ORIGINAL ARTICLE

A Longitudinal Follow-up Study of Anti-depressant Drugs Causing Hepatotoxicity in Patients with Major Depressive Disorders

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ABTRACT

Aim: To determine and compare hepatotoxic effects caused by escitalopram versus sertraline in patients with major depressive disorder.
Study Design: Comparative longitudinal study
Place and Duration of Study: Department of Pharmacology, Basic Medical Sciences Institute (BMSI) & Neuropsychiatry Ward of Jinnah Postgraduate Medical Centre (JPMC) Karachi from January 2017 to December 2017.
Methods: One hundred and twenty eight patients divided into four groups; group 1 (recent users for a period of >1 month to ≤3 months), group 2 (drug users for a period of >6 months to ≤9 months), group 3 (drug users for a period of >1 year to ≤2 years and group 4 (drug users for a period of >2years to ≤5 years.) and each group consists of 32 patients. Out of these 32 patients, 16 patients were escitalopram users (10-20mg) and 16 patients were sertraline users (50mg). Out of these 16 patients, 8 patients were males and 8 patients were females.
Results: The mean comparison of LFT parameters between two treatment groups results showed in escitalopram samples, mean±SD for Bilirubin was 0.91±0.38, SGPT 61.24±12.0, alkaline phosphatase 213.63±53.03, whereas in treatment group sertraline, mean±SD of bilirubin was 0.69±0.16, SGPT 36.88±9.34, alkaline phosphatase 221.69±108.9, there was significant mean difference observed for bilirubin and SGPT between two treatment groups with p-value less than 0.01.
Conclusion: Both escitalopram and sertraline can cause hepatotoxicity.
Keywords: Major depressive disorder (MDD), Selective serotonin reuptake inhibitors (SSRIs), Liver function test (LFT)

INTRODUCTION

Major depressive disorder or clinical depression, is an intense depressive attitude that persists for more than two weeks, severe enough for causing visible problems in the patient's capability to performing routine work, maintaining personal relationships and contributing in previously enjoyed communal activities.[1] It has an observable effect on individual's lives, which is categorized as cognitive, behavioral and somatic symptoms. The depression causes deleterious impact on quality of life, in addition, it is also related with a higher risk of illness and death.[2] Neurobiological findings considered as one of the major evidence on the etiology and pathophysiology of Major depressive disorder, that is probably pertinent for medical psychoanalysis[3].

There are various types of depression which could be mild, moderate or immensely severe condition; major depressive disorder (MDD), psychotic depression, melancholic depression, mysthymic disorder, seasonal affective disorder (SAD) and postpartum depression (PPD)[4].

Depression is likely to cause a 5.7% increase in the global burden of disease by 2020. The World Health Organization (WHO) estimates that, by 2030, MDD will be the 2nd most leading cause of economic liability and disability[5]. Depression is considered as a third common cause of debility affecting around 350 million people worldwide, with a lifetime risk of 7%[6].

Globally, the prevalence of major depressive disorder is expected to have increased considerably by 53% from 1990 approached to 253 million in 2013[7]. 24-02-2020 In addition co-morbidity complicates treatment seeking for mental disorder. Moreover mental disorders often go unrecognized by healthcare providers and therefore untreated in primary health settings.

Depression affects up to 15% of aging people >65 years age in United States and the prevalence may be as high as 42%[8]. The regional prevalence of depression in South East Asia is moderately high, as 6.9% in Bangladesh and 27.8% in India[9]. At National level, in Pakistan it is about 34%, which is greater than the 10% prevalence within the United States[10]. Different treatment modalities have been established to overcome depression. They can be divided into non pharmacological and pharmacological treatment. Majority of patients with depression prefer non drug strategies to manage their illness and feel healthier. Natural therapies and herbal remedies may be helpful for trivial forms of depression. But there is no any solid proof that they are effective for modest to severe depression**[11].**

Depression is a chronic and recurrent disease that often entails long lasting treatment with diverse modalities[12]. Ideal treatment has initiated with proper patient counseling about the nature of the disease and the

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nature of the suggested treatment. Precise psychological therapies are effective for major depression, with highest indication for trivial to modest depression, although no definite psychotherapy seemed to be superior to others. In moderately depressed patients the decision to recommend an antidepressant could be taken for about few weeks. In severe depression, the antidepressants usage is suggested, since the neurobiological chemicals are extremely disturbed therefore patients become un-responsive to psychotherapy alone[13].

Giving proposed equivalent of therapeutic outcome, the selection of antidepressant drug is established on the nature and severity of symptoms, avoidance of adverse drug reactions, coexisting psychological and medical problems, previous feedbacks and suitability to a particular antidepressant. Other concerns are the contraindications, drug interactions, toxicity and meanwhile drug cost. Furthermore, patient inclination once they become educated about the safety hazard quotient might be estimated to improve consistence[14]. Evidence based guidelines propose that SSRIs must be prescribed in trivial to modest depressive patients, and tricyclic antidepressants (TCAs) in severe depressive patients[15].

