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Venous thromboembolism as an adverse effect of antipsychotic treatment

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Summary

Many studies suggest an association between the use of antipsychotics (APs) and occurrence of venous thromboembolism (VTE). Thromboembolism is often related to a significant risk of disability or death. Despite many years of investigating the interrelations between use of APs and VTE, they have not been specified yet. This paper aims to summarize reports on the VTE risk factors in patients using APs. Based on the analyzed clinical studies, meta-analyses and data published by European Medicines Agency, it has been determined, that the main risk factors for VTE are duration of treatment and patient-related factors, such as gender, age, body mass, and physical activity. Current data do not allow to identify the prothrombotic potential for individual APs or indicate a higher risk for developing VTE in patients treated with newer atypical APs. Due to the complex pathogenesis of VTE it would be necessary to perform large, comparative studies, allowing to identify precisely differences in prothrombotic potential of individual APs. It is necessary to specify products with the lowest VTE risk, what

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would be useful in the treatment of high-risk patients. All patients treated with APs should be assessed with the risk of VTE and, if needed, appropriate prevention methods (including most of all the elimination of modifiable risk factors) should be implemented. Moreover, patients should be educated in scope of VTE prodromal symptoms. All patients with the higher VTE risk should be diagnosed as soon as possible and adequate treatment should be implemented.

Key words: antipsychotic drugs, venous thromboembolism

Introduction

First articles describing cases of VTE in patients treated with antipsychotics have been published soon after chlorpromazine was introduced to the treatment. Review article, describing 49 such cases was published in 1965 [1]. In the following years both case reports of VTE in patients treated with APs and results of clinical studies were published. Medicines and Healthcare products Regulatory Agency (MHRA) collected 303 description of cases describing cases of VTE in patients treated with APs (Table 1). Report summarizing all of this cases [2] became a basis for European Medicines Agency (EMA) to add the possibility of VTE to the information leaflets of all APs available on the market (Table 2).

Table 1. **Summary of PE and DVT reports in relation to APs treatment in UK in 1963-2008 [2]**

Medicinal product	PE	DVT	PE+DVT	Deaths
Chlorpromazine	9	1	2	9
Flupenthixol	4	1	0	4
Flufenazine	0	1	0	0
Haloperidol	6	0	0	4
Trifluoperazine	3	1	0	3
Zuclopenthixol	2	2	0	2
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	**146**	**101**	**56**	**112**

Point 4.4 of Summary of Product Characteristics (Special warnings and special precautions for use) has been supplemented by the following statement: „During use of antipsychotic drugs cases of venous thromboembolism (VTE). Due to the often

occurring VTE risk factors in patients treated with antipsychotics, before and during treatment with the medicinal product (name) all VTE risk factors need to be identified and preventive measures need to be taken". To point 4.8 (Undesirable effects) the following statement has been supplemented: "During treatment with antipsychotic medicines cases of venous thromboembolism have been reported, including w pulmonary embolism and deep venous thrombosis (frequency unknown)".

Table 2. **Antipsychotics registered in Poland.**

Classical	Phenothiazine derivates	Chlorpromazine Levomepromazine Perazine Promazine
	Butyrophenones	Haloperidol
	Thioxanthene derivates	Flupenthixol Tiapride Zuclopenthixol
	Benzamide	Sulpiride
Atypical		Amisulpride Aripiprazole Clozapine Quetiapine Olanzapine Risperidone Ziprasidone

Due to the lack of big prospective studies it is difficult to confirm a relationship between the use of APs and the occurrence of VTE. However, literature data suggest the potential possibility of presence of such a relationship, indicating various mechanism responsible for untoward effects observed in patients. The basic problem, considered both by clinicians and researchers is the differences in prothrombotic activity between classic and atypical APs. There are some doubts considering the role of the duration of the therapy and clinical situations, when anticoagulation prophylaxis should be introduced. Our article summarizes present knowledge about the risk of VTE in patients treated with APs with the special impact on aspects described above.

