PSYCHOTROPIC INTERACTIONS OF SOME ANTI-HYPERTENSIVES IN MALE ALBINO RATS AND MICE

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Summary

The psychotropic activities of commonly prescribed antihypertensives prazosin, propranolol and losartan are controversial. Also there are scanty reports on the psychotropic interaction of these antihypertensives with an antidepressant-anxiolytic, venlafaxine. The antidepressant and anxiolytic activities were elicited using forced swim test and tail suspension test paradigms for depression; elevated plus maze and light dark arena paradigms for anxiety. Propranolol and losartan showed significant antidepressant as well as anxiolytic activity, while prazosin though showed anxiolytic activity, significantly induced depression. In interaction studies anxiolytic activity of venlafaxine was potentiated by all the antihypertensives used in the study, while antidepressant activity was only potentiated by propranolol and losartan. In conclusion losartan and propranolol appears to be antihypertensives potentiating psychotropic activities of venlafaxine, thus may be effective combination in comorbid condition.

Keywords: Antidepressant, Anxiolytic, Interaction, Prazosin, Propranolol, Losartan, Venlafaxine.

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Introduction

Depression is the commonest mood disorder characterized by feelings of sadness, despair and discouragement. Anxiety, a normal phenomenon, which is acute and transient depending upon the situation an individual faces, but if excessive interferes with performance and constitutes a psychiatric disorder. [1]

Moreover anxiety and depression could also be secondary to a number of physical disorders like hypertension, myocardial infarction, stroke, dementia, epilepsy and endocrinal disorders like diabetes, hyperthyroidism (anxiety) and hypothyroidism (depression).[2,3] Major depressive disorder is described as an independent risk factor for hypertension and prevalence of depressive disorder in a population of hypertensive individuals has been reported between 18-37%.[4,5] Pharmacological treatment for co morbidity of depression with hypertension includes anti-hypertensives and antidepressants. Venlafaxine, an atypical antidepressant can raise the blood pressure dose dependently.[6] While losartan an anti-hypertensive is reported to possess anti-depressant and anxiolytic acyivity.[7] Whereas there are controversial reports on psychotropic activities of prazosin and propranolol. Prazosin has been shown to exhibit significant anxiolytic activity[8], while it is been reported to reduce anti-depressant activity of desipramine[9] in contrast to report where in it has potentiated the anti-depressant activity of imipramine[10]. Propranolol, is also been shown to possess significant anxiolytic activity[11], while its effect on depression is controversial[10, 12].

The treatment of such comorbid condition involving two or more drugs are expected to interact pharmacodynamically. There are scanty reports on interaction of anti-hypertensives like prazosin, propranolol, losartan with antidepressants like venlafaxine, amitriptyline and interaction between anti-adrenergic anti-hypertensive like prazosin and propranolol with losartan on psychotropic activities. So the present study was planned to elicit the psychotropic activity of prazosin, propranolol, losartan and their interaction with amitriptyline, venlafaxine.

Materials and methods

Animals

Healthy male adult Wistar rats weighing 150 ± 25 g and Swiss albino mice weighing 25 ± 5g were used for the study. The animals were obtained from the central animal house of the institute and were kept in the laboratory for about 10 days in 12-hour light and dark cycle. Throughout the experiment the animals were fed with laboratory Chow (Amrut Brand) and water ad libitum. A group of animals destined to receive alprazolam orally were fasted overnight prior to the day of experiment with free access to water.

The study was approved by Institutional Animal Ethical Committee constituted as per the CPCSEA guidelines.

Psychotropic studies: The anti-depressant activity were carried out using paradigms; forced swim test[13], in rats and tail suspension test[14], in mice as described earlier. The anxiolytic activities were carried out using paradigms; elevated plus maze[15] and light dark arena[16], in rats as described earlier.

Prazosin (0.65mg/kg), propranolol (26mg/kg), losartan (14.5mg/kg), venlafaxine (29mg/kg), amitriptyline (27mg/kg) and alprazolam (0.045mg/kg) were the rat equivalent doses used in the present study and the respective mice equivalent doses were calculated using Paget and Barnes conversion table described earlier[17]. Amitriptyline and alprazolam were used as standard anti-depressant and anxiolytic drugs respectively.

Sub effective dose (SED) for each drug was determined in separate set of experiments. The maximum dose which just failed to reduce immobility time significantly as compared to that of control was considered as sub effective dose.