Selective serotonin reuptake inhibitors and new generation antidepressants are well tolerated than TCAs and are harmless in overdose. Furthermore, their dose preparation tends to confirm suitable dosing, and they may be administered at the suggested dosage, following with maintenance at a lower dose[16]. Escitalopram and sertraline are Selective Serotonin Reuptake Inhibitors (SSRIs) that has revealed efficacy in both immediate and maintenance treatment of major depressive disorder**[17].**

It has been possible to attain two key opinions supporting the theory that somatodendritic 5-HT_{1A} auto receptors which are located in the raphe nuclei of central nervous system, performs a central role in the mechanism of action of SSRIs. Administration of SSRIs raises extracellular serotonin (5-HT) levels in the locality of the cell body and the dendrites of serotoninergic neurons of raphe nuclei[18].

Numerous studies have been shown that around 43% of patients with major depressive disorder may withdraw from antidepressants because of drug induced untoward effects[19], which include gastrointestinal upsets like vomiting, loose stools, GI bleeding, indigestion, hepatic toxicity, weightiness and cardiovascular instabilities (QT interval elongation, increased BP, orthostatic hypotension), urine retaining, incontinence, erotic dysfunction, osteoporosis, lowering of seizure threshold, sleep instabilities, glaucoma, cataract, hyperprolactinemia and electrolyte imbalance[20].

Most of the SSRIs go through extensive hepatic oxidative metabolism facilitated by CYP450 isoenzymes. Therefore several clinically important drug interactions (DDIs) are due to inhibition of these enzymes[21].

Drug interactions can be synergistic, antagonistic, or idiosyncratic. It can be further categorized as pharmacokinetic and pharmacodynamic interactions. Sertraline, citalopram, and escitalopram, at standard therapeutic dosages are unlikely to cause substantial modifications in CYP450 status. Nevertheless, these interactions can be clinically important in specific patient for e.g., in renal and hepatic impairment, slow CYP metabolizers, or drugs with a narrow therapeutic window[22].

Clinically evident liver injury with markedly elevated liver enzyme with or without jaundice has also been reported in patients treated with SSRI. Compared with other antidepressants, SSRIs remained least hepatotoxic. The frequency of hepatotoxicity is from 1.28 to 3.62 cases per patient year[23]. The liver injury observed usually within 12 to 24 weeks of treatment and the configuration of serum enzyme elevations varies from hepatocellular to mixed and cholestatic. Autoimmune and hypersensitivity reaction (rash, fever, and eosinophilia) are unusual. Acute liver failure due to SSRI is very rare. The patient's liver biochemical profile revealed elevated liver enzyme, investigation does not explain any other reason for their hepatitis. Liver function tests may normalize after terminating SSRI, indicating a possible relation between drug treatment and acute hepatic injury. Suggestive mechanism of hepatotoxicity may be an accumulation of drug or one of its metabolite in the body by inhibition of its own metabolism[24].

MATERIALS AND METHODS

This comparative longitudinal follow up study was conducted in Department of Pharmacology, Basic Medical Sciences Institute (BMSI) & Neuropsychiatry Ward of Jinnah Postgraduate Medical Centre (JPMC) Karachi from January 2017 to December 2017.One hundred and twenty eight patients divided into four groups; group 1 (recent users for a period of >1 month to ≤3 months), group 2 (drug users for a period of >6 months to ≤9 months), group 3 (drug users for a period of >1 year to ≤2 years and group 4 (drug users for a period of >2years to ≤5 years.) and each group consists of 32 patients. Out of 32 patients, 16 patients were Escitalopram users (10-20mg) and 16 patients were Sertraline users (50mg). Out of this 16 patient, 8patients were males and 8patients were females. We followed up patients on at least 3 occasions after every 6 weeks interval. The liver function test was measured on each follow up visit. The first sample of all participants was considered as a baseline sample. Liver function tests were estimated by using automatic chemistry analyzer. (Au 680-Beckman coulter) OR (Selectra-pro). The data was entered and analyzed through SPSS-20.

RESULTS

Table 1 shows that the mean comparison of LFT parameters between two treatment groups, with respect to 2-3 months users, results showed in Escitalopram samples mean and Standard deviation for Bilirubin was 0.91±0.38, for SGPT 61.24±12.0, for Alkaline phosphatase 213.63±53.03, whereas in treatment group Sertraline mean and Standard deviation for Bilirubin was 0.69±0.16 for SGPT 36.88±9.34, for Alkaline phosphatase 221.69±108.9 , there was significant mean difference observed for Bilirubin and SGPT between two treatment groups with p-value less than 0.01, however no significant mean difference was observed for Alkaline phosphatase for 2-3 months user samples.

Table 2 gives the mean comparison of LFT parameters between two treatment groups, with respect to

6-9 month users, results showed in Escitalopram samples mean and Standard deviation for Bilirubin was 1.03±0.26, for SGPT 70.38±8.79, for Alkaline phosphatase 226.25±83.77, whereas in treatment group Sertraline mean and Standard deviation for Bilirubin was 0.66±0.23 for SGPT 37.38±14.09, for Alkaline phosphatase 254.88±94.26 , there was significant mean difference observed for Bilirubin and SGPT between two treatment groups with p-value less than 0.01, however no significant mean difference was observed for Alkaline phosphatase for 6-9 month user samples.

