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RESEARCH ARTICLE

Comparison of effects of amitriptyline and venlafaxine on cognitive and psychomotor functions in healthy volunteers: A randomized parallel group study

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ABSTRACT

Background: Antidepressant drugs cause various degree of psychomotor and cognitive function impairment. **Aim and Objective:** The objective of the study was to compare effects of amitriptyline and venlafaxine on cognitive and psychomotor functions in healthy volunteer. **Materials and Methods:** A prospective double-blind parallel group study involving 28 participants was carried in the clinical pharmacology laboratory. Participants were divided in two groups of 14 each and given single oral doses of amitriptyline 100 mg and venlafaxine 75 mg. Participants undergone battery of cognitive-psychomotor function tests at baseline and 2, 6-, and 24-h post-drug administration and analyzed. **Results:** Mean age of the participants was 21.93 ± 0.47 years with no significant difference at baseline for psychomotor functions ($P > 0.05$). Both amitriptyline and venlafaxine affect psychomotor and cognitive function significantly ($P < 0.05$). On comparing the effects of two drugs on psychomotor functions, at 2 h only statistically significant difference found in memory test score (7.50 ± 1.51 with amitriptyline vs. 9.14 ± 1.10 with venlafaxine, $P = 0.003$). At 6 h, only statistically significant difference found in six letter cancellation test (SLCT) net score (116.21 ± 36.25 with amitriptyline vs. 145.43 ± 28.12 with venlafaxine, $P = 0.025$). Memory score improves at 2 h with venlafaxine as compared to amitriptyline while SLCT improves at 6 h with venlafaxine. Twenty-two participants (12 from Group A vs. 10 from Group B, $P < 0.05$) developed adverse drug event. Sedation and dry mouth were common among amitriptyline group while nausea, vomiting, and muscular pain were common among venlafaxine group. **Conclusions:** Both amitriptyline and venlafaxine affect psychomotor functions but deterioration is more in amitriptyline group. Venlafaxine can be better therapeutic option with less deteriorating effect on psychomotor functions and less adverse drug reactions.

KEY WORDS: Amitriptyline; Venlafaxine; Psychomotor and Cognitive Function; Critical Flicker Frequency; Choice Reaction Time; Six Letter Cancellation Test; Digit Symbol Substitution Test; Arithmetic Ability Test; Zigzag Test; Leeds Sleep Evaluation Questionnaire

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INTRODUCTION

Depression and anxiety disorders are the most common mental illnesses, each affecting in excess of 10–15% of the population at some time in their lives.[1] Depression is a common illness worldwide, with more than 264 million people affected.[2] Depression is different from usual

mood fluctuations and short-lived emotional responses to challenges in everyday life. Especially when long-lasting and with moderate or severe intensity, depression may become a serious health condition. It can cause the affected person to suffer greatly and function poorly at work, at school and in the family. At its worst, depression can lead to suicide. Close to 800,000 people die due to suicide every year. Suicide is the second leading cause of death in 15–29-year-old.

Antidepressant drugs in combination with the counseling and behavioral therapy are the mainstay of the treatment. According to a 2007 report by the Centers for Disease Control and Prevention, antidepressant drugs were the most commonly prescribed medications in the USA at the time of the survey.[3] However, the scenario is different in middle- and low-income countries. Although there are known, effective treatments for mental disorders, between 76% and 85% of people in low- and middle-income countries receive no treatment for their disorder.[4] Barriers to effective care include a lack of resources, lack of trained health-care providers and social stigma associated with mental disorders and adverse drug reactions (ADRs) and psychomotor dysfunction associated with all antidepressant drugs. Another barrier to effective care is inaccurate assessment. In countries of all income levels, people who are depressed are often not correctly diagnosed, and others who do not have the disorder are too often misdiagnosed and prescribed antidepressants.

Many of the antidepressant drugs are known to cause behavioral toxicity which can be defined as the extent to which a drug disrupts those abilities necessary for performance of the psychomotor and cognitive tasks of everyday life.[5] Several psychotropic drugs may adversely affect work performance that depends on psychomotor activities. Psychomotor performance results from the coordination of sensory and motor system through the integrative and organizational process of central nervous system (CNS). Central, sensory, and motor components of psychomotor performance can be evaluated by standard validated battery of psychomotor function tests.[6] Measuring the effects of a drug on psychomotor and cognitive ability is important to obtain an objective assessment of its psychotropic actions and to identify potential interference with every day activities such as driving, operating machinery, and performing daily routine tasks.[6]

