ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 15, Issue 10, 2022

Online - 2455-3891
Print - 0974-2441

Research Article

A PROSPECTIVE STUDY ON EFFECT OF FLUOXETINE ON PRIMARY HEMOSTASIS OF PATIENTS HAVING MAJOR DEPRESSIVE DISORDER

SHRUTHI KS, NARENDRANATH S, SUDHARSHAN CY, SANTOSH KUMAR M*, SHASHIKALA GH, DHANYA KUMAR G

Department of Pharmacology, JJM Medical College, Davangere, Karnataka, India. Email: sankumar20123@gmail.com

Received: 11 June 2022, Revised and Accepted: 23 July 2022

ABSTRACT

Objectives: The objectives of the study were to study the effect of fluoxetine on bleeding time, clotting time and platelet count of depressed patients.

Methods: Patients diagnosed with major depressive disorder were included in the study to fulfill a sample size of 60. Before starting the treatment with fluoxetine, laboratory tests were done which included bleeding time, clotting time, and platelet count. Patients were requested to return for follow-up after 4 weeks of treatment and the laboratory tests were repeated. All the study end point analysis was analyzed based on per-protocol population. Continuous variables were expressed as mean and standard deviations, paired t-test was used for within group comparison and unpaired t-test was used for between group comparisons. $p<0.05$ was considered to be significant. For categorical variable, frequency and percentage were calculated. For continuous variable, that is, bleeding time, clotting time, and platelet count, mean and standard deviation were calculated.

Results: At the end of 4 weeks, it was observed that there was a significant increase in bleeding time from 1.35±0.08 min to 1.46±0.08 min**. Similarly, there was a significant increase in clotting time from 3.30±0.15 min to 3.38±0.15 min**. It was also observed that there was a significant decrease in platelet count from 3.07±0.67 lakh cells/cu mm to 2.86±0.63 lakh cells/cu mm**.

Conclusion: Fluoxetine has shown to increase bleeding time, clotting time, and decrease platelet count. Hence, fluoxetine induced risk of bleeding and its cardio protective action has to be considered while individualizing therapy in management of depression.

Keywords: Fluoxetine, Depression, Bleeding risk, Cardio protection.

 DOI: http://dx.doi.org/10.22159/ajpcr.2022v15i10.45485. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

Major depressive disorder (MDD) is a mental disorder characterized by episodes of depressed mood, loss of interest or pleasure, feeling of guilt or low self-esteem, loss of energy, altered sleep patterns, and difficulty in concentration. The life time prevalence of MDD is approximately 17% [1].

At present, selective serotonin reuptake inhibitors (SSRIs) are the most widely prescribed antidepressants across the globe owing to their better adverse reaction profile and a higher safety margin compared to other antidepressants. However, it has been shown that at therapeutic doses SSRIs block the reuptake of serotonin by platelets, leading to decreased platelet serotonin and thereby diminishing platelet aggregation [2].

Serotonin is a strong vasoconstrictor and is also involved in platelet activation. It is taken up from the circulation by 5-HT transporters on the surface of platelets and stored within the platelets as granules at rest. On initiation of platelet aggregation, serotonin is released from the platelets which binds on 5HT-2 receptors on platelet membrane and enhances the aggregation process [3]. SSRIs share the same mechanistic target, the serotonin transporter (SERT), which is responsible for 5HT reuptake into serotonergic neurons. Inhibition of 5HT reuptake by an SSRI results in higher levels of 5HT in the synapse thus increasing their transmission and is considered as the basis of their antidepressant activity [4]. Since platelets themselves cannot produce serotonin, blockade of these transporters by SSRIs leads to diminished platelet serotonin levels causing abnormal bleeding and modification of hemostatic markers [5]. The most frequent hemostatic abnormalities are decreased platelet agreeability and activity, and prolongation of bleeding time [3].

There have been reports of SSRIs causing reductions in platelet count and sometimes resulting in thrombocytopenia [6]. Several case reports in the past have shown an association between SSRIs such as fluoxetine, paroxetine, and bleeding disorders such as epistaxis, ecchymoses, purpura, and few serious conditions such as gastrointestinal bleeding, genitourinary bleeding, and intracranial hemorrhage. Furthermore, an increased risk of gastrointestinal bleeding with the concurrent use NSAIDs with SSRIs was confirmed in population-based case–control study in the United Kingdom [2].

