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EFFECTS OF COMMONLY USED ANTIDEPRESSANTS ON PSYCHOMOTOR FUNCTIONS IN ADULT PATIENTS WITH DEPRESSION: A PROSPECTIVE OPEN LABEL OBSERVATIONAL STUDY

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ABSTRACT

Context: Cognitive and psychomotor functions are impaired often in patients with depression and their further impairment by antidepressants is undesirable Data on effect of commonly prescribed antidepressants on psychomotor functions in patients with depression in the Indian context are limited. **Aim**: Study aimed to determine the effects of commonly prescribed antidepressants (Doxepin, Fluoxetine, Citalopram, Sertraline) on psychomotor functions in patients with depression. **Materials and Methods**: 100 participants [20 healthy volunteers and 80 with depression being treated with one of following daily medication: doxepin (75 mg) / Fluoxetine (20 mg) / Citalopram (20 mg) / Sertraline (50 mg) for 12 weeks] were put to various psychomotor function tests (DSST, SDCT, CFFT, SVL, HST, Trail A and B). Results were compared and analyzed. **Statistical analysis used**: Comparisons were made using one–way analysis of variance [ANOVA] for all psychomotor tests except CFFT (Kruskal Wallis Test used), followed by Bonferroni multiple comparison test. **Results**: The psychomotor tests were impaired most by fluoxetine [20 mg/day] and doxepin [75 mg/day], followed by citalopram [20 mg/day] and sertraline [50 mg/day] in comparison to control group. **Conclusions**: Psychomotor impairment is an important consideration while treating patients with depression; participants treated with sertraline suffer lesser impairment in psychomotor function in comparison to many of the other commonly prescribed SSRIs.

KEY WORDS: Antidepressants, depression, psychomotor function.

Key messages: Drug induced psychomotor impairment should be considered while prescribing antidepressants. Sertraline causes least psychomotor impairment amongst commonly used SSRIs.

INTRODUCTION

Cognitive and psychomotor functions are impaired often in patients with depression[1] and their further impairment by drug treatment is undesirable.[2] Hence selective serotonin reuptake inhibitors (SSRI) are preferred over tricyclic antidepressants (TCA) as they claimed to have relatively non-sedating, non-cognition impairing profile.[3] However, amongst the SSRI group, differences with respect to their effects on cognitive and psychomotor functions exist due to their different structural, pharmacokinetic and pharmacodynamic profiles. This study was designed to determine the effect of commonly used SSRI (Fluoxetine, Citalopram, Sertraline) on psychomotor function, in comparison with TCA (Doxepin) and control group (healthy volunteer) and among the commonly prescribed SSRI, which SSRI has better profile as far as effect on psychomotor function is concerned.

MATERIALS AND METHODS

An open-label comparative clinical study was carried out after approval from the local institutional ethics committee. All participants gave written informed consent for participation in the study.

Based on the scrutiny of medical records, male patients of depression with Beck's depression inventory [BDI] test score <10 [to exclude the impairment caused by depression itself] , age between 20 to 45 years, education qualification of at least matriculation and visual acuity of 6/6 with or without glasses, receiving monotherapy with either of the following – fluoxetine [20 mg hs] or citalopram [20 mg hs] or sertraline [50 mg hs] or doxepin [75 mg hs] for less than 12 weeks duration were selected from psychiatric ward and OPD of tertiary care hospital in India were included in the study. The patients who were smokers or alcoholics, having any other abnormality on general and physical examination and those receiving other drugs having effect on cognitive

and psychomotor functions were excluded from the study.

In total, 20 apparently healthy volunteers and 80 patients of depression were enrolled after taking written informed consent. The patients fulfilling the inclusion criteria were familiarized with the battery of psychomotor tests by hands-on practice in order to preclude any learning curve effect. 03 sessions of hands-on-practice were given to each participant of 30 mins duration each as per their convenience. On completion of 12 weeks of respective drug intake, the subjects underwent various tests in the following sequence: Six-digit cancellation test [SDCT], Digit symbol substitution test [DSST], Critical flicker fusion test [CFFT], Serial verbal learning [SVL], Hand steadiness test [HST], Trail 'A' & 'B' test. The above tests were performed between 1000 hrs to 1300 hrs of a day for each participant so as to minimize the effect of time factor on psychomotor function.

