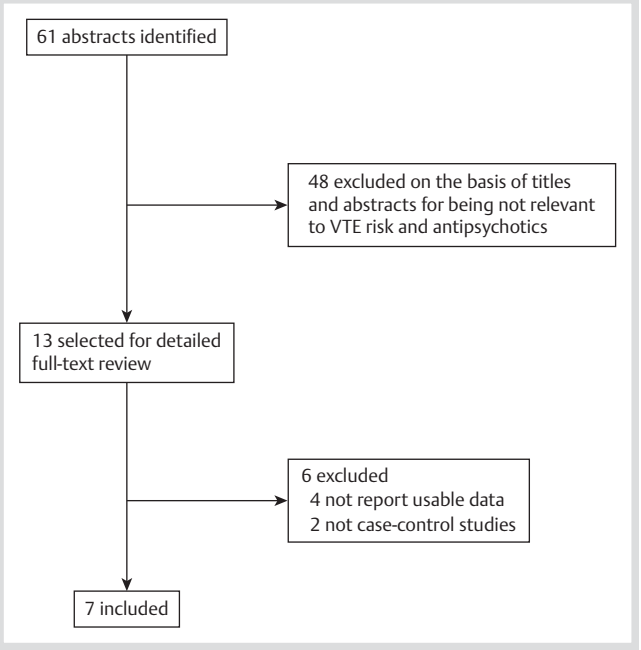

Fig. 1 Study identification: inclusion and exclusion criteria for meta-analysis.

Sensitivity analysis

Statistically similar results were obtained after sequentially excluding each study, suggesting the stability of the results of this meta-analysis.

Discussion

Identifying patients at risk for VTE so that effective prophylaxis can be provided in order to reduce morbidity from this sometimes fatal disease is now an important health-care priority. VTE is a complex disease involving multiple steps, multiple genes, and various gene-environment interactions. Thorough knowledge of risk factors for VTE is still limited. Because of their widespread use, in recent years interest in adverse reactions of antipsychotics has focused attention on an association with VTE. To date, results of investigations into this association are inconclusive, and to the best of our knowledge no previous meta-analysis has successfully established a relationship.

The current meta-analysis shows that exposure to antipsychotics is consistently associated with VTE, regardless of the type of drug used, with the overall risk being more than doubled compared to controls. Pooled estimates by drug type showed that use of low-potency antipsychotic drugs confers the highest risk for VTE, followed by atypical, conventional, and finally high-potency drugs.

Several biological mechanisms of action have been proposed to explain this relationship. One possible mechanism derives from research suggesting that antipsychotic drug treatment is associated with enhanced platelet aggregation, and elevated levels of prolactin correlate with platelet activation. One of the typical low-potency antipsychotics, clozapine, has been associated with platelet adhesion and aggregation in vitro [24–26]. A second possible explanation stems from the presence of raised levels of antiphospholipid antibodies, including lupus anticoagulantia and anticardiolipin antibodies, which have been observed in patients treated with antipsychotic drugs and have been associated with an increased VTE risk [27]. A third hypothesis is that venous stasis is exacerbated by sedation, commonly found in patients treated with low-potency antipsychotic drugs [28]. All

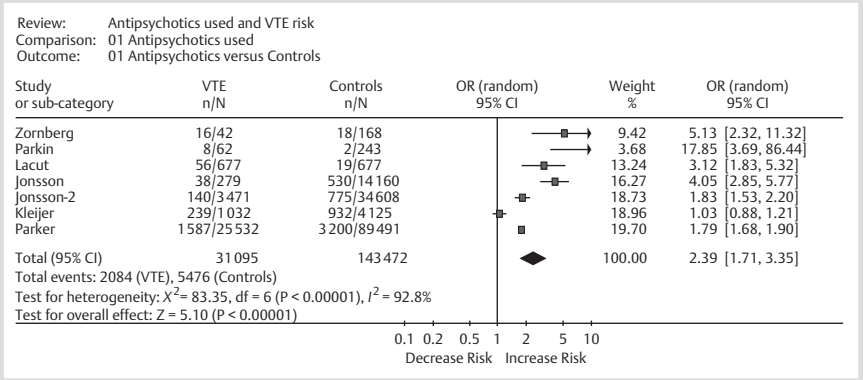

Fig. 2 Forest plot of studies reporting effect size on VTE due to exposure to antipsychotics.