On the other hand, SSRIs are considered as the first line agents in the treatment of depression associated with cardiovascular co-morbidity as they reduce the risk of thrombus formation. A number of case reports of association between treatment of depression with SSRIs and reduced events caused by intra-arterial thrombosis have been revealed in the recent past, since platelet aggregation is one of the major components of acute coronary syndromes, including sudden death [7].

Hence, understanding the effects of SSRIs on hemostasis plays an important role in individualizing the treatment for depression. This is done by assessing the risk benefit ratio of prescribing an SSRI. While prescribing an SSRI it is important to consider the co-morbid conditions and concomitant medications for better patient safety.

With very few prospective studies carried out on Indian population, particularly with fluoxetine, this study aims to investigate how significantly, the most commonly prescribed SSRI, fluoxetine affects the hemostasis of depressed patients.

Objectives of the study

The objectives of the study were to study the effect of fluoxetine on bleeding time, clotting time, and platelet count in depressed patients after 4 weeks of treatment.

METHODS

Study design

This was a prospective observational study conducted in the Department of Psychiatry, Bapuji Hospital and Chigateri General Hospital, Davangere over a period of 18 months after the approval of protocol from the institutional review board. All patients' attendants provided written informed consent before participation. The study was conducted after getting approval from Institutional Human ethics committee and in accordance to the approved protocol.

Study endpoints

At the end of 4 weeks, effect of fluoxetine on bleeding time, clotting time, and platelet count.

Subject selection

Inclusion criterion

The following criteria were included in the study:

1. Adult patients of either sex, aged >18 years and <65 years.
2. Newly diagnosed patients with MDD according to DSM-V criteria [8].
3. Patient's attendants willing to give written informed consent.

Exclusion criteria

The following criteria were excluded from the study:

1. Patients with other co-existing psychiatric conditions.
2. Patients with Type 1 or Type 2 diabetes mellitus.
3. Patients on anti-hypertensive drugs.
4. Patients with hepatic or renal disease.
5. Patients on aspirin, warfarin, heparin, NSAIDs and any other drug interfering with platelet function.
6. Patients with symptoms of bleeding due to any medical condition or diagnosed with any blood dyscrasias.
7. Pregnant and lactating mothers.

Study procedure

This clinical study was conducted on patients of MDD, diagnosed according to DSM-V criteria visiting psychiatry OPD of Bapuji Hospital and Chigateri General Hospital Davangere. Sample size was calculated using the formula, considering the prevalence [9]. At an anticipated dropout rate of 10%, a minimum of 60 patients fulfilling the inclusion criteria was taken in the study.

After the diagnosis, the patients were put on capsule fluoxetine as advised by the treating psychiatrist. The minimum dose prescribed was 10 mg twice daily and the maximum dose was 20 mg twice daily. At first visit patient's sociodemographic details were noted down in the case record form and were investigated to record the baseline values of the following laboratory tests:

1. Bleeding time - Duke's method [10].
2. Clotting time – Wright's method [11].
3. Platelet count - using an electronic automated cell counter.

Concomitant uses of benzodiazepines were allowed if necessary to treat insomnia in depressed patients. Patients were asked to report immediately in case of any symptoms of abnormal bleeding such as petechiae, purpura, ecchymosis, and epistaxis. Patients were also followed up after 1 week/15 days as advised by the treating psychiatrist to assess improvement in symptoms of depression and the dose of fluoxetine was accordingly increased or decreased. After 4 weeks, we noted down the cumulative dose of the medicine received during the 4-week period. Patients who have completed 4 weeks of treatment were investigated to reassess the above-mentioned laboratory tests and the values were recorded in the case record form. A self-designed pro forma to record sociodemographic details, laboratory test values and adverse events if any during the period of 4 weeks.

Statistical analysis

All the study end point data was analyzed based on per-protocol population. For categorical variable, frequency and percentage were calculated. For continuous variable, that is, bleeding time, clotting time, and platelet count, mean and standard deviation were calculated. Paired t-test was used to assess difference between before and after treatment within the groups. Difference between two groups was done using unpaired t-test. $p<0.05$ or less was considered for statistical significance. IBM SPSS software version 20 for windows was used for statistical analysis.

