Original Article

Effect of Fluoxetine on Some Cognitive Functions of Patients of Depression

Jaykaran, Pankaj Bhardwaj[1], N. D. Kantharia, Preeti Yadav, Arvind Panwar

ABSTRACT

Background: This study was carried out to evaluate the effect of long-term administration of a commonly prescribed antidepressant, fluoxetine from different group on memory and psychomotor functions in patients of various psychiatric disorders using a battery of simple tests that can be conveniently applied to the Indian population. **Materials and Methods:** Memory was evaluated using the PGI memory scale and psychomotor functions were evaluated using six letter cancellation test. Statistical analysis was carried out using Wilcoxon signed-rank test. **Results and Conclusion:** The results of the study reveal that there was significant improvement in some cognitive function. Cognitive functions are improved at first follow-up and they improved continuously up to last follow-up that is at one month. It is observed that there was improvement in the primary disease. So, final score of the cognitive parameters is because of the resultant activity of direct drug action and improvement in the underlying disease.

Key words: *Antidepressants, fluoxetine, PGI memory scale*

INTRODUCTION

Antidepressants are commonly used medications. They are used in various psychiatric conditions like depression (42.72%), anxiety disorders like obsessive compulsive disorder, panic attack, psychosomatic disorders and various phobias (11.89%), substance abuse withdrawn (4.61%), anorexia and weight disorders (0.97%), pain (10.44%), insomnia (10.19%), bipolar disorder (3.16%), schizophrenia (1.21%), and general medical conditions (14.81%).[1] Antidepressants like fluoxetine and other Selecive seretonergic uptake inhibitors (SSRIs) are known to improve cognition and memory in some studies.[2,4] Cognition and memory parameters are declined in some other studies.[3] Use of the antidepressants having cognitive and memory declining properties raises concern in employees of some critical jobs that require high level of alertness as drivers,[5] machinery operators,[6] aircraft pilots, etc. Older age patients are more prone to suffer the cognitive decline because of medications. Rockwood[7] reported delirium occurs in approximately 40% of hospitalized patients over age 65 years and is often treated with antipsychotic medications including antidepressants. In addition, it is estimated that 40% of the aged population suffer from depressive symptoms requiring medication.[8]

Antidepressants are widely used by ambulant patients, including geriatric age group, complete and quantitative evaluation of its effect on cognition and memory functions helps in making choice of drugs. Available tests for memory and psychomotor functions are cumbersome and not related to the Indian population but adaptations of tests meant for western population. There is a need to have simple objective tests to measure these functions by means that are easy to perform, less time consuming, and that do not require elaborate instrumentation. This study was therefore carried out to evaluate the effect of long-term administration of two commonly prescribed antidepressants from different group on memory and psychomotor functions in

Departmet of Pharmacology, New Civil Hospital, Government Medical College, Majura Gate, Surat-395 001,
[1]Department of Community Medicine, Era's Lucknow Medical College & Hospital, Lucknow, UP, India

Address for correspondence: Dr. Jaykaran
Departmet of Pharmacology, New Civil Hospital, Government Medical College, Majura Gate, Surat-395 001, India.
E-mail: drjaykaran@ahoo.co.in

DOI: 10.4103/0253-7176.53311

patients of various psychiatric disorders using a battery of simple tests that can be conveniently applied to the Indian population.

MATERIALS AND METHODS

This study was designed to evaluate the effect of antidepressant drugs for the period of one month on cognitive function (memory and psychomotor) in patient having major depressive disorders.

Subjects

Inclusion criteria:

1. Patients of either sex.
2. Within the age limit of 15–55 years.
3. Patients who were prescribed fluoxetine for at least one month.
4. Minimum educational qualification up to fifth year of schooling.
5. Patients who could read and write Gujarati, Hindi, or English.
6. Patients who were willing to be enrolled for the study and who gave the written informed consent.

The exclusion criteria for study group were as follows:

1. Patients who were on any other medications (e.g., antihypertensives, sedatives, antipsychotics, systemic steroid medication, etc.) that are known to affect memory and psychomotor functions. Topical medications were allowed.
2. Patients with any psychiatric illness or any other CNS disorder that could interfere with the memory and psychomotor functions except depression.
3. Patients with serious systemic disorders.
4. Patients who were on any antidepressant drugs at the time of enrollment to the study.

