WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 8, Issue 12, 1662-1674. Research Article ISSN 2277– 7105

INFLUENCE OF MAJOR DEPRESSIVE DISORDER AND THE USE OF ANTI-DEPRESSANTS ON DEVELOPMENT OF VENOUS THROMBOEMBOLISM

Lina El-haj Mousa, *Tarig Osman, Nahid Osman

College of Clinical and Industrial Pharmacy, National University- Sudan.

Article Received on
21 Sept. 2019,
Revised on 11 Oct. 2019,
Accepted on 01 Nov. 2019
DOI: 10.20959/wjpr201912-16245

***Corresponding Author**
Dr. Tarig Osman
College of Clinical and Industrial Pharmacy,
National University- Sudan.

ABSTRACT

Background: A venous thromboembolism (VTE) generally covers two interrelated conditions, deep venous thrombosis (DVT) and pulmonary embolism (PE). Thromboembolic disease is considered the third most common acute cardiovascular disease globally. Various studies have been reporting an observed increased risk of venous thromboembolism (VTE) associated with depressive disorder. **Objective**: The present study aims to evaluate the occurrence of this association between depressive disorder and antidepressant medications with the risk of subsequent development of venous thromboembolism. **Design:** A retrospective hospital-based descriptive study that was conducted in Khartoum state hospitals. **Methods:** Total Coverage purposive technique of available patients' records hospitalised with depressive disorder, deep vein thrombosis (DVT) or pulmonary embolism (PE) during the year 2018. The collected data was reviewed, extracted to excel sheets and analysed using the Statistical Package for the Social Sciences SPSS (IBM SPSS Statistics 24). **Results:** A total of 221 cases were covered. According to findings, the development of DVT was found to be significantly associated with the presence of depressive disorder and with the use of antidepressant medications (P=0.001 in both circumstances). While the occurrence of PE was found to be significantly associated with the existence of depressive disorder (p=0.007) and no association was found with the use of antidepressant medications. **Conclusion:** This study concluded that major depressive disorder is constituted a risk factor in developing venous thromboembolism. Moreover, the use of antidepressants, even if indicated for a disorder other than depression, is associated with the development of DVT. However, neither depression nor antidepressant use is

associated with pulmonary embolism but indirectly can contribute through DVT to develop PE.

1. INTRODUCTION

Cardiovascular disease (CVD) constitutes the leading cause of mortality worldwide, particularly in low- and middle-income countries. According to the World Health Organization in 2015, out of the 17 million premature deaths (under the age of 70) due to non-communicable diseases, 82% were in low- and middle-income countries, and CVDs caused 37% of these premature deaths.[1] Venous thromboembolism (VTE) which manifests clinically as deep vein thrombosis (DVT) and pulmonary embolism (PE) contributes as the third most common cause of death from cardiovascular diseases after heart attacks and strokes. VTE disorders are associated with a high mortality rate, substantial healthcare costs, and a high rate of recurrence.[2] The exact numbers of incidence and prevalence are often underestimated as the symptoms of these disorders are often silent, and thus the disease frequently goes by undiagnosed; however, some studies estimated an incidence rate of 1-2 per 1000 persons every year.[3]

Pulmonary embolism is a serious, life-threatening condition and most commonly derives from deep vein thrombosis of the lower extremities. Most DVTs originate in the calves, and 80% of distal DVTs are known to resolve spontaneously. PE reportedly occurs in up to 50% of patients.[4]

Knowledge of genetic and environmental risk factors is crucial for the effective application of diagnostic prophylactic and therapeutic interventions for VTE cases. Though depression is now being recognised as a possible risk factor for developing VTE, however, depression in Sudan is an unnamed disorder that is experienced and seen, yet rarely acknowledged. Access to mental health care is considered a challenge to those without access to health insurance services or funds and the role of environmental risk factors in the development of VTE in the Sudanese population is poorly characterised.

In the current work we are trying to assess the association between depressive disorder and antidepressant medications with the risk of subsequent development of venous thromboembolism in Sudanese population.