Amitriptyline, a tricyclic antidepressant, apart from inhibiting reuptake of serotonin (5-HT) and norepinephrine, also antagonize α_1 adrenergic, H_1 histaminic, and muscarinic cholinergic receptors, and thus compromise the quality of life of the patients by causing psychomotor impairment, somnolence, and tremors etc.[7] Increased understanding of neurotransmitter and receptor interactions led to the development of newer antidepressants with more selective activity such as selective serotonin reuptake inhibitors (SSRIs) and more recently serotonin-norepinephrine reuptake inhibitors (SNRIs). Venlafaxine hydrochloride is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and weak inhibitor of dopamine reuptake. Venlafaxine has no significant affinity for muscarinic, histaminergic, or adrenergic receptors *in vitro*. These new generation of the antidepressants used very widely in current practice with limited evidence on their comparative safety. It would be worth observing whether venlafaxine has any central effects that could interfere with the psychomotor functions and thus with the patient's ability to perform skilled works or daily routine activities. This study has been taken up to compare the effect amitriptyline and venlafaxine on psychomotor function and cognitive ability using standard battery of tests on healthy human volunteers.

MATERIALS AND METHODS

Study Design and Ethical Considerations

This was a randomized double-blind parallel group study. The study protocol was approved by institutional ethics committee. All the participants were explained the general aim and nature of the study and the risk of possible untoward side effects in the language they understood (vernacular language). They were allowed to clarify any issues related to study. Participants were included only after they gave written informed consent. The study was conducted in clinical CNS laboratory, Department of Pharmacology, of a tertiary care teaching hospital in western India.

Participant Selection

Thirty healthy volunteers willing to participate in the study were included after applying inclusion and exclusion criteria. Brief medical history and a complete physical examination of each participant were carried out by a qualified physician before inclusion in the study to declare them as healthy. Participants of any gender and of age 18–35 years were included while participants having history of epilepsy, depression, psychosis or other CNS disorders, cardiac diseases, peptic ulcer, respiratory disease, liver disease, pregnant or lactating woman, and also participants taking any CNS affecting drugs or any other drugs were excluded from the study. Any participant involved in any other trial till 2 weeks before during the study period was also excluded from the study.

Drugs

Single oral doses of venlafaxine (75 mg) and amitriptyline (100 mg) were used.

Experimental Design

A double blind, parallel group study was carried out in the clinical CNS laboratory. All the participants had undergone training sessions with the battery of psychomotor function

tests to preclude any learning curve effect. Subjects participated in training sessions before actual drug administration and experimental testing. At the beginning of these sessions, they were fully informed about the protocol, received the physical and psychiatric interview and spent 1–2 h practicing each of the six psychomotor tests. The purpose of the training sessions was to ensure proficiency at less than a 10% error rate in each of the information processing tasks and to improve tracking skills to a level where major learning effects were excluded.

Participants were divided randomly into two groups of 14 each. Randomization was carried out using computer generated random number table for test drug administration. On the study day, participants were asked to have breakfast at 8 a.m. and report to laboratory at 10 a.m. After 15 min of acclimatization period, the control parameters were tested using standard battery of psychomotor function test by all the participants. After that, the test drug was administered orally as single dose along with a full glass of water (250 ml). Thereafter, the psychomotor functions were tested at 2, 6, and 24 h post-drug administration, as shown in Figure 1. Sleep questionnaire was evaluated only after 24 h of drug administration to evaluate effect of the drug on sleep pattern and compared with baseline. Participants were not allowed to eat any food for 2 h of post-drug administration; however, drinking water was allowed. Participants were instructed to strictly avoid mechanical work or driving a vehicle during study period. Participants were instructed to refrain from smoking, drinking alcohol, or taking any medication 1 week prior and during the study period.

ADRs if any observed during the study period was identified reported and analyzed. Appropriate treatment for the ADRs was immediately given by a physician. All the reported adverse drug events were analyzed using the World Health Organization – Uppsala Monitoring Centre (WHO-UMC) scale.[8]

All the participants had undergone following tests for evaluation of psychomotor functions.

