Original Article

Comparison of Effect of Antidepressants on Psychomotor Functions

Pranjali P. Mendhe, Samidh P. Shah, Mira K. Desai, Minakshi N. Parikh[1]

ABSTRACT

Objective: The comparison of the effect of antidepressants on psychomotor functions in patients with endogenous depression. **Materials and Methods:** This prospective interventional study was carried out at a tertiary care teaching hospital on 95 literate patients with newly diagnosed endogenous depression matching inclusion and exclusion criteria. Patients were prescribed either desvenlafaxine (50 mg) or fluoxetine (40 mg) or sertraline (50 mg). Psychomotor functions were assessed by digit letter substitution, six letter cancellation, choice reaction time, hand steadiness and flicker fusion test at the baseline 1st month and 3rd month. Efficacy of drugs was also measured by Hamilton rating scale for depression. Data were analyzed by using ANOVA and $P < 0.05$ was considered as statistically significant. **Results:** A total of 95 patients were enrolled. Fluoxetine, desvenlafaxine, and sertraline were prescribed in 32, 32, and 31 patients, respectively. At the end of 3 months, a significant improvement in psychomotor functions was observed in patients treated with sertraline ($P < 0.05$), while desvenlafaxine-treated patients did not show any significant change in any of the tests. Surprisingly, fluoxetine-treated patients showed deterioration in all psychomotor tests ($P < 0.05$). Hamilton rating score improved at the end of 3 months treatment as compared to baseline. Most commonly observed adverse reactions in all three drug groups were nausea ($n = 20$), dizziness ($n = 3$), headache ($n = 20$), and diarrhea ($n = 3$). **Conclusion**: Sertraline significantly improves psychomotor function as compared to desvenlafaxine while fluoxetine impairs.

Key words: *Desvenlafaxine, fluoxetine, psychomotor function, sertraline*

INTRODUCTION

Depression is a common mood disorder characterized by sadness, loss of interest or pleasure, feelings of guilt of low self-worth, disturbed sleep or appetite, feelings of tiredness, and poor concentration.[1] According to the global burden of diseases, the prevalence of depression is 5.8% in men and 9.5% in women.[2] The treatment options mainly include nonpharmacological therapies and pharmacological therapy. Pharmacotherapy mainly consists of antidepressants. The monoamine oxidase inhibitors and tricyclic antidepressants (TCAs) comprise the first-generation antidepressants. Whereas, antidepressants such as the selective serotonin reuptake inhibitor (SSRI), for example, fluoxetine, and sertraline; serotonin–norepinephrine reuptake

Access this article online	
Website: www.ijpm.info	Quick Response Code
DOI: 10.4103/0253-7176.198946	

How to cite this article: Mendhe PP, Shah SP, Desai MK, Parikh MN. Comparison of effect of antidepressants on psychomotor functions. Indian J Psychol Med 2017;39:69-75.

Departments of Pharmacology and [1]Psychiatry, B.J. Medical College, Ahmedabad, Gujarat, India

Address for correspondence: Dr. Mira K. Desai
Department of Pharmacology, B.J. Medical College, Ahmedabad, Gujarat, India.
E-mail: desaimirak@yahoo.co.in

inhibitors such as desvenlafaxine and duloxetine mainly comprise the second generation. The second-generation antidepressants have proven greater efficacy and safety than the first generation.[3] The efficacy can be measured as changes from baseline or remission on an investigator-rated diagnostic depression scale such as Hamilton Depression (HAM-D) Rating Scale for depression. As depression is a chronic condition and the treatment has to be given for a longer duration, the adverse reactions deserve special attention mostly those affecting the daily activities like behavioral toxicity.[4] Behavioral toxicity is defined as the extent to which a drug disrupts those abilities necessary for the safe performance of cognitive and psychomotor tasks of everyday life.[4] A meta-analysis of controlled studies of antidepressants showed that some TCAs could disrupt these functions.[5] Cognitive function is the brain's ability to acquire process, integrate, store, and retrieve information.[6] Psychomotor function includes sensorimotor processes such as reaction time and sensorimotor accuracy. Disturbance in these processes leads to patient maladjustment and may impair psychomotor performance, which plays an important role in driving and operating complex machinery. Various tests for the assessment of different aspects of the psychomotor function are available. This includes six letter cancellation test (SLCT), digit letter substitution test (DLST), flicker fusion test, hand steadiness test, choice reaction time test, etc., The efficacy and effect of conventional first-generation antidepressants on psychomotor function are established. Hence, the present study was aimed at comparing the efficacy and effect of the second-generation antidepressants on psychomotor functions with newer antidepressants in patients with endogenous depression at a tertiary care hospital, Ahmedabad.