Venous thromboembolism – clinical presentation

Venous thromboembolism (VTE) is a common hospitalization reason [3]. It is estimated that over 25% of patients die because of VTE within a week of falling

sick, and almost 30% suffer from complications [4] VTE includes two disease entities – pulmonary embolism (PE) and deep vein thrombosis (DVT) [5]. Superficial thrombophlebitis (located above deep fascia) and thromboembolism of other deep veins (i.e. portal vein, renal vein) are treated as separate disease entities. Due to a high risk of VTE complications (including severe – such as patient's death, chronic thromboembolitic pulmonary hypertension, myocardial infarction) and high treatment cost. It is important to remember the risk of VTE in everyday practice and to promptly confirm or exclude this option.

Thromboembolism promoting factors are:

- slower blood flow (e.g. due to mechanical pressure, immobilization of extremities)
- predominance of thromboembolism promoting factors over factors causing suppression of coagulation and fibrinolysis promoting factors (e.g. effect of some drugs, thrombophilia)
- cell wall damage (e.g. caused by trauma) [6].

Risk factors can be divided into patient-related (personal characteristics, clinical presentation) and iatrogenic factors (diagnostic procedures, treatment) (2). As much as one-third of all PE cases is diagnosed in its idiopathic (essential) form, which means that it is not possible to identify significant contibuting factor [7]. Along with increased medical knowledge, we can expect that more thromboembolism inducing factors will be identified.

Lower extremities deep vein thrombosis (DVT) includes three clinical variants – distal thrombosis, proximal thrombosis and painful swelling. Distal thrombosis affects fibular veins and frontal and posterior tibial veins. It is the most common form of DVT, in most cases asymptomatic, with spontaneous resolution and related to a low risk of pulmonary embolism, however it can take the form of proximal thrombosis. Proximal thrombosis affects the popliteal vein, femoral veins, iliac veins, or the inferior vena cava. It is related to a high risk of pulmonary embolism. Usually accompanied by symptoms (Table 3), but can also be asymptomatic. Sometimes the first symptoms of proximal thrombosis is a pulmonary embolism episode. Painful swelling (phlegmasia dolens) is an acute form of thrombosis, related to simultaneous closing of multiple vein vessels, accompanied by strong pain and severe swelling of extremities. It can lead to loss of extremities, and even death [8].

Differential diagnosis of DVT includes: trauma, hematoma, chronic venous insufficiency, superficial veins thrombosis, inflammation of: subcutaneous tissue, muscles, tendons or joints, lymphatic swelling, swelling after administration of some drugs (typical calcium channel blockers, e.g. amlodipine), and the broken Baker's cyst.

If particles of clots from lower extremities get with the blood flow to the pulmonary circulation, they can manifest in form of pulmonary embolisms. Pulmonary embolisms can be the first and only symptom of deep vein thrombosis.

Pulmonary embolism (PE) is a clinical manifestation of a narrowing or closing of the pulmonary artery (or its occlusions) by clotting material. Most often these are caused by clots, but it is important to remember the less common blockages caused by fat tissue (e.g. broken pipe bones), air (e.g. after catheterization of large vessels), cancer tissue, or amniotic fluid. PE cause approx. 10% of all deaths in hospitalized patients. At the same time it is the most common cause that could be prevented. An early detection of PE episodes is very important, as even with effective treatment methods the death rate cannot be reduced completely – i.e. in clinically stable patients, with accompanying right cardiac ventricle dysfunction, the death rate is still 3-15%, and with accompanied by hypotension or concussion is over 15% [9].

