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ORIGINAL ARTICLE

Effect of Selective Serotonin Reuptake Inhibitors on Psychomotor Function in Patients of Depression: A Comparative Study of Sertraline and Fluoxetine

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ABSTRACT

Aims and objectives: Depression is a most common and widespread of all psychiatric disorders. Treatment of depression includes the use of antidepressants, commonly used clinically, such as tricyclic antidepressants, selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitor, and monoamine oxidase inhibitors. Certain antidepressants apart from improvement in the symptoms found to have detrimental effect on cognitive and psychomotor functions. Objective of this study was to assess and to compare the effect of sertraline and fluoxetine on cognitive and psychomotor functions.

Materials and methods: Effect of sertraline and fluoxetine on psychomotor function was assessed by using critical flicker fusion frequency (CFF) and reaction time (RT) in patients of mild to moderate depression at the end of 2nd and 4th week of monotherapy.

Results: Patients in both the group have their RT remained significantly higher ($p < 0.001$) in comparison with control and CFF remained significantly lower at the end of both the week except sertraline group in which CFF did not differ significantly from control at the end of 4th week. There was a significant rise in CFF ($p < 0.05$) in sertraline group as compared to fluoxetine. Sertraline showed a significant improvement ($p < 0.01$) in visual reaction time (VRT) at both the follow-ups and auditory reaction time (ART) ($p < 0.01$) at 4th week of monotherapy. Both the groups did not differ with respect to their effect on choice reaction time (CRT).

Conclusion: Findings of this study support the use of sertraline which had shown less impairment of psychomotor function in patients of depression as compared to fluoxetine, in special subgroups of population who operate machinery, drive vehicle or require alertness for the work.

Keywords: Antidepressants, Cognitive functions, Critical flicker fusion frequency, Reaction time.

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INTRODUCTION

Depression is a most common and widespread of all psychiatric disorders characterized by depressed mood for at least 2 weeks and or loss of interest or pleasure in most of the routine activities. In addition, depression is characterized by disturbances in sleep, appetite as well as deficit in cognition; thoughts of guilt, worthlessness and suicide are also common.[1] Antidepressants commonly used clinically are tricyclic antidepressants, selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitor, and monoamine oxidase inhibitors.

Depression related cognitive impairment is a condition that is under-recognized, undiagnosed and undertreated.[2] Cognitive impairment ranges from deficit in short-term, long-term memory or alteration in decision making process and impairment of information processing.

The largest population-based study to date of late onset depressive illness (65–84 years) documented severe cognitive impairment in 10% of depressed patients.[3] Approximately 70% of elderly depressed patients have measurable cognitive deficits, although a physician may be unaware of any overt signs.[4] It is well established that antidepressants can improve patient's well-being and functioning but many have demonstrable detrimental effect on range of cognitive functions. The optimum profile of antidepressant includes no detrimental effect on cognitive and psychomotor functions.[5]

With moves toward continuation and maintenance therapy for depression antidepressants with relatively non-sedating, non-cognition impairing profiles, such as selective serotonin reuptake inhibitors (SSRIs) are preferred in patients of depression.[6] However, antidepressant like fluoxetine and other SSRI's are known to improve cognition and memory in some studies,[7,8] whereas in contrast, in some studies cognition and memory parameters have shown decline.[9]

There are differences emerging amongst the SSRI group with respect to their effects on cognitive and psychomotor function. In another study, fluoxetine has demonstrated significant impairment of sustained attention in healthy volunteers.[10] Sertraline has demonstrated cognition enhancing effects in healthy volunteers.[11]

The lack of a placebocontrol in many of the studies, particularly those in depressed patients, means that the apparent differences amongst SSRIs in their cognitive and psychomotor effects require further confirmation. Use of these antidepressants having cognitive and psychomotor function impairing properties may raise concern amongst employees of some critical job that require high level of alertness such as drivers,[12] students, factory workers, machinery operators.[13] Since, antidepressants have to be used on chronic basis, it is important to evaluate the effect of these antidepressants on cognitive and psychomotor functions, such assessment would help in selecting a particular drug based on the individual patient requirements.

This study has been undertaken to determine the effect of commonly used antidepressants such as SSRIs on cognitive and psychomotor functions and to compare the effect of sertraline *vs* fluoxetine with healthy unmedicated adults as control group.

MATERIALS AND METHODS

The present study was an open label prospective comparative clinical study. It was carried out from Jan 2013-June 2013 and was approved by Institutional Ethics committee. Aim of the study was to evaluate the effect of commonly prescribed SSRIs sertraline and fluoxetine on cognitive and psychomotor functions. Assessment was carried out using CFF and RT. The present study included objective measures from various divisions of psychomotor performance, viz. sensory, central integration, and motor component.