MATERIALS AND METHODS

This was an interventional, continuous, prospective study carried out at the Department of Pharmacology and Department of Psychiatry, Civil Hospital, Ahmedabad. The study protocol was approved by the Institutional Ethics Committee (Reference number - EC/Approval/51/14 date: February 7, 2014). Newly diagnosed patients with endogenous depression, aged 15–55 years of either gender, living in Ahmedabad city, could read and write in Gujarati, Hindi, or English and consented to follow-up were included in the study. Patients suffering from chronic diseases or diseases affecting psychomotor function, patients on any drug (s) known to affect memory and psychomotor function, having a history of alcohol or any other substance abuse, pregnant, and lactating women were excluded from the study. The new patients diagnosed with endogenous depression by the consultant psychiatrist were included in the study. They were randomly assigned to either sertraline and fluoxetine or desvenlafaxine groups using a random table. Tablet desvenlafaxine was obtained from Abbott Pharmaceuticals, Ahmedabad. Tablet fluoxetine and sertraline were available from the hospital pharmacy. The patients were followed for 1st month and at the end of the 3rd month of starting the treatment. The drug was dispensed by the investigator at each follow-up, and compliance was maintained by using a drug dispensing record sheet and checking the pill count. The baseline data such as demographic details, clinical examinations, laboratory investigations, any concomitant diseases and drug therapy, and details of the drug treatment were recorded in a predesigned case record form. The tests used for the evaluation of psychomotor function includes SLCT,[7] DLST,[7] critical flicker fusion test,[8] choice reaction time audio-visual,[9] and hand steadiness test.[10] HAM-D rating scale[11] is a 17-item clinician-rated scale used to measure the efficacy of these antidepressants. These were administered at the baseline and at the end of the 1st and 3rd month treatment.

Statistical analysis

Data were analyzed as per the protocol analysis. A sample size of thirty in each group was calculated considering the power of study as 95% and level of significance 0.5%. Data were analyzed using repeated measures and one-way ANOVA. The data are represented as mean ± standard error of mean. $P < 0.05$ was considered statistically significant.

RESULTS

A total 109 patients diagnosed as endogenous depression by a consultant psychiatrist and who fulfilled the inclusion–exclusion criteria were enrolled in the study [Figure 1]. The mean age of the patients was 39 ± 10.14 years. The male to female ratio was 1:1.15. All the 95 patients were literate. Maximum numbers of graduates were in the fluoxetine group. Majority of patients were homemaker followed by students, businesspeople, and few were unemployed. The group-wise distribution of demographic details is as mentioned in Table 1.

Effect of drug on psychomotor functions

The three groups were comparable ($P > 0.05$) at the baseline in the choice reaction time test audio-visual, hand steadiness, and flicker fusion test.

Patients treated with sertraline showed a significant increase in SLCT and DLST scores at the first and second follow-up as compared to the baseline ($P < 0.001$). In the flicker fusion test, an increase in threshold was

