MHRA PUBLIC ASSESSMENT REPORT

The risk of venous thromboembolism associated with antipsychotics

June 2009

EXECUTIVE SUMMARY

(Please note that this summary is intended to be accessible to all members of the public, including health professionals)

Background

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating the effectiveness and safety of medicines and medical devices in the UK. We continually review all medicines and regularly inform healthcare professionals and the public of the latest safety updates. The following MHRA Public Assessment Report discusses the risk of venous thromboembolism (VTE) associated with the use of antipsychotic medicines.

Antipsychotics are used primarily to treat schizophrenia, and are also used to treat other mental health conditions such as agitation, anxiety, mania and aggression. Given in the form of tablets, solutions or injections, they act on the brain to change the levels of neurotransmitters (natural chemicals), which has a calming effect on the patient.

Antipsychotics can be classified into two groups: conventional (or typical/first-generation) antipsychotics lower the levels of a neurotransmitter called dopamine; atypical (or second-generation) antipsychotics lower dopamine and also act on other neurotransmitters, particularly serotonin (increasing its levels). The antipsychotic drugs licensed for use in the UK include: (atypicals) amilsulpride (brand name Solian), aripiprazole (Abilify), clozapine (Clozaril), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), sertindole (Serdolect) and zotepine (Zoleptil); (conventionals): chlorpromazine (Largactil), flupenthixol (Depixol), fluphenazine (Modecate), haloperidol (Haldol), trifluoperazine (Stelazine) and zuclopenthixol (Clopixol).

As with all medicines, antipsychotics may lead to side-effects in some individuals, which are described in the patient information leaflets that accompany the individual drugs, and on the Electronic Medicines Compendium (product information) website http://emc.medicines.org.uk/. One potential risk associated with the use of antipsychotics is the condition VTE. Venous thrombosis is a condition in which a blood clot (thrombus) forms in the 'deep veins' of the legs or pelvis – known as deep vein thrombosis (DVT). Part of the clot may break off from the site where it is created and travel through the venous system. If the clot lodges in the lung a very serious condition, pulmonary embolism (PE), arises. DVT and PE are known as venous thromboembolism (VTE). A relationship between antipsychotic medicines and VTE was first suggested around 50 years ago, but a true link has not been clearly established. Currently, warnings for VTE association are contained in the product information for the atypical antipsychotics aripiprazole, clozapine and olanzapine. This assessment report reviews the data available from case reports and published literature on DVT and PE, for evidence of a possible association with all antipsychotic agents.

Results

Between 1 July 1963 and 25 June 2008, the MHRA received a total of 303 reports of suspected adverse reactions[a] of either DVT or PE associated with antipsychotic use. Although the majority of reports were either confounded[b] or did not have enough

[a] Reports of adverse drug reactions submitted to MHRA through our Yellow Card Scheme

[b] Where the presence of one risk factor changes the effects that another risk factor has on the development of a medical condition; this can affect the results of a study

information that could definitely establish a link, there is a possibility that antipsychotic treatment may have led to a VTE in a number of cases.

The number of studies on VTE and antipsychotics is small (11 in total), and there are limitations with some of the methods used. However, all of the studies concluded that there appeared to be an increased risk of VTE with antipsychotics.

Conclusions
A Europe-wide review of UK Yellow Card data and worldwide published epidemiological studies on antipsychotics and VTE has concluded that an increase in risk of VTE cannot be excluded. Product information for healthcare professionals and patients for all antipsychotics will be updated across the EU to include information about this risk.

Advice for healthcare professionals is:

- Antipsychotic use may be associated with an increased risk of VTE
- At present there are insufficient data available to determine any difference in risk between atypical and conventional antipsychotics, or between individual drugs
- All possible risk factors for VTE should be identified before and during antipsychotic treatment and preventive measures undertaken

1. INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating the effectiveness and safety of medicines and medical devices in the UK. We continually review all medicines and regularly inform healthcare professionals and the public of the latest safety updates. The following MHRA Public Assessment Report discusses the risk of venous thromboembolism (VTE) associated with the use of antipsychotic medicines.

Antipsychotic drugs are used primarily to treat schizophrenia, and are also used to treat many other mental health conditions such as agitation, anxiety, mania and aggression. They can be broadly classified into two groups: conventional (or typical/first generation) antipsychotics lower dopamine levels; atypical (or second-generation) antipsychotics not only lower dopamine, but also act on other neurotransmitters, particularly increasing serotonergic activity.

The antipsychotic drugs licensed for use in the UK include: (atypicals) amilsulpride (brand name Solian), aripiprazole (Abilify), clozapine (Clozaril), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), sertindole (Serdolect) and zotepine (Zoleptil); (conventionals): chlorpromazine (Largactil), flupenthixol (Depixol), fluphenazine (Modecate), haloperidol (Haldol), trifluoperazine (Stelazine) and zuclopenthixol (Clopixol).

As with all medicines, antipsychotics may lead to adverse drug reactions (ADRs) in some individuals. Common ADRs of antipsychotic use include: extrapyramidal movement disorders resembling the symptoms of Parkinson's disease; dry mouth, constipation and blurred vision, caused by their anticholinergic actions; and dizziness and weight gain. Rarer side effects of these drugs include diabetes or metabolic syndrome; neuroleptic malignant syndrome; and cardiac arrythmias. Recent evidence also suggests there is an increased risk of stroke and a small increased risk of mortality in elderly patients who receive antipsychotic therapy for dementia (only one antipsychotic, risperidone, is licensed for treatment of dementia-related behavioural disturbances: and then only specifically for short-term (up to 6 weeks') treatment of persistent aggression in Alzheimer's dementia unresponsive to non-pharmacological approaches and where there is a risk of harm to the patient or others).

Another risk which might be associated with antipsychotic use is the occurrence of VTE. In venous thrombosis, a thrombus forms in the 'deep veins' of the legs or pelvis – known as deep vein thrombosis (DVT). Part of the thrombus may break off from the site where it is created and travel through the venous system. If the thrombus lodges in the lung, pulmonary embolism (PE) arises. DVT and PE are known as venous thromboembolism (VTE). A relationship between antipsychotic medicines and VTE was first suggested around five decades ago; however, despite early descriptions and subsequent reports of VTE associated with antipsychotic use, evidence for a true link has not been clearly established. Reviews of the available data for aripiprazole, clozapine and olanzapine have led to warnings about VTE being added to their Summaries of Product Characteristics (SPCs). This report will assess the data available from reports of suspected adverse reactions[a] and published literature on all antipsychotic drugs and VTE.

[a] Reports of adverse drug reactions submitted to MHRA through our Yellow Card Scheme

2. BACKGROUND

2.1. Antipsychotics

Antipsychotic drugs are primarily indicated for the treatment of psychosis which is typically characterised by schizophrenia. They can also be used in the short-term for various other conditions including mania, anxiety, bipolar affective disorder and depression with agitation. Antipsychotics are mainly available as oral preparations. Some are available as long-acting depot formulations for injection, given intramuscularly; these are considered advantageous for use in patients with poor compliance, but require an extended period of time (typically 3–6 months) before reaching useful therapeutic ranges and are therefore not useful for acute episodes.

Drugs in the antipsychotic class are broadly divided into two groups: conventional and atypical. Conventional antipsychotics can be further divided into five sub-groups based on their chemical structures: a) phenothiazines; b) butyrophenones; c) diphenylbutylpiperidines; d) thioxanthenes; and e) the substituted benzamides. The phenothiazine group can be further subdivided into three groups depending on the type of side chain attached to the phenothiazine ring. Atypical antipsychotics (also known as second-generation antipsychotics) are a newer group of drugs unrelated to each other by structure.