Logistics of the administration of the various tests to evaluate the cognitive functions were organized and pilot work was performed to ensure the suitability.

Method

The investigator visited the Psychiatry OPD daily in the morning from 9:00 A.M. to 1:00 P.M. for screening the patients, those who met with the inclusion and exclusion criteria were enrolled in the study. The aim and procedure of the study and the tests were explained. Written informed consent was obtained from the patient. The baseline evaluation carried out on the zero day, i.e. before starting of the drug treatment. The patients were then evaluated in the same manner at 15th day and at the one month of drug treatment. Patients were evaluated in the morning hours after ensuring that drug has been taken as per the schedule. Patient's personal data like name, age, registration number, educational status, occupation, mother tongue were noted at the first visit. Other things like symptoms, illness duration, past history, family history, and past drug history were also noted. Vital data and detail of systemic examination were recorded. A note of the diagnosis and treatment prescribed was recorded in the pro forma at each visit. Adverse drug reaction and clinical progress observed by investigator or reported by the patient was also recorded in pro forma.

Tests

Tests for memory

The PGI memory scale (PGIMS)[9,10] was employed to assess memory function of patients. The PGIMS consists of 10 subtests. Each subtest has maximum score of 6, 5, 9, 15, 10, 12, 5, 15, 13, and 10, respectively. The total score is 100. These tests measure different aspects of memory and employ different methods of recall. These tests are as follows:

1. Remote memory: It comprises of six simple questions relating to personal and current information. Scores are allotted as per the correct responses given by the patient.
2. Current memory: It consists of five questions that assess the patient's ability to recall information and events in the recent past.
3. Mental balance: This test gives an idea of balance over one's mental functioning. The learned materials (alphabet and numbers) were recalled in backward and forward series.
4. Attention and concentration: This function was evaluated by the test of digit span forward and backward repetition.
5. Delayed recall: In this test, the investigator reads out the names of common objects (two series of five each) at a uniform interval. The patient was instructed to recall the same after one minute and score of correct recall recorded.
6. Immediate recall: This test included sequential reproduction of the sentence in verbatim. Patient was asked to recall the sentences immediately.
7. Verbal retention for similar pairs: A series of similar associative pairs of words were administered to the patient. Patient was asked to mention the associate words in response to the stimulus word.
8. Verbal retention for dissimilar pairs: It is similar to the previous test. However, the associate pair of words was unrelated and dissimilar. Patients were allowed up to three trials in the test.
9. Visual retention: In this test, the investigator displayed some cards containing geometrical figure. Each card was shown for 15 s and after 30 s patient instructed to reproduce the drawing from memory. No time limit was set for this test. Correct reproductions of figures were scored.

10. Recognition: In this test, the investigator showed a card containing common objects. The patient was allowed to observe this card for 30 s. Two minutes later a second card containing another set of pictures having some picture appeared in first card shown to the patient. Patient was asked to identify and name the picture that appeared in both the cards. Correct responses were recorded and scores allotted accordingly.

Psychomotor function tests

Six letter cancellation test

Six letter cancellation test (SLCT)[11] is a psychomotor function test in which perceptual processing of sensory information can be readily assessed. It is a pencil and paper test, easy to replicate. It is a useful indicator of drug-induced changes. The worksheet for this test was prepared in Gujarati, English, or Hindi. The worksheet of this test consists of three parts: First part consists of name, age, sex of a patient with date and instructions. Second part includes the key that mentioned six target letters, while the third part is having working section. The working section displays randomized alphabets arranged in 22 rows and 14 columns. Within 90 s, patient asked to cancel as many target alphabets as possible. The letter cancellation was undertaken in a horizontal, vertical, or randomized manner. Total number of cancellations and wrong cancellations were scored. To avoid the effect of memory, parallel worksheets were prepared by changing the six letter key.

Statistical analysis

Data obtained in the various tests was analyzed using the following tests:

1. Distribution of data is analyzed by histogram, kurtosis, skewness, using Kolmogorov-Smirnov and Shapiro-Wilk tests.
2. Wilcoxon signed-rank test was used to compare post treatment scores (15 days and 1 month) of memory and psychomotor function test with pretreatment scores (baseline).