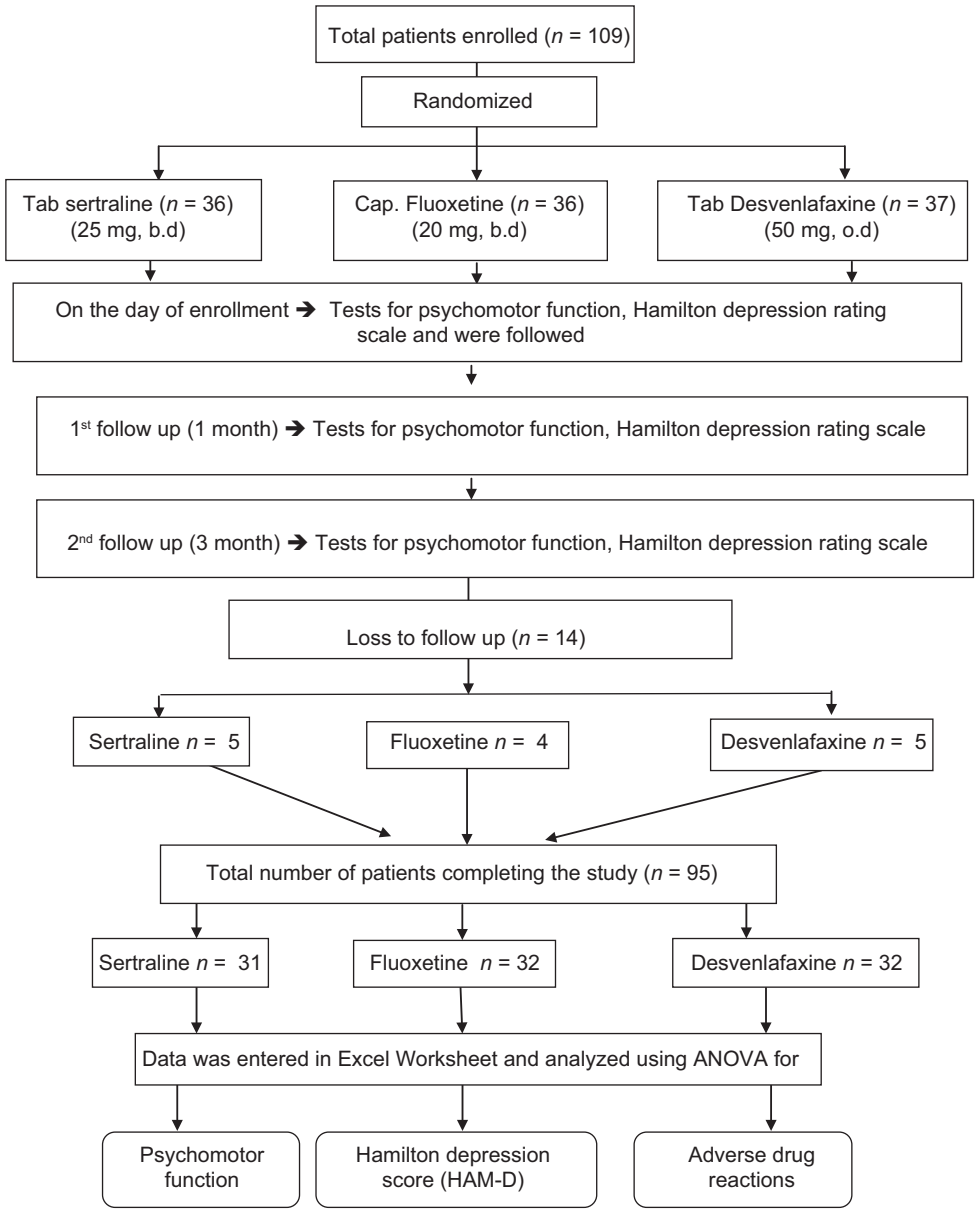

Figure 1: Details of patients enrolled

Table 1: Demographic details and Hamilton depression rating scale at baseline of patients in the study (*n*=95) (values expressed as mean±SEM)

Variable	Sertraline (*n*=31)	Fluoxetine (*n*=32)	Desvenlafaxine (*n*=32)	*P* value
Mean age	39.59±1.18	39.45±1.79	39.62±1.78	>0.99
Gender (M: F)	15:16	17:15	19:13	0.6802
Educational qualification (%)				
Upto 5th standard	9 (29)	7 (21.8)	8 (25)	
Upto 10th standard	7 (22)	4 (12.5)	9 (28)	-
Upto 12th standard	4 (12)	5 (15)	8 (25)	-
Graduate	11 (35)	16 (50)	7 (21)	-
Hamilton depression rating scale	17.96±1.47	18.31±1.30	17.68±1.65	>0.05

observed in the first follow-up as compared to the baseline ($P < 0.01$). A significant decrease in the choice reaction time test audio and visual component was observed at each follow-up as compared to the baseline. In hand steadiness test, a significant decrease in scores as compared to the baseline and subsequent follow-ups were observed at the first ($P < 0.01$) and second follow-up ($P < 0.001$) [Table 2].

Fluoxetine-treated patients showed a significant decrease SLCT and DLST scores at all the follow-ups as compared to the baseline ($P < 0.001$). In the flicker fusion test, a significant decrease in threshold was observed at the first and second follow-up as compared

to the baseline ($P < 0.001$). In choice reaction time test audio, a significant increase in scores was observed at the first follow-up as compared to the baseline ($P < 0.001$) and second follow-up as compared to the baseline and first follow-up ($P < 0.001$). In the visual test, all the follow-ups showed a significant increase in scores as compared to the baseline ($P < 0.001$). In hand steadiness test, a significant increase in scores was observed at each follow-up as compared to the baseline ($P < 0.001$) [Table 2].