2. METHOD AND MATERIALS

Study design: A retrospective descriptive hospital-based study.

Study area: The study was conducted in specialised hospitals in Khartoum state.

Study period: The study was conducted during the period from September 2018 till February 2019.

Study population: Total coverage of all patients diagnosed with either of; deep vein thrombosis or pulmonary embolism in the year 2018.

Data collection techniques and tools

Data were collected using a predesigned, pretested data collection form that was formulated by the researcher. The form was composed of patients' demographic information, past medical history –focusing on comorbidities known for increasing risk of VTE occurrence- and past medications history. The researcher acquired permission to enter hospitals from the Federal Ministry of Health research ethics committee and the hospital's authorisation committee, patients' records from 2018 were categorized, and the patients' files that matched the research criteria were chosen. The data collection was done by the researcher to ensure the accuracy of the obtained data, and a total of 221 patients' records were selected.

Data Analysis: The collected data was reviewed, extracted to excel sheets and prepared for statistical analysis using the Statistical Package for the Social Sciences SPSS (IBM SPSS Statistics 24). Descriptive and inferential statistics were used. Comparison between qualitative variables was made using the person's chi-square to test significance; $p < 0.05$ was considered significant.

Ethical Considerations

Ethical clearance was obtained from the National University research ethics committee and the Federal Ministry of Health research ethics committee. Records used were numbered to preserve the anonymity of patients' identity information. Data obtained were handled for the research purposes only and disseminated as statistic numbers, tables and charts without preaching the confidentiality of the data.

3. RESULTS

The following represents the statistical analysis for the data acquired from patients' records. The first section introduces the patients' demographic data while the second section presents the disease-related data which was covered from hospitals' records archive for 2018.

3.1. General Demographic Data

A total of 289 cases were covered yet, 68 of them were excluded for they missed some of the primary required data; as a result, 221 cases have been chosen and analysed; The age ranged from 18 to 90 with the majority being above 60 years old. The female gender covered almost more than half of the total cases. While more than a third of the covered patients were considered overweight, and nearly a quarter of the participants were found to be current smokers, and 14.5% were past smokers. Below are the tables and graphs demonstrating the exact numbers contributing the demographic data from patients' records.

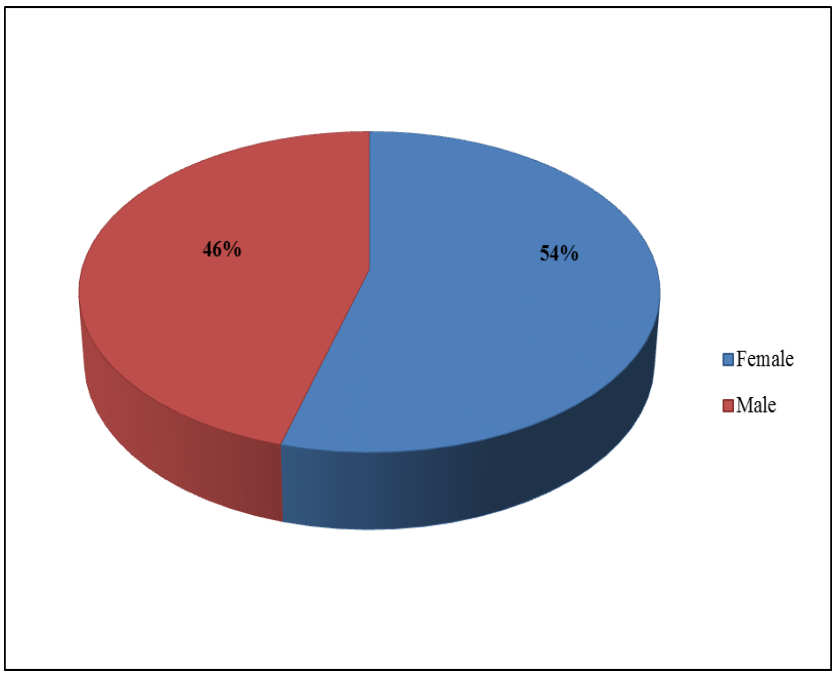

Figure (1): Distribution of Participated Patients' Gender.