The most widely-prescribed antipsychotics include 14 conventional and nine atypical drugs as listed in the British National Formulary (BNF), which are summarised in Table 1.

Table 1. Most widely-prescribed antipsychotics* classified according to chemical structure.

	Drug group		Drug substance
		Side group	
Conventional	Phenothiazines	Propylamine	Chlorpromazine Levomepromazine Promazine
		Piperidine	Pericyazine
		Piperazine	Fluphenazine Perphenazine Prochlorperazine Trifluoperazine
	Butyrophenones		Benperidol Haloperidol
	Diphenylbutylpiperidines		Pimozide
	Thioxanthenes		Flupentixol Zuclopenthixol
	Benzamides		Sulpiride
Atypical			Amisulpride Aripiprazole Clozapine Olanzapine Paliperidone Quetiapine Risperidone Sertindole Zotepine

*as listed in the BNF

At the time of this review (October 2008), the latest guidelines from the National Institute for Clinical Excellence (June 2002) recommended that the oral atypical antipsychotic drugs amilsulpride, olanzapine quetiapine, risperidone and zotepine were considered when choosing first-line treatment for individuals with newly-diagnosed schizophrenia.

2.2 Pharmacology of antipsychotics

Most antipsychotics act by limiting or decreasing dopamine neurotransmission, which is particularly necessary for controlling hallucinations and delusions; however, it is unlikely that dopamine-blockade is their only mechanism of action. Indeed, many studies have confirmed a variety of molecular targets for antipsychotic drug actions.

The introduction of clozapine in the 1950s proved to be a major breakthrough in the understanding of antipsychotic pharmacology. As clozapine appeared to have a low propensity for extrapyramidal side effects, it became the template for the design of new antipsychotics. The term ‘atypical’ was coined to describe clozapine, and has subsequently been applied to all second-generation antipsychotics despite their widely differing pharmacological actions. One common attribute for all atypical antipsychotics however is serotonergic activity (except for amisulpride). In general, atypical antipsychotics are better-studied compared to conventional agents.

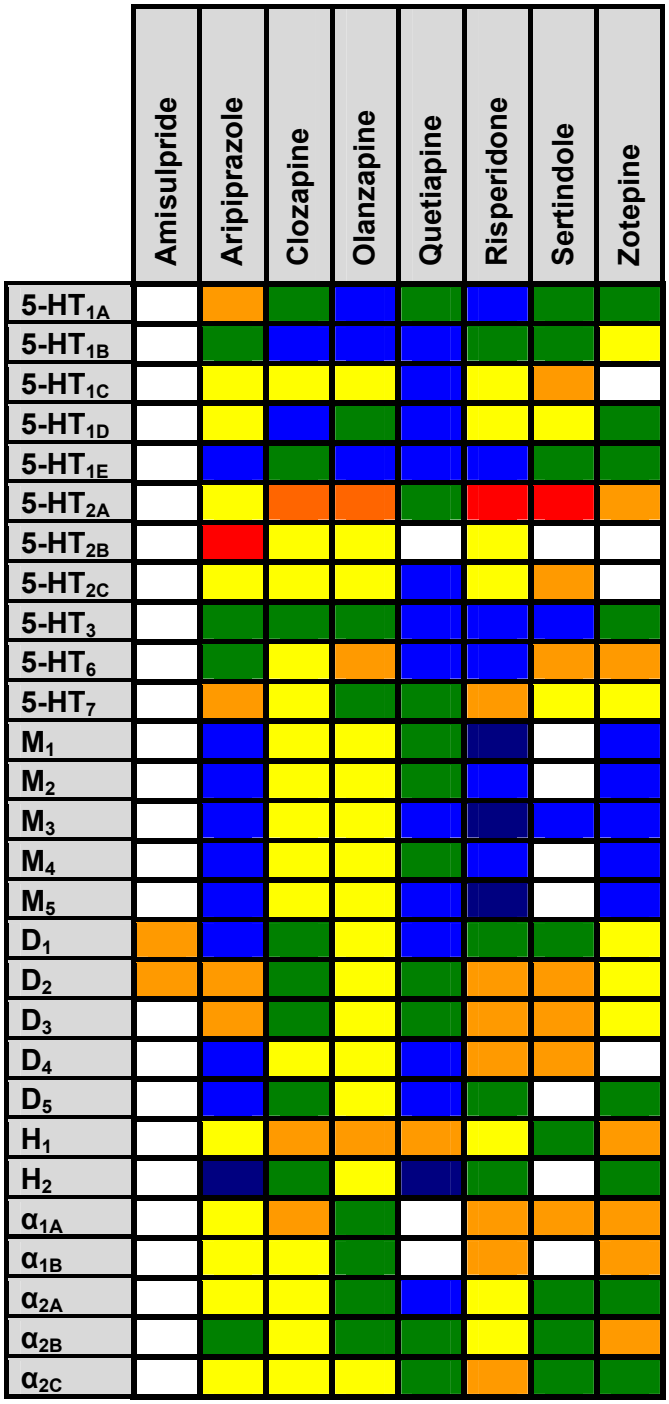
Tables 2a and 2b summarise the receptor-binding profiles of the antipsychotics reviewed in this report. The affinity values for these compounds can be found at the Psychoactive Drug Screening Program (PDSP) Ki Database (part of the National Institute of Mental Health PDSP) which, despite being the largest database of this kind in the public domain is not exhaustive; for example, zuclopenthixol and paliperidone are not included. The affinity K_i values for all antipsychotics in the tables are derived from the PDSP K_i database (http://pdsp.med.unc.edu/kidb.php) which collects all known published studies for a given combination of receptor-ligand. Colours indicate the level of affinity of the drug for the receptor and are calculated using the means of all matching experimental values. A cell without colour indicates that there are no experiments matching the conditions specified.

Table 2a. Receptor-binding profiles of conventional antipsychotics.

Ki Colour Code
<1
>1 <10
>10 <100
>100 <1000
>1000 <10000
>10000

	Benperidol	Chlorpromazine	Flupentixol	Fluphenazine	Haloperidol	Levomepromazine	Pericyazine	Perphenazine	Pimozide	Prochlorperazine	Promazine	Sulpiride	Trifluoperazine
5-HT$_{1A}$													
5-HT$_{1B}$													
5-HT$_{1C}$													
5-HT$_{1D}$													
5-HT$_{1E}$													
5-HT$_{2A}$													
5-HT$_{2B}$													
5-HT$_{2C}$													
5-HT$_{3}$													
5-HT$_{6}$													
5-HT$_{7}$													
M$_{1}$													
M$_{2}$													
M$_{3}$													
M$_{4}$													
M$_{5}$													
D$_{1}$													
D$_{2}$													
D$_{3}$													
D$_{4}$													
D$_{5}$													
H$_{1}$													
H$_{2}$													
α$_{1A}$													
α$_{1B}$													
α$_{2A}$													
α$_{2B}$													
α$_{2C}$													

Table 2b. Receptor-binding profiles of atypical antipsychotics.



Key: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_3, 5-HT_6, 5-HT_7: serotonin receptors; M_1, M_2, M_3, M_4, M_5: muscarinic receptors; D_1, D_2, D_3, D_4, D_5: dopamine receptors; H_1, H_2: histamine receptors; α_{1A}, α_{1B}, α_{2A}, α_{2B} α_{2C}: adrenergic receptors.

As with all medicines, there is a potential risk of ADRs associated with antipsychotic use.

2.3 DVT and PE

VTE develops from one or more of three major factors: blood stasis, changes in the endothelial vessel wall, and hypercoagulability[1]. It is thought that all pro-thrombotic factors, whether systemic or molecular, influence one of these three mechanisms.