RESULTS

Study population

A total of 69 patients diagnosed with MDD were enrolled in the study to fulfill the sample size of 60. A total of 60 patients returned for follow-up at the end of 4 weeks. The percentage of loss to follow-up in our study was 13% (9 patients).

Sociodemographic details

The frequency of distribution of MDD was more in the population aged between 31 and 40 years (49%) followed by population between 21–30 years (31.9%). The distribution of MDD was least in the population aged below 20 years. The frequency distribution of age is tabulated in Table 1. In our study, it was seen that MDD was more common in females (75.4%) than males (24.6%). In our study, it was observed that depression was more common in married individuals (78.3%) when compared to unmarried individuals (21.7%).

Changes in hemostatic markers in the study population

Bleeding time

It was observed that there was a significant increase in bleeding time from a baseline value of 1.35±0.08 min–1.46±0.08 min. The difference was found to be statistically significant** (Table 2)

Clotting time

It was observed that there was a significant increase in clotting time from a baseline value of 3.30±0.15 min–3.38±0.15 min. The difference was found to be statistically significant** (Table 2).

Platelet count

It was observed that there was a significant decrease in platelet count from a baseline value of 3.07±0.67 lakh/cu mm to 2.86±0.63 lakh/cu mm. The difference was found to be statistically significant** (Table 2).

Influence of gender on hemostatic markers

The change in hemostatic markers following 4 weeks of treatment with fluoxetine, was compared between males (n=16) and females (n=44) to evaluate the influence of gender on change in hemostatic parameters (Table 3). The mean increase in bleeding time was greater in males (14 s) than females (9 s). The difference was statistically significant

Table 1: Frequency distribution of age in MDD

Age (years)	Frequency	Percent
20 and below	4	5.8
21–30	22	31.9
31–40	34	49.3
41–50	9	13.0

MDD: Major depressive disorder

Table 2: Change in bleeding time, clotting time and platelet count before and after treatment

Hemostatic markers	n=60	Mean	SD	Paired t-test	
Bleeding time (min)	Before	1.35	0.08	–8.284	p<0.000
	After	1.46	0.08		
Clotting time (min)	Before	3.30	0.15	–3.596	p<0.001
	After	3.38	0.15		
Platelet count (lac/cu mm)	Before	3.07	0.67	–5.807	p<0.000
	After	2.86	0.63		

(p<0.05). The mean increase in CT was not significantly different between males and females. Similarly, the mean decrease in platelet count was also not significantly different between males and females.

Influence of age on hemostatic markers

The change in hemostatic markers following treatment with fluoxetine in different age groups, that is, <30 years (n=22) versus more than 30 years (n=28) were compared to evaluate its influence of on hemostatic markers. It was observed that the mean increase in bleeding time, clotting time and the mean decrease in platelet count were not significantly different in different age groups (Table 4).

Influence of cumulative dose of fluoxetine on hemostatic markers

The influence of cumulative dose of fluoxetine on changes in hemostatic parameters was evaluated by comparing the changes in hemostatic parameters in patients who received a cumulative dose (at the end of 4 weeks) of <1000 mg (min 600 mg) with those who received more than 1000 mg (max 1200 mg).

Bleeding time (intra group comparison)

Patients in both the groups, (Group 1<1000 mg, Group 2>1000 mg) dose showed an increase in bleeding time which was statistically significant p<0.000. Thus, the increase in bleeding time due to fluoxetine observed in this study was independent of the cumulative dose (Table 5).

Clotting time (CT) (intra group comparison)

The mean increase in clotting time was statistically significant (p<0.002) in Group 1 patients (<1000 mg), whereas the increase in clotting time in Group 2 patients (>1000 mg) was not statistically significant (Table 6).

Platelet count (intra group comparison)

The mean decrease in platelet count was statistically significant (p<0.000) in both group 1 (<1000 mg) and Group 2 (>1000 mg) patients. Thus, the decrease in platelet count due to fluoxetine was found to be independent of the cumulative dose in this study (Table 7).

Intergroup comparison

The mean difference in increase in BT, CT and the mean difference in decrease in platelet count was not significantly different between Group1 (<1000 mg) and Group 2 (>1000 mg) (Table 8).