The perception and recognition aspects of sensory component were tested by SDCT and DSST, respectively. [4] In SDCT, participants were given a sheet consisting of 1200 randomised digits and 6 digits key and was asked to cancel as many digits as possible which are appearing in the key given. Scoring was given on the basis of number of correct cancellations in 2 minutes. In DSST, participants were given a sheet consisting of 200 randomized digits and a symbol key. Participants were required to insert the corresponding symbol in the space above each digit and scoring was done on the basis of number of correct substitutions.[4]

The fine motor component of psychomotor function was tested by using HST.[5] The participants were asked to use his dominant hand to insert the whole metallic portion [about an inch] of the stylus into the holes made in metallic plate, without touching the sides of the hole, starting from the largest hole and progressing towards the smaller ones in a total duration of 15 secs. The participant was asked to ensure that probing is being done at uniform speed. The time for which probe was in touch with holes was displayed as error time. Three such readings were taken with a brief rest of 10 seconds in between the readings and mean value was calculated.

The integration and memory aspect of CNS component were tested by CFFT and SVL, respectively.[6] For CFFT, the participants were told to view a flickering light source through the eyepiece and frequency of flickering increased till participants reported that he can no longer see flicks but a steady source of light. The test was reversed by reducing frequency of the steady light source to the level that participant notes flickering again. A mean of three such readings was taken.

The short-term memory was assessed by the memory drum apparatus. The participants were shown a list of 10 nonsense syllables one by one; each syllable being displayed only for 2 seconds. The participants were given 20 sec to recall the entire list as shown without any error. The processes [trials] were repeated till the participants recalled the entire list of nonsense syllables without error. The number of attempts to recall the list correctly was recorded.

All the components of psychomotor function were assessed together using Trail 'A' and 'B' test.[6 - 8] In Trail 'A', the participants were instructed to draw lines to connect the encircled numbers 1-25 in ascending order. In Trail 'B', the encircled numbers [1–13] and letters [A – L] were used and the participants were instructed to draws lines to connect the circles in a progressive order, alternating between the numbers and letters [i.e., 1-A-2-B-3-C, etc.]. Time taken by the participants to complete the trail 'A' and 'B' was recorded.