Table 3. **Venous thromboembolism risk factors (VTE) [3].**

Patient-related	Iatrogenic
Age >40 years (risk increases significantly with age)	
Obesity (BMI > 30 kg/m2)	
Pregnancy and labour	
Varicose veins in lower extremities (in patients older than 60 years)	
Class III and IV (NYHA class) cardiac failure	
VTE history	Use of oral anticonception (OCT)
VTE family history	Use of hormonal replacement therapy (HRT) or selective estrogen receptor modulators (SERM)
Trauma (in particular multiple organ, pelvis fractures, lower extremities pipe bone fractures)	
Brain stroke with paralysis or significant paresis of lower extremities	Anticancer treatment (chemotherapy, hormonal drugs, angiogenic inhibitors)
Long immobilization	
Bedridden patient treated preventatively (e.g. severe pneumonia, COPD)	Use of erythropoiesis stimulating agents
Malignant cancer	
Ventilatory failure	Significant surgical procedures (in particular in the abdominal cavity, pelvis and lower extremities area) – the risk depends on the location, technique applied and duration of procedure, type of anaesthetic, and duration of post-surgical immobilization.
Nephrotic syndrome	
Acute inflammation and sepsis	
Autoimmune diseases (i.e. rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, primary idiopathic thrombocytopenic purpura)	
Thrombophilia	
Polycythemia vera	Catheter in a large vein vessel
Essential thrombocytosis	
Compression of vein vessels (e.g. hematoma)	
Marchiafava-Micheli anemia	
Presence of antiphospholipid antibodies	
Long airplane travel (longer than 6 hours)	

PE risk factors are the same as in case of DVT (Table 5). Symptoms reported by patients and observed signs are not specific (Table 5) and can be related to other diseases (i.e. pneumonia, COPD, asthma, esophagus diseases, intercostal nerve neuralgia, Da Costa's syndrome, acute coronary syndrome, pneumothorax, aortic dissection, cardiogenic shock, heart tamponade).

Deviations in laboratory tests in patients with PE may include: a higher concentration of the D-dimers, and sometimes also troponin, natriuretic peptides (BNP, proBNP), changes in ECG (e.g. tachycardia, supraventriucular arrhythmia, dextrogram, appearance of the complete or incomplete right bundle-branch block, some fresh alterations of the ST sector and T-wave), in the chest radiogram (which is correct in one-fourth of all patients), can help determine if there is fluid in the pleura, enlargement of heart, collapsed lung air pockets, parenchymal concentrations, broadening of the pulmonary artery, or elevated hemidiaphragm. Imaging studies still hold highest diagnostic value – angio-CT, heart ECHO, USG of lower extremities veins [9].

Table 4. **Deep vein thrombosis symptoms [6].**

Reported by patients	Deviations in physical examination
Pain in calf when walking Pain when resting in the afflicted extremity.	One-sided swelling of the lower leg or swelling of extremity, visible as thickening (circumference measured at about 10 cm below the thickening of the shin > by 2 cm) Pain or sensitivity to compression Excessive warming of the extremity Positive Homans' sign (passive bending of foot dorsum causes pain in calves) Elevated body temperature and fever Widening of superficial veins despite elevation of extremity to a 45^{O} degree Sometimes skin discoloration (white or grey-blue with a painful swelling, reddened with vein inflammation).

Table 5. **Signs and symptoms of pulmonary embolism [8].**

Reported by patients	Deviations in physical examination
Dyspnoea (approx. 80%) – particularly with a sudden onset Chest pain of pleural character (approx. 50%) – stinging, sharp, can be one-sided, increased with deeper inhalation, coughing, chest movements, can radiate to the area between shoulder blades, decreased when lying on the side of the pain. Coughing (approx. 20%) – in particular dry cough Chest pain or discomfort of coronary character (approx. 10%) – compressing or burning, increased with exertion, stress, can radiate to the lower jaw, neck, shoulders, abdomen Fainting Spitting out blood	Increased breathing frequency (tachypnoe) >20/min Increased heart rhythm (tachycardia) > 100/min Hypotension (systolic RR < 90 mmHg, or decrease by ≥40 mmHg for longer than 15min) Shock Widening of neck veins, signalling right ventricular failure. Tricuspid valve regurgitation murmur (not frequent) Increased partial pulmonary volume II hart sounds (P2>A2)

Each patent with suspected PE should be diagnosed as soon as possible. Treatment strategy depends on patient's state and diagnostic possibilities of the health care facility. In everyday practice it is useful to apply clinical assessment instruments for PE – Padwa Risk Assessment Scale (Table 6) and the Well's Criteria (Table 7). It should be emphasized that VTE is not the only serious adverse effect of APs' therapy. Indications of all the APs are especially limited in elderly patients with dementia, mainly due to increased risk of the ischemic stroke.