DISCUSSION

Depression is a disorder of major public health importance, in terms of its prevalence and the suffering, dysfunction, morbidity, and economic burden [9]. The common symptoms of depression include somatic symptoms, guilt and other depressive ideations, suicidal behavior, phenomenology of delusions, and sleep architecture [9]. The life time prevalence of MDD is approximately 17% [1]. MDD has been estimated to be the fourth major cause of disability worldwide, and may become second only to cardiovascular diseases by around 2020 [12].

At present, SSRIs are the most widely prescribed antidepressants across the globe owing to their better adverse reaction profile and a higher safety margin compared to other antidepressants. However, it has been shown that at therapeutic doses SSRIs block the reuptake of serotonin by platelets, leading to decreased platelet serotonin and thereby diminishing platelet aggregation [2]. Serotonin stored within the platelets is released on platelet activation, which in turn causes activation of other platelets. Activation of platelets themselves causes the release of serotonin from dense granules, which causes further aggregation, mediated by stimulation of the $5\text{-}HT_{2A}$ receptors on the surface of the platelet [13,14].

In our study, it was observed that depression is more common in females than male which was in accordance with a study done by Kendler *et al*. They concluded that females have a higher life time risk of developing major depression than males which can, however, not be explained by differing rates or sensitivities to stressful life events [15].

Table 3: Influence of gender on hemostatic markers

Blood Investigations	Sex	n	Mean difference	SD	Unpaired t-test
BT (min)	Male	16	0.14	0.06	1.97,
	Female	44	0.09	0.10	p<0.05
CT (min)	Male	16	0.06	0.16	−0.45, NS
	Female	44	0.09	0.17	
Platelet count	Male	16	0.24	0.28	0.426, NS
lakh/cu mm	Female	44	0.20	0.29	

NS: Non significant

Table 4: Influence of age on hemostatic markers

Blood Investigations	Age (years)	n	Mean difference	SD	Unpaired t-test
BT (min)	<30	22	0.08	0.09	−1.59, NS
	>30	38	0.12	0.10	
CT (min)	<30	22	0.03	0.17	−1.62, NS
	>30	38	0.11	0.17	
PLT (lac/cu mm)	<30	22	0.23	0.31	0.397, NS
	>30	38	0.20	0.27	

NS: Non significant

Table 5: Effect of cumulative dose on bleeding time

Cumulative dose (mg)	Measure	BT Mean value (min)	SD	Paired t-test
Group 1:	Before	1.37	0.06	−7.41,
≤1000 (n=31)	After	1.48	0.08	p<0.000
Group 2:	Before	1.34	0.09	−4.603,
>1000 (n=29)	After	1.43	0.08	p<0.000

Table 6: Influence of cumulative dose on clotting time

Cumulative dose (mg)	Measure	CT mean value (min)	SD	Paired t-test
≤1000 (n=31)	Before	3.31	0.14	−3.307,
	After	3.41	0.15	p<0.002
>1000 (n=29)	Before	3.29	0.16	−1.78, NS
	After	3.35	0.15	

Table 7: Influence of cumulative dose on platelet count

Cumulative dose (mg)	Measure	Platelet count Mean value (lakh/cu mm)	SD	Paired t-test
≤1000 (n=31)	Before	3.11	0.53	4.074,
	After	2.94	0.58	p<0.000
>1000 (n=29)	Before	3.03	0.80	4.289,
	After	2.76	0.68	p<0.000

Table 8: Inter group comparison of change in hemostatic markers

Blood Investigations	Cumulative Dose	n	Mean	SD	Unpaired t-test
BT (min)	≤1000	31	0.11	0.09	0.895, NS
	>1000	29	0.09	0.11	
CT (min)	≤1000	31	0.10	0.17	0.988, NS
	>1000	29	0.06	0.17	
PLT (lakh/cu mm)	≤1000	31	0.17	0.23	−1.377, NS
	>1000	29	0.27	0.33	

NS: Non significant

In our study, there were significant changes in bleeding time, clotting time, and platelet count at the end of 4 weeks of treatment with fluoxetine. It was observed that fluoxetine caused a significant increase in bleeding time which was statistically significant ($p<0.000$). However, the increase in bleeding time was not beyond the normal range. This finding was similar to a study done by Riyaz Siddiqui *et al.*, treatment with fluoxetine (20 mg/day) for 3 months showed a significance increase in bleeding time which was within the normal range. In our study, it was observed that increase in bleeding time was significant with both minimum (600 mg) and maximum (1200 mg) cumulative dose. These changes observed with BT in our study were also in accordance with a literature review by Halperin and Rebar. Several case reports by Humphries *et al.*, Evans *et al*. have also been published where patients treated with fluoxetine showed increased bleeding time [16,17].