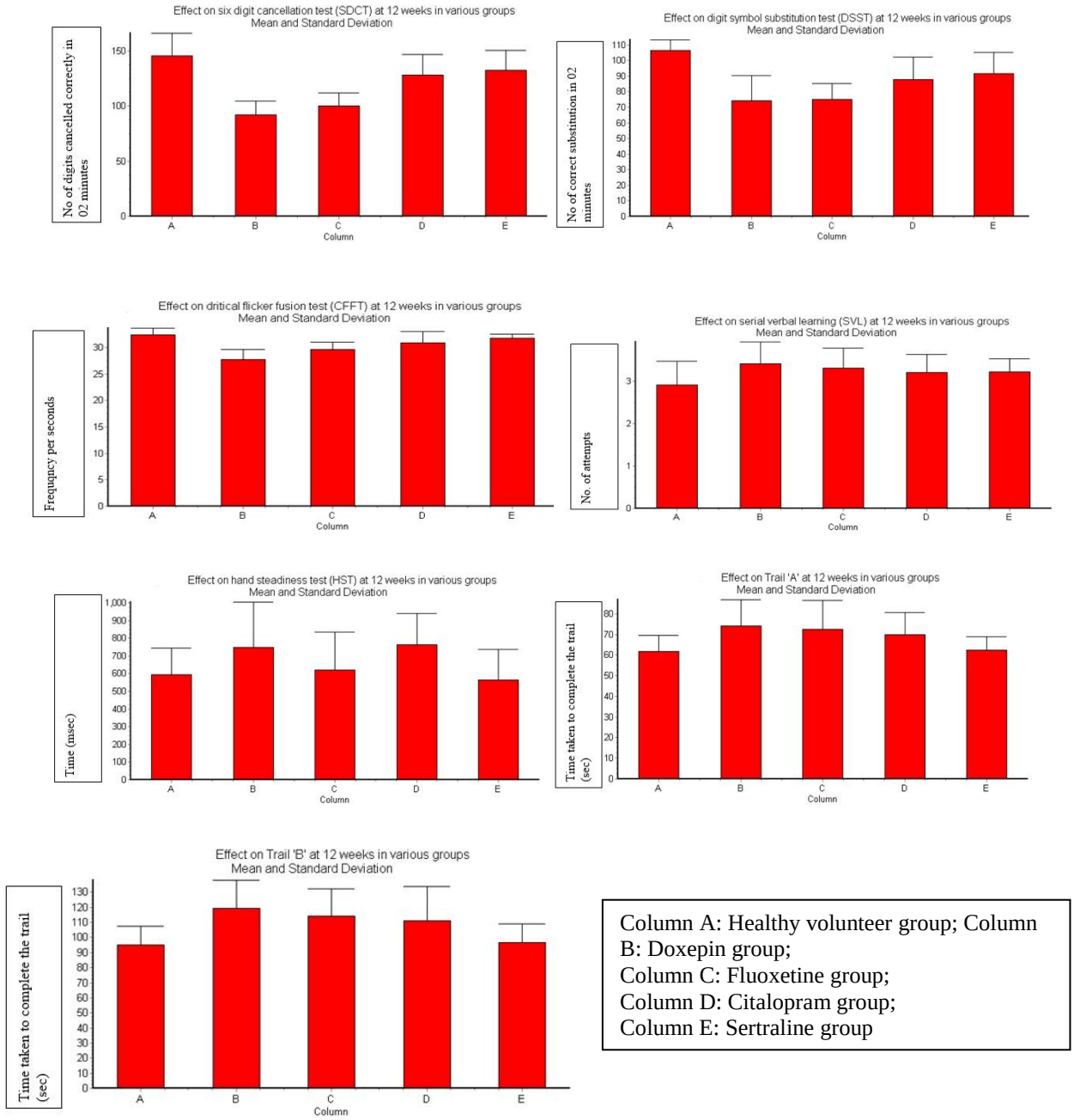
Statistical analysis

The comparisons were made using one–way analysis of variance [ANOVA] for all psychomotor tests except CFFT, followed by Bonferroni multiple comparison test. To find the significance in CFFT scores of different groups, Kruskal Wallis Test was used. P-value <0.05 was considered significant. The statistical tests were performed using GraphPad prism 7 software.

RESULTS

A total of 100 male participants (80 with depression and 20 healthy volunteers) were included in the study. The mean age of the healthy volunteer and participants with depression was 30.3 and 34 years, respectively. Participants underwent various psychomotor function tests. Figure 1 summarizes the findings on each psychomotor function tests amongst various groups with help of graphs. Table-1 summarizes the data along with inter-group comparison significance level. Fluoxetine significantly decreased scores on SDCT, DSST and CFFT when compared to control [$p<0.01$ for all tests]. Fluoxetine also impaired SDCT & CFFT in comparison to sertraline [$p<0.05$ for both tests] and SDCT in comparison to citalopram [$p<0.05$]. Citalopram group when compared with healthy control had no significant impairment of psychomotor performance except in DSST [$p<0.05$]. The performance in SDCT was significantly better than fluoxetine and doxepin groups [$p<0.05$ for both]. The CFFT performance in citalopram group was also better than doxepin group [$p<0.05$]. Sertraline group did not have significantly difference in the psychomotor performance on all objective measures, in comparison to healthy volunteers. However, performance in SDCT and CFFT is much better than in both fluoxetine [$p<0.05$] and doxepin group [$p<0.05$]. The performance in DSST of sertraline was also significantly better than doxepin [$p<0.05$]. Hand steadiness test and short-term memory were not significantly different in any of the study groups indicating that both SSRIs [fluoxetine, citalopram, sertraline] and TCA [doxepin] treated groups had fine

motor function and short-term memory not significantly different to that of healthy control group.



Column A: Healthy volunteer group; Column B: Doxepin group;
Column C: Fluoxetine group;
Column D: Citalopram group;
Column E: Sertraline group

Figure 1: Graphs showing results of psychomotor function tests of different groups.

Table-1: Results of various psychomotor function tests performed in different groups after 12 weeks of anti-depressants therapy and healthy control [values shown are Mean ± SEM]

Tests ↓ / Group →	Control (n=20)	Doxepin 75 mg (n=20)	Fluoxetine 20 mg (n=20)	Citalopram 20 mg (n=20)	Sertraline 50 mg (n=20)
SDCT	145.70 ± 6.48	92.00 ± 4.00 [**,Φ,#]	100.00 ± 3.79 [**,Φ,#]	128.10 ± 6.01 [£,■]	132.90 ± 5.67 [£,■]
DSST	106.50 ± 2.13	74.30 ± 5.07 [**,#]	75.20 ± 3.21 [**]	87.90 ± 4.58 [*]	91.40 ± 4.42 [£]
CFFT	32.43 ± 0.38	27.71 ± 0.61 [**,Φ,#]	29.61 ± 0.45 [**,#]	30.88 ± 0.66 [£]	31.68 ± 0.24 [£,■]
HST	593.40 ± 47.80	747.20 ± 81.29	620.10 ± 68.26	761.80 ± 56.79	563.60 ± 55.29
SVL	2.90 ± 0.18	3.40 ± 0.16	3.30 ± 0.15	3.20 ± 0.13	3.10 ± 0.10
Trail A	61.70 ± 2.49	74.00 ± 4.03	72.60 ± 4.41	69.80 ± 3.38	62.50 ± 2.04
Trail B	95.20 ± 3.83	119.40 ± 5.87 [*]	114.20 ± 5.71	111.10 ± 7.15	96.40 ± 4.04