Table (1): Age Distribution of Participated Patients.

Age Group		Frequency	Percent
	<40	62	28.1
	40-49	37	16.7
	50-59	52	23.5
	<60	70	31.7
	Total	221	100.0

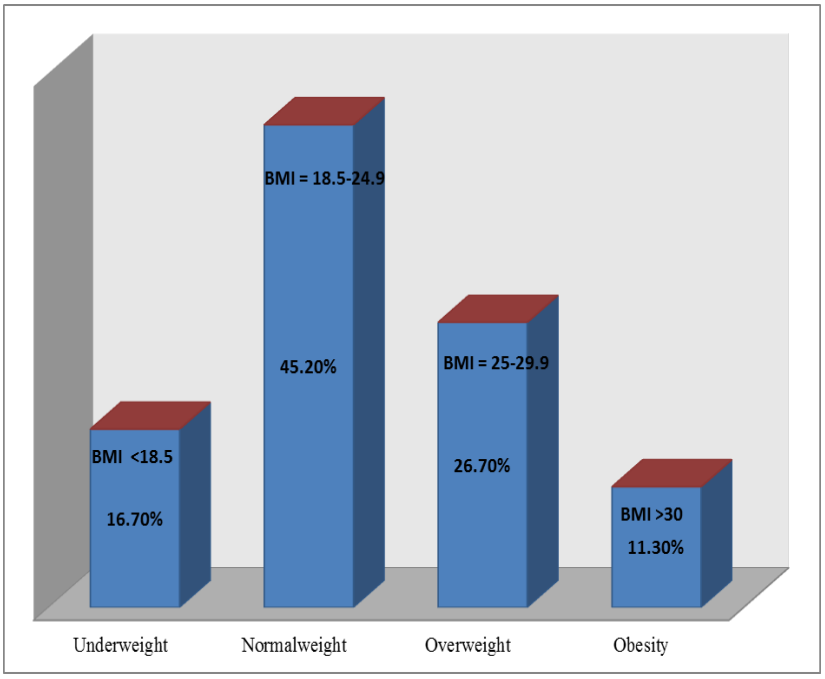

Figure (2): Body Mass Index Measurement of Participated Patients' Weight.

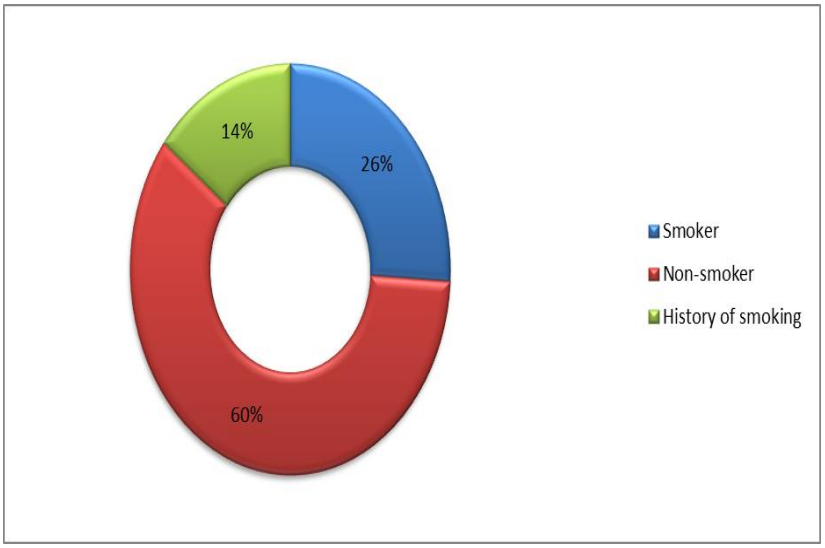

Figure (3): Distribution of Participant Patients According to Their Smoking Status.