DVT and PE are part of the VTE process. PE usually arises from thrombi (or blood clots) originating in the deep venous system of the lower extremities and pelvis. Occasionally they may also originate in the renal veins, or veins of the upper extremities, and in the right heart. In many cases, these clots are completely asymptomatic and are gradually broken down with no long-term effects. However, the presence of larger thrombi is normally accompanied by swelling, pain, redness and skin discolouration, and these clots can dislodge from the veins and cause an eventual embolism in the pulmonary arteries. Common symptoms when this occurs are chest pain, dyspnoea, haemoptysis, and in more severe cases collapse and sudden death. Despite the potential serious complications of these conditions, if diagnosed quickly they can be treated effectively. Moreover, PE is to a large extent preventable.

2.4 Epidemiology

The incidence of VTE in recent years has remained relatively constant, with rates slightly higher than one in 1000 people. Mortality rates associated with these conditions are probably underestimated however, and it has been suggested that in nearly 25% of patients with PE the initial clinical manifestation is sudden death[2].

The rate of VTE occurrence is roughly equal between men and women, with possibly higher rates occurring among women in younger age groups, and among men in older age groups. The incidence of venous thrombosis is strongly age-dependent: it is extremely uncommon (one in 100 000 per year) in childhood, but rises to nearly one in 100 per year in old age. VTE incidence rises sharply after age 60 years in both men and women, with cases of PE accounting for the majority of the increase[3]. Patients with VTE also commonly have an underlying genetic predisposition; the major genetic thrombophilic factors include the expression of: factor V Leiden; prothrombin gene mutation; and deficiencies of antithrombin III, protein C, or protein S. Important environmental risk factors for VTE include (apart from advancing age): personal or family history of VTE; obesity; surgery and accompanying risks including trauma and immobilisation [including hospitalisation]); cancer; pregnancy; and use of exogenous hormones.

VTE therefore usually occurs as a culmination of environmental and genetic risk factors. The genetic risk factors may enhance the occurrence of VTE either during risk periods or in the absence of environmental triggers. Whilst the majority of patients present with a combination of risk factors, a large percentage of patients with first-time VTE are classified as idiopathic (presenting with no readily identifiable risk factor). Table 3 shows the pooled data from various studies on the risk for VTE occurrence associated with some of the most widely-studied risk factors.

Table 3. Ranges of VTE risk according to patients' general characteristics and major risk factors (adapted from Samama et al, 2003[4]).

Risk factor	Risk*
Age	1·8 to 14·8
Oral contraceptives	2·2 to 6·9
Personal history of VTE	1·1 to 4·7
Obesity	1·0 to 4·5
Secondary antiphospholipid syndrome	4·3
Family history of VTE	3·3 to 3·4
Smoking	1·0 to 3·3
Hormone replacement therapy	2·1 to 2·7
Recent surgery	3·7 to 21·7
Non surgical hospitalisation or immobilisation	5·7 to 11·1
Congestive heart failure	1·4 to 9·6
Malignancy and chemotherapy	6·5
Venous catheter	5·6 to 6·0
Myocardial infarction	5·9
Malignancy	2·4 to 5·6
Venous insufficiency	0·9 to 4·2
Ischaemic stroke	2·0 to 3·0

*Risks include odds ratios, relative risks, relative hazards and hazard ratios
VTE=venous thromboembolism

A further risk factor for VTE (discussed in this report) is the use of antipsychotic drugs.[5,6,7,8]

2.5 Current product information for antipsychotics related to VTE occurrence

The SPCs for the atypical antipsychotics clozapine, olanzapine and aripiprazole include specific warnings of the risk of immobilisation and thromboembolism.

Clozapine:
Section 4.4: Since Clozaril (clozapine) may be associated with thromboembolism, immobilisation of patients should be avoided.

Section 4.8: Thromboembolism has been reported with clozapine use after licensing. The occurrence of this adverse reaction is greater than one in 10 000 of all reported adverse reactions, but less than one per 1000, and is classed as rare.

Olanzapine:
Section 4.4: Temporal association of olanzapine treatment and venous thromboembolism has very rarely (< 0.01%) been reported. A causal relationship between the occurrence of venous thromboembolism and treatment with olanzapine has not been established. However, since patients with schizophrenia often present with acquired risk factors for venous thromboembolism all possible risk factors of VTE, eg, immobilisation of patients, should be identified and preventive measures undertaken.

Section 4.8: Thromboembolism (including PE and DVT) has been reported with olanzapine use after licensing (frequency unknown).

***Aripiprazole**:*
Section 4.8: Thromboembolic events have been reported with aripiprazole use (frequency unknown).

Research of the literature and data from case reports received by the MHRA indicate that an increased risk of VTE cannot be excluded across the antipsychotic drug class as a whole. These data are discussed below, and evidence is presented in favour of a VTE warning to be included in the SPCs of all antipsychotics.

3. DATA FROM UK REPORTS OF SUSPECTED ADVERSE REACTIONS

Reports of suspected adverse drug reactions (ADRs) related to VTE received through our Yellow Card Scheme from 1 July 1963–25 June 2008 for all of the drugs included in this review are summarised in this section. The total number of reports, including fatal reactions, of respiratory and vascular ADRs classified as PE and DVT are provided. The reports are also separated into those received for conventional versus atypical agents.

Note about data interpretation: A comparison of the number of reports of suspected ADRs received with different drugs is of limited value, as these data do not take into account the level of usage of a drug or the length of time it has been on the market. Generally, older drugs are associated with a greater level of under-reporting of suspected ADRs compared to newer drugs.

Data relating to clozapine reports in particular should be interpreted with caution since the use of this drug is restricted to patients registered with the clozapine patient-monitoring service. Clozapine is, therefore, under an increased level of scrutiny[a] compared to other antipsychotic drugs in this report. This is illustrated by the fact that out of a total of 53 182 total reports for all antipsychotics up to 25 June 2008, approximately 50% were for clozapine.

3.1 Reports of VTE events

Table 4 summarises all UK antipsychotic ADR case reports containing the reactions classified as ‘PE’ and ‘DVT’.

[a] Clozapine use in the UK is monitored by the Clozaril Patient Monitoring Service (please direct all Healthcare Professional enquiries to: Tel - UK 0845 7698269; Eire – [01] 662 1141
Fax - UK 0845769 8379 or 08467698541; Eire – [01] 662 5961)

Table 4. Summary of all reports of VTE suspected to be associated with antipsychotics received in the UK from 1 July 1963–25 June 2008.

Antipsychotic drug	Pulmonary embolism	Deep vein thrombosis	Both	Fatal
Conventional				
Chlorpromazine	9	1	2	9
Flupenthixol	4	1	0	4
Fluphenazine	0	1	0	0
Haloperidol	6	0	0	4
Trifluoperazine	3	1	0	3
Zuclopenthixol	2	2	0	2
Total	**24**	**6**	**2**	**22**
Atypical				
Aripiprazole	2	2	0	1
Clozapine	89	62	35	61
Olanzapine	12	14	9	13
Quetiapine	1	5	5	6
Risperidone	16	12	5	7
Sertindole	1	0	0	1
Zotepine	1	0	0	1
Total	**122**	**95**	**54**	**95**
Total for atypicals w/o Clozapine	**33**	**33**	**19**	**34**
Total	**146**	**101**	**56**	**112**
Total for antipsychotics w/o Clozapine	**56**	**39**	**21**	**56**

w/o=without

3.2 Overview of reports of VTE events

The MHRA received a total of 303 unique reports of VTE associated with antipsychotics up to 25 June 2008. Of these, 146 reported PE, 107 reported DVT, and the remaining 50 reports contained both terms. The majority of these reports concerned atypical antipsychotics (271), with only 32 reports associated with conventional antipsychotics. 69% of the atypical reports were related to clozapine use (186 out of 271 reports), reflecting the unique nature of reporting for this drug. Since the product information for clozapine already contains warnings relating to VTE, these cases will not be reviewed further in this report. Olanzapine product information also contains warnings for VTE; however, cases for this drug will be

reviewed here to provide a useful comparison between olanzapine and risperidone, the two most widely-prescribed atypical antipsychotics.