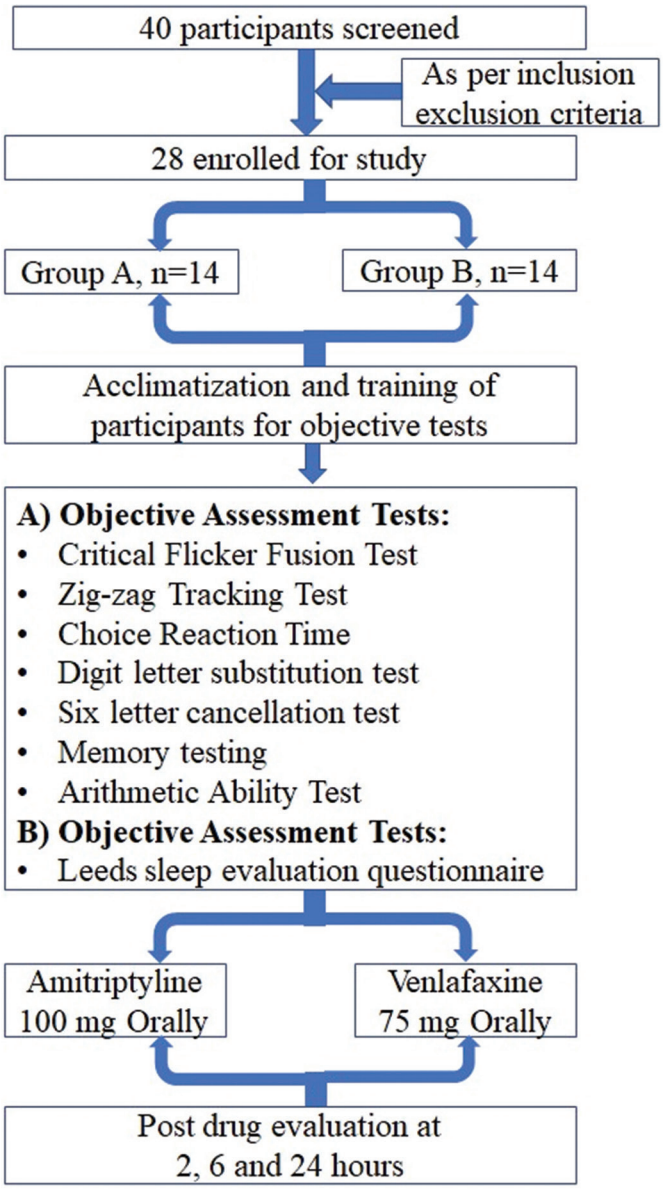

Figure 1: Study design

Tests for Psychomotor Functions

Objective assessment

1. Critical flicker fusion (CFF) test:[9-12] CFF threshold is the test of choice for investigating the change in overall integrative activity of the CNS produced by psychoactive drugs. The critical flicker frequency may be defined as the fastest rate at which a flickering source of light appears to be flickering as opposed to being steady or as the point at which a flickering light gives rise to the subjective sensation of a steady light. The CFF threshold was assessed by CFF apparatus. The participants were allowed adaptation to a least flickering frequency for 1 min. After this period of accommodation, the frequency was progressively increased or decreased until the subject reported a change in his perception of flicker (i.e., from fusion to flicker and from flicker to fusion). Six such readings were taken (three with increasing frequency and three with decreasing frequency). The mean of the six observed CFF frequency (hertz) was noted
2. Zig-zag Tracking Test (ZZTR):[13] The ZZTR has been designed to facilitate version generation using a repetitive shape. The total time to complete the ZZTR was recorded, and an error score was calculated by adding one point each time the pen touched the side of the track or an obstacle, two points if it crossed or penetrated the boundary. The results were compared before and after drug administration
3. Choice reaction time (CRT):[14] The test was performed on CRT apparatus. There were four bulbs of different colors

and four different voices in the apparatus for visual and auditory CRT estimation. The bulb was lighted or sound was played by the investigator by pressing a switch on his side. Volunteer sitting on opposite side was asked to extinguish the light or mute the sound by pressing the switch on his side. The time required in extinguishing the light or muting the sound was noted on apparatus. This was taken as reaction time and noted before and after the drug administration

4. Digit letter substitution test (DLST):[15] This test assesses recognition capacity of brain. Participants were provided a working sheet consisting of digits arranged randomly in rows and columns. Participants were required to substitute as many digits with letters from the key as possible within 90 s. The letters in the key and the digits in the working section were changed randomly to avoid the effect of memory on repeated testing. Scoring will be done on the basis of number of correct substitutions
5. Six letter cancellation test (SLCT):[16] This test assesses perceptual processing of sensory information. Participants were provided a working sheet, consisting of randomized letters arranged in rows and columns. Participants had to cancel as many target letters from key, as possible within 90 s, going systemically either row wise or column wise. The six letters in the key were changed randomly to avoid the effect of memory or practice during repeated administration of test. Scoring will be done on the basis of number of correct cancellations
6. Memory testing: Ten articles were kept in a tray. Volunteer were asked to look at them for 1 min and memorize. Then, the attention of the volunteer was diverted by asking him to perform SLCT and DLST. After that he/she was asked to name the articles which were shown in the tray. Number of articles that he recollects correctly was taken as memory score. The test was performed before drug administration which will give baseline memory score. The memory scores before and after the drug administration will be compared. Articles kept in the tray were changed after every test
7. Arithmetic ability test (AAT):[17] This is a test for assessing central processing capacity. There were four problems of mathematical calculation, that is, addition, subtraction, multiplication, and division, randomly distributed in rows and columns. Participants were asked to solve the problems either row wise or column wise in 90 s. Two points were awarded for each correct division and multiplication, whereas one point each for correct addition and subtraction. Total score was calculated.

