(International Print/Online Journal)

SJIF IMPACT FACTOR: 4.617
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume2, Issue 3, Page No: 374-383
May-June 2019

Acute effect of anti-anxiety drugs on psychomotor performance in healthy volunteers: a prospective, crossover study

Dr Ankita Jire[1], Dr. Chindhalore Chaitali[1], Dr. Motghare Vijay[1], Dr. Dakhale Ganesh[1], Dr. Kalikar Mrunalini[1], Dr. Turankar Avinash[1], Dr. Sontakke Smita[1], DrSonal Arsude[2]

[1] Department of Pharmacology, GMC, Nagpur; [2] Departments of Respiratory Medicine, NKPSIMS, Nagpur

***Corresponding Author:**
Dr. Chindhalore Chaitali
Department of Pharmacology, GMC, Nagpur

Type of Publication: Original Research Paper
Conflicts of Interest: Nil

ABSTRACT

Context: The cognitive and psychomotor functions may become impaired in patients of anxiety disorders due to anxiety itself or as side-effects of antianxiety drugs. It is desirable for the drug to have a minimal effect on cognition

Objective: To evaluate effects of single dose of Alprazolam, Escitalopram and Venlafaxine on psychomotor performance in healthy volunteers.

Study Design: Randomized, prospective, open label, single dose, crossover study

Methods and Material: A total of 22 volunteers were included to administer single dose of Escitalopram 20 mg, Alprazolam 0.5 mg and Venlafaxine 37.5 mg. Parameters were tested at 0, 2 and 4 hours after drug administration. A wash out period of 21 days was given. Test used were- 6 digit cancellation test, digit symbol substitution test, critical flicker fusion test, arithmatic ability test, digit span test, hand steadiness test, visual analogue scale and mean reaction time. Statistical analysis used: Repeated measures ANOVA and One way ANOVA was used for statistical analysis.

Results: Escitalopram significantly improved the scores of objective and subjective tests at the end of 2 and 4 hours as compared to baseline, whereas Alprazolam significantly deteriorated the scores. Venlafaxine did not show significant change in scores as compared to baseline.

Conclusions: Escitalopram had improved whereas Alprazolam significantly deteriorated psychomotor performance. Venlafaxine had neutral effect on psychomotor performance

Keywords: Antianxiety drugs, Escitalopram, Alprazolam, Venlafaxine, psychomotor performance

INTRODUCTION

Anxiety is defined as "A state of intense apprehension, uncertainty and fear resulting from the anticipation of a threatening event or situation, often to a degree that normal physical and psychological functioning is disrupted".[1]Psychomotor performance results from the coordination of sensory and motor system through integrative and organizational process of brain and central nervous system. Central, sensory and motor components of psychomotor performance can be evaluated by standard validated battery of psychomotor function tests.

Patient of anxiety has an impaired information-processing ability, when compared with age and gender-matched controls. [2]Antianxiety drugs should have minimal or no effect on cognitive abilities.Among antianxiety drugs, Benzodiazepines are considered as the standard drug category and Alprazolam is the most frequently used benzodiazepine for the treatment of anic disorder and anxiety. [3] Main problems associated with the clinical use of benzodiazepine as an anxiolytic are drowsiness, dizziness, impairment of psychomotor and cognitive functioning. [4] Currently, the evidence base for pharmacological treatment of anxiety disorders is greatest for selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), because they are

relatively safe, lack the potential for dependence and abuse and can also improve cognitive function. [5,6,7]

It is desirable that antianxiety drug should have greater efficacy, lesser behavioural toxicity with minimum or no potential for developing tolerance and dependence.[8] Study by Drabant S et al.[9] had shown that single dose of Alprazolam impaired psychomotor performance. A study by Paul MA et al. reported that Citalopram and Escitalopram had no impact on psychomotor performance. [10] However, results of another study demonstrated that Citalopram improved psychomotor performance.[11] According to previous study, Venlafaxine which is a SNRIfailed to impair psychomotor performance.[12]

Since antianxiety drugs have to be used on chronic basis, it is important to evaluate their effects on cognitive and psychomotor function. Single dose study in healthy volunteers gives us preliminary idea about the level of cognitive and psychomotor impairment due to the study drug. Very few studies have reported head to head comparison between SSRIs, SNRIs and benzodiazepines for their effects on psychomotor performance. Hence this study was carried out to evaluate and compare acute effects of single dose of Alprazolam, Escitalopram& Venlafaxine at 0 hr, 2 hr& 4 hr interval on psychomotor performance using battery of psychomotor function tests in healthy volunteers. Secondary objective was to evaluate and compare side effects profile of these drugs.