Inclusion and Exclusion Criteria

Inclusion Criteria

(i) Patients of either sex; (ii) Patients within the age limit 18 to 60 years; (iii) A known cases of mild to moderate depression diagnosed by DSM-IV criteria and HDRS scale;[14] (iv) Patients who were on monotherapy with either SSRIs (fluoxetine 20 mg, sertraline 50 mg); and (v) Patients who were willing to participate in the study and willing to give written informed.

Exclusion Criteria

(a) Patients who were on any other medications (antihypertensive, sedative and systemic steroid, etc.) that are known to affect cognitive and psychomotor functions; (b) Patients with serious systemic disorders (diabetes, hypertension, etc.); (c) Patients with any psychiatric illness or any other CNS disorder that will interfere with cognitive and psychomotor functions except depression; (d) Patients who were not willing to participate and not given written informed consent; and (e) Patients with severe depression with HDRS score >17.

Outpatient department patients diagnosed with depression and meeting with inclusion criteria were enrolled in the study. Age and sex matched healthy adult volunteers were assigned to control group. Aim, procedure of the study and tests were explained to the study participants. The enrolled patients were explained about the importance of this study and written informed consents were obtained.

Each patient was familiarized with CFF and RT tests. Tests were carried out between 10:00 am and 1:00 pm. Before beginning of the study, patient's vital data, such as name, age, sex, educational status, occupation were noted on first visit. Other things like symptoms, illness duration, past history family history, past drug history were also noted. Vital data and details of systemic examination were recorded. A note of the diagnosis and treatment was recorded in the performa during each visit. General and systemic examinations were carried out to exclude any systemic disease. Enrolled subjects were grouped in 3 as follows:

Test Performed

Critical flicker fusion frequency test; and (ii) Reaction time performance test: (a) Visual reaction time; (b) Auditory reaction time; and (c) Choice reaction time.

Critical Flicker-Fusion Test

It was assessed by the critical flicker-fusion apparatus (Techno Electronics, LalbaughLucknow-226001). The apparatus is housed in a metal cabinet having two sloping sides the light source flickers at the rate set by the experimenter. The flicker frequency range of the instrument is 5 to 50 Hz the CFF (Fig. 1).

Subjects were asked to indicate when a red-light-emitting flickering source increasing in frequency, is perceived to become a continuous signal. They were also required to distinguish the threshold at which a flickering signal was perceived from a continuous signal, when frequency decreased. This fusion and flicker are a reliable measure of cortical alertness and arousal and reasonably stable in a given subject. Decreases in thresholds is indicative of altered CNS function.[15]

Determination of 'Critical Fusion Frequency

The 'flicker per second' knob of the instrument was kept at minimum frequency of 5 Hz. The volunteers

Fig. 1: Techno flicker-fusion apparatus

were told to view a flickering light source through the eyepiece. They were allowed adaptation to the least flicker frequency for 1 minute. Then frequency was increased slowly by rotating the flicks per second knob clockwise. The frequency increase was stopped as soon as patient responded by pressing the response switch, when he saw fusion, i.e. no more flickering or a steady light source. Frequency from the dial setting was noted. Three such readings were taken and the score was calculated as the mean of these 3 readings.[16]

Determination of 'Critical Flicker Frequency'

After determination of critical fusion frequency, the flicks per second knob was adjusted to maximum frequency of 50 Hz, after 1 minute adaptation frequency was decreased slowly, by rotating the flicks per second knob anticlockwise. The frequency reduction was stopped as soon as the subject responded when he saw flickering. Three reading were taken and the score was calculated as the mean of these 3 readings.[16]

Mean of both (a) and (b) was then calculated.

Mean CFF value is decreases with age, also with the antidepressants impairing cognitive and psychomotor function and hypnotics,[17] while CNS stimulant drugs increases critical flicker fusion frequency.[17,18]

Reaction Time Performance Test

Reaction time performance test was assessed using (Digital Display Multiple Choice 4-visual+4- Aural Type MCR-444) Lalbaugh Lucknow-2220. It measures reaction time, i.e. time interval after which subject responds to stimulus either visual/auditory.

Four different stimuli of different colors and four aural stimuli of different tones, with independent operation were provided. Chronoscope is a four segment LED Display with a minimum count of 00.10 seconds and maximum of 99.99 seconds.

The techno digital display multiple choice is a compact portable unit with sloping operating panel. On both sides for ease of operation, a removable partition effectively shields the operation side from each side. It operates from 220V 50 Hz AC (Fig. 2).

Experimenter's side contains (a) red, green, yellow and amber colored LED's lights or any four different colors, (b) The bottom row has eight press buttons four for visual stimuli four for auditory stimuli. Subject's side contains: red, green, yellow and amber colored visual stimuli (or matching different colors) and eight press buttons four for visual four for aural stimuli.