Table 6. **VTE risk factors in hospitalized patients (high risk of thrombosis – score of ≥4) [42].**

Risk factor	Points
Active neoplasmic processes	3
History of VTE (excluding superficial vein thrombosis)	3
Immobilization (remaining in bed longer than 3 days)	3
Congenital thrombophilia (deficiency of antithrombin, C or S protein; Type Leiden gene Factor V or mutation of the G20210A prothrombin gene, antiphospholipid syndrome).	3
Injury or surgical procedure in the past 2 months	2
Advanced age (older then 70)	1
Ventilatory or cardiovascular failure	1

table continued on the next page

Myocardial infarction or ischemic brain stroke	1
Acute infection or rheumatologic disease	1
Obesity (BMI above 30)	1
Current hormonal treatment	1

Table 7. **Clinical probability assessment for PE in accordance with the Well's score [9]**

Variable	Points
Predisposing factors: – history of VTE (PE, or DVT) – recent surgical procedure or immobilization – malignant cancer	 1.5 1.5 1
Signs: – spitting out blood	 1
Symptoms: – tachycardia >100/min – symptoms of deep vein thrombosis	 1.5 3
Clinical presentation: – diagnosis less probable than pulmonary embolism	 3
Result interpretation: Clinical probability (out of 3 levels) – total of points 0-1 small 2-6 average ≥7 large Clinical probability (out of 2 levels) – total of points 0-1 small probability of pulmonary embolism > 4 pulmonary embolism probable	

Association between use of APs and VTE

The prominent natural death cause in patients with schizophrenia are cardiovascular diseases [10]. It is estimated that death rate caused by cardiovascular problems is twice as high in schizophrenic patients, than in the general population. Until now no definite causes explaining this situation have been identifie [11]. It has been suggested that more frequent occurrence of obesity, arterial hypertension and dyslipidaemia in these patients might be responsible. Smoking and APs administration is

an important detrimental coincidence [12, 13]. VTE is one of the most dangerous of the all APs' adverse effects, apart from the metabolic syndrome and the neuroleptic malignant syndrome.

Until now results of several retrospective studies, meta-analyses and VTE case studies of patients treated with APs have been published. The temporal association between the antipsychotic treatment and emergence of VTE has been the main focus. The significance of type of treatment on development of VTE has also been studied.

Duration of APs' administration and VTE risk

Duration of AP's administration is one of the leading considered risk factors of development of VTE. Majority of studies emphasise highest risk of VTE development during the introduction of the treatment which decreases with the duration of treatment. The risk of VTE has been shown to be 20% higher in patients during first 3 months of treatment than in the following 9 months (comparing with patients not-treated with antipsychotics, the total risk is estimated to be 85% and 65%) [14]. Moreover a double increase in the risk of VTE has been described in patients currently treated with APs, (defined as treatment within 90 days before hospitalization due to VTE), compared to the patients not-treated with APs. The one and a half increase in VTE risk has been identified in patients treated with APs for more than 180 days before the admission [15].

Similarly, the temporal association between APs use and VTE has been described in a study published in 2010 in the British Medical Journal. More than 25,500 of the first-time VTE episodes have been analysed and it has been found that in patients treated with APs in the last 24 months the risk of VTE has been 32% higher, than in patients not using APs. Patients who started treatment with APs three months ago, had VTE risk twice as much, than patients not using APs. Moreover, this research confirmed earlier publications showing double increase in the risk fo VTE in patients starting APs therapy within three months [16].

However, some retrospective observational studies, with cohorts followed for 7-11years proved that long-term treatment with APs decreases the cumulated death risk, when compared with non-treated patients (risk 0.81 vs.1.0) [17]. These studies suggest, that unfavourable influence of APs on VTE development is quantitatively limited and moderated by various additional factors. Effectiveness of the treatment remains the leading protective factor. In the cited study, treatment with clozapine and olanzapine, which are considered the most effective APs, was associated with the lowest death risk, while both drugs were reported as most frequent risk factor for VTE (Table 1, Table 8)

Table 8. **Number of VTE cases during APs treatment reported to the WHO database [2, 17].**