MATERIALS AND METHODS

This was a randomized, prospective, open label, single dose, crossover study in 22 healthy volunteers. Study was carried out from January 2016 to July 2017 in the Department of Pharmacology of a tertiary care teaching institute after taking approval from the institutional ethics committee. (IEC Registration No. 856)

Healthy volunteers of either gender with age 18-52 years with minimum education upto secondary school certificate (SSC) and ready to give written informed consent were included in the study. Written informed consent were taken from participants after explaining nature of the study. Participants having history of bleeding disorders, hypertension, smoking, alcoholism, seizures, allergy, hypersensitivity or reaction to any medication, h/o receiving chronic medication for any type of illness, h/o decreased visual acuity without correction, Pregnant and lactating women were excluded.This study was registered in the Clinical Trial Registry of India (CTRI/2017/10/010301)

Depending on history given by the participant and general as well as systemic examination, participants fulfilling the inclusion criteria were enrolled in the study.Eligible participants were randomly allocated into the following three treatment groups using simple random number table and were given single oral dose of Alprazolam (0.5 mg) [3] or Escitalopram (20 mg)[10] or Venlafaxine (37.5 mg). [13] The parameters were tested at 0, 2 and 4 hours. Once all tests are over, participants were allowed for lunch with advice to take rest for that day and not to engage in any mechanical work for the day. If necessary, the participants were escorted to their place. After a wash out period of 21 days, the participants were again called and the same procedure was repeated for the second drug and similarly for the third drug respectively. Volunteers were asked to note down any side-effects experienced after study drug administration.

Assessment of psychomotor functions were done using following tests.[14,15]

A) OBJECTIVE MEASURES

1. Sensory component:

Test for perception: Six-digit cancellation test (6DCT) [16]

Participants were given a sheet of 300 randomized digits. Six target digits were given on the top of each sheet. Participants were instructed to cancel as many target digits as possible in 2 minutes. The number of correct cancellations was scored.

Test of Recognition: Digit symbol substitution test (DSST) [17]

Participants were provided with a sheet of 200 boxes in 20 rows and 10 columns. Randomized digits (0-9) were arranged.Participants were given 2 minutes for substituting corresponding symbol.

Test for central integration: Critical flicker fusion test (CFFT) [18]

It is a reliable psychometric test as there is no learning curve effect. This test was assessed by

Volume 2, Issue 3; May-June 2019; Page No.374-383

critical flicker fusion apparatus. Frequency of light used was 5 to 50 Hz.

Test for central processing: Arithmetic ability test (AAT) [19]

Participants were asked to solve mathematical problems involving addition, subtraction, multiplication and division (4 of each) in 2 minutes. Two points were awarded for multiplication and division, while one point for subtraction and addition. Score was given depending on number of correct problems solved.

Test for Memory and learning: Digit span test (DST) [19]

This test was used to study short term memory.The participants were asked to write down a nine digit sequence after 10 seconds of hearing it. Five such different sequences were repeated and the score was given on number of correct number placements in each sequence.

2. Motor component:

Test for steadiness: Hand Steadiness Test (HST) [16]

The hand steadiness was tested on the steadiness tester. Performance index was calculated as product of error recorded by the instrument and time taken to complete the test.

3. Sensory-motor performance:

Reaction Time**:** The test was performed on Reaction time application (Google version 8.3.01) from android mobile (4.4.4 version) operating systems which helped in the assessment of simple visual reaction time.

B) SUBJECTIVE MEASURES

Visual analogue scale (VAS): VAS for sedation, alertness and concentration was used. The volunteers were asked to indicate the state of their current feeling by marking on a 100 mm horizontal line. Any change in position of the mark on each scale at 2 hours and 4 hours from baseline was considered as shift to right or left by mm.