3.2. Disease Data: The data considering patients' clinical status and treatment patterns were collected, analysed and summarized in (table 2).

Table (2): Clinical Characteristics and Treatment Patterns of the Study Cases Patients.

Clinical Characteristics	Frequency	Per cent
Myocardial Infarction	9	4.1
Malignancy	16	7.2
Congestive Heart Disease	1	0.5
Ischemic Stroke	10	4.5
Haemorrhagic Stroke	30	13.6
Thrombophilia	4	1.8
Hyperthyroidism	2	0.9
Hypothyroidism	5	2.3
Hypertension	46	20.8
High cholesterol	12	5.4
Diabetes mellitus	23	10.4
General Surgery in the last six months	2	0.9
Major trauma in the last six months	17	7.7
Infectious disease in the last six months	5	2.3
Hip surgery in the last six months	5	2.3
Hip/lower limb fracture in the last six months	16	7.2
Pregnancy in the last six months	5	2.3
Epilepsy	2	0.9
Guillain-Barré syndrome	1	0.5
Antihypertensive medications	49	22.2
Oral hypoglycaemic medications	17	7.7
Insulin therapy	14	6.3
Statin therapy	16	7.2
Anticoagulant medication	12	5.4
Non-Steroidal Anti-Inflammatory medications	26	11.8
Musculotropic antispasmodic medications	2	0.9
Carbimazole	2	0.9
Thyroxine medications	5	2.3

The findings were further categorised into subdivisions; 1) DVT/PE association with Depression and/or Antidepressant Medications and 2) DVT/PE related findings and associations;

1) DVT/PE association with Depression and Antidepressant Medications

According to findings, the development of DVT was markedly and significantly associated with the presence of depressive disorder and with the use of antidepressant medications (P=0.001 in both circumstances). Whilst, there was no association (P=.193) was found with neither the use of antidepressant medications nor presence of the disease. These findings are more prominent in females, in patients ageing sixty years and above and in patients with BMI measurements in the range.[18.5-24.9]

Table (3): Occurrence of Deep Venous Thrombosis.

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Present	156	70.6	70.6	70.6
	Not-present	65	29.4	29.4	100.0
	Total	221	100.0	100.0	

Table (4): Occurrence of Pulmonary Embolism.

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Present	57	25.8	25.8	25.8
	Not-present	164	74.2	74.2	100.0
	Total	221	100.0	100.0	

Table (5): Occurrence of Depression Disorder.

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Present	66	29.9	29.9	29.9
	Not-present	155	70.1	70.1	100.0
	Total	221	100.0	100.0	

Table (6): Occurrence of Use of Antidepressant Medications.

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Present	57	25.8	25.8	25.8
	Not-present	164	74.2	74.2	100.0
	Total	221	100.0	100.0	

Table (7): Association between DVT/PE and Depressive Disorder.

		Deep Vein Thrombosis		Pulmonary Embolism	
		Present	Not-present	Present	Not-present
Depressive Disorder	Not-Present	16	50	9	57
	present	140	15	48	107
Total		156	65	57	164

Table (8): Association Between DVT/PE and Antidepressants Use.

		Deep Vein Thrombosis		Pulmonary Embolism	
		Present	Not-present	Present	Not-Present
Antidepressant Medications	Not-Using	17	40	11	46
	Using	139	25	46	118
Total		156	65	57	164

2) Depression and Antidepressant Medications Related findings

Depression and use of antidepressant medications were more common among females than males, and in two groups of patients aging (>60 years) and (<40 years). Patients demographic

characteristics-namely age, BMI and smoking status- were found to be positively significance with the occurrence of depression and disorder and the use of antidepressant medications (p=0.042, 0.047 and 0.05 respectively).

The most commonly prescribed antidepressant medications were; Selective Serotonin Re-uptake Inhibitors (SSRIs) (25.3%) -Sertraline- followed by Tricyclic Antidepressants and Tetracyclic Antidepressants. Other medications that were found to be commonly prescribed for depression disorder were; Antipsychotics (23.5%) -Olanzapine- and anticonvulsants (10.4%) mainly Sodium Valproate.