Sensory component is an important aspect of psychomotor performance. Detection, perception, and recognition of a stimulus are three levels of information processing which together account for the majority of sensory activity. Thus, reaction time performance measure the processing of sensory information.

Reaction time is impaired/increased with drugs declining cognitive functions, depression, with increasing age[18] (time taken to respond to stimuli is increased with cognitive and psychomotor impairment could be due to drug or depression itself). Certain antidepressants, caffeine[19] and CNS stimulant, such as amphetamine produces reduction reaction time.[20]

In the present study, patients were included in such a way so as to exclude any extraneous influence on psychomotor function like drugs (e.g. antiepileptic, sedative-hypnotics, antipsychotic) and diseases (serious systemic disorder, for example diabetes mellitus.) Thus, the changes observed in the study if any could be attributed to two factors, first the effect of drugs on psychomotor function parameters and second improvement in the disease, i.e. depression.

STATISTICAL ANALYSIS

Data presented using charts and descriptive statistics, such as mean, standard deviation (SD), standard error (SE).

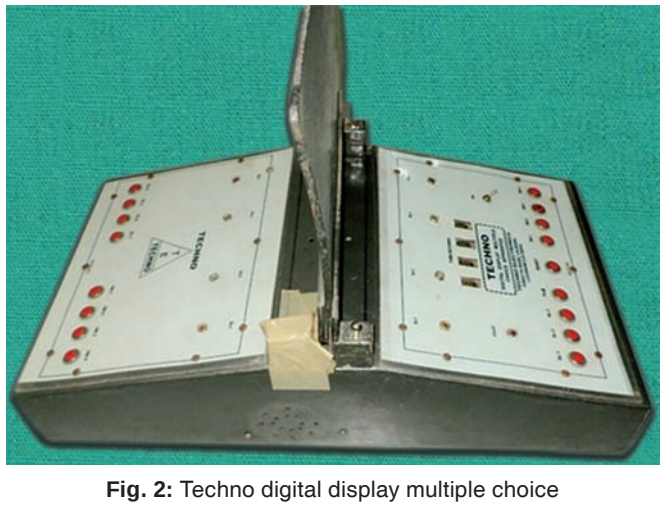

Fig. 2: Techno digital display multiple choice

Further statistical analysis was being done using one-way analysis of variance (ANOVA), followed by Tukey's post hoc test. The significance level was set at 5%, p-value less than 0.05 was considered as a significant.

RESULTS

In this study, there were 55% males and 45% females. Out of 60 study subjects 55% were in the age group of (18-40) and 45% were in the age group of (41–60) (Table 1).

At 2nd and 4th week of monotherapy when both the drug groups compared with control, mean CFF, mean VRT and mean CRT was decreased significantly ($p < 0.001$), except sertraline at 4th week in which CFF did not differ significantly from control group (Table 2).

Mean CFF in sertraline group increased significantly when compared with fluoxetine ($p < 0.05$) at 2nd week (31.68 ± 0.21) and 4th week (33.1 ± 0.20) of treatment. Effect of sertraline on visual reaction time did not differ significantly from fluoxetine. However, it was reduced (159.77 ± 4.44) significantly at 4th week ($p < 0.05$). Mean ART was significantly low in sertraline group when compared with fluoxetine at the end of both 2nd (209.85 ± 2.24) and 4th week (146.33 ± 4.51) of treatment. Effect of sertraline on choice reaction time did not differ significantly from fluoxetineat both the follow-ups.

Table 1: Sociodemographic profile of study participants

	Sertraline (n = 20)	*Fluoxetine (n = 20)*	*Control (n = 20)*
Sex			
Male	12 (60)	10 (50)	11 (55)
Female	8 (40)	10 (50)	9 (45)
Age group			
18–40	12 (60)	10 (50)	11 (55)
41–60	8 (40)	10 (50)	9 (45)
Occupation			
Student	3 (15)	5 (25)	4 (20)
Household worker	4 (20)	3 (15)	3 (15)
Factory worker	5 (25)	4 (20)	3 (15)
Laborer	4 (20)	4 (20)	4 (20)
Office worker	3 (15)	2 (10)	4 (20)
Others	1 (5)	2 (10)	2 (10)

Note: Figures in parenthesis show percentages

DISCUSSION

Depression affects 121 million people worldwide; it has life time prevalence of 16.2% and 12 months prevalence of 6.6% in developed countries,[21] and is a leading cause of disability worldwide. As far as the burden of depression in India is concerned, many studies have estimated the prevalence of depression in community samples and the prevalence rates have varied from 1.7 to 74 per thousand in Indian population.[22,23] The largest population-based study to date of late onset depressive illness (65–84 years) documented severe cognitive impairment in 10% of depressed patients.[3] Approximately, 70% of elderly depressed patients have measurable cognitive deficits, although a physician may be unaware of any overt signs.[4] It is well established that antidepressants can improve patient's well-being and functioning but many have demonstrable detrimental effect on range of cognitive functions. The optimum profile of antidepressant includes no detrimental effect on cognitive and psychomotor functions.[5]

