

# Depression, antidepressants and pulmonary embolism

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A 66-year old male, ex-smoker (10 pack/years), with no known history from the respiratory system, was admitted to our department due to right-sided pleuritic chest pain and progressive dyspnea on exertion during the last 20 days. With regards to his medical history, the patient was receiving escitalopram due to depression, antihypertensive drugs and had a history of acute ischemic stroke.

On admission, clinical examination unveiled: body's temperature 37,4°C, SaO<sub>2</sub> 97% FiO<sub>2</sub> 21%, heart rate 80 beats per minute, blood pressure 125/65 mmHg and reduction in the intensity of breath sounds in the right side. A computed tomography pulmonary angiogram (CTPA) was performed demonstrating an embolus in the right pulmonary artery, as well as pleural effusion in the right side. Based on PESI score, pulmonary embolism was considered as low risk (class II). Blood tests for mutations in homocysteine, V-Leiden, prothrombin G20210A, protein C & S, antithrombin were performed. At his exit, patient was in good condition. He was asked to continue his treatment for pulmonary embolism at least for 3 months (a reevaluation was scheduled) and to perform a new chest computerized tomography and possibly a Positron Emission Tomography in the next month for the evaluation of the nodule.

Based on that case, we aimed to highlight the current evidence about the association of antidepressants and the spectrum of venous thromboembolism (VTE) (pulmonary embolism and deep vein thrombosis). Several factors including immobilization, cancer, trauma, surgery, obesity, hormonal therapy and inherited thrombophilia have been associated with VTE<sup>1,2</sup>; yet, several cases of VTE present with no known risk factors and thus there is still interest for identification of more causes.

A plethora of studies have investigated the association among anxiety, stress, depression, antidepressants and VTE development. The majority of previous studies, but not all, have reported increased VTE risk for patients with depression and/or antidepressant use<sup>3-10</sup>. Importantly, a recent meta-analysis had further corroborated the evidence that depression and use of antidepressants are associated with an increased risk of VTE<sup>11</sup>.

In particular, there are both studies investigating the risk for VTE in patients with depression and patients with no depression and studies comparing antidepressants use versus no use (Table 1). Patients with depression presented with increased risk for VTE, as the relative risk ranged between 1.19

**TABLE 1.** Table 1 shows studies investigating the relative risk for venous thromboembolism for patients with depression or for patients receiving antidepressants

Study	Number of participants	Groups	RR (95% CI)	Reference
Enga et al, 2012	25964	Depression vs no Depression	1.60 ( 1.02, 2.50)	(3)
Lee et al, 2015	105822	Depression vs no Depression	1.38 ( 1.09, 1.73)	(5)
Parkin et al, 2017	734092	Depression vs no Depression	1.19 ( 0.95, 1.49)	(7)
Ray et al, 2002	75649	Antidepressants vs no Antidepressants	1.04 ( 0.94, 1.15)	(9)
Parkin et al, 2003	263	Antidepressants vs no Antidepressants	4.90 (1.10, 22.50)	(12)
Lacut et al, 2007	1354	Antidepressants vs no Antidepressants	1.10 (0.90, 1,50)	(10)
Jick et al, 2008	3867	Antidepressants vs no Antidepressants	1.20 (0.90, 1.40)	(8)
Wu et al, 2013	13102	Antidepressants vs no Antidepressants	1.59 (1.27, 2.00)	(6)
Parkin et al, 2017	734092	Antidepressants vs no Antidepressants	1.39 (1.23,1.56)	(7)

Abbreviation: CI: Confidence Interval, RR: Relative Risk

and 1.60<sup>3,5,7</sup>. Use of antidepressants was also associated with increased risk for VTE, with the relative risk ranging between 1.04 and 4.90<sup>6-8,10,12</sup>.

Special attention needs to be drawn in the recently published, largest study conducted to date, which comprised more than 700.000 women followed for an average of approximately 7 years<sup>7</sup>. It was shown that women receiving antidepressants had an increased risk of VTE. Nonetheless, women reporting treatment for depression but not on antidepressants presented with no significantly increased risk of VTE. The key strength of that study compared to others was the number of participants, as well as the fact that they had robust long-term information both on depression and on regular use of antidepressants. However, the puzzling outcome was that the risk was similar regardless of the type of antidepressant. Tricyclic antidepressants, selective serotonin reuptake inhibitors and other antidepressants were associated with risk of similar magnitude, even though they are pharmacologically distinct compounds<sup>7,13</sup>. Several speculations could be made based on that outcome, including the fact that VTE risk is may be actually related to the depression itself and not the drug; yet, a definite conclusion cannot be drawn.

Pathogenetic mechanisms connecting depression, antidepressants and VTE remain elusive. It is still a matter of ongoing debate whether statistical significance is associated with causality or not. This debate remains mainly due to the fact that epidemiological studies are limited the relative risks were low in the majority of them<sup>13-15</sup>. In case depression itself is the key driver, it has been proposed that

depression driven lack of mobility, or depression driven obesity could contribute to VTE development, as these are known risk factors for VTE<sup>16-21</sup>. Furthermore, depression has been associated with increased homocysteine levels and thus with increased platelet activation, procoagulant activity and thromboembolic risk<sup>22-24</sup>. With regards to antidepressants, it has been suggested that association between antidepressant use and risk of PE could be due to the chemical similarities between tricyclic antidepressants and phenothiazines, which are antipsychotics already associated with increased risk for VTE through increased platelet aggregation, presence of anticardiolipin antibodies and venous stasis as a result of their sedative effect<sup>12,25,26</sup>. Moreover, it has been proposed that antidepressants and especially selective **serotonin reuptake inhibitors (SSRIs)**, might increase the risk for VTE through modulation of levels of peripheral serotonin<sup>27,28</sup>. In particular, it has been shown that antidepressants not only affected neuronal serotonin (5-HT) uptake, but also modulate peripheral serotonin, resulting in an increase in serotonin near specific serotonin receptor subtypes in discrete regions of the body where relevant physiological processes were regulated<sup>29</sup>. **Serotonin** itself represented a platelet agonist, and in the presence of proaggregatory factors (e.g., collagen, adenosine diphosphate, adrenaline), it could potentiate platelet aggregation. Therefore, a rise in serotonin levels might lead to an increase in the risk of hypercoagulability<sup>30</sup>. However, all these data represent speculations. There is an amenable need for well -designed studies investigating a possible mechanistic

link between antidepressants and thromboembolic risk in order to have a definite conclusion.

Collectively, depression represents a disorder with a gradually increasing incidence and antidepressants are increasingly being prescribed<sup>31,32</sup>. Consequently, the last years have seen an increase in the interest for the impact of depression and antidepressants in patients' quality of life. Epidemiological studies provided evidence that depression and use of antidepressants were associated with increased risk for VTE. It is still unclear whether statistical significance means also causality. Furthermore, it remains to be addressed whether the key driver for the thromboembolic event is the depression itself or the drug. Towards this direction, there is amenable need for large, long term, well-designed studies including highly characterized participants and recording the exact type of the antidepressant used, as well as the time point of the thromboembolic event in association with the start of the drug.

Before definite conclusion is drawn, it will be important for the prescribers of such compounds to consider the **increased VTE risk** reported. Similarly to the prescription of estrogen-containing hormone modulating therapy, providers may ask about VTE, bleeding history and family history before prescribing antidepressants in such an easy way. Applying a personalized medicine approach and weighting the benefits and risks of such a prescription would be an important step, while the results of well-designed studies are anticipated.

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