- Extremely sleepy - Wide awake
- Inability to concentrate - Ability to concentrate
- Dull - Alert

Statistical analysis

Sample size was calculated as 22 based on CFFT score as primary efficacy variable with level of significance (α) 5%, power 80%, significant difference in score of 1.2 & SD of 1.8, considering 10% dropout rate.(20) Sample size was calculated using PS:Power and Sample Size Calculation software version 3.0.43.

Graph pad prism version 5.01 was used for statistical analysis. Repeated measures ANOVA followed by post hoc Tukey's test was used to compare the difference in mean score from baseline & One way ANOVA followed by Tukey's test was used for inter-drug comparison. Chi square test was used for analysis of adverse events $P < 0.05$ was considered as statistically significant. There was no conflict of interest in this study.

RESULTS

Thirty healthy volunteers were screened for participation in the study. Out of these, 22 healthy volunteers satisfied the inclusion criteria and were enrolled in the study. Among 22 participants, M:F ratio was 9:13 with mean age 26.95±7.5 years. Majority of participants were graduate (68.18%) followed by HSC holders (27.28%) and SSC holders (4.54%).

In various psychomotor performance tests (6DCT, DSST, CFFT, AAT, DST, HST) statistically significant difference in the scores was observed at the end of 2nd and 4th hour in Escitalopram and Alprazolam group when compared with baseline. The difference was not statistically significant in Venlafaxine group when compared with baseline suggesting that Venlafaxine do not affect psychomotor performance.[Table 1]

Inter-drug comparison of Escitalopram, Alprazolam and Venlafaxine at 2 and 4 hours on psychomotor performance is as shown in Table 2. Intergroup comparison of Escitalopram, Alprazolam & Venlafaxine showed that Escitalopram significantly increased CFF threshold whereas Alprazolam significantly reduced CFF threshold when compared with each other.

Table 3 demonstrate effect of these drugs on mean raction time. Escitalopram significantly improved mean reaction time at the end of 4hrs whereas

Volume 2, Issue 3; May-June 2019; Page No.374-383

alprazolam deteriorated mean reaction time at the end of 2 & 4hrs significantly. Interdrug comparison showed that escitalopram significantly improved mean reaction time as compared to alprazolam.

Table 1: Effect of Escitalopram, Alprazolam & Venlafaxine at 0, 2 and 4 hours on sensory and motor component of psychomotor performance (n=22)

Test	Drug	Mean±SD		
		0 hour	2 hours	4 hours
6 DCT	Escitalopram	100±27.37	104.9±30.75*	111.7±32.54***
	Alprazolam	107.2±32.82	102.7±31.95	90.86±24.92***
	Venlafaxine	98±30.34	95.95±30.04	97.41±31.1
DSST	Escitalopram	48.77±13.39	53.05±14.01**	58.41±16.25***
	Alprazolam	56.23±17.45	54.32±18.79	48.95±15.52***
	Venlafaxine	53.82±15.91	54.95±15.62	53.86±15.98
CFFT	Escitalopram	39.23±0.53	39.73±0.77**	40.59±0.59***
	Alprazolam	40.09±0.61	39.64±0.79	38.5±1.18***
	Venlafaxine	39.77±0.61	39.68±0.78	39.91±0.53
AAT	Escitalopram	12.27±3.38	13.09±3.50**	14.86±3.56***
	Alprazolam	13.5±3.43	13.23±3.54	11.64±2.87***
	Venlafaxine	12.32±2.93	13±3.39	12.68±3.36
DST	Escitalopram	30.27±4.66	30.68±4.62	33.09±4.83***
	Alprazolam	32.64±5.09	31.23±4.95***	29.18±4.68***
	Venlafaxine	32.05±5.65	31.73±5.14	31.91±5.00
HST	Escitalopram	142±27.04	138.5±22.34	127.5±26.15*
	Alprazolam	143.5±23.49	146.8±19.47	159.9±30.69*
	Venlafaxine	138.5±19.82	141.2±20.42	139.5±19.82

*P <0.05; ** P<0.01; ***P<0.001Repeated measures ANOVA followed by post hoc Tukey's test.