Subjective assessment

Leeds sleep evaluation questionnaire (LSEQ)[18] was used to rate subjective impressions of the ease of getting to sleep (GTS), the quality of sleep (QOS), the ease of waking from sleep (awakening from sleep), and the co-ordination of behavior following waking (BFW) on 10 cm line analog rating scales. Subjects completed the LSEQ forms before the drug administration and on the morning following the day of medication and results compared.

Statistical Analysis

Data were analyzed using SPSS software version 16. Data were represented as actual frequencies, mean and standard deviation. Unpaired "*t*-test" was used for analysis of effect on psychomotor functions for the two groups before and after drug administration. Within group analysis for comparing the effect of drug at multiple time points was performed using analysis of variance (ANOVA) test. A repeated measure ANOVA with a Greenhouse-Geisser correction was used to compare the mean at different time points and *Post hoc* tests using the Bonferroni correction were applied. Chi-square test was used for analysis of ADRs in the two groups. $P < 0.05$ was considered significant.

RESULTS

Out of total 40 participants evaluated, 28 were enrolled and randomized for the study after applying inclusion and exclusion criteria [Figure 1]. Mean age of the participants was 21.93 ± 0.47 years. The majority of them were male (26, 92.86%) and only two (7.14%) were female. Baseline characteristics of the study participants are shown in Table 1 and there was no significant difference between the two groups at baseline for psychomotor functions ($P > 0.05$).

Effect of amitriptyline on psychomotor performance is shown in Table 2. No statistically significant difference was found on CFF test, visual choice reaction time (VCRT), SLCT, and memory test at different time points. A repeated measures ANOVA with a Greenhouse-Geisser correction determined that mean auditory choice reaction time (ACRT) differed statistically significantly between time points (F [1.956, 25.434] = 4.140, P = 0.028). *Post hoc* tests using the Bonferroni correction revealed that amitriptyline elicited a slight reduction in ACRT from baseline to 2- and 6-h post-drug administration (1.57 ± 0.73 s vs. 1.39 ± 0.52 s and 1.18 ± 0.22 s, respectively) which was not statistically significant (P = 1.00 and 0.72, respectively). However, post-drug ACRT had been reduced to 1.03 ± 0.41 s at 24 h which was statistically significantly different to baseline (P = 0.028). Amitriptyline elicits a statistically significant reduction in ACRT but after only 24 h of post-drug administration. A repeated measures ANOVA with a Greenhouse-Geisser correction determined that mean AAT score differed statistically significantly between time points (F [3, 39] = 4.227, P = 0.011). *Post hoc* tests using the Bonferroni correction revealed that amitriptyline elicited a decline in net AAT score from baseline to 2- and 6-h post-drug administration (25.21 ± 12.94 vs. 24.00 ± 10.61 and 22.86 ± 10.89, respectively) which was not statistically significant (P = 0.44 and 0.11, respectively). However, post-drug AAT had

Table 1: Study participant baseline characteristics

Parameter	Amitriptyline group (Mean±SD)	Venlafaxine group (Mean±SD)	*P*-value
Age	21.93±0.47	21.93±0.47	1.00
Gender (Male/female)	14/0	12/2	0.16
Critical flicker frequency	40.12±5.22	41.26±5.24	0.56
Visual CRT	0.33±0.08	0.37±0.07	0.18
Auditory choice reaction time	1.57±0.73	1.65±0.53	0.75
SLCT	122.00±42.86	151.50±39.71	0.07
AAT	25.21±12.94	26.14±11.11	0.840
Digit symbol substitution test	58.43±9.24	63.93±8.77	0.11
Memory score	8.71±1.27	8.64±1.50	0.89
Zigzag test (error score)	3.50±3.67	5.50±4.72	0.22

Values are displayed as Mean±SD. Values compared using independent "t-test" and $P<0.05$ were considered significant. SLCT: Six letter cancellation test, CRT: Choice reaction time, AAT: Arithmetic ability test