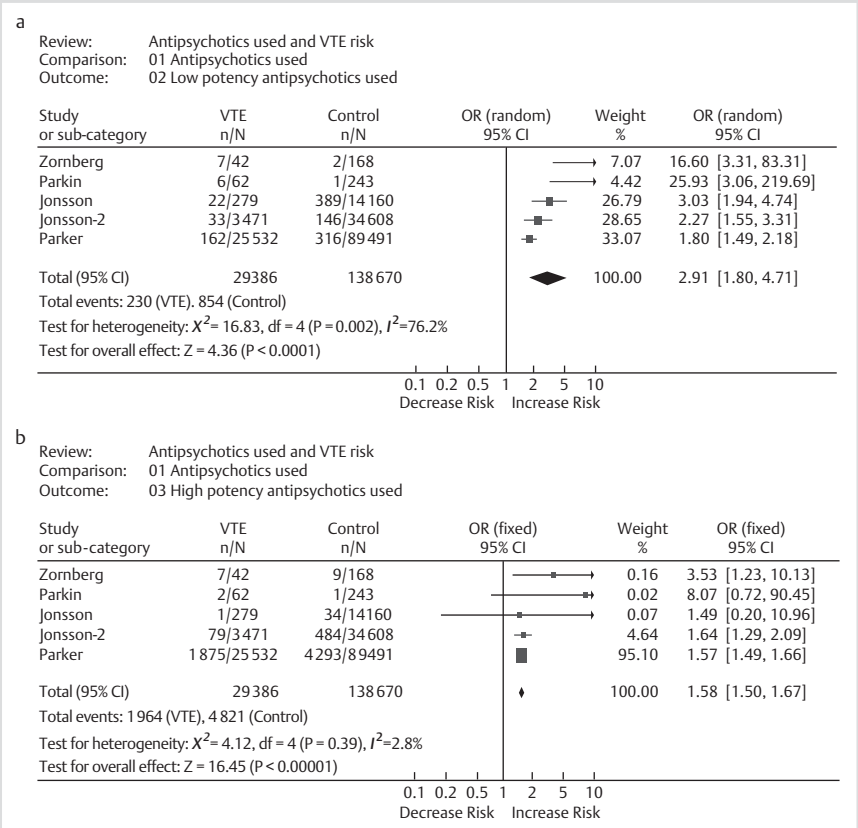

Fig. 3 Forest plot of studies reporting effect size on VTE due to exposure to (**a**) low- and (**b**) high-potency antipsychotics.

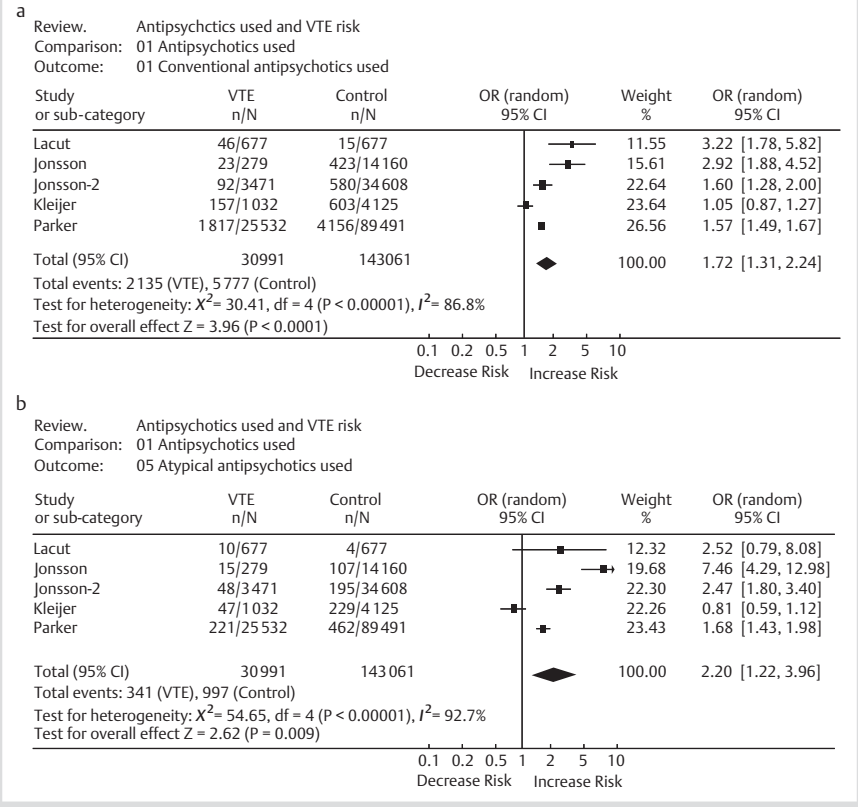

Fig. 4 Forest plot of studies reporting effect size on VTE due to exposure to (**a**) conventional and (**b**) atypical antipsychotics.

these may contribute to the pathogenesis of VTE, especially in patients using low-potency antipsychotics.