Table 2: Inter-drug comparison of Escitalopram, Alprazolam and Venlafaxine at 2 and 4 hours on Sensory and motor components of psychomotor performance (n=22)

Test	Drug	Mean difference	
		2 hours	4 hours
6 DCT	Escitalopram vs Alprazolam	2.13	20.86
	Escitalopram vs Venlafaxine	8.91	14.32
	Alprazolam vs Venlafaxine	6.78	-6.54

Volume 2, Issue 3; May-June 2019; Page No.374-383

DSST	Escitalopram vs Alprazolam	-1.27	9.46
	Escitalopram vs Venlafaxine	-1.91	4.55
	Alprazolam vs Venlafaxine	-0.64	-4.91
CFFT	Escitalopram vs Alprazolam	0.09	2.09***
	Escitalopram vs Venlafaxine	0.04	0.68*
	Alprazolam vs Venlafaxine	-0.04	-1.41***
AAT	Escitalopram vs Alprazolam	-0.14	3.23**
	Escitalopram vs Venlafaxine	0.09	2.18
	Alprazolam vs Venlafaxine	0.23	-1.04
DST	Escitalopram vs Alprazolam	-0.55	3.9*
	Escitalopram vs Venlafaxine	-1.04	1.18
	Alprazolam vs Venlafaxine	-0.50	-2.73
HST	Escitalopram vs Alprazolam	-8.32	-32.36***
	Escitalopram vs Venlafaxine	-2.77	-12.05
	Alprazolam vs Venlafaxine	5.55	20.32*

One way ANOVA followed by post hoc Tukey's test. *P <0.05; ** P<0.01; ***P<0.001

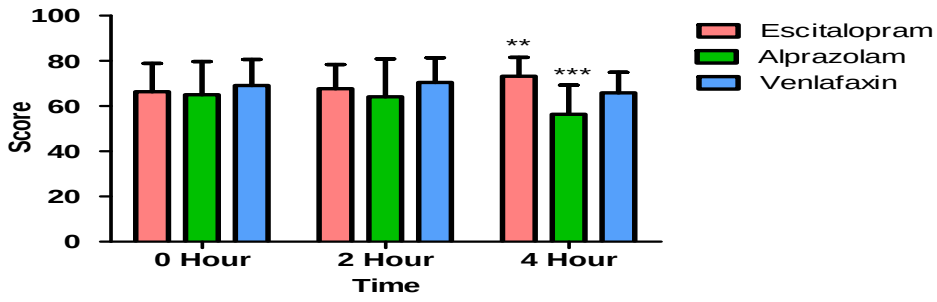
Table 3: Effect of Escitalopram, Alprazolam & Venlafaxine at 0, 2 and 4 hours on Reaction time (n=22)

Drug	Mean±SD		
	0 Hour	2 Hours	4 Hours
Escitalopram	532.3±91.67	511.3±78.23	475±83.66***
Alprazolam	483.5±97.89	519.7±97.83**	570.3±86.19***
Venlafaxine	513±89.95	513.3±67.68	512.9±86.67

Repeated measures ANOVA followed by post hoc Tukey's test. ** P<0.01; ***P<0.001

Figure 1, Figure 2 and Figure 3 shows effect of Escitalopram, Alprazolam and Venlafaxine on scores of VAS-Sedation, VAS-alertness and VAS-concentration respectively.

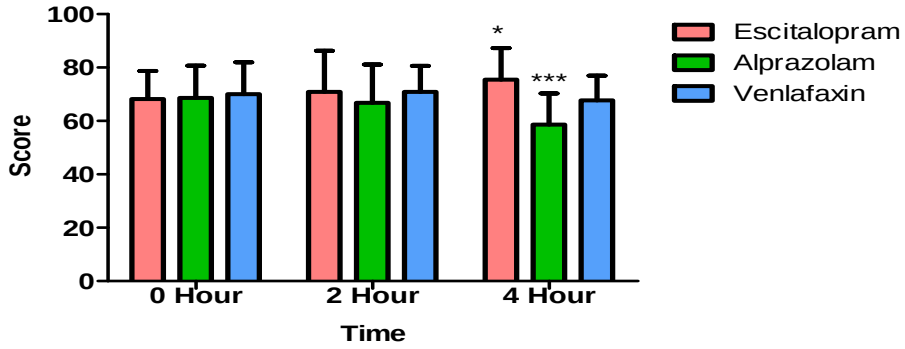
FIG 1: Effect of Escitalopram, Alprazolam and Venlafaxin on VISUAL ANALOGUE SCALE-SEDATION (VAS-SED) (N=22)