Table 2: Effect of amitriptyline on psychomotor performance

Test	Time after test drug (Amitriptyline) administration				*P*-value (Repeated measure ANOVA test)
	0 h	2 h	6 h	24 h	
Critical flicker frequency	40.12±5.22	40.78±5.26	41.21±5.44	42.24±4.49	0.299
Critical fusion frequency	41.16±4.47	41.31±3.63	42.12±5.10	41.29±5.75	0.817
Visual CRT	0.33±0.08	0.33±0.10	0.29±0.06	0.29±0.05	0.193
Auditory reaction time	1.57±0.73	1.39±0.52	1.18±0.22	1.03±0.41	0.028*
SLCT	122.00±42.86	131.21±37.28	116.21±36.25	128.93±34.01	0.178
AAT	25.21±12.94	24.00±10.61	22.86±10.89	28.00±12.51	0.01*
Digit symbol substitution test	58.43±9.24	56.21±7.57	52.07±7.03	59.93±9.33	0.015*
Memory score	8.71±1.27	7.50±1.51	7.93±1.33	8.36±1.45	0.08
Zigzag test (error score)	3.50±3.67	7.21±4.23	6.21±4.59	4.57±3.46	0.004*

Values are displayed as Mean±SD. Values compared using repeated measure ANOVA: Analysis of variance test and $P<0.05$ was considered significant. SLCT: Six letter cancellation test, CRT: Choice reaction time, AAT: Arithmetic ability test

been increased to 28.00 ± 12.51 at 24 h which was statistically significantly different to baseline, 2 h and 6 h ($P < 0.05$). Amitriptyline elicits a reduction in AAT initially at 2 and 6 h but causes statistically significant increase after only 24 h of post-drug administration. When using an ANOVA with repeated measures with a Greenhouse-Geisser correction, the mean scores for DSST were also statistically significantly different (F [3, 39] = 3.918, $P = 0.15$). A repeated measures ANOVA with a Greenhouse-Geisser correction determined that mean Zigzag error score differed statistically significantly between time points (F [3, 39] = 5.137, $P = 0.004$). *Post hoc* tests using the Bonferroni correction revealed that amitriptyline elicited an increase in error score of zigzag test from baseline to 2 h post-drug administration (3.50 ± 3.67 vs. 7.21 ± 4.23) which statistically significant ($P = 0.029$). However, post-drug zigzag error score at 6 and 24 h had also been increased to 6.21 ± 4.59 and 4.57 ± 3.46, respectively, but was not statistically significantly different to baseline ($P > 0.05$). Amitriptyline causes increase in error score of zigzag test but was statistically significant at 2 h only.

Overall, amitriptyline causes decrease in auditory CRT at 2, 6, and 24 h. SLCT improved at 2, 6, and 24 h but not significantly. Critical flicker-fusion frequency and VCRT not affected much. Decrease in arithmetic ability test at 2 and 6 h but returned to normal at 24 h decrease in DSST at 2, 6, and 24 h. Error score has been increased at 2, 6, and 24 h. This suggests depression of CNS. Memory score also decreases but not significant.

On evaluating the effect of venlafaxine on psychomotor performance, it was not affecting any of the psychomotor function tests (CFF, VCRT, SLCT, DSST, AAT, zigzag test, and Memory test) except auditory CRT [Table 3]. A repeated measures ANOVA with a Greenhouse-Geisser correction determined that mean ACRT differed statistically significantly between time points (F [3, 39] = 8.251, $P = 0.001$). *Post hoc* tests using the Bonferroni correction revealed that venlafaxine elicited a slight reduction in ACRT from baseline to 2 h post-drug administration (1.65 ± 0.53 s vs. 1.35 ± 0.71 s) which was not statistically significant ($P = 0.95$). However, post-drug ARCT had been reduced to 1.02 ± 0.45 s at 6 h and 0.99 ± 0.43 s at 24 h which was statistically significantly different to baseline ($P = 0.001$ for both). Thus, amitriptyline elicits a statistically significant reduction in ARCT but only 2 h of post-drug administration.

Overall, venlafaxine improves ACRT and VCRT at 2, 6, and 24 h. SLCT improves at 2 h but decrease at 6 and 24 h. Memory score improves at 2 h and comes back to baseline at 6 and 24 h. CFF frequency and AAT were not affected. DSST reduces at 2, 6, and 24 h. Error score increases at 2, 6, and 24 h but not significantly.

On comparing the effects of two drugs on psychomotor functions at different time points, at 2 h only statistically significant difference found in memory test score (7.50 ± 1.51 with amitriptyline vs. 9.14 ± 1.10 with venlafaxine, $P = 0.003$). At 6 h post-drug administration, only statistically significant difference found in SLCT net score (116.21 ± 36.25 with amitriptyline vs. 145.43 ± 28.12 with venlafaxine, $P = 0.025$). Memory score improves at 2 h with venlafaxine as compared to amitriptyline while SLCT improves at 6 h with venlafaxine. At 24 h post-drug administration, none of the psychomotor function tests revealed any significant difference between the two drug groups [Table 4].