Antipsychotic drug	Cases reported
Haloperidol	41
Flupenthixol	9
Zuclopenthixol	10
Chlorpromazine	14
Perazine	7
Levomepromazine	6
Amisulpride	2
Aripiprazole	4
Clozapine	385
Olanzapine	99
Quetiapine	20
Risperidone	91
Sertindole	6
Ziprasidone	13

Type of treatment and risk of VTE

Not enough data has been published so far to distinguish the prothrombotic potential of single APs. Most of the research summarising both clinical studies results and cases reports includes tables with the number of thrombosis cases in patients treated with one AP. However, it should be remembered, that VTE is a multi-factorial disease and it is difficult to indicate the role of the single drug in the pathogenesis of VTE. Even big head-to head clinical studies comparing the frequency of VTE cases between users of APs could not give the answer to this question. Data showed below should be considered as preliminary and approximate.

However, some metaanalyses published in prestigious journals indicate APs with higher procoagulant activity than others. Some articles just confirm increased risk of VTE in patients treated with APs, however, not mentioning about differences among Aps [18].

It should be emphasised, that according to present knowledge, procoagulant activity in not proportional to antipsychchotic activity of the APs. VTE was diagnosed more frequently in patients treated with weak or moderate antipsychotics (chlorpromazine, quetiapine) than in patients treated with drugs with a stronger antipsychotic effect (risperidone, haloperidol, olanzapine, trifluoperazine) [17].

However, the results of a retrospective study, with more than 450,000 patients who at least once were treated with APs, showed that the highest risk for pulmonary embolisms was related to treatment with clozapine, risperidone, ziprasidone, and haloperidol. No such relationship was identified for quetiapine and aripiprazole [19]. The study did not however take into account the association between a PE episodes and use of APs, and did not include a control group.

There were also published cases of VTE in patients treated with olanzapine [20], as well as of pulmonary embolisms in patients treated with amisulpride [21].

Analysis of the safety profile of atypical APs showed a significant increase in hospitalization rate of patients treated with clozapine, risperidone and olanzapine, compared to patient not treated with Aps [22].

The MHRA report including summary of individual reports from healthcare professionals, concluded that VTE complications were most frequent when using clozapine, risperidone, chlorpromazine, and haloperidol (Table 1). Similarly, the results of an analysis of the WHO adverse effects database, published in 2008, showed that almost half of all VTE cases in patients treated with APs were related to clozapine (Table 8). An increased risk of VTE has been also identified in patients using olanzapine, risperidone, haloperidol, quetiapine, ziprasidone, and chlorpromazine [23].

No studies comparing the number of APs taken simultaneously and the risk of VTE have been published so far. The analysis of death risk due to natural reasons in patients suffering from schizophrenia have not shown any association with APs polypharmacy [24, 25].

Moreover, no studies analysed frequency of cases of VTE in patients treated with APs in depot form. However, injection application has been extracted as a risk factor for VTE development [26]. Lack of such data may result from low reporting rate of adverse events by GPs. Due to specific pharmacokinetic properties and mechanism of action, patients treated either with APs in depot form or more than one APs simultaneously should be monitored.

Mechanisms of thrombosis mediated by APs

Despite many studies indicating an association between the use of APs and VTE, there is not enough data to explain prothrombotic activity of APs. It should be remembered that mechanisms of prothrombotic activity may be as different as different are mechanisms of its antipsychotic action. Available data do not, however, indicate any association between the binding affinity of APs to serotonine $5HT_{2A}$, histamine H_1

and dopamine D_2 receptors and its prothrombotic activity. Moreover, no association between the dose of APs and the risk of VTE development has been shown [27].

Considered risk factors for VTE also include a variety of biologic mechanisms, such as hormonal abnormalities (hiperprolactinemia), increased platelet aggregation, increased concentration of antiphospholipid antibodies and hiperhomocystynemia [28].

Hiperprolactinemia is a common adverse effect of APs. In patients treated with APs both hiperprolactinemia and activation of platelets have been described [29]. Hiperprolactinemia is considered as one of possible VTE-promoting factor due to prothrombotic action of prolactine [30].