For interaction studies animals were divided into 10 groups containing 6 animals in each group, to study effect on depression (6 groups) and anxiety (4 groups). Treatment followed as shown below.

For interaction with prazosin; all the drugs were used in their therapeutic equivalent doses.

To evaluate effect on depression:

Group 1: prazosin + losartan
Group 2: prazosin + venlafaxine
Group 3: prazosin + amitriptyline

To evaluate effect on anxiety:

Group 4: prazosin + losartan
Group 5: prazosin + venlafaxine

For interaction with propranolol all the drugs were used in SEDs.
To evaluate effect on depression

Group 1: propranolol + losartan
Group 2: propranolol + venlafaxine
Group 3: propranolol + amitriptyline

To evaluate effect on anxiety:

Group 4: propranolol + losartan
Group 5: propranolol + venlafaxine

Statistical Analysis: All the results of the various experiments carried out in the present study were analyzed by ANOVA followed by Dunnet's posthoc test . The 'p' value ≤ 0.05 was considered as significant.

Results

In the present study prazosin, propranolol, losartan and venlafaxine were investigated for their psychotropic activity. In the interaction study as described earlier prazosin or propranolol was coadministered with either losartan or venlafaxine or amitriptyline to evaluate effect on depression. Whereas they were co-administered with either losartan or venlafaxine only to evaluate effect on anxiety.

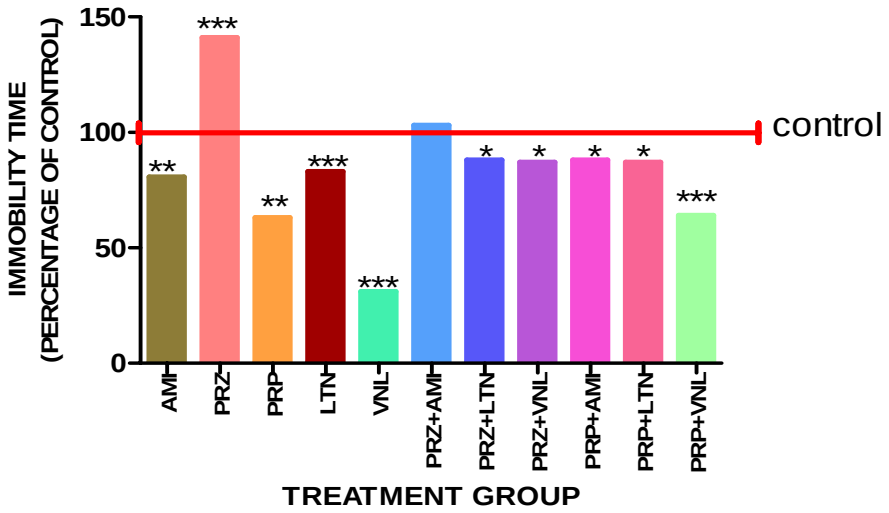
The SEDs of prazosin, propranolol, losartan, venlafaxine and amitriptyline were determined to be 0.2 mg/kg, 8 mg/kg, 5 mg/kg, 6.6 mg/kg and 15mg/kg respectively and the corresponding mice doses were calculated as described earlier.

Anti-depressant activity

Forced swim test

The duration of immobility time in seconds was noted over a period of 5 minutes. In the control group it was 176.0±5.26, while 142±3.19, 112.5±11.97, 147.7±2.49 and 55.0±11.44 in amitriptyline, propranolol, losartan and venlafaxine treated groups respectively. All the treatments significantly ($p<0.05$, $p<0.01$) decreased immobility, whereas prazosin with mean value of 249±8.35 was significantly ($p<0.001$) increased as compared to that of control. (Table 1, Fig 1)

Fig 1. FORCED SWIM TEST



***p<0.05, ** p<0.01, ***p<0.001**
VNL: Venlafaxine, PRZ: Prazosin, PRP:Propranolol, LTN: Losartan, AMI: Amitriptyline

Prazosin coadministered with venlafaxine and with losartan significantly ($p<0.05$) decreased immobility time with mean value of 153.7±4.86 and 155.3±4.43 as compared to that of control; whereas prazosin coadministration with amitriptyline failed to do so with mean value of 182.0±4.44, which was comparable to that of control. (Table 1, Fig 1)