Patients of desvenlafaxine group did not show any significant change in the scores of any tests at any follow ups [Table 2].

Comparison of three groups at the end of 3 months

The effect of 3 months treatment with sertraline and fluoxetine desvenlafaxine was determined. The difference of the values between baseline and at the end of the study period was calculated. The mean value of this difference for all psychomotor tests was compared using one-way ANOVA with *post hoc* analysis. The mean difference of the baseline to the last follow-up scores in sertraline group was statistically significant as compared to fluoxetine group in all the psychomotor tests [Table 3]. The difference in sertraline group was significant as compared to desvenlafaxine in all tests except flicker fusion test [Table 3] ($P < 0.05$). Whereas, the mean difference between baselines to last follow-up scores of desvenlafaxine group was significant as compared to fluoxetine [Table 3] ($P < 0.05$).

Hamilton depression rating scale

Comparison of all the three groups at the baseline

Mean score at the baseline for all three groups was comparable [Table 1]. All the three groups showed a significant reduction in mean scores was observed at the end of the 1st month and 3rd month as compared to the baseline values ($P < 0.01$, 0.001) [Table 4]. Further, the 3rd month follow-up also showed a significant reduction in the score as compared to the 1st month follow-up ($P < 0.01$) [Table 4]. However, no statistically significant difference was observed at the end of 3 months treatment between the three groups.

Adverse drug reactions

A total of 42 adverse drug reactions (ADRs) were observed during the study period. The causality was assessed using the WHO-UMC criteria and preventability using modified Schumock and Thronton preventability scale.

Sertraline

In the sertraline group, a total of 14 adverse events were reported. The most common ADR was headache (6) followed by nausea (5), diarrhea (2), and dizziness (1). The WHO-UMC causality was possible for all the reactions expect diarrhea for which it was probable.

Fluoxetine

In this group, a total of 16 ADRs were reported. The most common ADR was headache (8) followed

Table 2: Effect of sertraline, fluoxetine and desvenlafaxine on psychomotor functions at the end of study period (*n*=95)

Psychomotor tests	Sertraline (*n*=31)			Fluoxetine (*n*=32)			Desvenlafaxine (*n*=32)		
	Baseline	1 month	3rd month	Baseline	1 month	3rd month	Baseline	1 month	3rd month
Six letter cancellation test	26.4±1.19	31.48±1.27**	33.03±1.31**	31.96±1.64	26.84±1.27*	25.46±1.78*	28.84±0.9	28.81±0.86	28.68±0.89
Digit letter substitution test	23.03±1.0	27.06±1*	28.8±1.04*	29.12±1.28	24.12±1.37*	23.03±1.73*	22.7±1.0	23±1.05	22.62±1.02
Flicker fusion test	43.1±0.22	44±0.24**	43±0.3	43.03±0.18	41.81±0.37*	41.48±0.29*	42.81±0.21	43.03±0.23	43.37±0.9
Choice reaction time-audio	1.65±0.06	1.26±0.06*	1.08±0.06*^	1.58±0.04	1.83±0.08*	2.02±0.05*,^	1.67±0.05	1.61±0.04	1.64±0.05
Choice reaction time-visual	1.6±0.07	1.23±0.03*	1.14±0.05*	1.68±0.05	1.91±0.07*	2±0.1*	1.5±0.03	1.5±0.03	1.5±0.02
Hand steadiness test	47±1.86	40±2.03	39±2.04	45.8±1.49	53.4±1.97*	57.81±2.3*,^	44.0±1.76	43.34±1.63	43.65±1.7

*P value<0.01 as compared to baseline ** P value<0.001 as compared to baseline ^ P value<0.001 as compared to 1st follow up

Table 3: Comparison of effect of sertraline, fluoxetine and desvenlafaxine on psychomotor functions at the end of study period (*n*=95)