Excluding clozapine, there were 117 reports of VTE occurrence with antipsychotic use. The most frequently-reported drugs (excluding clozapine) were (in order of total number of reports):

Olanzapine (35)
Risperidone (33)
Chlorpromazine (12)
Quetiapine (11)
Haloperidol (6)
Flupenthixol (5)
Trifluoperazine, zuclopenthixol, and aripiprazole (4)

One report of VTE was received for sertindole and zotepine, and no reports of either PE or DVT were received for the following nine drugs: benperidol, levomepromazine, paliperidone, pericyazine, perphenazine, pimozide, prochlorperazine, sulpiride and amisulpride.

Table 5 shows data on the three antipsychotic drugs most frequently-reported in association with PE or DVT, or both.

Table 5. Antipsychotics ranked according to frequency of case reports for PE and DVT.

Reaction	First highest frequency	Second highest frequency	Third highest frequency
PE	Risperidone (14)	Olanzapine (12)	Chlorpromazine (9)
DVT	Olanzapine (14)	Risperidone(12)	Quetiapine(5)
Both	Olanzapine(9)	Risperidone(5) Quetiapine(5)	Aripiprazole(2) Zuclopenthixol(2)

PE=pulmonary embolism; DVT=deep vein thrombosis

Analysis of the MHRA's ADR database showed that none of the drugs represented a safety signal[a] for either DVT or PE. However, the possibility of under-reporting should be taken into account, as most of these drugs are old, and reporting rates for a given drug declines with age. Moreover, there are a number of unexplained reports of sudden death on the database, which may have masked possible events of PE.

3.3 Characteristics of VTE events

The characteristics of the 32 and 85 reports relating to conventional and atypical drugs, respectively, are summarised in tables 6a and 6b below.

[a] No specific cause for concern for either ADR with the drugs under review (see MHRA website for further details: http://www.mhra.gov.uk/Safetyinformation/Howwemonitorthesafetyofproducts/Medicines/TheYellowCardScheme/WhathappenstoaYellowCard/index.htm)

Table 6a. Summary of characteristics of VTE reports for conventional antipsychotics.

		n (%)*
Gender	Female	14 (44)
	Male	18 (56)
Age (age range: 24–82 years)	21–30	3 (9)
	31–40	7 (22)
	41–50	6 (19)
	51–60	4 (13)
	61–70	5 (16)
	71–80	1 (3)
	81–90	1 (3)
	Unknown	5 (16)
Time to onset of VTE (days)	0–7	2 (6)
	8–30	4 (13)
	31–90	4 (13)
	>1 year	4 (13)
	Unknown	18 (56)
Outcome of event	Fatal	22 (69)
	Recovering	2 (6)
	Recovered	4 (13)
	Unknown	4 (13)
Co-suspect medication	Other antipsychotics	4 (13)
	Sedatives	2 (6)
	Others	4 (13)
	None	22 (69)
Concomitant medication type†	Drugs known to cause DVT (oestrogen)	1 (3)
	Other antipsychotics	5 (16)
	To treat risk factors	1 (3)
	Sedatives	3 (9)
	Antidepressants	4 (13)
	Other	5 (16)
	None stated	13 (40)
Relevant medical history or other risk factors†	Pregnancy	1 (3)
	Obesity	1 (3)
	Surgery	1 (3)
	Immobility/hospitalisation	7 (22)
	Drugs known to cause DVT	3 (9)
	Other	2 (9)
	None stated	17 (53)

Table 6b. Summary of characteristics of VTE reports for atypical anti-psychotics.

		n (%)*
Gender	Female	43 (51)
	Male	41 (48)
	Unknown	1 (1)
Age (age range: 24–82 years)	11–20	2 (2)
	21–30	13 (15)
	31–40	15 (18)
	41–50	12 (14)
	51–60	17 (20)
	61–70	8 (9)
	71–80	4 (5)
	81–90	2 (2)
	Unknown	12 (14)
Time to onset of VTE (days)	0–7	4 (5)
	8–30	11 (13)
	31–90	12 (14)
	91–364	13 (15)
	>1 year	6 (7)
	Unknown	39 (46)
Outcome of event	Fatal	31 (37)
	Not recovered	6 (7)
	Recovering	12 (14)
	Recovered	11 (13)
	Unknown	24 (28)
Co-suspect medication	Other antipsychotics	3 (9)
	Sedatives	1 (1)
	Antidepressants	3 (9)
	Others	2 (2)
	None	76 (89)
Concomitant medication type†	Drugs known to cause DVT (oestrogen)	2 (2)
	Other antipsychotics	12 (14)
	To treat risk factors	7 (8)
	Sedatives	11 (13)
	Antidepressants	7 (8)
	Other	13 (15)
	None stated	32 (38)
	Unspecified	1 (1)
Relevant medical history or other risk factors†	Previous history of DVT	4 (5)
	Obesity	5 (6)
	Surgery	2 (2)

	Pregnancy	1 (1)
	Immobility/hospitalisation	10 (12)
	Drugs known to cause DVT	2 (2)
	Other	13 (15)
	None stated	48 (56)

*Population percentages have been rounded to the nearest whole number, therefore totals may not equal 100

†In cases where more than one confounding factor present, only the factor with the strongest association with VTE was noted

VTE=venous thromboembolism; DVT=deep vein thrombosis

Details of report characteristics:

Gender

There were a similar percentage of reports for females (49%) and males (50%). The percentage of reports was slightly higher for males taking conventional antipsychotics (56%) compared to females, but those reports only represented approximately a quarter of the total number of reports (32 out of 117 reports).

Age

Patient age was provided in 86[a] % reports (100 out of 117). An unexpectedly high percentage of reports concerned patients aged up to 40 years (40 out of 117 or 34%) with similar numbers of reports for both typical and atypical drugs (30% and 35% of the total, respectively). Patients aged over 60 years accounted for only 18% of the reports (21 out of 117); reports for this age group were slightly higher for conventional antipsychotics compared to atypicals (22 and 16% respectively).

Time to onset of VTE

For the cases when time to onset of VTE was provided, there appeared to be a good temporal relationship between exposure to the antipsychotic and occurrence of VTE. The risk appeared to be higher in the first 3 months of treatment (32% of cases, or 65% of cases where onset was known), with an additional 11% cases (23% where onset was known) occurring within the first year of treatment. This is not entirely surprising as events which occur in close temporal relationship to starting a medicine are more likely to be reported.

Co-suspect and concomitant medication

In 84% (98 out of 117) of reported cases, no other co-suspect medication was reported. The most commonly reported co-suspect medication was another antipsychotic, in seven out of 117 or 6% of the cases. Sedatives and antidepressants were each reported as a co-suspect drug in three cases (3%), and use of various other drugs were reported in six cases (5% of the cases). With regards to concomitant medication, there were confounding factors present in 11 cases (9%), such as drugs known to cause DVT or drugs used to treat a known risk factor for DVT. Again, the most commonly used concomitant medications were other psychiatric drugs: antipsychotics (17 out of 117 or 15%); sedatives (14 out of 117 or 12%); and antidepressants (11 out of 117 or 9%). The majority of cases however did not state any other concomitant medication (45 out of 117 or 39%).