Volume 2, Issue 3; May-June 2019; Page No.374-383

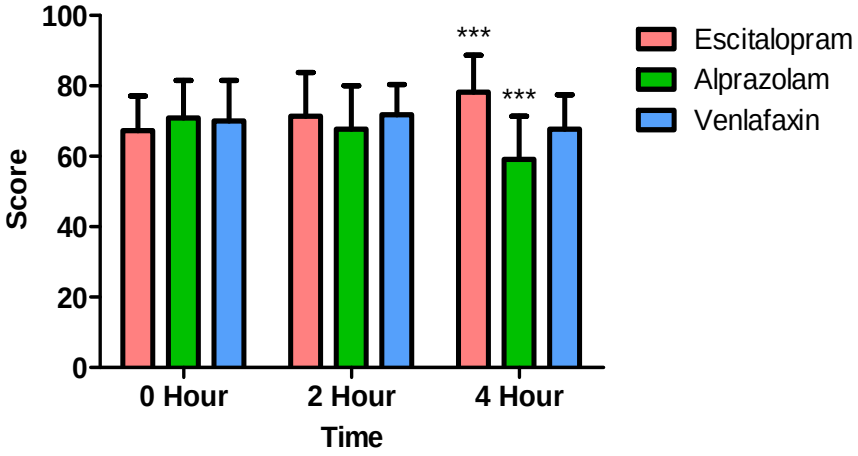
Values expressed as mean ± S.D. ** P < 0.01,*** P < 0.001 Repeated measures ANOVA followed by Tukey's test

FIG 2: Effect of Escitalopram, Alprazolam and Venlafaxin on VISUAL ANALOGUE SCALE-ALERTNESS (VAS-ALERT) (N=22)



Values expressed as mean ± S.D. * P < 0.05, *** P < 0.001 Repeated measures ANOVA followed by Tukey's test

FIG 3: Effect of Escitalopram, Alprazolam and Venlafaxin on VISUAL ANALOGUE SCALE-CONCENTRATION (VAS-CONC) (N=22)



Values expressed as mean ± S.D. *** P < 0.001 Repeated measures ANOVA followed by Tukey's test

Adverse events

Most common ADR reported was dizziness in 86.36% participants in Alprazolam group which was statistically significant as compared to other drugs. Nausea was reported by 50% participants in Escitalopram group and 22.72% in Venlafaxine group. Other ADRs reported were dry mouth, insomnia, restlessness, constipation, headache and irritability.

Discussion:

Efficacy, dosage forms, availability, side effects and cost of the drug are some important factors considered while prescribing antianxiety drugs. Antidepressants, particularly the SSRIs, are generally used as first-line agents for anxiety disorders, not only because anxiety is highly associated with depression but also due to less side effects and improved cognitive and psychomotor function due to selectivity of action.[7]

Study in healthy volunteers gives us preliminary idea about the level of cognitive and psychomotor impairment due to the study drug. If we directly study effects of antianxiety drugs on psychomotor performance in patients then it becomes difficult to

Volume 2, Issue 3; May-June 2019; Page No.374-383

decide whether altered psychomotor performance is due to drug or underlying disease itself. Since anxiety itself is associated with impaired cognitive function, any treatment with a detrimental effect on cognitive functions will be counter-therapeutic and might be responsible for increasing the severity of the disease. [2]So the present study evaluated and compared the effects of single dose of Escitalopram (SSRI), Alprazolam (Benzodiazepine) and Venlafaxine (SNRI) on cognitive and psychomotor performance in healthy volunteers.

Majority of participants were graduates. The difference in the basic educational levels of all the participants enrolled in study was not significant, hence no confounding factor of intellectual level on paper and pencil test are likely to be present. The crossover design of the study ensured that participants acted as their own control thereby nullifying the effect of intellectual level among the participants. Impact of practice effects was reduced by prior training.

In present study, Escitalopram showed statistically significant improvement in 6 DCT at the end of 2 hours and 4 hours suggesting improvement of sensory processing mechanism. Previous study conducted by Khan SarfarazAlam et al[11] had also found the similar results.