On analyzing effect on sleep, net sleep score was significantly affected by amitriptyline ($P < 0.02$) while it was not significantly affected by venlafaxine ($P > 0.05$). GTS score was affected by both the amitriptyline and venlafaxine administration ($P < 0.05$). Baseline sleep score was not significantly different among the two group ($P = 0.05$) but after drug administration, significant difference was found between the effects on GTS score, QOS score, and net score ($P < 0.05$) among the two groups [Table 5].

Out of total 28 participants, 22 (12 from Group A vs. 10 from Group B, $P < 0.05$) developed one or another adverse drug event. Total 36 events were reported in these 22 participants. Sedation and dry mouth were more common among amitriptyline group while nausea, vomiting, and muscular pain were more common among venlafaxine group, as shown in Table 6. All the reactions were in the category of "probable" according to the WHO-UMC criteria of causality assessment.

Table 3: Effect of venlafaxine on psychomotor performance

Test	Time after test drug (venlafaxine) administration				*P*-value (Repeated measure ANOVA test)
	0 h	2 h	6 h	24 h	
Critical flicker frequency	41.26±5.24	40.67±4.24	41.21±6.85	40.47±7.54	0.88
Critical fusion frequency	41.17±5.26	42.24±3.38	42.95±6.30	42.67±5.94	0.46
Video CRT	0.37±0.07	0.32±0.08	0.31±0.07	0.31±0.06	0.05*
Audio reaction time	1.65±0.53	1.35±0.71	1.02±0.45	0.99±0.43	0.001*
SLCT	151.50±39.71	154.93±32.30	145.43±28.12	147.64±24.87	0.65
AAT	26.14±11.11	25.00±10.47	27.64±8.92	28.36±10.10	0.09
Digit symbol substitution test	63.93±8.77	59.78±7.21	58.21±9.89	62.93±6.59	0.12
Memory score	8.64±1.50	9.14±1.10	8.64±0.84	8.64±1.15	0.49
Zigzag test	5.50±4.72	6.71±5.50	7.00±6.92	6.14±9.04	0.56

Values are displayed as Mean±SD. Values compared using ANOVA: Analysis of variance test and $P<0.05$ was considered significant. SLCT: Six letter cancellation test, CRT: Choice reaction time, AAT: Arithmetic ability test

Table 4: Comparison of effects of amitriptyline and venlafaxine on psychomotor functions: (***n***=14 in each group)

Test	Time after test drug administration								
	2 h		*P*-value	6 h		*P*-value	24 h		*P*-value
	Amitriptyline group	Venlafaxine group		Amitriptyline group	Venlafaxine group		Amitriptyline group	Venlafaxine group	
Critical flicker frequency	40.78±5.26	40.67±4.24	0.94	41.21±5.44	41.21±6.85	1.000	42.24±4.49	40.47±7.54	0.46
Critical fusion frequency	41.31±3.63	42.24±3.38	0.48	42.12±5.10	42.95±6.30	0.70	41.29±5.75	42.67±5.94	0.53
Video CRT	0.33±0.10	0.32±0.08	0.76	0.29±0.06	0.31±0.07	0.56	0.29±0.05	0.31±0.06	0.29
Audio reaction time	1.39±0.52	1.35±0.71	0.85	1.18±0.22	1.02±0.45	0.24	1.03±0.41	0.99±0.43	0.83
SLCT	131.21±37.28	154.93±32.30	0.08	116.21±36.25	145.43±28.12	0.025*	128.93±34.01	147.64±24.87	0.10
AAT	24.00±10.61	25.00±10.47	0.80	22.86±10.89	27.64±8.92	0.21	28.00±12.51	28.36±10.10	0.93
Digit symbol substitution test	56.21±7.57	59.78±7.21	0.21	52.07±7.03	58.21±9.89	0.06	59.93±9.33	62.93±6.59	0.33
Memory score	7.50±1.51	9.14±1.10	0.003*	7.93±1.33	8.64±0.84	0.10	8.36±1.45	8.64±1.15	0.56
Zigzag test	7.21±4.23	6.71±5.50	0.78	6.21±4.59	7.00±6.92	0.72	4.57±3.46	6.14±9.04	0.54

Values are displayed as Mean±SD. Amitriptyline and venlafaxine groups are compared using independent "*t*-test" and $P<0.05$ was considered significant. SLCT: Six letter cancellation test, CRT: Choice reaction time, AAT: Arithmetic ability test