We also have to mention the importance of heterogeneity. Heterogeneity is an important issue when interpreting the results of meta-analyses. In this study, significant heterogeneity existed in overall comparisons. Possible explanations may relate to differences among the studies analyzed in the severity of psychotic disorders, in dosage and duration of the drugs used, and in

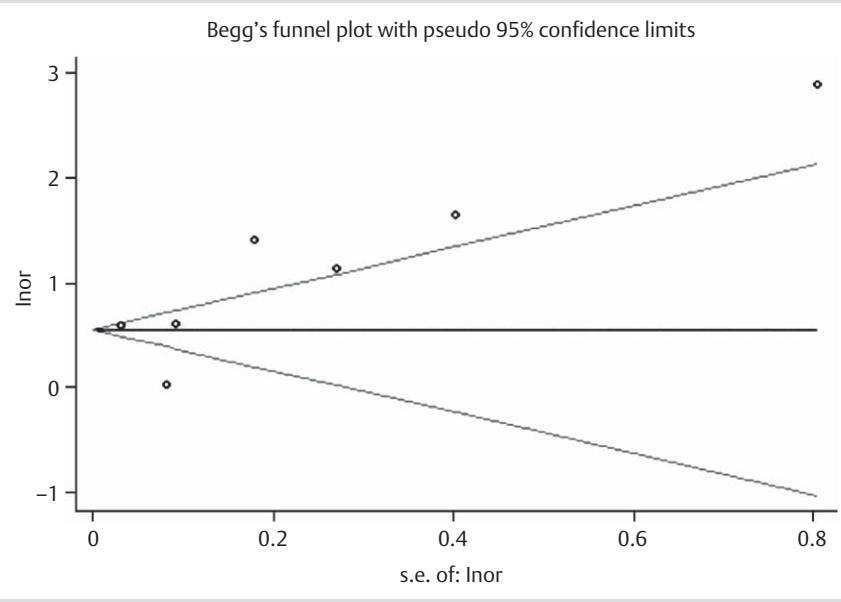

Fig. 5 Begg's funnel plot with pseudo-95% confidence limits.

actual VTE etiology. In addition, homogeneity in the case and control groups was uncertain. Ideally, all cases and controls should be matched for age, sex, and environmental exposures, among other variables. In this meta-analysis, such factors could not be taken into account because sufficient information for individual patients was not available. Potentially further complicating our meta-analysis is the fact that studies conducted in different populations may lead to dissimilar results.

Some limitations of this meta-analysis should be acknowledged. First, the exclusion of conference abstracts, letters to editors, and non-English language studies may lead to publication bias, and perhaps an inflation of risk estimates due to preferential acceptance of papers reporting positive results. Second, data were not stratified by other factors, such as atopic status, because sufficient information could not be extracted from the primary publications. Third, some of the individual studies analyzed have a small number of cases, which may affect statistical power, increasing publication bias. However, we minimized the likelihood of bias by creating a detailed protocol before initiating our study, by performing a meticulous search for publications, and by using explicit methods for publication selection, data extraction, and data analysis. In addition, different definitions for users were used in the case control studies of the present analysis. It is not very reasonable, but it is inevitable because of the insufficient information provided by the case control studies.

To the best of our knowledge, this study is the first comprehensive meta-analysis to assess the relationship between exposure to antipsychotics and VTE susceptibility. It provides evidence for such an association, supporting the hypothesis that using antipsychotics could increase the risk of VTE. Although at this point in time we can only state that this is an association, we think it would be prudent to alert patients using antipsychotics about the possibility of developing VTE. Regular determination of the serum concentration of D-dimer may be useful for early diagnosis in long-term users. However, additional studies in large cohorts are required to validate our findings. Future analyses should look for potential effect modifications by different doses and durations of antipsychotic exposure in various populations.

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Conflict of Interest Statement

None of the authors have a financial relationship with a commercial entity that may have an interest in the subject of this manuscript.

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