Escitalopram significantly improved DSST score in present study which suggest that Escitalopram has potential to improve recognition and recoding capacity. These findings were supported by previous study.[11] In contrast, study conducted by Nathan P et al[21] reported that Citalopram and Escitalopram did not show significant improvement in DSST score Escitalopram significantly increased CFF threshold at the end of 2 hours and 4 hours suggesting improvement in information processing and overall integrative capacity. These findings are in accordance with previous studies. [11,21]

Escitalopram significantly improved scores of Arithmetic ability test in present study suggesting improvement in central processing mechanism of perception. However, Khan SarfarazAlam et al[11]reported that Citalopram (20 mg) did not produce significant effect on Arithmetic ability test score.Escitalopram is more potent and effective at half the dose of Citalopram and is relatively safe.This lack of improvement in psychomotor performance with Citalopram (20 mg) might be due to low dose of citalopram in reference study.[11]

Escitalopram significantly improved the scores of Digit span test suggesting improvement in memory and learning. These findings were supported by study conducted bySoczynska JK et al [22] The present study found significant diminution in errors during hand steadiness test with Escitalopram suggestive of improvement in the tasks involving sensory-motor coordination. In contrast, previous study showed that Citalopram did not decrease the errors during hand steadiness test. [11]

In present study, Escitalopram significantly increased awakeness, alertness and concentration capacity on visual analogue scale at the end of 4 hours. Whereas, in a previous study a trend towards increased awakeness and activity was observed with Citalopram but could not reach statistically significant level at the end of 3 hours. [11] There was significant decrease in reaction time in Escitalopram group which is in accordance with previous study.[21] However, Study by Paul MA et al [10] reported that neither Citalopram nor Escitalopram affects reaction time.

In present study Esitalopram improved psychomotor performance probably because it inhibits reuptake of serotonin (5HT) in serotonergic neurons by blocking serotonin transporter(SERT) leading to increased serotonin concentration in the synapse, potentiating neurotransmission.

In our study, Alprazolam produced significant detrimental effect on sensory component (6 DCT, DSST,CFFT and AAT), motor component (HST), sensorimotor component (Reaction time) & subjective component (VAS) score at the end of 2 hours or 4 hours suggesting overall significant impairment in psychomotor performance.Similar study by Drabant S et al. [9]concluded that Alprazolam showed serious driving impairment, decreased mental alertness and significantly impaired psychomotor performance. In contrast, study conducted by Hart P et al [23] concluded that Alprazolam had minimal effects on psychomotor speed and memory.In subjective scales using visual analogue scales (VAS) for sedation, alertness and concentration, in Alprazolam group, participants experienced increased sedation, reduced alertness and

Volume 2, Issue 3; May-June 2019; Page No.374-383

concentration at the end of 4 hours which is similar to previous study.[24]

Alprazolam acts as positive allosteric modulator on gamma amino butyric acid ($GABA_{A)}$ receptor. This $GABA_A$ receptor is a ligand-gated chloride-selective ion channel.reducing the excitability of neurons producing a calming effect on the brain. So administration of Alprazolam might be responsible for impairment of psychomotor performance. [25,26]

In present study, Venlafaxine had no significant effect on psychomotor functions which is in accordance with the findings reported by previous study. [12,21,27]Whereas, a study by Trick L et al [28]concluded that Venlafaxine significantly raised CFF scores compared to baseline but had no effect on any other measure. .Simillarly, Venlafaxine didnot altered subjective feeling for sedation, alertness and concentration ability which is similar to the previous study findings. [27] Effect of Venlafaxine on reaction time was not significant similar to previous studies.[21,27]

Intergroup comparison of Escitalopram, Alprazolam & Venlafaxine showed that Escitalopram significantly increased CFF threshold whereas Alprazolam significantly reduced CFF threshold when compared with each other. However Venlafaxine did not affect CFF threshold significantly when compared with other two drugs. These findings are in accordance with the results of study conducted by Nathan Pet al. [21]

The lack of effect of Venlafaxine on psychomotor performance can be explained by its relative potency for inhibition of serotonin and noradrenaline reuptake. Venlafaxine is approximately 160 times less potent than Citalopram. Hence, relative potentiation of 5-HT neurotransmission, after uptake inhibitionwith Venlafaxine may not be sufficient to influence performance significantly. [21]

Escitalopram significantly improved scores of AAT and DST at the end of 4 hours as compared with Alprazolam. Whereas interdrug comparison between Escitalopram vs venlafaxine and alprazolam vs venlafaxine was found to be non-significant. Whereas there was no significant difference in the score of 6 DCT & DSST when intergroup analysis was done between these three drugs.