RESULTS

Out of all patients attending Psychiatry OPD, 35 patients who fulfill the inclusion criteria were enrolled in the study. All patients were evaluated at baseline (pretreatment), 15 days and one month of treatment. Four patients were dropped out of study as they did not report for follow-up. The findings of study reveal the following data.

Sociodemograhic distribution of patients

In this study, there were 58% males and 42% females. Among 31 patients, 16 (52%) were of age group 15–29 years while 11 (35%) were in 30–44 years and the remaining 4 (13%) were of 45 or above age group. Out of all respondents, 22 (71%) patients were primary school passed while 5 (16%) were senior secondary passed. Only 1 (3%) patient was in the graduation level [Table 1].

Effect of fluoxetine on memory and psychomotor function

A total of 35 patients were enrolled in this group. Four patients did not turn up for follow-up while 31 patients completed the study.

Memory

Patients on fluoxetine showed statistically significant improvement in attention and concentration ($P < 0.05$), delayed recall ($P < 0.05$), verbal retention ($P < 0.05$), and visual retention ($P < 0.05$) [Table 2].

These trends persist after one month. After one month, there was statistical improvement in attention and concentration ($P < 0.05$), delayed recall ($P < 0.05$), verbal retention ($P < 0.05$), and visual retention ($P < 0.01$) [Table 2].

Other memory subtests are not significant statistically.

Psychomotor function

There was no improvement in psychomotor function at 15th day ($P > 0.05$) but after one month from baseline SLCT showed statistically significant improvement ($P < 0.05$) [Table 2].

Table 1: Sociodemographic profile of patients included in the study

	Fluoxetine (n = 31)
Sex	
Male	18 (58)
Female	13 (42)
Age group	
15–29 years	16 (52)
30–44 years	11 (35)
≥ 45 years	4 (13)
Educational status	
5^{th}–10^{th}	22 (71)
11^{th}–12^{th}	5 (16)
Higher secondary to graduation	3 (10)
Postgraduation	1 (3)
Occupation	
Textile worker	6 (19)
Student	9 (29)
Government employee	7 (23)
Household work	8 (26)
Labor work	0 (0)
Others	1 (3)

Figures in parenthesis denote percentages

Table 2: Effect of fluoxetine (20 mg daily) on PGI memory scale

Subtest	Baseline (n = 31)	15 days (n = 31)	1 month (n = 31)
Remote memory	6.0±0.0	6.0±0.0	6.0±0.0
Recent memory	4.9±0.01	4.9±0.01	4.9±0.01
Mental balance	5.94±0.32	6.55±0.30	7.16±0.35
Attention and concentration	7.19±0.33	7.74±0.43*	8.29±0.41**
Delayed recall	3.19±0.21	3.9±0.25**	4.35±0.23**
Immediate recall	8.97±0.25	8.94±0.27	8.9±0.22
Verbal retention for similar pair	4.32±0.11	4.71±0.13*	4.87±0.10**
Verbal retention for dissimilar pair	13.98±0.23	14.15±0.16	14.79±0.18
Visual retention	3.68±0.21	4.68±0.24**	5.19±0.30***
Recognition	8.3±0.17	8.6±0.16	8.7±0.15
Psychomotor functions	11±0.34	12±0.37	13±0.35*

Value indicate mean ± SE; *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$; Wilcoxon signed-rank test (two-tailed) for two related samples

DISCUSSION

Cognitive function is the brains ability to acquire process, integrate, store, and retrieve information. It may be impaired with age, due to depressive disorder and as a result of drug treatment, including some forms of antidepressant drug treatment.

Cognitive function decline is associated with various kind of psychiatric disorders like depression,[12] anxiety,[13] somatization,[14] migraine,[15] etc.

Memory impairments and psychomotor retardation are among the classic features of major depressive disorder.[16] Cognitive impairment in depressed patients ranges from deficits in short- and long-term memory to alterations in the decision-making process and impairment of information processing. Reaction time and sensorimotor accuracy may also be disrupted.[16] It is well established that antidepressants can improve patient well-being and functioning but many drugs have a demonstrable detrimental effect on a range of cognitive functions.[17]

In this study, patients were included in such a way so as to exclude any extraneous influence on memory and cognition like drugs (e.g., antiepileptic, sedative-hypnotics, antipsychotics, etc.) and diseases (serious systemic disorder, for example diabetes mellitus, etc.). Thus, the changes observed in the study, if any, could be attributed to two factors, first the effect of drugs on cognition and memory parameters and second improvement in the disease, i.e. depression with or without other psychiatric disorders.