4. DISCUSSION

Venous thrombosis a severe disease and a fatal one, because fragments of the thrombi may detach and occlude branches of the pulmonary artery; which may sometimes lead to cardiac arrest. Our findings provided that 70.6% of the total cases were diagnosed with DVT and 25.8% were diagnosed with PE. The spectrum of disease ranged from clinically unsuspected to clinically unimportant to massive embolism, causing death.

Age**:** Cases were more prominent in elderly patients and female since most VTE patients in developed countries are over 65 years of age. With ageing, the severity of VTE also increases, i.e. the venous thrombosis will be more frequent and more extensive.[18] In old age patients the main triggering factor of VTE is long periods of immobilisation; furthermore, elderly patients with VTE often suffer from associated chronic diseases which make VTE diagnosis challenging and symptoms sometimes overlap and are confused or misinterpreted which may worsen their prognosis.

Depression disorder and use of anti-depressant medications, the prevalence of major depressive disease increased with age in both males and females.[19] This could be due to dealing with common late-life issues: social isolation, significant life losses such as the death of a partner, financial stress, and major health problems.

Gender: Venous thrombosis is a reproductive health risk for females. During the perinatal period, the risk of VTE increases by up to 5-fold, and the risk further increases by 60-fold postpartum. Furthermore, a large number of females worldwide are at a high risk of developing VTE because of the use of hormonal contraceptives or hormone replacement therapy (HRT) and undergoing infertility treatment. Although VTE is a specific reproductive

health risk for women, there is also strong evidence that male gender also is a significant risk factor for VTE. It was estimated that the incidence of DVT, PE or both was significantly higher in males than in females particularly at an older age.[20] Hence with advancing age, the risk for developing VTE in males increases while females at child-bearing age are more susceptible than males.

In depression, many decades of epidemiologic studies on depression indicated that females are more likely to meet criteria for major depression than males, and the prevalence of depression among females is approximate twice the prevalence of depression among males, this could be attributed to many reasons like hormonal changes which occur throughout their lives, biological factors, inherited traits, and personal life circumstances and experiences.[21]

Body Mass Index: Obesity appears to be associated with an increased risk for VTE. Although the association between obesity and VTE appears to be moderate, obesity can interact with other environmental or genetic factors and pose a significantly higher risk of VTE among individuals who are obese and who are exposed simultaneously to several other risk factors for VTE.[22] It was concluded that a relationship does exist between obesity and depression; this relationship will be described as mutual interaction, which makes it unclear whether obesity causes depression or is it depression, which eventually leads to obesity.

Smoking: Heavy smoking is considered a risk factor for provoking VTE, although studies show conflicting opinions regarding the strength of this relationship.[23] Similarly, in depression, studies have shown that depression and smoking often go hand in hand. People with depression are not only more likely to smoke but may also find it harder to quit smoking than those who are not depressed, also. It was suggested that smoking and depression might perpetuate each other; meaning that smoking makes people more depressed and depression makes people turn to smoke.[24]

Depressive Disorder: Mental health services in the country remain poorly developed and under-resourced. Although Sudan's mental health policy was re-formulated in 2008, mental health continues to receive very little attention from the government and is not high on the list of priorities for policy-makers. A large proportion of the population still depends on alternative or traditional medicine as their first remedy when they feel ill. Also, with poor social insurance scheme, people of low-income cannot afford the prescribers' fees and even when they are diagnosed they struggle greatly to pay for the expensive medicines. In

Sudanese society, the view about mental illness was stereotyped; this often leads to discrimination and social isolation of affected patients. In many regions in Sudan, women are expected to work and at the same time take care of children, do all the housework and often be the prime carer for parents, making them more vulnerable to depression. Religious believes, illiteracy, poor living conditions and daily life stress all applies more pressure on people who might drive them to develop and maintain negative mental state that could evolve into clinical depressive state, and as it was said in an article published the AFRICAN ARGUMENTS "Sudan is a country plagued by war, poverty and incompetent political leadership. Amidst these more obvious challenges the increasing burden of mental health should not be ignored". With the new knowledge that keeps pouring daily linking existing disorders together, depression and VTE cases should receive more consideration to avoid losing patients when it is possible to preserve their lives.