[a] Please note that all percentages have been rounded to the nearest whole number, therefore totals may not equal 100

4. LITERATURE

The association between VTE and the use of antipsychotic drugs was reported in literature as early as 1953[5] shortly after the introduction of phenothiazines for the treatment of psychotic disorders. The first study however, to try to objectively quantify this association, using relevant control groups, was not until 1997[6]. The following section reviews all of the published studies which investigate the possible association of VTE with antipsychotic use.

4.1 Clozapine-specific studies

A record-linkage study investigated rates of various causes of death in 67 072 current and former clozapine users in the US Clozaril National Registry[a] between 1991 and 1993[6]. Although the absolute risk of death by PE was small (19 cases in 85 399 person-years in the full cohort), almost all of the cases (18 out of 19) were confined to current clozapine users; relative risk (RR) was 5·2 in current versus past users. No confidence intervals (CI) were calculated due to the rarity of this event. Overall mortality rates were lower in current users compared to former users, mainly due to the lower risk of suicide (RR 0·17, 95% CI: 0·10–0·30). Interestingly, this study reported more deaths from PE than agranulocytosis (18 vs two, respectively), which is a serious side effect most commonly associated with clozapine use. However, this could be due to the success of the Clozaril Registry or a lack of recording agranulocytosis as an underlying cause on death certificates. The authors of this study also suggested that the increase in weight and sedation associated with the use of clozapine could increase the risk of DVT and subsequent PE.

Data from the Swedish Adverse Reactions Advisory Committee (SADRAC) also suggested an association between the use of clozapine and VTE complications[7]. Even though this was based on case reports which did not allow for a conclusive causal relationship, the authors noted that over the same reporting period 12 cases were reported to SADRAC for clozapine and only three cases for all antipsychotics other than clozapine. During that period (1989–2000), only 4% of sales of all antipsychotic drugs in Sweden were for clozapine.

4.2 Other studies

A nested case-control study by Zornberg and Jick (2000) demonstrated an increased risk for VTE in association with typical antipsychotics[8]. Using the UK General Practice Research Database (GPRD), the authors studied a baseline population of 29 952 patients younger than 60 years in 1998, who had used at least one conventional (chlorpromazine, trifluoperazine, thioridazine, mesoridazine, fluphenazine, perphenazine, pericyazine, methotrimeprazine, pipothiazine, zuclopenthixol, flupenthixol, thiothixene, haloperidol, benperidol, sulpiride, pimozide, loxitane) or atypical (risperidone, olanzapine, quetiapine, clozapine) antipsychotic between 1 January 1990–31 October 1998.

The study identified 42 individuals with a first-time diagnosis of VTE who were classified as idiopathic cases. 168 matched controls were also randomly selected. After adjusting for confounders, current exposure to conventional antipsychotics was associated with a significant increase in the risk for VTE. Low-potency antipsychotic

[a] A register monitoring the safety of all patients in the US currently treated with Clozaril (a brand of clozapine)

drugs such as chlorpromazine and thioridazine were more strongly associated with VTE compared to high-potency antipsychotics such as haloperidol. Table 7 summarises the findings of this study.

Table 7. Odds ratios of developing VTE associated with use of antipsychotic and antidepressant drugs[8].

	Cases (%) (n=42)	Controls (n=168)	Odds Ratio* (95% CI)
Exposure†			
None	26 (62)	150 (89)	1·0
Current use (0–60 days)	14 (33)	11 (7)	7·1 (2·3–21·9)
Recent use (61–120 days)	2 (5)	7 (4)	2·1 (0·4–11·8)
Duration†			
Never or past use	28 (67)	157 (93)	1·0
Current use:			
0–11 months	12 (29)	3 (2)	28·7 (4·9 –169·5)
≥12 months	2 (5)	8 (5)	1·0 (0·1–7·3)
Potency			
None or past	28 (67)	157 (93)	1·0
Current use:			
Low potency	7 (17)	2 (1)	24·1 (3·3 –172·7)
High potency	7 (17)	9 (5)	3·3 (0·8–13·2)
Daily dose			
None or past	28 (76)	157 (93)	1·0
Current use:			
0–99mg	11 (26)	7 (4)	12·4 (3·2–48·3)
≥100mg	3 (7)	4 (2)	2·3 (0·4–14·9)

*Adjusted for smoking, body mass index, hypertension, oestrogen use and antidepressant use.
†All antipsychotic drug classes, with or without antidepressant use.

CI=confidence interval

Despite the attempts of the authors to exclude patients with risk factors, reduction in physical activity, which is of crucial importance in the occurrence of VTE, was not addressed in this study. In addition, the lack of a dose-response between antipsychotic exposure and VTE prompted arguments against the association[9]. Another limitation of the study is that only 3% of the cohort was exposed to an atypical antipsychotic. Nevertheless, this study renewed interest in establishing a link between antipsychotics and VTE.

Another case-control study attempted to address this association by conducting a historic literature overview of 474 incident cases with a first episode of DVT between 1990 and 1993 selected from three anticoagulation clinics[10]. The control group was matched for sex and age, and study participants with a history of thrombosis or malignant disorders, or who had used coumarins were excluded. This study was limited to outpatients which, according to the authors, removed confounding due to sedation and immobility. However, only four patients using antipsychotic medication

were identified with VTE from the 474 cases; no odds ratios (ORs) could be derived for these data as there were no cases of VTE in the control population. This paper raised the possibility that thromboembolism might be an expression of some other underlying risk factors of the disease itself. An alternative mechanism proposed was an enhancement of coagulation due to the increase of adrenaline secretion during an acute psychotic episode.

A large retrospective cohort study of adults aged 65 years and older was performed to complement the Jick study, which had excluded this age group[11]. Patients receiving thyroid-replacement hormones were chosen as the control group. The authors found a small but significant increase in the risk for VTE (hazard ratio [HR]:1·43, 95% CI 1·18–1·74) in patients receiving butyrophenone antipsychotics (haloperidol, benperidol and droperidol) compared with the control group. However, in common with the Jick paper, this study did not account for each participant's degree of mobility. Co-morbid illnesses and previous history of VTE were also not considered, and individuals who died during the study period were excluded. In addition, the primary outcome of this study was limited to DVT.

Parkin et al[12] conducted a national case-control study similar to the Jick paper, identifying all fatal cases in patients aged 15–59 years of PE and infarction or phlebitis and thrombophlebitis or venous embolism, recorded in New Zealand between 1990–1998. They reached similar conclusions to Jick, that low-potency antipsychotics appeared to carry the highest risk (OR: 20·8 [95% CI: 1·7–259.0]). The 62 cases without major risk factors were non-users of atypical agents. The controls selected were matched for age and sex, but not for other risk factors. Table 8 summarises the results from this study.

Table 8. Odds ratios of fatal PE associated with use of antipsychotic and antidepressant drugs (adapted from[12]).

Exposure	Cases (exposed/total)	Controls (exposed/total)	Adjusted odds ratio* (95% CI)
Any antipsychotic†			
All study particpants	9/75	3/300	9·7(2·3–40·9)
Participants without major risk factors for VTE‡	8/62	2/243	13·3(2·3–76·3)
Low-potency antipsychotic			
All study participants	7/75	1/300	29·3(2·8–308·2)
Participants without major risk factors for VTE‡	6/62	1/243	20·8(1·7–259·0)

*Adjusted for weight (four categories, including missing values, for both sexes), combined oral contraceptive use and hormone replacement therapy during the 3 months before the index date.
†Non-users of antipsychotics (never-used and past-users combined) are the reference group.
‡No history of venous thromboembolism or of prolonged immobility, severe injury, major surgery or pregnancy during the 2 months before the index date.