Studies are available which show the effect of antidepressants on cognitive and psychomotor functions but most of these studies are single-dose studies and healthy volunteers were used as study subjects.[16] Few studies reveal the effect of Selective serotonin reuptake inhibitors like fluoxetine on cognitive and psychomotor performance in depressed patients. Cognitive and psychomotor dysfunctions are symptoms of depression and they improve along with mood during effective therapy. During treatment, the cognitive and psychomotor effects of an antidepressant will be superimposed upon any effects of the depressive disorder itself. The net effect in a patient whose depressive symptoms respond will reflect the balance between persistent or emergent impairing antidepressant side effects and the drugs therapeutic activity. Fluoxetine is one of the commonly prescribed antidepressant and it is used in various kind of psychiatric disorders like OCD, social phobia, generalized anxiety disorder, etc. so this drug was selected as a test drug.

The occupation of these patients was varied household work, studying, office work, laborers, machine operator, and farmers. These occupations require the use of memory and psychomotor skills to a varying extent. Drugs that interfere with those functions can affect these daily occupations as in case of students and machine operators.

In the present study, fluoxetine shows highly significant improvement in the cognitive parameters. Subtest of PGIMS, mental balance, attention and concentration, delayed recall, verbal retention of similar pair, visual retention, and psychomotor functions are improved not only at the first follow-up but also at second follow-up where effects became more significant.

Similar results shown by study conducted by Fairweather *et al*,[18] in 66 elderly depressed patients, comparing fluoxetine (20 mg every morning) to amitriptyline (75 mg at night), results revealed that despite comparable antidepressant efficacy, performance testing by using psychometric tests like Critical flicker fusion (CFF) and choice reaction time (CRT) at weekly intervals showed differential drug effects. The mean CFF threshold in the fluoxetine group improved significantly at every week, relative to the amitriptyline group. Both treatments improved CRT but the rate of change was greater in the fluoxetine group resulting in a significant difference between groups at the end of the first week of treatment.

Even some animal studies confirmed our results. Kumar *et al*.,[19] investigated the effect of antidepressant drugs (amitriptyline, imipramine, and fluoxetine) on cognitive functions, impaired by the muscarinic antagonist scopolamine were in mice. The changes in learning and memory tasks were studied using transfer latency on

elevated plus maze and employing number of descents in passive avoidance paradigms. Amitriptyline and imipramine showed significant memory impairment. Fluoxetine, however, showed no effect on learning and memory. It significantly reversed the scopolamine-induced memory impairment in both the tests.

In our study, cognitive and psychomotor functions are improved in the fluoxetine-treated group, this improvement is highly significant as compared to the baseline score of the same group. These findings are significant and of clinical importance. As can be interpreted from the sociodemographical profile of the patients in this study, most patients who had been prescribed these drugs were student/machine operators/ office workers—occupations that demand optimum memory and psychomotor functions. Because of the availability of various classes of antidepressants, the choice of the drug for the prescriber then rests on other criteria like adverse events, compliance, cost availability of drugs, etc.

In such situation, drugs like fluoxetine could be preferred choice if adverse events alone taken into consideration. Compliance to drug therapy is also likely to be better because of their convenient dosing schedule and lesser incidence of adverse effects.

Finding of the study supports the concept that long-term use of fluoxetine does not impair memory and psychomotor function but improves it significantly. It may be preferred in patients who operate machinery, drive vehicle, or require alertness for the work.

This study also validates the tests used for evaluating the memory and psychomotor functions. The observations of this study are similar to those in other studies that employed other tests for evaluating these functions. The tests employed in this study are simple, reproducible, easy to perform, less time consuming. Since they are easy to understand and simple in content they have been found to be suitable for the literate or semiliterate Indian population. Hence their use may be recommended, particularly in OPD settings of the hospitals and in postmarketing surveillance.