In general, both venous thromboembolism and depression seem to share the level of occurrence when it comes to demographic risk factors, which could be a possible factor that intensifies the strength of the association between developing of VTE in depression patients. The significantly increased VTE risk was observed for antidepressant medications users regardless of their use of other medications for managing depression (antipsychotic medications). Also, the type of antidepressant did not seem to make a difference, even though these drugs are pharmacologically distinct. These facts could suggest that increased VTE risk may be related to the depression itself and not the treatment. This is supported by previous studies which suggested that depressive feelings were associated with increased risk of occurrence of first time and recurrent VTE.[7,11,12,15]

The statistics measurements between this study and the previous studies mentioned in the literature review are different; our overall findings are related with the studies that confirmed a presence of a significant relationship between depressive disorder and the use of antidepressant medications with deep vein thrombosis occurrence, and the presence of depressive disorder with the development of pulmonary embolism.[7][8][9][10][11][12][13][14] While the previous studies in the literature review that reported no association between antidepressant medications and VTE confirm partially with our finding that antidepressant medications are not associated with the development of PE.[16][17] These findings suggest the presence of an association yet; a causative relationship cannot be suggested for it was difficult to determine whether depression or antidepressant medications use drove the

increased VTE risk or even if another related factor was the principal stimulus that caused some patients to develop VTE.

This study needed more time to assess more data from years previous to 2018 to strengthen the outcomes. Also, 68 records were eliminated from analysis because of poor recording techniques; much time was consumed while verifying the accuracy of recorded data on the 221 records used in this study.

5. CONCLUSION

This study concluded that major depressive disorder is constituted as a risk factor to develop venous thromboembolism. Moreover, the use of antidepressants, even if indicated for a disorder other than depression, is associated with the development of DVT. However, neither depression nor antidepressant use is associated with pulmonary embolism but indirectly can contribute through DVT to develop PE. Because antidepressant medications are increasingly being used to treat depression, anxiety, and other gastric/neurologic conditions, it will be necessary for prescribers of these drugs to consider the increased risk of VTE reported in this stud and the literature and more studies of the thrombotic and haemorrhagic potential of antidepressant medications in various patient populations are needed before specific recommendations can be confidently expressed. Increased attention to mental health by governments and researchers, is highly recommended as it is considered a human right essential for wellbeing and social development. Further studies are needed to establish the role of depression, and antidepressant medications use in VTE development, their potential causative pathways, and if there is a class effect of antidepressants on VTE.

REFERENCES

1. Danwang C. etal. Epidemiology of venous thromboembolism in Africa: a systematic review. *Journal of Thrombosis and Haemostasis,* 2017; 15: 1770–81.
2. Goldhaber S. and Bounameaux H. Pulmonary embolism and deep vein thrombosis. *The Lancet,* 2012; 379: 1835–1846.
3. Centers for Disease Control and Prevention. *Data and Statistics on Venous Thromboembolism.* Available from: https://www.cdc.gov/ncbddd/dvt/data.html
4. Turpie A., Chin B. and Lip G., Venous thromboembolism: pathophysiology, clinical features, and prevention. *The British Medical Journal BMJ,* 2002; 325: 887–90.