Psychomotor tests	Sertraline (*n*=31)			Fluoxetine (*n*=32)			Desvenlafaxine (*n*=32)		
	Baseline	3rd month	Difference	Baseline	3rd month	Difference	Baseline	3rd month	Difference
Six letter cancellation test	26.4	33.03	−6.63*,**	31.96	25.46	6.5	28.84	28.68	0.16#
Digit letter substitution test	23.03	28.8	−5.77*,**	29.12	23.03	6.09	22.78	22.62	0.16#
Flicker fusion test	43.1	43	−0.1*	43.03	41.48	1.55	42.81	43.37	0.94#
Choice reaction time-audio	1.65	1.08	0.57*,**	1.58	2.02	−0.44	1.67	1.64	0.03#
Choice reaction time-visual	1.6	1.14	0.46*,**	1.68	2	−0.32	1.5	1.5	0.0#
Hand steadiness test	47.7	39	8.7*,**	45.8	57.81	−12.01	44.09	43.65	0.4#

*Significant increase in sertraline as compared to fluoxetine ($P<0.05$) ** Significant increase in sertraline as compared to desvenlafaxine ($P<0.05$)
#Significant increase in desvenlafaxine as compared to fluoxetine ($P<0.05$)

Table 4: Comparison of Hamilton depression rating scale at different time intervals in the study (*n*=95)

	Sertraline	Fluoxetine	Desvenlafaxine
Baseline	17.94±1.47	18.31±1.30	17.68±1.65
End of 1 month	17.08±1.38*	17.43±1.34*	16.87±1.43*
End of 3rd month	11.90±1.57*.**	11.81±1.42*.**	11.84±1.47*.**

*$P<0.05$ as compared to baseline **$P<0.05$ as compared to 1 month follow up Value are expressed as mean±SEM

by nausea (6), diarrhea (1), and dizziness (1). The WHO-UMC causality was possible for all the reactions expect diarrhea for which it was probable.

Desvenlafaxine

A total of 19 ADRs were reported. The most common ADR was nausea (9) followed by headache (6), drowsiness (2), and dizziness (2). The WHO-UMC causality was possible for all the reactions.

All the reactions were not preventable according to modified Schumock and Thronton preventability scale.

After comparing the three groups, using Chi-square test, no significant difference was observed between the three groups for ADRs ($P < 0.25$).

DISCUSSION

This study evaluated the effect of sertraline, fluoxetine, and desvenlafaxine on psychomotor function in patients with endogenous depression. The three groups were comparable at the baseline in choice reaction time audio–visual, flicker fusion test, and hand steadiness test. While in the six letter cancellation, digit letter substitution the three groups were not found to be comparable. The patients in fluoxetine group showed higher baseline values for these test. This may be because of the higher number of literate (graduate) patients. It has been reported that the results of these tests can be affected by the education level.[12] Our results are supported by Lawlor *et al*. (1991) a double-blind, 12-week study on sertraline 50–100 mg and fluoxetine 20–40 mg.[13] Similar results for flicker fusion test and reaction time have been obtained by a meta-analysis by Sherwood on the comparative behavioral toxicity of SSRIs.[14] A study by Ghodke *et al*. on SSRIs also showed that sertraline improved the choice reaction time audio and visual components at the end of 1 month as compared to 2nd week follow-up.[15]

Patients treated with fluoxetine showed a significant deterioration of all the psychomotor functions by the end of study period. A similar observation has been reported by Nicholson and Pascoe with fluoxetine.[16] Our findings on flicker fusion test are supported by Ramaekers *et al*. (1997) a double-blind, crossover study with fluoxetine.[17]

Desvenlafaxine-treated patients did not show any significant change in any psychomotor tests till the end of study period. Our observations have been supported by a study by Nichols *et al*. a single ascending dose of desvenlafaxine did not significantly affect the digit letter substitution scores or choice reaction time scores over the dose range studied.[18]

Psychomotor performance is the result of coordination of sensory and motor system through integrated and organized process in the brain and central nervous system (CNS). The processing of sensory input may be influenced by personality, memory, individual motivation, and the state of arousal of the CNS.[19] Real life tasks such as car driving and machine operating require coordinated sensorimotor systems. This coordination was assessed by using choice reaction time audio and visual test. Hand steadiness test assesses fine tremors in hand.[6] The patients treated with sertraline thus had improved perceptual processing, recording and recognition, improved psychomotor speed, and sensorimotor stimulation at the end of the study period. However, patients treated with fluoxetine showed deterioration in the above-mentioned functions, and those of desvenlafaxine group did alter these functions by the end of the study period.

Surprisingly, sertraline and fluoxetine belong to the same group, i.e., SSRIs; they have opposite effect on the psychomotor functions. Probably, this can be attributed to the different chemical structure, receptor binding, and pharmacokinetic profiles of these drugs. According to Plenge *et al*. 1991, different SSRIs bind to different areas of 5-HT transport proteins.[20] Sertraline has shown to have a high affinity toward the sigma-1 binding site of 5-HT transport protein, as well as a high affinity for human dopamine transporter.