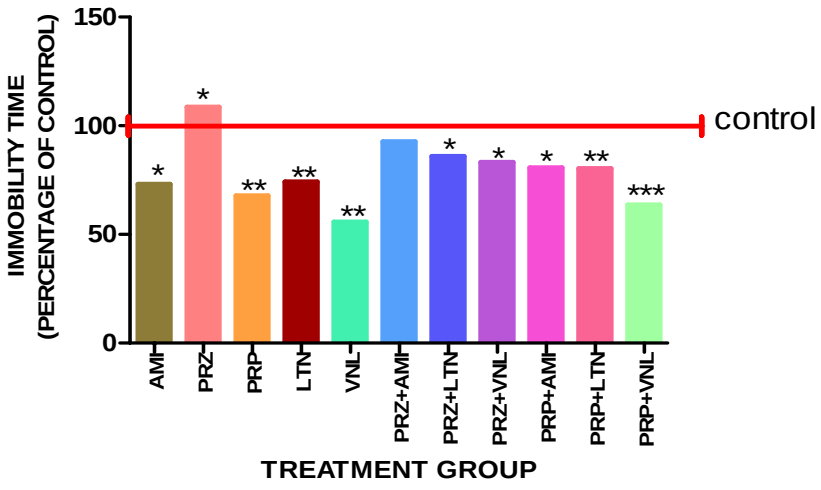
Propranolol coadministration with amitriptyline or losartan or venlafaxine showed significant ($p<0.05$, $p<0.001$) decrease in immobility time with mean values of 155±5.08, 113.2±5.58 and 154.2±6.19 as compared to that of control. (Table 1, Fig 1)

Tail suspension test

The mean duration of immobility over a period of 6 min evaluation was 218.7±12.25 in control, while that of amitriptyline group was 159.7±2.33 which was significantly ($p<0.05$) decreased compared to that of control. The mean immobility time in propranolol, losartan and venlafaxine treated groups were 148.3±12.63, 162.8±3.49 and 121.8±22.35 respectively, which were significantly ($p<0.01$) decreased as compared to that of control. In prazosin treated group with a mean value of 233.5±19.04 was significantly ($p<0.01$) increased as compared to that of control. (Table 1, Fig 2)

Prazosin when coadministered with venlafaxine or losartan in separate group of animals showed significant ($p<0.05$) decrease as compared to that of control with mean values of 182.0±10.75 and 187.8±6.16 respectively; whereas its coadministration with amitriptyline failed to decrease immobility significantly with a mean value of 202.8±13.96 as compared to that of control. (Table 1, Fig 2)

Fig 2. TAIL SUSPENSION TEST



***p<0.05, ** p<0.01, ***p<0.001**
VNL: Venlafaxine, PRZ: Prazosin, PRP:Propranolol, LTN: Losartan, AMI: Amitriptyline

Propranolol co administration with amitriptyline or losartan or venlafaxine in separate groups showed a mean value of 176.5±6.49, 175.7±5.71 and 139.0±8.05 respectively, which were significantly ($p<0.05$, $p<0.01$) decreased as compared to that of control. (Table 1, Fig 2)

Anxiolytic activity

Elevated plus maze.

a) Open arm entry

The mean percentage of entry into open arm in the control group was 24.71±4.54; while it was 48.92±6.79, 41.24±3.23, 47.41±4.64, 42.55±1.87 and 47.17±4.53 in alprazolam, prazosin, propranolol, losartan and venlafaxine treated groups respectively, indicating significant ($p<0.05$, $p<0.01$) increase as compared to that of control. (Table 1, Fig 3)

The mean percentage of entries in prazosin co administered with losartan or with venlafaxine in separate groups were 43.75±4.86 and 45.6±4.82 respectively which were significantly ($p<0.05$) increased as compared to that of control. (Table 1, Fig 3)

The groups receiving propranolol with losartan or venlafaxine separately showed significant ($p<0.05$) increase in percentage of entries with mean values of 42.83±5.15 and 49.42±6.79 respectively as compared to that of control. (Table 1, Fig 3)

b) Percentage of time spent in open arm

The mean percentage of time spent in the open arm in alprazolam, prazosin, propranolol, losartan and venlafaxine were 22.06±3.43, 17.72±1.31, 19.78±0.69, 19.32±1.51 and 19.72±1.27 respectively, which were significantly ($p< 0.05$, $p< 0.001$) increased as compared to 9.17± 3.24 of control. (Table 1, Fig 4)

In prazosin co administered with losartan or with venlafaxine separately, significantly ($p<0.05$, $p< 0.01$) increased percentage of time spent in light arena with mean values of 17.22± 1.19 and 21.44± 1.14 respectively as compared to that of control value was observed. (Table 1, Fig 4)

In groups receiving propranolol with losartan or venlafaxine separately, the mean percentage of time spent in open arm were 18.45± 1.54 and 23.78± 2.45 respectively which were significantly ($p< 05$, $p< 0.01$) increased as compared to that of control.