In our study, we observed an increase in clotting time which was statistically significant ($p<0.000$) and this increase was within the normal range of clotting time. However, the increase in CT was significant only in those patients who received a cumulative dose of <1000 mg, whereas it was insignificant in patients who received more than 1000 mg. Such insignificant increase in CT was also observed in a study by Riyaz Siddiqui *et al.* However, it has been studied that platelet serotonin is released during coagulation cascade and hence decreased intra platelet 5-HT levels caused by fluoxetine may affect the clotting mechanisms in our body.

The platelet count of patients was decreased in our study which was statistically significant ($p<0.000$). The decrease in platelet count was independent of the cumulative dose, that is, all 60 patients irrespective of the cumulative dose received. However, the platelet counts though reduced were within the normal range. Furthermore, the decrease in platelet count was independent of the dose. A study by Song *et al.*, demonstrated decrease in platelet count in depressed patients treated with escitalopram, which is also an SSRI [18].

Several case reports documented by Anderson *et al.*; Arnath *et al.* where patients treated with fluoxetine showed decreased platelet count. Decreased platelet agreeability due to treatment with fluoxetine was also demonstrated by Laine-Cessac *et al*.

SSRI induced change in hemostatic markers is due to inhibition of platelet SERTs leading to decreased intra-platelet serotonin. This was demonstrated by Alvarez *et al.* in a study where depressed patients treated with fluoxetine showed decreased expression of platelet SERT, decreased intra platelet 5-HT levels [19].

Such decrease in intra-platelet serotonin levels was also observed with other SSRIs like paroxetine. Hergovich *et al*. showed decreased intra-platelet 5-HT concentration by 83% in 16 healthy male volunteers receiving paroxetine, 20 mg/d over 2 weeks. It also decreased epinephrine induced platelet activation by 31% [20]. Furthermore, study conducted by Gil *et al.* demonstrated, a significant decrease in serotonin induced platelet aggregation following treatment with imipramine [21].

In the past, many case reports of abnormal bleeding manifestation such as ecchymosis, subdural hematomas, and hemoptysis with fluoxetine have been reported [16,17,21]. An increased risk of gastrointestinal bleeding with SSRIs when coprescribed with NSAIDs has also been reported.

However, in our study, no such adverse bleeding manifestations were reported by patients during the treatment period. In general, decreased platelet counts induced by SSRI are not associated with severe bleeding such as thrombocytopenia. This can be attributed to the wide normal ranges for platelet count. Potential adverse effects of the combination of nonsteroidal anti-inflammatory drugs and anti-platelet agents, however, should be considered.

Influence of age and sex on the primary outcome was also evaluated. The changes observed in markers of hemostasis after treatment with fluoxetine, did not show significant differences with respect to a particular age group or gender, except that bleeding time was increased in males to a greater extent than females. Presence of more amounts of estrogens in females may suppress platelet function and prolongs bleeding time. Higher clotting time in females may be due to presence of estrogens which prolongs clotting time by decreasing plasma fibrinogen levels [22,23].

Based on the mechanism of SSRI induced reduction in platelet 5-HT and its functions, several research works have been published emphasizing the cardio protective nature of SSRI in humans [24-26]. Menys *et al*. demonstrated a statistically significant decrease in both plasma 5-HT levels and 5-HT induced platelet aggregation, with fluoxetine. This suggests a higher inhibition of platelet activity by SSRIs than tricyclic antidepressants, and therefore a more suitable treatment for depressed patients with cardiovascular disease [27]. Animal models have also demonstrated that $5HT_{2A}$ antagonism is effective in abolishing intracoronary platelet-rich thrombosis and also improves blood flow even after withdrawing the thrombolytic agent [24]. It has also been suggested that SSRIs, and especially fluoxetine, may be responsible for the inhibition of platelet aggregation, which may lead to low platelet activity.