The issue of potential direct proagreggative action of APs is still studied. Platelet agreggation and adhesion (due to the action of superficial receptors) are important factors for VTE development. 5HT2A receptor, present on platelets, binds some of APs (risperidone, chlorpromazine, flufenazine, haloperidole, quetiapine, aripiprazole) [23]. In patients suffering from schizophrenia, treated actually with these APs increased platelets aggregation has been described. It's worth stressing, that among a variety of APs only clozapine caused increased platelets aggregation in vitro. On the contrary, haloperidole and olanzapine decreased platelets aggregation in vitro. However, clinical relevance of this laboratory finding is not clear [16].

Increased concentration of antiphospholipid antibodies (including lupus anticoagulants) and anticardiolipin antibodies have been noted for patients treated with antipsychotics [31]. The presence of both types of antibodies is associated with increased risk of VTE [32].

It has also been suggested that psychotic disorders themselves can be conditions with increased procoagulation activity. In patients with acute psychosis a significant increase in D-Dimers (marker of thrombogenesis) was found in psychotic patients. P-selectin (thrombocytes activity marker) and an increase in GPIIb/IIIa platelet receptor expression have been also identified. In women with acute psychosis a significant increase in concentration of blood-clotting factor VIII was found, what is associated with an increased risk of VTE [33].

Many researchers indicate the role of indirect factors in prothrombotic activity of APs. One of the major factor considered is decreased physical activity, resulting either from primary disease or its complications (mainly associated with untoward effects of the treatment), such as increased body mass, metabolic syndrome [34] or sedation. Sedation, resulting mostly from concurrent blocking of many receptors (dopaminergic, histaminergic, adrenergic, muscarinic), is most frequently reported in case of classical APs (chlorpromazine, haloperidol) and some atypical medicines (clozapine, olanzapine, quetiapine). Increased body mass, most probably a result of the blocking of H1 histamine, adrenergic alpha 1 and serotonin 5-HT2c and 5-HT6, receptors, is the adverse effect observed in patients treated with clozapine, olanzapine, risperidone, and chlorpromazine [35]. Obesity, being one of the most important factors for VTE may

be a reason for decreased physical activity, which may futher cause decrease in plasma fibrynolytic activity. Additionally, obesity is associated with development of heart coronary disease and higher incidence of acute myocardial infarction, both being risk factors for VTE. However, it should be emphasised, that increased risk of VTE may persist despite of weight reduction. It is probably caused by irreversible inflammatory changes in blood vessels of obese patients suffering from artherosclerosis.

Secondary factors associated closely with the specificity of psychiatric treatment may also play important role. These include physical restrain (especially with injury of blood vessels), deficiency in fluid intake (for example, due to catatonia) or fewer and rhabdomyolysys (during neuroleptic malignant syndrome) [36]. All of these factors may result in increased prothrombotic activity in patients, resulting in VTE development.

Assessment of VTE risk in patients treated with APs

One of the key elements of VTE prevention is identification of risk factors, both related to the patient and to the treatment itself. In a study which included approximately 15,000 VTE cases (including 39% PE and 61% DVT), an increased VTE risk was identified in women, as well as positively related to age, BMI and number of cigarettes smoked daily. Similarly, an increased risk was identified in case of congestive heart failure or varicose veins (increase by 40%), chronic renal failure (increase by 60%), cancer (increase by 85%), COPD (increase by 41%), inflammatory bowel disease (increase by 45%) and in patients hospitalized in the past six months (increase by 86%). No difference in VTE risk was identified for men and women treated with antiplatelet drugs, auricular fibrillation, cardiovascular disorders, asthma and family history for VTE. An important VTE risk factor was also the use of different drugs. The highest increase risk was found in relation to APs (almost by 55%), tamoxifen (48%), anti-contraceptives (33%), and hormone replacement therapy (20%) [36]. The authors of the cited study developed an algorithm, for quick assessment of VTE risk. It is available on the website: www.thrombosis.org.

Despite the fact, that data shown above apply to general population, it may be considered important for VTE risk assessment in patients treated with APs. Proposed algorithm includes treatment with APs as one of the risk factors for VTE development.

It's worth stressing, that some studies show higher risk of VTE development in men comparing to women. In women risk increases when other risk factors, such as hormonal replacement therapy, obstetrical complications or pregnancy exists [38].