Table 3 gives the mean comparison of LFT parameters between two treatment groups, with respect to 1-2 years users, results showed in Escitalopram samples mean and Standard deviation for Bilirubin was 1.02±0.32, for SGPT 71.50±11.61, for Alkaline phosphatase 215.75±84.96, whereas in treatment group Sertraline mean and Standard deviation for Bilirubin was 0.61±0.22 for SGPT 32.94±11.04, for Alkaline phosphatase 203.88±104.27 , there was significant mean difference observed for Bilirubin and SGPT between two treatment groups with p-value less than 0.01, however no significant mean difference was observed for Alkaline phosphate for 1-2 years user samples.

Table 4 gives the mean comparison of LFT parameters between two treatment groups, with respect to 2-5 years users, results showed in Escitalopram samples mean and Standard deviation for Bilirubin was 1.16±0.27, for SGPT 64.50±15.18, for Alkaline phosphatase 238.25±75.10, whereas in treatment group Sertraline mean and Standard deviation for Bilirubin was 0.67±0.25 for SGPT 43.19±12.62, for Alkaline phosphatase 202.63±72.97 , there was significant mean difference observed for Bilirubin and SGPT between two treatment groups with p-value less than 0.01, however no significant mean difference was observed for Alkaline phosphatase for 2-5 years user samples.

Table 1: Mean comparison of LFT parameters between treatment with respect to 2-3 months users

Parameter	Escitalopram (n=16)	Sertraline (n=16)	P value
Bilirubin	0.91±0.38	0.69±0.16	0.04*
SGPT	61.25±12.00	36.88±9.34	<0.01*
Alkaline phosphate	213.63±53.03	221.69±108.90	0.79

*p<0.05 (Significant)

Table 2: Mean comparison of LFT parameters between treatment with respect to 6-9 Month users

Parameter	Escitalopram (n=16)	Sertraline (n=16)	P value
Bilirubin	1.03±0.26	0.66±0.23	<0.01*
SGPT	70.38±8.79	37.38±14.09	<0.01*
Alkaline phosphate	226.25±83.77	254.88±94.26	0.37

*p<0.05 (Significant)

Table 3: Mean comparison of LFT parameters between treatment with respect to 1-2 years users

Parameter	Escitalopram (n=16)	Sertraline (n=16)	P value
Bilirubin	1.02±0.32	0.61±0.22	<0.01*
SGPT	71.50±11.61	32.94±11.04	<0.01*
Alkaline phosphate	215.75±84.96	203.88±104.27	0.72

*p<0.05 (Significant)

Table 4: Mean comparison of LFT parameters between treatment with respect to 2-5 years users

Parameter	Escitalopram (n=16)	Sertraline (n=16)	P value
Bilirubin	1.16±0.27	0.67±0.25	<0.01*
SGPT	64.50±15.18	43.19±12.62	<0.01*
Alkaline phosphate	238.25±75.10	202.63±72.97	0.18

p<0.05 (Significant)

DISCUSSION

Depression is a heterogeneous disorder frequently mistaken for a single clinical mental disorder. There are definitely various forms of depression which are either be mild or enormously severe conditions like psychotic depression in which the patient presents with symptoms like hallucinations, delusions and suicidal thoughts. Diagnosis of this condition is difficult because of the concomitant mental disorders for example anxiety disorders, panic agoraphobia syndrome, severe phobias, generalized anxiety disorder (GAD), social anxiety disorder (SAD), post-traumatic stress disorder (PTSD) and obsessive compulsive disorder (OCD). SSRIs have essentially replaced older tricyclic antidepressants (TCA) as a medicine of choice for the management of depression.

Abdullah et al[24] reported in his study that SSRIs use in major depressive disorder is associated with hepatotoxicity which is in favor of our study, as our study reveals disturbed LFTs with elevated levels of bilirubin and SGPT in all four groups. Cristopher et al[25] also reported in his study that SSRIs used in depression and anxiety disorders can cause increased levels of transaminases. Biopsy of liver shows lobular hepatitis, which is in accordance of our study, as our study results showed raised SGPT levels in all four groups.

Billioti et al[26] in his cohort study compared venlafaxine, duloxetine, mianserine, mirtazapine, tianeptine and agomelatine with SSRIs and declared that SSRIs does not causes drug induced liver injury. This is in conflict with our study as our samples showed abnormal levels of bilirubin and SGPT in all study subjects.

CONCLUSION

Both selective serotonin reuptake inhibitors (escitalopram and sertraline) can cause abnormal liver function test, but in comparison escitalopram is more hepatotoxic than Sertraline. Selective serotonin reuptake inhibitors are disturbing liver function test by increasing serum bilirubin and SGPT levels in patients with major depressive disorder. We suggest regular surveillance of LFTs in these patients and re-adjust dosages or discontinue the drug as needed.

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