Fluoxetine has also shown to reduce the risk of intravascular thrombosis, myocardial infarction, and stroke [28,29]. Use of SSRIs was associated with 43% lower risk of death or nonfatal MI and 43% lower risk of all-cause mortality [30]. This makes SSRI a suitable drug in treating depression in patients with cardiovascular risks.

Hence, we conclude that SSRI induced alteration in hemostasis can increase the risk of bleeding. This has to be considered while treating depression in patients, who are concomitantly using other drugs which increase the risk of bleeding, for example: NSAIDs, warfarin and clopidogrel. On the other hand, SSRIs are shown to be safer in patients with cardiovascular risk as they reduce the intravascular platelet formation and also decrease the risk of stroke and MI in depressed patients. An effective risk benefit ratio analysis, with this background will help us to ensure patient safety and in practicing personalized therapy.

Limitations of this study include lack of specific platelet function tests like platelet function analyzer fibrinogen, platelet functional assessment; we used older methods to record bleeding time and clotting time.

CONCLUSION

SSRIs are commonly prescribed in the management of MDD. SSRIs reduce the intra platelet serotonin levels by inhibition of SERT transporters present on platelets, which have shown to significantly alter the hemostatic mechanisms. In this study it was observed that depressed patients treated with fluoxetine showed significant increase in bleeding time, clotting time, and decreased platelet count. However, the hemostatic markers were within the normal range. SSRI induced risk of bleeding has to be kept in mind while co-prescribing drugs like NSAIDs which also increase the risk of bleeding. On the other hand, SSRI could be the drug of choice in patients with history of cardiovascular disease as they have shown to reduce the risk of intravascular thrombosis. Hence, while prescribing SSRIs; its effect on hemostasis has to be considered while evaluating the risk benefit ratio in individualizing therapy.

AUTHOR'S CONTRIBUTION

All authors have contributed equally for study planning, execution, monitoring, analysis, and writing the final study report.

CONFLICT OF INTEREST

None.

AUTHORS FUNDING

This was a self-funded project, none of the authors received funding.