Studies are available which show the effect of antidepressants on cognitive and psychomotor function but most of these studies are single-dose studies and healthy volunteers were used as a study subjects.[24] Few studies reveal the effect of selective serotonin reuptake inhibitors on cognitive and psychomotor performance in depressed patients.[24,26]

In the present study, at 2nd and 4th week of monotherapy, when both the drug groups compared with control, mean CFF of all patients was significantly less except sertraline group in which CFF did not differ significantly from control at 4th week. Present results considering the effect of fluoxetine on cognitive and psychomotor performance in comparison with control as measured by CFF is in commensurate with findings of Sabbe et al (1997),[25] in which they had assessed sensory-motor programming, coordination, initiation and execution of muscle commands and feedback processing. The performances of patients receiving fluoxetine were compared to a control group of

Table 2: Effect on CFF and RT at the end of 2nd and 4th week between various groups (mean ± SEM)

Test ↓ *Group* →		*Sertraline (n = 20)*		*Fluoxetine (n = 20)*	
Time interval	*Control (n = 20)*	*2nd week*	*4th week*	*2nd week*	*4th week*
CFF	33.34 ± 0.17	31.68 ± 0.21[ac]	33.1 ± 0.20[ac]	28.43 ± 0.25[b]	28.92 ± 0.22[b]
VRT	163.06 ± 2.69	222.35 ± 2.26[a]	209.85 ± 2.24[ad]	232.66 ± 3.83[b]	230.30 ± 3.97[b]
ART	111.27 ± 4.48	159.77 ± 4.44[ae]	146.33 ± 4.51[ae]	212.25 ± 3.11[b]	207.20 ± 2.97[b]
CRT	335.20 ± 12.95	388.36 ± 3.71[a]	375.20 ± 4.11	411.40 ± 3.24[b]	408.50 ± 3.33[b]

Time in millisecond (msc) and frequency in Hz

CFF: Critical flicker fusion frequency; RT: Reaction time; VRT: Visual reaction time; ART: Auditory reaction time; CRT: Choice reaction time; [a]$p < 0.001$ as compared with control; [b]$p < 0.001$ as compared with control at both the weeks, [c]$p < 0.05$ as compared with fluoxetine at 4th week, [d]$p < 0.01$ as compared with fluoxetine at both the weeks, [e]$p < 0.01$ as compared with fluoxetine at the end of 2nd and 4th week

22 individuals. The significant slowing of motor processes in the depressed in-patients decreased but did not disappear after treatment. At the end of treatment significant differences persisted between the patient group and the control group. Significant slowing of motor processes in depressed inpatients receiving fluoxetine decreased but did not disappear at the end of 6th week.[25]

Improvement in mean CFF (33.1 ± 0.20) in sertraline group at 4th week is in agreement with the study done by Schrijvers (2009), in which they reported that the patients psychomotor slowing had improved after 6 weeks on sertraline reflected by reductions in initiation and movement times on simple line and figure copying task and decreased initiation times for complex figure copying task relative to their baseline outcome.[26]

Mean (VRT, ART and CRT) of all drug groups were remained significantly on higher side as compared to control. Mean CFF in sertraline group was increased as compared to fluoxetine at the end of 2nd (31.68 ± 0.21) and 4th week (33.1 ± 0.20). It is in consistence with findings of the study done by Newhouse (1996).[27] In their study, there was a significant improvement in the parameters of cognition such as DSST in sertraline group relative to baseline from week 1 and relative to fluoxetine at 6th and 12th week. Fluoxetine only significantly improved DSST relative to baseline at 12th week. Both the treatment improved shopping list task however the improvement was greater in sertraline group and it was significantly greater than fluoxetine 6th week.

Effect of sertraline on visual reaction time did not differ significantly from fluoxetine group at 2nd week. However; it was significantly low at 4th week of monotherapy. Mean ART in sertraline group was significantly low when compared to fluoxetine at both the follow-ups. Effect of both the groups on choice reaction time didnot differ significantly from each other at 2nd and 4th week.

Sertraline showed a significant improvement in cognitive and psychomotor functions as far as its effect on parameters, such as CFF and RT were concerned.

CONCLUSION

Findings of this study support the use of sertraline which had shown less impairment of psychomotor function in patients of mild to moderate depression as compared to fluoxetine. Drugs which have low behavioral toxicity should therefore be preferred as they are less disruptive of patients everyday activities produce better quality of life. It may be preferred in patients who operate machinery, drive vehicle or require alertness for the work. However, our findings need confirmation by using larger number of patients with repeated follow-up.

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