5. Ibrahim N., Hassan F., Elgari M. and Abdallah S., Risk factors for deep vein thrombosis of lower extremities in Sudanese women. *Vascular Health and Risk Management,* 2018; 14: 157–164.
6. Zhou H., Tang, Y., Yan Y., Yi Q. and Liang Z., Antidepressant Drugs and Risk of Venous Thromboembolism: A Case Report and Literature Review. Bulletin of Clinical Psychopharmacology, 2011; 21(3): 237-41.
7. Halperin D. and Reber G., Influence of antidepressants on haemostasis. *Dialogues in Clinical Neuroscience,* 2007; 9(1): 47-59.
8. Enga K., Brækkan S., Hansen I. and Hansen J., Emotional states and future risk of venous thromboembolism. *Thrombosis and Haemostasis,* 2012; 107(3): 485-493.
9. Jick S. and Lin Li, Antidepressant Drug Use and Risk of Venous Thromboembolism, *PHARMACOTHERAPY,* 2008; 28(2): 144-150.
10. Parkin L., Balkwill A., Sweetland S., Reeves G., Green J., Beral V., Antidepressants, Depression, and Venous Thromboembolism Risk: Large Prospective Study of UK Women. Journal of the American Heart Association, 2017; 6(5): 1-8.
11. Sheng Lee C., Liao C., Lin C., Liang J., Sung F. Kao. Depression and Risk of Venous Thromboembolism: A Population-Based Retrospective Cohort Study. *The American Psychosomatic Society,* 2015; 77: 591-598.
12. Känel R., Margani A., Stauber S. and Biasiutti F., Depressive Symptoms as a Novel Risk Factor for Recurrent Venous Thromboembolism: A Longitudinal Observational Study in Patients Referred for Thrombophilia Investigation. *PLOS ONE,* 2015; 10(5): 1-12.
13. Ishida T., Katagiri T., Uchida H., Suzuki T., Watanabe K. and Mimura M., Case Report: Asymptomatic Deep Vein Thrombosis in a Patient with Major Depressive Disorder. Hindawi: Case Reports in Psychiatry, 201; 2012; Article ID 261251: 2.
14. Kurne A., Ertugrul A., Yagcioglu E. and Kazim M., Venous thromboembolism and escitalopram. *General Hospital Psychiatry,* 2004; 26: 481–483.
15. Kunutsor S., Seidu S., and Khunti K., Depression, antidepressant use, and risk of venous thromboembolism: systematic review and meta-analysis of published observational evidence. *Annals of Medicine,* 2018; 5(6): 529-537.
16. Ray J., Mamdani M., and Yeo E., Antipsychotic and Antidepressant Drug Use in the Elderly and the Risk of Venous Thromboembolism. *Thrombosis and Haemostasis,* 2002; 88: 205–209.
17. Lacut K., Le Gal G., Couturaud F., Cornily G., Leroyer C. and Mottier D., Association between antipsychotic drugs, antidepressant drugs and venous thromboembolism: results

from the EDITH case–control study. *Fundamental and Clinical Pharmacology*, 2008; 21(6): 643-650.

18. Tritschler T, Aujesky D., Venous thromboembolism in the elderly: A narrative review. Thrombosis Research, 2017; 155: 140-147.
19. Chun T., Yi-Cheng C., Jing-Yang H. *et, al*., Incidence of Major Depressive Disorder: Variation by Age and Sex in Low-Income Individuals. *Medicine (Baltimore)*, 2016; 95(15): e3110.
20. ESHRE Capri Workshop Group, Eichinger S., *et. al*, Venous Thromboembolism in Women: aspecific reproductive health risk. *Human Reproductive Health Risk*, 2013; 19(5): 471-482.
21. James Y., Exploring Gender Difference in Depression. *Psychiatric Times*, 2001; 18(3).
22. Margaret A., Obesity and Venous Thrombosis: A Review. *Seminars in Thrombosis and Hemostasis*, 2011; 38(8): 903-907.
23. Cheng Y., Liu Z., *et. al.*, Current and Former Smoking and Risk for Venous Thromboembolism: A Systematic Review and Meta-Analysis. *Public Library of Science Medicine*, 2013; 10(9): e1001515.
24. David F., Renee D., John L., Major Depression and cigarette smoking: results of a 21-year longitudinal study. Psychological Medicine, 2003; 33(8): 1357-1367.