REFERENCES

1. Golan DE, Tashjian AH Jr., Armstrong EJ, Armstrong AW. Principles of Pharmacology. 3rd ed. New Delhi: Wolters Kluwer; 2012.
2. De Abajo FJ, Montero D, Rodríguez LA, Madurga M. Antidepressants and risk of upper gastrointestinal bleeding. Basic Clin Pharmacol Toxicol 2006;98:304-10.
3. Halperin D, Reber G. Influence of antidepressants on hemostasis. Dialogues Clin Neurosci 2007;9:47-59.
4. Blakely RD, Berson HE, Fremeau RT Jr.,Caron MG, Peek MM, Prince HK, *et al.* Cloning and expression of a functional serotonin transporter from rat brain. Nature 1991;7:354:66-70.
5. Hougardy D, Egberts TC, Van Der Graaf F, Brenninkmeijer VJ, Derijks LJ. Serotonin transporter polymorphism and bleeding time during SSRI therapy. Br J Clin Pharmacol 2008;65:761-6.
6. Andersohn F, Konzen C, Bronder E, Klimpel A, Garbe E. Citalopram-induced bleeding due to severe thrombocytopenia. Psychosomatics 2009;50:297-8.
7. Belcher PR, Drake-Holland AJ, Noble IM. Serotonin reuptake inhibitors and cardiovascular disease. Vasc Dis Prev 2005;2:67-76.
8. Chatterjee RN, Mukherjee SP, Nandi DN. Life events and depression. Indian J Psychiatry 1981;23:333-7.
9. Grover S, Dutt A, Avasthi A. An overview of Indian research in depression. Indian J Psychiatry 2010;52:S178-88.
10. Dacie JV, Lewis, SM. Bleeding time-investigation of the hemorrhagic disorders. In: Practical Hematology. 5th ed. Churchill Livingstone: London; 1975. p. 324-5.
11. Ghai CL. A Textbook of Practical Physiology Haematology. 5th ed. New Delhi: Jaypee Brothers; 1999. p. 84-101.
12. Mathers CD, Vos ET, Stevenson CE, Begg SJ. The Australian burden of disease study: Measuring the loss of health from diseases, injuries and risk factors. Med J Aust 2000;172:592-6.
13. Blockmans D, Deckmyn H, Vermylen J. Platelet actuation. Blood Rev 1995;9:143-56.
14. Saltzman AG, Morse B, Whitman MM, Ivanshchenko Y, Jaye M, Felder S. Cloning of the human serotonin 5-HT2 and 5-HT1C receptor subtypes. Biochem Biophys Res Commun 1991;181:1469-78.
15. Kendler KS, Thornton LM, Prescott CA. Gender differences in the rates of exposure to stressful life events and sensitivity to their depressogenic effects. Am J Psychiatry 2001;158:587-93.
16. Yaryura-Tobias JA, Kirschen H, Ninan P, Mosberg HJ. Fluoxetine and bleeding in obsessive compulsive disorder. Am J Psychiatry 1991;148:949.
17. Humphries JE, Wheby MS, VandenBerg SR. Fluoxetine and the bleeding time. Arch Pathol Lab Med 1990;114:727-8.
18. Song HR, Jung YE, Wang HR, Woo YS, Jun TY, Bahk WM. Platelet count alterations associated with escitalopram, venlafaxine and bupropion in depressive patients. Psychiatry Clin Neurosci 2012;66:457-59.
19. Alvarez JC, Gluck N, Arnulf I, Quintin P, Leboyer M, Pecquery R, *et al*. Decreased platelet serotonin transporter sites and increased platelet inositol triphosphate levels in patients with unipolar depression: Effects of clomipramine and fluoxetine. Clin Pharmacol Ther 1999;66:617-24.
20. Hergovich N, Aigner M, Eichler HG, Entlicher J, Drucker C, Jilma B. Paroxetine decreases platelet serotonin storage and platelet function in human beings. Clin Pharmacol Ther 2000;68:435-42.
21. Gomez-Gil E, Gasto C, Carretero M, Díaz-Ricart M, Salamero M, Navinés R, *et al*. Decrease of the platelet 5-HT_{2A} receptor function by long-term imipramine treatment in endogenous depression. Hum Psychopharmacol 2004;19:251-8.
22. Cramer SC, Schiller GJ. Acquired abnormalities of platelet function. N Engl J Med 1991;324:1670-2.
23. Kumar SS, George J, Mukkadan JK, Jasira Mchamed VK. Bleeding time and clotting time in healthy male and female college students of Karukutty Village, Kerala. Health Prospect J Public Health 2013;12:7-9.
24. Noble MI, Drake-Holland AJ. The possible role of serotonin 5HT2 receptor antagonism in cardioprotection. Neth J Med 1992;41:183-9.
25. Vikenes K, Farstad M, Nordrehaug JE. Serotonin is associated with coronary artery disease and cardiac events. Circulation 1999;100:483-9.
26. Serebruany VL, Gurbel PA, O'Connor CM. Platelet inhibition by sertraline and N-desmethylsertraline: A possible missing link between depression, coronary events, and mortality benefits of selective serotonin reuptake inhibitors. Pharmacol Res 2001;43:453-62.
27. Menys VC, Smith CC, Lewins P, Farmer RD, Noble MI. Platelet 5-hydroxytryptamine is decreased in a preliminary group of depressed patients receiving the 5-hydroxytryptamine re-uptake inhibiting drug fluoxetine. Clin Sci (Lond) 1996;91:87-92.
28. Pollock BG, Laghrissi-Thode F, Wagner WR. Evaluation of platelet activation in depressed patients with ischemic heart disease after paroxetine or nortriptyline treatment. J Clin Psychopharmacol 2000;20:137-40.
29. Rasmussen A, Hindberg I, Mellerup E. Does sertraline induced platelet dysfunction protect stroke patients against cardiovascular comorbidity. Int J Neuropsychol Pharmacol 2000;3:S372.
30. Taylor CB, Youngblood ME, Catellier D, Veith RC, Carney RM, Burg MM, *et al*. Effects of antidepressant medication on morbidity and mortality in depressed patients after myocardial infarction. Arch Gen Psychiatry 2005;62:792-8.