Escitalopram significantly improved performance in HST when compared with Alprazolam whereas Alprazolam significantly deteriorated the performance of HST when compared with Venlafaxine. Escitalopram significantly improved subjective feeling of awakeness, alertness & concentration when tested on visual analogue scale as compared to Alprazolam whereas Alprazolam significantly reduced the scores of Visual analogue scale for these three parameters as compared to Venlafaxine.

Escitalopram significantly decreased mean reaction time when compared with Alprazolam. Whereas interdrug comparisons between Escitalopram vs Venlafaxine and Alprazolam vs Venlafaxine were not significant.

Dizziness was the most commonly observed adverse event with Alprazolam which was statistically significant compared to other groups. This finding was supported by previous study.[29]Side effects like nausea, insomnia, dry mouth were common with Escitalopram which were as reported in the literature. [10]

Limitations of the study

Since this is a single dose study, effect of drug on long term basis cannot be predicted from this study.The effects on psychomotor performance obtained are for particular dose of the drug. Studies with different doses of the drug will be more useful.

Conclusion

Escitalopram had favourable effects on psychomotor performance whereas Alprazolam significantly deteriorated psychomotor performance. Venlafaxine had no effect on psychomotor performance.Thus present study will be helpful in deciding drug therapy for anxiety considering effects on psychomotor performance. But these findings need to be explored in separate set of long term studies in future to evaluate chronic effects on psychomotor performance.

References:

1. Doukkali Z, Taghzouti K, Bouidida ELH, Nadjmouddine M, Cherrah Y, Alaoui K. Evaluation of anxiolytic activity of methanolic extract of Urtica urens in a mice

Volume 2, Issue 3; May-June 2019; Page No.374-383

model. Behav Brain Funct [Internet]. 2015;11(1):19.
2. Hindmarch I. Cognition and anxiety: the cognitive effects of anti-anxiety medication. Acta Psychiatr Scand. 1998;98:89–94.
3. Isbister GK, O'Regan L, Sibbritt D, Whyte IM. Alprazolam is relatively more toxic than other benzodiazepines in overdose. Br J Clin Pharmacol. 2004;58(1):88–95.
4. Leufkens TRM, Vermeeren A, Smink BE, Van Ruitenbeek P, Ramaekers JG. Cognitive, psychomotor and actual driving performance in healthy volunteers after immediate and extended release formulations of alprazolam 1 mg. Psychopharmacology (Berl). 2007;191(4):951–9.
5. Dunlop B, Davis P. Combination Treatment With Benzodiazepines and SSRIs for Comorbid Anxiety and Depression: A Review. Prim Care Companion J Clin Psychiatry. Prim Care Companion J Clin Psychiatry; 2008;10(3):222–8.
6. Biringer E, Rongve A, Lund A. A Review of Modern Antidepressants' Effects on Neurocognitive Function. Curr Psychiatry Rev. 2009;5(3):164–74.
7. Outhoff K. The pharmacology of anxiolytics. South African Fam Pract . 2010;52(2):99–105.
8. Emamghoreishi M, Khasaki M, Aazam MF. Coriandrum sativum: Evaluation of its anxiolytic effect in the elevated plus-maze. J Ethnopharmacol. 2005;96(3):365–70.
9. Drabant S , Tömlo J, Tóth M, Péterfai E KI. The cognitive effect of alprazolam in healthy volunteers. Acta Pharm Hung. 2006;76(1):25–31.
10. Paul MA, Gray GW, Love RJ, Lange M. SSRI effects on pyschomotor performance: Assessment of citalopram and escitalopram on normal subjects. Aviat Sp Environ Med. 2007;78(7):693–7.
11. Khan Sarfaraz alam, Mukesh chunnilal Mehta , Anand kade A turankar. Acute Effects of Citalopram and Imipramine on Psychomotor Performance in Healthy Volunteers : A Comparative Study. J Pharm Sci Res. 2011;3(6):1269–75.
12. Hanlon O, James F, Hindrik WJ, Ms A, Leeuwen V, Philippe E. Venlafaxine's Effects on Healthy Volunteers Driving , Psychomotor , and Vigilance Performance During 15-Day Fixed and Incremental Dosing Regimens. J Clin Psychopharmacol. 1998;18:212–21.
13. Katz IR, Reynolds ICF, Alexopoulos GS, Hackett D. Venlafaxine ER as a treatment for generalized anxiety disorder in older adults: Pooled analysis of five randomized placebo-controlled clinical trials. J Am Geriatr Soc. 2002;50(1):18–25.
14. Hindmarch I. PSYCHOMOTOR FUNCTION AND PSYCHOACTIVE DRUGS. Br J Clin Pharmac. 1980;10:189–209.
15. Broadbent DE. Performance and its measurement. Br J Clin Pharmac. 1984;18:5–9.
16. Khade A, Bashir MS, Kale A, Turankar A. Study of the effect of nortriptyline and fluvoxamine on psychomotor functions in healthy volunteers. Indian J Psychol Med . 2010;32(2):104.
17. Stone BM. Pencil and paper tests- sensitivity to psychotropic drugs. Br J Clin Pharmac. 1984;18:15S–20S.
18. Parkin C, Kerr JS, Hindmarch I. The effects of practice on choice reaction time and critical flicker fusion threshold. Hum Psychopharmacol. 1997;12(1):65–70.
19. Worlikar P, Shaligram S V, Saraf AP. Effect of multiple doses of diazepam and promethazine on psychomotor performance of human volunteers. Indian J Pharmacol. 1985;17(1):30–3.
20. Jaiswal K, Pimpalkhute S, Sontakke S, Bajait C, Gaikwad A. Comparative study of effects of gabapentin, vigabatrin and sodium valproate on psychomotor performance in healthy volunteers. Int J Nutr Pharmacol Neurol Dis [Internet]. 2013;3(4):341–6.
21. Nathan P, Sitaram G, Stough C, Silberstein R, Sali A. Serotonin, noradrenaline and cognitive function: A preliminary investigation of the acute pharmacodynamic effects of a serotonin versus a serotonin and noradrenaline reuptake inhibitor. Behav Pharmacol . 2000;11:639–42.
22. Soczynska JK, Ravindran LN, Styra R, McIntyre RS, Cyriac A, Manierka MS, et al. The effect of bupropion XL and escitalopram