VTE=venous thromboembolism; CI=confidence interval

Two similar studies from Japan demonstrated a disproportionately high number (44 and 29%) of patients receiving antipsychotics among patients with confirmed PE[13,14]. In the first study, records of patients transferred to a Japanese emergency centre were reviewed for acute massive PE. After excluding all confounded cases, 16 cases were identified, of which seven (44%) had taken some antipsychotic medication; in most cases a conventional agent. Risperidone had been prescribed in two cases. Of particular interest is one case where the patient died from PE within 40 days of adding risperidone to his chronic treatment with benperidol. The second study reviewed records of autopsies performed between1998–2002 to investigate the cause of sudden unexpected death. From 1125 forensic autopsies, PE was indicated as cause of death in 28 cases (3%). Eight of these patients (29%) had taken antipsychotics; all were female. Chlorpromazine or other phenothiazines had been prescribed in six cases, haloperidol and other butyrophenones in five, and atypical antipsychotics (risperidone, zotepine and perospirone) in six. Only one subject had a risk factor for thrombotic disease. Time to onset was not provided in any of the cases.

In a retrospective study of a cohort of nursing home non-schizophrenic residents aged over 65 years, 19 940 new users of antipsychotics were compared to 112 078 residents not using antipsychotics[15]. Analyses of the two populations were adjusted for all reasonable possible confounders. The study was restricted to cases confirmed by hospital diagnosis and therefore did not include fatal cases prior to hospitalisation or events where hospital referral was not deemed necessary. The results of this study are summarised in table 9.

Table 9. Effect of antipsychotics on the risk of hospitalisation with VTE[15].

Antipsychotic drug	Cases	Crude incidence rate per 100 person-years	Adjusted HR (95% CI)*
Atypical	64	1·24	2·01(1·50–2·70)
Risperidone	43	1·25	1·98(1·40–2·78)
Olanzapine	15	1·17	1·88(1·06–3·27)
Clozapine-Quetiapine†		1·35	2·68(1·15–6·28)
Conventional	28	0·84	1·02(0·67–1·55)
Phenothiazines	15	0·83	1·03(0·60–1·77)
Other	13	0·86	0·98(0·52–1·87)
>1 antipsychotic†		2·80	4·80(2·28–10·10)
Non-users	439	0·87	Reference group

*Adjusted for age, sex, body mass index. activities of daily living score, Cognitive Performance Scale score, history of DVT, history of hip fracture, chronic obstructive pulmonary diseases, cancer, dementia, depression, peripheral vascular disease, cerebrovascular disease, heart failure, diabetes mellitus, and concomitant drug use including anticoagulants, aspirin or antiplatelets, and oestrogens.
†Number of events <11; unable to report the actual number under agreement with the US Centers for Medicare and Medicaid Services.
HR=hazard ratio; CI=confidence interval; DVT=deep vein thrombosis

Atypical antipsychotics appeared to increase the risk of VTE, in contrast to phenothiazines or other conventional agents. Although this study seems to contradict previous studies, by demonstrating an increased risk associated with atypical agents, two points should be noted. Firstly, the cohort in this study was different to the others in that it completely excluded schizophrenic patients, which comprised most of the cohorts in all other studies. The majority of the patients included suffered from dementia, which, especially in an advanced age, may predispose to immobility. Secondly, prescribing patterns over the years have probably changed in favour of newer atypical agents. As the authors of this study point out, most antipsychotic prescriptions among patients with dementia are for atypical drugs, although, as mentioned earlier, recent evidence suggests an increased risk of stroke and a small increased risk of mortality in elderly patients who receive antipsychotic therapy for dementia (only one antipsychotic, risperidone, is licensed for treatment of dementia-related behavioural disturbances: and then only specifically for short-term (up to 6 weeks') treatment of persistent aggression in Alzheimer's dementia unresponsive to non-pharmacological approaches and where there is a risk of harm to the patient or others).

A hospital based case-control study designed to test interactions between genetic and environmental risk factors for VTE also concluded that exposure to antipsychotic drugs was associated with an increased risk of VTE[16]. A total of 677 patients hospitalised with well-documented DVT were included in this study, who were sex-matched and age-matched with controls selected from the roster of patients hospitalised in the same ward. Patients presenting major risk factors were excluded, but oral contraceptive use, smoking and mobility levels were not accounted for. More

importantly, although patients in 210 cases reported a personal history of VTE they were still included in the study. Table 10 summarises the results of this study.

Table 10. Odds ratios and 95% CIs for VTE related to neuroleptic and antidepressant drugs[16].

Exposure	Exposed patients among 677 cases, n (%)	Exposed patients among 677 controls, n (%)	OR (95% CI)
All neuroleptics	84 (12·4)	44 (6·5)	2·1(1·4–3·2)
All antipsychotics	56 (8·3)	19 (2·8)	3·5(2·0–6·2)
Conventional	46 (7·2)	15 (2·3)	4·1(2·1–8·2)
Atypical	10 (1·7)	4 (0·6)	2·7(0·7–10·0)
Sleeping pills	34 (5·4)	23 (3·5)	1·6(0·9–2·7)
Other neuroleptics	4 (0·6)	4(0·6)	1·0(0·3–4·0)
Antidepressants	135 (19·9)	123(18·2)	1·1(0·9–1·5)

OR=odds ratio; CI=confidence interval

Conditional logistic regression adjusted for body mass index (which was slightly higher in the cases cohort), factor V Leiden and prothrombin G20210A gene variations (both genetic factors implicated in the thrombotic process) did not alter the results, hindering interpretation. Almost a third of the cases should have been excluded due to medical history. In addition, inclusion in the study required informed consent. Patients with dementia or acute severe psychotic disorders, and patients who died suddenly because of massive PE were not included. Most importantly, this study was not designed to investigate the association between VTE and antipsychotics but rather to evaluate interactions between risk factors for VTE.

Data mining of the World Health Organization (WHO) database has also been used to investigate the association between antipsychotics and VTE in a recent study[17]. By November 2004, 754 cases of VTE during treatments with anti-psychotics were identified in the database. Of these, 375 concerned clozapine. The advantage of this study that it is able to investigate and calculate a risk for individual drugs. However, the reliability of the results is severely compromised by the varying quality of the reports included. Moreover reporting is influenced by several factors such as the use and the age of the drug, public attention to specific problems associated with a particular drug. Therefore it cannot be used to establish a conclusive causal relationship between an event and a drug. Table 11 shows the results of this study as information component (IC) values, a logarithmic measure of association, which can be viewed as the strength of dependency between a drug and an adverse event relative to background.

Table 11 Cases of VTE during treatment with antipsychotic drugs reported to the WHO database, with IC values*(adapted from[17])

Antipsychotic drugs	Reports for drug (n)	Case reports (n)	VTE IC value	Lower 95% credibility interval of the IC value (IC_{025})
High-potency conventionals	**19 277**	**88**	**–0·2**	**–0·5**
Benperidol	132	2	0·8	–0·9
Bromperidol	219	2	0·5	–1·2
Clopenthixol	284	2	0·3	–1·4
Flupenthixol	1561	9	0·2	–0·8
Fluphenazine	2438	8	–0·6	–1·6
Haloperidol	9428	41	–0·2	–0·7
Perphenazine	1549	7	–0·2	–1·2
Pimozide	596	1	–1·0	–3·1
Tiotixene	847	0	–2·4	–5·3
Trifluoperazine	1794	6	–0·5	–1·6
Trifluperidol	20	1	0·9	–1·3
Zuclopenthixol	848	10	1·0	0·2
Low-potency conventionals	**13 419**	**46**	**–0·6**	**–1·0**
Chlorpromazine	5785	14	–1·0	–1·8
Cyamemazine	665	4	0·2	–1·1
Levomepromazine	2103	6	–0·8	–1·8
Melperone	300	4	1·0	–0·3
Perazine	567	7	1·0	0·0
Thioridazine	4330	12	–0·8	–1·6
Atypicals	**69 598**	**620**	**0·8**	**0·7**
Amilsulpride	945	2	–1·0	–2·6
Aripiprazole	597	4	0·3	–1·0
Clozapine	36 739	385	1·0	0·9
Olanzapine	11 480	99	0·7	0·5
Quetiapine	2857	20	0·4	–0·2
Remoxipride	319	1	–0·4	–2·5
Risperidone	15 064	91	0·2	–0·1
Sertindole	316	6	1·4	0·3
Sultopride	65	1	0·6	–1·5
Ziprasidone	1678	13	0·6	–0·2
Zotepine	249	3	0·8	–0·6

*Table shows the number of case reports and IC values prior to exclusion of suspected duplicates
IC=information component; VTE=venous thromboembolism.