CONCLUSION

During the study period of one month, there was significant improvement in some cognitive function. Cognitive functions improved at first follow-up and they improved continuously up to last follow-up that is at one month. It is observed that there was improvement in the primary disease. So, final score of the cognitive parameters are because of the resultant activity of direct drug action and improvement in the underlying disease.

ACKNOWLEDGMENT

Dr. Ritumbhara Mehta, Professor and Head, Department of Psychiatry, Dr. Kamlesh Dave, Associate Professor, Department of Psychiatry, Dr. Devendra Chaudhary, Resident Doctor, Department of Psychiatry, New Civil Hospital, Government Medical College for necessary support in enrollment, interviewing, and interection with patients in OPD. Dr. S.D. Mistry, Professor, Dept of Pharmacology for logistic support.

REFERENCES

1. Joseph J, Keene JR, Galt T, Martin F. Antidepressants use in psychiatry and medicine. J Am Dent Assoc 2003;134:71-9.
2. Doraiswamy PM, Krishnan KR, Oxman T, Jenkyn LR, Coffey DJ, Burt T, *et al*. Does antidepressant therapy improve cognition in elderly depressed patients? J Gerontol A Biol Sci Med Sci 2003;58:1137-44.
3. Jacqueline D. Memory loss in a patient treated with fluoxetine. Ann Pharmacother 2003;37:1800-3.
4. Spring B, Gelenberg AJ, Garvin R, Thompson S. Amitriptyline, clovoxamine and cognitive function: A placebo-controlled comparison in depressed outpatients. Psychopharmacology (Berl) 1992;108:327-32.
5. Wingen M, Ramaekers JG, Schmitt JA. Driving impairment in depressed patients receiving long-term antidepressant treatment. Psychopharmacology 2006;188:84-91.
6. Haslam C, Atkinson S, Brown S, Haslam RA. Perceptions of the impact of depression and anxiety and the medication for these conditions on safety in the workplace. Occup Environ Med 2005;62:538-45.
7. Andrew MK, Rockwood K. Psychiatric illness in relation to frailty in community-Dwelling elderly people without dementia: A report from the Canadian study of health and aging Can J Aging 2007;26:33-8.
8. Kennedy, Frazier GJ, Amy. Medical comorbidity and mental disorders in older adults. Curr Opin Psychiatry 1999;12:451-5.
9. Pershad D, Wig NN. A battery of simple tests of memory for use in India. Neurol India 1976;24:86-93.
10. Pershad D, Wig NN. Relationship between PGI- Memory scale and WAIS verbal I.Q. Neurol India 1979;27:69-72.
11. Natu, Agarwal. Six letters cancellation test. Indian J Pharmacol 1997;29:11-14.
12. Forsel Y, Palmer K, Fratiglioni L. Psychiatric symptoms, syndromes in elderly persons with mild cognitive impairment: Data from a cross-sectional study. Acta Neurol Scand 2003;107:25-8.
13. DeLuca AK, Lenze EJ, Mulsant BH, Butters MA, Karp JF, Dew MA, *et al*. Comorbid anxiety disorder in late life depression: Association with memory decline over four years. Int J Geriatr Psychiatry 2005;20:848-54.
14. Niemi PM, Portin R, Aalto S, Hakala M, Karlsson H. Cognitive functioning in severe somatization: A pilot study. Acta Psychiatr Scand 2002:106:461-3.
15. Leijdekkers ML, Passchier J, Goudswaard P, Menges LJ, Orlebeke JF. Migraine patients cognitively impaired? Headache 1990;30:352-8.
16. Roger M, James F. Cognitive and psychomotor effect of antidepressants with emphasis on selective reuptake inhibitor and the depressed elderly patient. German J Psychiatry 1999;18;332-350.

17. Amado-Boccara I, Gougoulis N, Poirier-Littre MF, Galinowski A, Lôo H. Effects of antidepressants on cognitive functions: Review of the literature. Encephale 1994;20:65-77.
18. Fairweather DB, Ashford J, Hindmarch I. Effects of fluvoxamine and dothiepin on psychomotor abilities in healthy volunteers. Pharmacol Biochem Behav 1996;53:265-9.
19. Kumar S, Kulkarni SK. Influence of antidepressant drugs on learning and memory paradigms in mice. Indian J Exp Biol 1996;34:431-5.

Source of Support: Nil, **Conflict of Interest:** None.