On the other hand, fluoxetine has been shown to have a greater affinity for 5-HT_{2C} receptors. Probably, the interaction of fluoxetine with 5-HT_{2C} receptors may result in impairment of psychomotor function. The pharmacological manipulation of 5-HT_{2C} receptors functions affects food intake and anxiety in animals. Moreover, the drugs interacting with 5-HT_{2C} receptors (nefazodone and trazodone) have been shown to potentiate the cognitive deficits produced by scopolamine in healthy elderly individuals.[6]

Desvenlafaxine is a novel drug in the treatment of depression. Very few studies on the effect of desvenlafaxine on psychomotor function have been published. In general, desvenlafaxine treatment did

not modify any psychomotor function. However, further research and long-term follow-up of patients on desvenlafaxine are essential to confirm this observation.

The effect of antidepressants was assessed using HAM-D rating scale. All the three groups were found to be equally efficacious. The patients treated with sertraline, fluoxetine, and desvenlafaxine showed a significant reduction in scores at the end of first follow-up and end of the study period as compared to the baseline. Similar observations for sertraline have been reported by Lyketsos *et al*.[21] A randomized, double-blind, placebo-controlled trial in depressed diabetic patients by Lustman *et al*. showed a significant decrease in HAM-D scores from 3 weeks onward to the end of 8-week period in patients treated with fluoxetine.[22] Soares *et al*. have reported that desvenlafaxine 50 mg showed a significant improvement in depression symptoms by the end of 8 weeks of treatment.[23] Thus, all the three antidepressant drugs were found to be efficacious in improving the symptoms of depression from 3 weeks onward with progressive improvement till the end of the study. All the three antidepressant drugs were well tolerated. However, few ADRs were reported. The most common ADRs in each group were headache followed by nausea, diarrhea, and dizziness. Similar results have been reported by Rabkin *et al*. 2004,[24] and Tourian *et al*. 2009.[25] Stimulation of 5-HT_3 receptors in the CNS and periphery may account for the gastrointestinal side effects, and the excessive stimulation of brain 5-HT_2 receptors may result in CNS adverse reactions.

Like any other study, the present study also had some limitations. The number of patients enrolled in each group was less. A strict inclusion criterion for patients suffering only from endogenous depression not associated with any other comorbidity and concomitant medication was excluded from the study. This was the major reason for enrolling less number of patients. Second, the duration of the study was short, and we could not follow the patients till the complete remission of the disease. Moreover, some of the psychomotor tests such as SLCT and DLST are subjective in nature, and the result may vary according to the education level of the patients. However, the importance of the present study cannot be undermined. It is one of the few studies conducted in India on comparative effect of antidepressants on psychomotor function. This work may prove to be a foundation for future research on depressive illness and may also help clinicians in deciding treatment options based on it.