Note: SDCT- Six Digit Cancellation Test; DSST – Digit symbol substitution test; CFFT- Critical Flicker Fusion Test; HST – Hand Steadiness Test; SVL- Serial Verbal Learning

* : In comparison to control; **£** : In comparison to doxepin; ■ : In comparison to fluoxetine

Φ : In comparison to citalopram; # : In comparison to sertraline; Single symbol denotes P < 0.05; Double symbol denotes P < 0.01

DISCUSSION

Cognitive and psychomotor impairment are part of pathophysiology of depression. Antidepressant drugs can improve as well as aggravate these impairments due to their antidepressant and sedative effects, respectively.

At present, only limited number of studies exists on the effects of SSRIs on cognitive and psychomotor performance in patients of depression.[9 - 13] The present study was designed to assess the effects of fluoxetine [20 mg hs], citalopram [20 mg hs], sertraline [50 mg hs], and doxepin [75 mg hs] on various divisions of psychomotor performance viz. sensory, central integration, memory and motor component.

Sensory component is an important aspect of psychomotor performance. Pencil and paper tests such as SDCT & DSST measure processing of sensory information.[14] CFFT is a commonly used and validated psychometric test that is used to measure the integrative capacity of CNS.[15] The assessment of short-term memory was done using SVL test. For the assessment of fine motor control, HST was used.

In the present study, fluoxetine significantly decreased scores on SDCT, DSST and CFFT when compared to control [p<0.01 for all tests]. Fluoxetine also impaired SDCT & CFFT in comparison to sertraline [p<0.05 for both tests] and SDCT in comparison to citalopram [p<0.05]. The results of fluoxetine in all tests were not significantly different from doxepin group which is known to cause impairment due to its ability to readily cross the blood-brain barrier and produce sedation by blocking central H1, muscarinic and serotonin receptors. [16] Similar results were shown by studies conducted by other workers using fluoxetine.[10, 12]

Citalopram group when compared with healthy control had no significant impairment of psychomotor performance except in DSST [p<0.05]. The performance in SDCT was significantly better than fluoxetine and doxepin groups [p<0.05 for both]. The CFFT performance in citalopram group was also better than doxepin group [p<0.05]. The obtained results in comparison with healthy control were similar to those by Lader et al.[17]

Thus, in our study, the psychomotor tests were impaired most by fluoxetine [20 mg/day] and doxepin [75 mg/day], followed by citalopram [20 mg/day] and sertraline [50 mg/day] in comparison to control group. Similar results were obtained by other studies while comparing effect of sertraline and fluoxetine on psychomotor function.[18-20] Psychomotor function of sertraline group was not significant different from that of healthy control group. Citalopram group had significant impairment in the sensory component of the psychomotor function.

However, our study had some limitations too. Small sample size of patients (n=80 , divided in 4 groups), exclusion of females, shorter duration of the study (12 weeks) and comparison with healthy volunteers instead of pretreatment and post treatment comparison were some of the main limitations of the study. In addition, though the participants with BDI <10 were included, the psychomotor impairment due to residual depression cannot be ruled out.[21] The result of the study needs to be confirmed by study involving large number of participants including females over larger duration of therapy, preferably pre and post comparison.

Drugs causing lesser impairment of cognitive and psychomotor function are to be preferred, more so in patients with depression, to prevent the disruption of

patient's everyday activities and improve their quality of life. Antidepressants like sertraline may be preferred in patients who operate machinery, drive vehicle, or require alertness for the work.

CONCLUSION

Our study indicates that participants treated with sertraline suffer lesser impairment in psychomotor function in comparison to many of the other commonly prescribed SSRIs. Citalopram appears to be superior to Fluoxetine but inferior to Sertraline so far as effect on psychomotor function is concerned. However, our findings need confirmation by studies using larger number of patients.

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