VTE was reported more often in combination with atypical antipsychotic drugs, particularly olanzapine, sertindole, zuclopenthixol and clozapine than would be expected based on general reporting patterns in the database. However, confounding factors such as the underlying disease, smoking, obesity and immobilization could all have contributed to disproportional reporting. Possibly-confounding drugs were present in three of the six reports for sertindole, making the causal association between sertindole and VTE less likely.

5. DISCUSSION

Reports of suspected adverse reactions related to VTE
The majority of the cases reported through the Yellow Card Scheme to the MHRA of antipsychotic exposure and thromboembolic events either mentioned other conditions or medicines which may be associated with VTE or had incomplete data to assess causality. The main concerns with these data were potential confounding factors, such as sedation and weight gain, which are commonly present in antipsychotic users and are risk factors for VTE. Despite these limitations some conclusions can be drawn:

- The reports are evenly split between female and male patients. The association between gender and VTE is controversial, with most studies suggesting a slightly increased risk for males[4].

- Almost half of the reports, where age was reported, refer to patients younger than 40 years. Advanced age is one of the most-characterised independent risk factors for VTE, and most studies demonstrate a marked increase in VTE incidence with age, both in hospitalised patients and outpatient settings. Two studies have quantified that VTE risk increases by approximately 2-fold per decade[18,19]. Although available case reports may suggest that VTE occurs at a younger age in patients receiving antipsychotics, this should be interpreted with caution as the typical age of onset for schizophrenia, bipolar disorders and psychotic disorders is early to late twenties. In addition, adverse reactions occurring in this population may be more likely to be suspected to be associated with the medicine and therefore reported.

- Temporal relationships between antipsychotic exposure and onset of reported events were good in most cases. Consistent with findings from the first case-control study to demonstrate the association between antipsychotics and VTE[8], almost a third of the reported cases showed onset of the event was within 3 months. However it is recognised that a reaction may be more likely to be identified as a possible ADR if it occurs soon after starting a new treatment.

- Potential confounding factors in a number of cases could be attributed to side-effects of antipsychotics (such as sedation and weight gain). For these cases, causality assessment is very difficult.

Although many of the cases are confounded or lack sufficient information to determine causality between antispsychotic exposure and thromboembolic events, the possibility that antipsychotic medicine may have contributed to the occurrence of VTE cannot be excluded in a number of cases, particularly with atypical agents. The number of reports is quite small for most antipsychotics, although some of the cases of sudden death reported for the antipsychotics may have been due to VTE.

Published literature
There are few published studies on this subject and most have limitations. All available studies are retrospective, so to some extent they are susceptible to incomplete records of exposure; an inability to completely identify confounding factors; and recall bias.

Moreover, there is substantial heterogeneity among these studies with different endpoints, populations included, age groups, criteria for selection of controls and

drugs studied. Such heterogeneity makes a meta-analysis of antipsychotic-related VTE risk impossible. Despite these limitations, it is worth noting that all of the studies conclude that there appears to be an increased risk for VTE with exposure to antipsychotics.

Biological plausability
An important criterion for causality association between a drug and an ADR is biological plausibility. A number of possible explanations have been proposed for the role of antipsychotics in the thrombotic process. They include:

- the sedating properties of these drugs which increase the risk for DVT and PE
- similarly, weight gain is a also risk factor for DVT and PE (and is a side-effect of antipsychotic use)
- platelet aggregation
- hyperprolactinaemia
- antiphospholipid syndrome

Sedation is a common side-effect of conventional antipsychotics, especially low potency-agents (eg chlorpromazine, pericyazine, sulpiride) as well as several atypical antipsychotics (such as clozapine, olanzapine and quetiapine). Studies have indicated that sedation may also be related to the variable affinity of antipsychotics to block the histamine H_1 receptor[20]. As illustrated in tables 3.1 and 3.2., the drugs with the highest affinity for this receptor are: flupenthixol and levomepromazine; chlorpromazine, perphenazine, clozapine and olanzapine. The product information for clozapine and olanzapine already contain warnings about thromboembolism, and chlorpromazine and flupenthixol have been implicated in two of the studies mentioned above. Antipsychotic drugs are quite commonly used in combination with benzodiazepines which also cause sedation, leading to reduced activity contributing to venous stasis.

The exact molecular mechanisms responsible for antipsychotic drug-induced weight gain are unknown but a recent study has indicated a role for the H_1 receptor, as well as the α_{1A} adrenergic receptor and 5-HT_{2C} and 5-HT_6 serotonin receptors [20]. Sertindole has the highest affinity for 5-HT_{2c}, whereas olanzapine, sertindole and zotepine have the highest affinity for 5-HT_6. Chlorpromazine has the highest affinity for α_{1A} followed by fluphenazine, clozapine, risperidone, sertindole and zotepine. These drugs, with the exception of fluphenazine, are the antipsychotics most commonly associated with weight gain.

Platelet aggregation is a key step in the haemostatic process. Serotonin plays a crucial role in this process since it is able to induce and amplify platelet aggregation. This has been demonstrated in patients with schizophrenia treated with the conventional agents chlorpromazine, fluphenazine, flupenthixol, trifluoperazine and haloperidol[21]. Most of the atypical antipsychotics also have a high affinity for the 5-HT_{2A}, especially risperidone and sertindole. However, an antipsychotic-induced increase in platelet aggregation has not yet been associated with a clinical case of VTE. Recently, prolactin has been recognized as another potent platelet aggregation coactivator, and hyperprolactinaemia has been suggested as an important risk factor for VTE in patients receiving antipsychotic drugs[22], although the precise mechanism has not been fully clarified. Moreover, the evidence is based on single observations in patients receiving antipsychotics, pregnant women or in vitro experiments.

Circulating antibodies to phospholipids, including lupus anticoagulants and anticardiolipin antibodies have been associated with an increased risk of thrombosis.

Antiphospholipid syndrome is recognised as the most common form of acquired hypercoagulability, appearing most commonly as DVT. However, this hypothesis seems to be unlikely since elevated titres of these antibodies have also been found in patents with psychosis who are not receiving antipsychotics[23]. Moreover, in contrast to autoimmune diseases, the presence of these antibodies induced by antipsychotics seldom seems to be associated with thromboembolism[24].

6. CONCLUSIONS

A possible relation between use of antipsychotic medicines and venous thromboembolic events (VTE) was first suggested approximately 50 years ago, after the introduction of phenothiazines. Since then, reports of suspected adverse reactions related to VTE and antipsychotics have been received periodically through the Yellow Card Scheme and further studies have been completed that investigated this issue[8,15]. A Europe-wide review of UK Yellow Card data and worldwide published epidemiological studies on antipsychotics and VTE has concluded that an increase in risk of VTE cannot be excluded.