Volume 2, Issue 3; May-June 2019; Page No.374-383

on memory and functional outcomes in adults with major depressive disorder: Results from a randomized controlled trial. Psychiatry Res [Internet]. Elsevier; 2014;220(1–2):245–50.
23. Hart P, Colenda C, Hamer R. Effects of buspirone and alprazolam on the cognitive performance of normal elderly subjects. Am J psychiatry. 1991;148(1):73–7.
24. Wright E, Sisson T, FIeishaker J, Antal E. Pharmacokinetics and Psychomotor Performance of Alprazolam : Concentration-Effect Relationship. J Clin Pharmacol. 1997;37:321–9.
25. Gilhotra N, Dhingra D. Neurochemical modulation of anxiety disorders. Int J Pharm Pharm Sci. 2010;2:1–6.
26. Griffin C, Kaye A, Bueno F, Kaye A. Benzodiazepine pharmacology and central nervous system-mediated effects. Ochsner J [Internet]. 2013;13:214–23.
27. T. Siepmann, M. Mueck-Weymann , R. Oertel , W. Kirch , D. Pittrow MS. The Effects of Venlafaxine on Cognitive Functions and Quantitative EEG in Healthy Volunteers. Pharmacopsychiatry. 2008;41:146–50.
28. Trick L, Stanley N, Rigney U, Hindmarch I. A Double-Blind, Randomized, 26-Week Study Comparing the Cognitive and Psychomotor Effects and Efficacy of 75 mg (37.5 mg b.i.d.) Venlafaxine and 75 mg (25 mg Mane, 50 mg Nocte) Dothiepin in Elderly Patients with Moderate Major Depression Being Treated in . J Psychopharmacol. 2004;18:205–14.
29. Verster JC, Volkerts ER, Verbaten MN. Effects of Alprazolam on Driving Ability, Memory Functioning and Psychomotor Performance : A Randomized, Placebo-controlled Study. Neuropsychopharmacology. 2002;27(2):260–9.

Volume 2, Issue 3; May-June 2019; Page No.374-383