Table 5: Analysis of Leeds' sleep evaluation questionnaire (LSEQ)

Parameter	Amitriptyline group			Venlafaxine group			P value (comparing both groups)	
	Before drug	After drug	*P*-value (paired *t*-test)	Before drug	After drug	*P*-value (paired *t*-test)	Before drug – at baseline (unpaired *t*-test)	After drug –after 24 h (unpaired *t*-test)
GTS score	4.89±1.79	6.82±1.52	0.004*	4.57±0.95	5.51±1.92	0.01*	0.56	0.05*
QOS	5.46±1.71	7.07±1.30	0.24	5.57±1.14	5.25±2.05	0.58	0.70	0.009
AFS	5.07±1.25	4.49±2.21	0.35	4.89±1.21	4.82±2.18	0.93	0.84	0.69
BFW	5.57±1. 03	5.05±1.17	0.2	5.64±1.13	5.17±1.76	0.41	0.86	0.84
Net score	5.25±0.49	5.86±0.74	0.02*	5.16±0.67	5.19±0.99	0.93	0.72	0.05*

GTS: Time for going to sleep; QOS: Quality of sleep; AFS: Awakening from sleep; BFW: Behavior following awakening, LSEQ: Leeds sleep evaluation questionnaire, GTS: Getting to sleep

Table 6: Analysis of ADRs among participants (*n*=35 events)

Adverse drug event	Amitriptyline group (*n*, %)	Venlafaxine group (*n*, %)	Total (*n*, %)	*P*-value
Sedation	10 (28.57)	4 (11.43)	14 (40)	
Headache	1 (2.86)	0	1 (2.86)	
Dry mouth	2 (5.71)	1 (2.86)	3 (8.57)	
Acidity/gastritis	6 (17.14)	1 (2.86)	7 (20)	
Nausea	2 (5.71)	5 (14.29)	7 (20)	
Vomiting	0	1 (2.86)	1 (2.86)	
Muscle pain	0	1 (2.86)	1 (2.86)	
Fatigue	0	1 (2.86)	1 (2.86)	
Total	21 (60)	14 (40)	35 (100)	<0.05

Chi-square test, $P<0.05$ was considered significant. ADR: Adverse drug reaction

DISCUSSION

The tricyclic anti-depressant like amitriptyline has been used as effective treatment for depression. Furthermore, SSRI and SNRI can also be used for the management of depression for selective subject improvement but it has certain adverse reactions such as impairment of CNS function, and sedation. The present study was conducted with the objective of comparing the effects on psychomotor performance of amitriptyline and venlafaxine in healthy human volunteers. Patients of depression may have underlying psychomotor impairment and it would be difficult to differentiate that the psychomotor function impairment was because of drug or underlying disease process.[12] According to Wittenborn, psychomotor function assessment with respect to drug therapy in patient can be difficult and in certain cases it is misleading. In patients under treatment symptomatic improvement can yield an improved score on psychomotor test which is not necessarily a consequence of an enhancement of psychomotor behavior *per se*.[19] On single dose administration, the antidepressant drugs give same cognitive impact in depressive patient as in healthy volunteers.[20]

Psychomotor performance is the coordination of a sensory or cognitive process and motor activity through brain and CNS. The influence of personality, memory, and individual motivation is called as sensory information while the overall function of the integrative mechanism is governed by the state of arousal of CNS. Complex feedback and adaptive systems complete the process by which environmental stimuli produce appropriate, coordinated behavioral responses. The three levels of information processing are detection, perception, and recognition which together account for the majority activity of sensory organism. Change in the level of activity of the sensory input brought about by the administration of a drug can have a disruptive effect on total psychomotor performance and reduce the responsiveness of an individual to changes in his environment. The perceptual processing of sensory information can be readily assessed using a letter or number cancellation task, providing the motor components are not too great. Recognizing sensory information involves the matching of the perceptual figuration with a pre-existing or stored stimulus pattern. Digit symbol substitution performance test can be used to recoding and recognition of sensory information. The central component of CNS activity is central processing. The arithmetic or number handing task can be considered as one of the easiest ways for measuring cognitive ability of person.[5] In this study, *per se* effect of the drugs was noted as well as inter-drug comparison of psychomotor effects was done.