CONCLUSION

Sertraline significantly improves the psychomotor function as compared to desvenlafaxine and fluoxetine. On the contrary, fluoxetine deteriorates it over a period of 3 months. Further studies till the remission of the disease are necessary to correlate the effect of these antidepressants on psychomotor function with the improvement of depression.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. World Health Organization. Mental Health Depression. Available from: http://www.who.int/mental_health/management/depression/en/. [Last cited on 2016 Jan 11].
2. The Global Burden of Disease, 2010 Update. Department of Health Statistics and Informatics in the Information, Evidence and Research Cluster of WHO. Geneva: WHO Press, World Health Organization; 1995.
3. O'Donnell JM, Shelton RC. Drug Therapy of Depression and Anxiety Disorders. In: Brunton LL, Chabner BA, Knollmann BC, editors. Goodman and Gilman's the Pharmacological Basis of Therapeutics. 12th ed. New York, USA: The McGraw-Hill Companies Inc.; 2011. p. 397-415.
4. Kerr JS, Powell J, Hindmarch I. The effects of reboxetine and amitriptyline, with and without alcohol on cognitive function and psychomotor performance. Br J Clin Pharmacol 1996;42:239-41.
5. Hindmarch I, Kerr J. Behavioural toxicity of antidepressants with particular reference to moclobemide. Psychopharmacology (Berl) 1992;106:S49-55.
6. Roger ML, O'Hanlon JF. Cognitive and psychomotor effects of antidepressants with emphasis on selective reuptake inhibitors and the depressed elderly patient. Ger J Psychiatry 1999;1:28.
7. Stone BM. Pencil and paper tests – Sensitivity to psychotropic drugs. Br J Clin Pharmacol 1984;18 Suppl 1:15S-20S.
8. Turner P. Critical flicker frequency and centrally-acting drugs. Br J Ophthalmol 1968;52:245-50.
9. Parkin C, Kerr JS, Hindmarch I. The effects of practice on choice reaction time and critical flicker fusion threshold. Hum Psychopharmacol 1997;12:65-70.
10. Seth GS. Techniques in Pharmacology. Mumbai: Med Coll and KEM Hosp.; Manual Pharmatech; 1996.
11. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56-62.
12. Elst WV, Boxtel MP, Breukelen GJ, Jolles J. The letter digit substitution test: Normative data for 1858 healthy participants aged 24-81 from the Maastricht aging study: Influence of age, education and sex. Neuropsychology 2006;28:998-1009.
13. Lawlor BA, Newhouse PA, Balkin TJ, Molchan SE, Mellow AM, Murphy DL, *et al.* A preliminary study of the effects of nighttime administration of the serotonin agonist, m-CPP, on sleep architecture and behavior in healthy volunteers. Biol Psychiatry 1991;29:281-6.
14. Sherwood N. Comparative behavioural toxicity of the selective serotonin reuptake inhibitors. Hum Psychopharmacol 1995;10:S159-62.
15. Ghodke BV, Mohanty IR, Ghilduyal R, Shounak A, Deshmukh YA. Effect of selective serotonin reuptake

inhibitors on psychomotor function in patients of depression: A comparative study of sertraline and fluoxetine. MGM J Med Sci 2015;2:72-7.
16. Nicholson AN, Pascoe PA. Studies on the modulation of the sleep-wakefulness continuum in man by fluoxetine, a 5-HT uptake inhibitor. Neuropharmacology 1988;27:597-602.
17. Ramaekers JG, Ansseau M, Muntjewerff ND, Sweens JP, O'Hanlon JF. Considering the P450 cytochrome system in determining the effects of antidepressant and benzodiazepine treatment on actual driving performance of outpatients suffering from major depression. Int Clin Psychopharmacol 1997;12:159-69.
18. Nichols AI, Jessica Behrle A, Virginia P, Lyette Richards S, Stephanie McGrory B, Joel P, *et al*. Pharmacokinetics, pharmacodynamics, and safety of desvenlafaxine, a serotonin-norepinephrine reuptake inhibitor. J Bioequiv 2013;5:022-30.
19. Hindmarch I. Psychomotor function and psychoactive drugs. Br J Clin Pharmacol 1980;10:189-209.
20. Plenge P, Mellerup ET, Laursen H. Affinity modulation of [3H] imipramine, [3H] paroxetine and [3H] citalopram binding to the 5-HT transporter from brain and platelets. Eur J Pharmacol 1991;206:243-50.
21. Lyketsos CG, Sheppard JM, Steele CD, Kopunek S, Steinberg M, Baker AS, *et al*. Randomized, placebo-controlled, double-blind clinical trial of sertraline in the treatment of depression complicating Alzheimer's disease: Initial results from the depression in Alzheimer's disease study. Am J Psychiatry 2000;157:1686-9.
22. Lustman PJ, Freedland KE, Griffith LS, Clouse RE. Fluoxetine for depression in diabetes: A randomized double-blind placebo-controlled trial. Diabetes Care 2000;23:618-23.
23. Soares CN, Fayyad RS, Guico-Pabia CJ. Early improvement in depressive symptoms with desvenlafaxine 50 mg/d as a predictor of treatment success in patients with major depressive disorder. J Clin Psychopharmacol 2014;34:57-65.
24. Rabkin JG, Wagner GJ, McElhiney MC, Rabkin R, Lin SH. Testosterone versus fluoxetine for depression and fatigue in HIV/AIDS: A placebo-controlled trial. J Clin Psychopharmacol 2004;24:379-85.
25. Tourian KA, Padmanabhan SK, Groark J, Brisard C, Farrington D. Desvenlafaxine 50 and 100 mg/d in the treatment of major depressive disorder: An 8-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial and a *post hoc* pooled analysis of three studies. Clin Ther 2009;31 Pt 1:1405-23.