Decreased risk of VTE development has been observed in elderly patients treated with low doses of classic APs [16], compared to young patients. Elderly patients with dementia, treated with APs are separately studied. However, in this group of patients highest risk of VTE development during 90 days of treatment has been confirmed. Moreover, decreased risk of VTE has been shown both after withdrawal of the therapy

or during chronic treatment [39]. It should be emphasised, that elderly patients with dementia, treated with APs should be monitored for symptoms of VTE during first three months of treatment, especially when other risk factors (such as hip bone fracture, history of VTE, simultaneous treatment of classic and atypical APs) exist.

VTE prevention in patients treated with APs

Before start of an antipsychotic treatment, a VTE risk assessment is mandatory. In case of the high risk of VTE (a result of 4 points or more, Table 6), it is necessary to consult a general practitioner and evaluate the need of anticoagulant prevention. An effective VTE prevention is considered the most important element of providing patients with safe treatment. In accordance with „Polish guidelines on prevention and treatment of venous thromboembolism – amended in 2012." [8] and the NICE recommendations [40] there is no need for routine anticoagulation treatment in patients treated with APs. In the recommendation of the American College of Chest Physicians in immobilized patients, without other VTE risk factors, pharmacological treatment is also not recommended. It is however emphasized that there is a need for pharmacological VTE prevention in patients hospitalized due to acute medical conditions (without a defined cause), terminally ill patients, cancer patients, chronically immobilized, persons travelling for a long and with diagnosed, asymptomatic thrombophilia [25]. The recommendations do not identify patients on APs therapy as a separate group. In each case of APs' use, the need to exclude other procoagulation factors such as dehydration, smoking, use of anti-contraceptives or a hormonal replacement therapy, has to be considered. It is also important to notify the patient about a need for increased physical activity and keeping of a proper body weight, to prevent undesirable thrombosis events. In case of VTE suspicion the anticoagulation treatment should be introduced immediately.

In relation to physical restrain accompanying APs treatment the above recommendations could be concluded, that additional pharmacological prevention of VTE might be indicated only in case of prolonged restraint. Association between physical restraint and sudden death of psychiatric patients has not been proven yet [41]. The conclusive analyses of coincidence of so many risk factors, such as simultaneous restraint, APs treatment, behavioral disorders, primary disease, electrolyte disturbances, etc. is very difficult.

Summary

1. Despite a long-term use of APs, the information on their safety of use is still incomplete. Thromboembolic complications in form of DVT, PE and ischemic

brain stroke are among the most serious adverse reactions to APs and may be associated with the risk of death in psychiatric patients. Increased risk of VTE during APs' treatment is widely described, however with frequency not exceeding 4-10/10000. The highest risk of VTE development was observed during first three months of the APs' treatment.

2. Based on currently published data and spontaneous reports it is impossible to identify a specific antipsychotic medication largely exceeding prothrombotic activity of other APs. Postulated differences between prothrombotic action of classic and atypical APs have not been definitely proven yet. Available data is often incomplete. Each of the studies described had many limitations and their results should be treated as preliminary. Since no study was performed comparing head-to-head safety of individual APs, the question which treatment has the lowest risk for undesirable effects remains without answer.
3. It is necessary to perform a careful risk assessment for thrombosis and to attempt eliminating modifiable risk factors. Each hospital should develop internal VTE prevention standards and treatment in accordance with guidelines updated by relevant associations and expert groups. Sensible VTE prevention practices are important not only because of the significant decrease of general treatment costs, but foremost because of assurance of patients' safety. Appropriate prevention will not completely eliminate the risk of VTE. In case of appearance of symptoms, which could suggest a thromboembolic episode in a patient under VTE prevention treatment, the possibility of deep vein thrombosis and pulmonary embolisms should always be taken into account in differential diagnosing.
4. It also bears emphasis that each severe adverse event, and VTE is such an adverse reaction, shall be reported to the Department for Pharmacovigilance at the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products. Reports submitted by healthcare professionals are a valuable source of post-authorization data on the safety of use of a medicinal product, and based on them the Summary Products Characteristics are being amended by new, significant information.

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