The cognitive and psychomotor impairment is also associated with depression. The cognitive dysfunction may be followed by reduced quality of life, poor compliance, and risk of accidents during depression. Hence, psychomotor effects and side effect should be kept in mind while prescribing

antidepressant drug. The most commonly used antidepressant drugs are tricyclic group associated with varying degrees of anticholinergic side effects and sedation. This present study employed amitriptyline as a positive control in this respect which significantly impaired psychomotor function even in healthy volunteers. Overall, amitriptyline causes decrease in auditory CRT at 2, 6, and 24 h and VCRT and CFF is not affected much. SLCT improved at 2, 6, and 24 h but not significantly. Decrease in arithmetic ability test at 2 and 6 h but returned to normal at 24 h. Decrease in DSST score at 2, 6, and 24 h. Error score has been increased at 2, 6, and 24 h. This suggests depression of CNS. Memory score also decreases but not significant. Net sleep score was also significantly affected as compared to venlafaxine group. Other studies have shown the similar findings suggesting patients treated with amitriptyline deteriorated all psychomotor functions. Amitriptyline, apart from inhibiting reuptake of 5HT and NE, also antagonizes histaminic H1 and muscarinic receptors, which is responsible for sedation and psychomotor impairment. As amitriptyline has shown detrimental effects on sensory (DLST and SLCT) and central processing (flicker fusion test) mechanism, this could also be the reason for impairment of fine motor performance with amitriptyline during HST and choice reaction test.[21]

Overall, venlafaxine improves ACRT and VCRT at 2, 6, and 24 h. SLCT improves at 2 h but decrease at 6 and 24 h. Memory score improves at 2 h and comes back to baseline at 6 and 24 h. CFF frequency and AAT were not affected. DSST reduces at 2, 6, and 24 h. Error score increases at 2, 6, and 24 h but not significantly. Findings are similar to other studies. Venlafaxine, when given to healthy volunteers, did not affect neuropsychological functions such as choice reaction, psychomotor performance, or memory.[22] This could also be seen when given to elderly depressed patients.[23] One randomized, placebo-controlled crossover-study on venlafaxine in healthy subjects indicated neither acute nor sub-chronic treatment effects on a standard on-road driving test.[24] There is, however, little evidence that there may be selectively impairing effects especially in vigilance tasks with venlafaxine.[24,25] This effect of venlafaxine can be explained by its mechanism of action. Although the exact mechanism of action of venlafaxine is unknown, appears to be associated with the potentiation of neurotransmitter activity in the CNS. Venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV), inhibit the reuptake of both serotonin and norepinephrine with a potency greater for the 5-HT than for the NE reuptake process.[26] Both venlafaxine and the ODV metabolite have weak inhibitory effects on the reuptake of dopamine but, unlike the tricyclics and similar to SSRIs, they are not active at histaminergic, muscarinic, or alpha(1)-adrenergic receptors. Various antidepressants available in Indian market with wide price variation; therefore, selection should be made based on efficacy and adverse effects.[27]

Major adverse effects in amitriptyline group were sedation and dry mouth as reflected by other literature while nausea, vomiting, and muscular pain were more common among venlafaxine group. All the reactions were in the category of "probable" according to the WHO-UMC criteria of causality assessment. When we choose an adequate antidepressant, a profile of side effects which influence use of medicine is important as well as co-operation of a patient. The purpose of clinical researches is the detection of efficient antidepressants with the profile of side effects which do not influence quality of patient's life.

This study has highlighted the effects of two antidepressants drugs on cognitive and psychomotor functions in clinical pharmacology laboratory on healthy human volunteers. There are inbuilt difficulties in conducting such type of studies like there is marked variation within and between subjects in autonomic and CNS functions, associated with a bewildering array of physiological, psychological, and environmental factors. Therefore, experimental conditions should be strictly controlled, including ambient temperature, humidity, noise, and other distractions. The sensitivity of the method in the hands of the investigator should be established for each study, whenever possible. The time course of an experiment must be so designed to permit adequate time for acclimatization of subjects to the environmental conditions. If too much information is sought by means of a number of tests which cannot easily be accommodated within the experimental period, the inevitable haste and harassment that ensue can produce their own autonomic effects and prejudice the experimental results. It will be ideal to conduct a combine pharmacokinetic with pharmacodynamic studies of this kind but it may lead to failure because the trauma of venesection may produce a degree of arousal in the subject which interferes with test results. This study has been completed successfully, overcoming all the problems associated with such studies. Few limitations of this study are small sample size and single center for conduction of the study. Moreover, healthy volunteer's cognitive and psychomotor functioning cannot be extrapolated directly to the depressive patients as there are disease related changes in the CNS function also. Such studies on patients with larger study participants are required for betterment in therapeutic decision making.

CONCLUSION

This study has shown effect of amitriptyline and venlafaxine on cognitive and psychomotor functions in healthy human volunteers. Venlafaxine was not associated with detectable anticholinergic side effects and appeared to be the better tolerated treatment under these study conditions. Thus, venlafaxine can be preferred to amitriptyline in clinical practice.

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