Many of the cases reported to us via the Yellow Card Scheme were potentially confounded by other risk factors or contained too limited information to allow a clear causal relation to be established for antipsychotics and risk of VTE. Some of the known side effects of antipsychotics (eg, sedation, weight gain) are known risk factors for VTE, and a direct or indirect causal association between antipsychotic use and VTE could not be excluded.

Information from the literature is limited by a lack of randomised controlled trial data and by heterogeneity among the available observational studies. However, despite these limitations, all of the published studies to June 2008 conclude that there is an increased risk of VTE with exposure to antipsychotics[8,15]. Product information for healthcare professionals and patients for all antipsychotics will be updated across the EU to include information about this risk; (currently, product information for the antipsychotics clozapine, olanzapine, and aripiprazole already contains a warning about this risk).

Advice for healthcare professionals:

- Antipsychotic use may be associated with an increased risk of VTE
- At present there are insufficient data available to determine any difference in risk between atypical and conventional antipsychotics, or between individual drugs
- All possible risk factors for VTE should be identified before and during antipsychotic treatment and preventive measures undertaken

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GLOSSARY

Acetylcholine
A chemical found in the nerves of the body known as ‘parasympathetic’

Adrenergic receptors
Receptors in nerves known as ‘sympathetic’ that bind to chemicals in the body called adrenaline and noradrenaline

Affinity
The strength of binding between a substance and its receptor

Agranulocytosis
A disorder where the level of blood cells called neutrophils is below normal, causing fever and ulcers in the mouth and throat

Akinesia
Absence of movement

Anticholinergic
A substance that blocks the effects of **acetylcholine**

Antithrombin
A protein that inhibits the activity of **thrombin** so that blood does not **coagulate** (clot)

Antiphospholipid syndrome
A disease characterised by **hypercoagulability**, which causes frequent thrombosis or blood clots

Autopsy
An examination of a body after death

Bipolar affective disorder
A mental disorder which causes episodes of both depression and mania

Case-control study
A study in which cases and controls (patients with and without a certain condition, respectively) are grouped before the study begins, and are then compared during the study.

Cardiac arrhythmia
Abnormality in the electrical activity of the heart that appears as an abnormality in the heart rhythm or rate

Causal relationship
A direct link between a factor and the onset of a disease or medical condition or event

Cellulitis
A bacterial infection of deep tissue and muscle that spreads through the body, causing inflammation

Cerebrovascular disease

A disease of the arteries supplying the brain

Chemotherapy
The prevention or treatment of diseases such as cancer, using chemical substances

Chronic obstructive pulmonary disease
A disease characterised by airflow obstruction in the lungs

Coagulate
To form a blood clot

Cognitive Performance Scale
Gives scores for combined information on memory loss, consciousness and brain function

Concomitant medications
Two or more medicines given or taken approximately at the same time (eg, one after the other on the same day)

Conditional logistic regression
A statistical method for determining relationships between variables in a study

Confounded
Where the presence of one **risk factor** changes the effects of another risk factor on the development of a medical condition; this can affect the results of a study

Coumarin
A drug that prevents blood clotting

Deep vein thromboembolism
A blood clot in the veins of the leg

Dementia
A brain disease characterised by the loss of intellectual abilities

Dyspnoea
Difficulty in breathing

Embolism
A blockage in an artery which obstructs blood flow

Endothelial vessel wall
A layer of cells that lines the inside of blood vessels

Epidemiology
The study of the occurrence, distribution and control of diseases in populations

Exacerbated
Made worse

Exogenous
External to the body

Extrapyramidal movement disorders
Involuntary movements that can occur as a side effect of antipsychotic medicine

Factor V Leiden
An inherited disorder that affects Factor V, a protein found in blood that helps the clotting process

First-line treatment
The first type of treatment a person receives for a disease or medical condition

Haemoptysis
Coughing up blood

Hazard ratio
A measure of risk of an event occurring. Hazard ratios >1 suggest increased risk, =1 suggest equal risk, <1 suggest decreased risk. Usually accompanied by a 95% confidence interval (CI)—indicates there is a 95% chance that the real difference between the two groups lies within this interval. If the 95% CI does not cross 1, then the hazard ratio is statistically significant

Heterogenity
Dissimilarity (between groups)

Histamine
A chemical in the body involved in immune responses and functioning of the gut

Hormone replacement therapy
The use of female hormones to relieve symptoms of the menopause

Hypercoagulability
A tendency of the blood to **coagulate** (clot) more rapidly than normal

Hyperprolactinaemia
Increased levels of a substance in the body called prolactin (which stimulates breast milk production)

Ischaemic stroke
Reversible or irreversible paralysis caused by a blood clot interrupting bloodflow to the brain resulting in a lack of oxygen. (A haemorrhagic stroke results from a blood vessel bursting in the brain)

Ligand
A molecule that binds to a **receptor**

Malignancy
A disorder that can become life-threatening if untreated

Metabolic syndrome
A combination of medical conditions that increase the risk of developing heart and circulatory disease

Mortality
Death rate; ie, the total number of deaths in a group compared to the total population

Muscarinic receptors
A subset of the **acetylcholine receptor** group

Myocardial infarction
Death of a segment of heart muscle after its blood supply is interrupted due to a blood clot in an artery (also known as a heart attack)

Neuroleptic malignant syndrome
A combination of unstable blood pressure, fever, profuse sweating, incontinence, stiffness and rigidity

Odds ratio
A measure of risk for one group compared with another. Odds ratios >1 suggest increased risk, =1 suggest equal risk, <1 suggest decreased risk. Usually accompanied by a 95% confidence interval (CI), which indicates there is a 95% chance that the real difference between the two groups lies within this interval. If the 95% CI does not cross 1, then the odds ratio is statistically significant

Parkinson's disease
A disease that occurs in the brainstem causing nerve cell loss. Symptoms include trembling of the limbs and difficulties with speech

Peripheral vascular disease
A disease of the arteries supplying the arms and legs

Person-years
The total sum of the number of years that a member of a study population has been under observation, eg, years of treatment with a certain drug

Phlebitis
Inflammation of a vein

Platelet aggregation
A mass or 'clump' of platelets (cells in the bloodstream) which form a clot

Potency
The power of a medicine to produce the desired effects

Proteins C and S
Proteins that are part of the blood clot formation process

Prothrombin
A substance in the blood from which **thrombin** is formed

Psychosis
Mental disorders characterised by impairment in reality and awareness testing, and mental functioning, which reduces the capacity of the patient to meet ordinary demands of life

Pulmonary embolism
A blood clot in the lungs

Recall process
The process of study participants remembering information required for the study

Receptor
A structure on the surface of a cell to which specific substances can bind, causing a change within the cell resulting in an effect on the body

Renal
Of the kidney

Retrospective cohort study
A study in which past medical records of groups of individuals who are alike except for one certain characteristic (ie, antipsychotic users vs non-users) are compared for a particular outcome (such as VTE).

Respiratory
Related to breathing

Risk factor
A substance or activity that leads an individual to have a greater likelihood of developing an illness or medical condition

Roster
Register

Serotonergic
Describes the actions of a chemical in the body known as serotonin

Stasis (venous)
Slowing or stoppage of blood flow due an obstruction

Temporal
Related to the timing of when a drug is taken

Time to onset
The time between starting the use of a medicine, and the symptoms or medical condition being studied occurring

Thrombin
A substance which is made during the blood clotting process to help form the clot in the final stage

Vascular
Related to blood vessels

Venous insufficiency
A condition in which blood flow is inadequate through the veins, particularly those of the legs