Fig 3. ELEVATED PLUS MAZE (Entries)

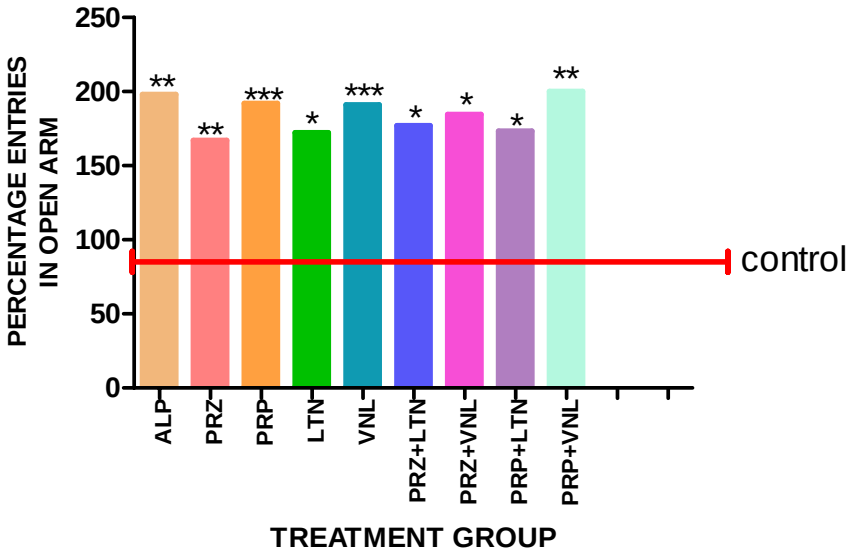
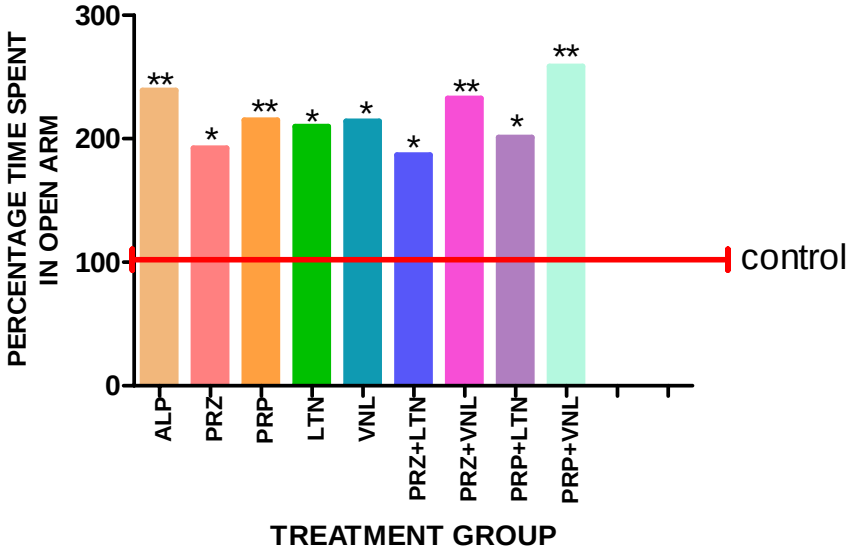


Fig 4. ELEVATED PLUS MAZE (Time spent)



p<0.05, ** p<0.01,p<0.001**

VNL: Venlafaxine, PRZ: Prazosin, PRP:Propranolol, LTN: Losartan, ALP: Alprazolam

Table 8. Effect (in percentage of control) of various treatments on depression and anxiety paradigms.

Paradigms / Treatment	FST (Time immobility)	TST (Time immobility)	EPM (open arm)		LDA(light arena)	
			Time spent	Entries	Time spent	Entries
Amitriptyline	80.7**	73*	Not tested	Not tested	Not tested	Not tested
Alprazolam	Not tested	Not tested	239**	198**	179.3**	159.9*
Prazosin	141.5***	108.5*	192.4*	166.9**	159.8*	169.5*
Propranolol	63.9**	67.8**	215.2**	191.9***	166.3*	139.5*
Loasrtan	83.9***	74.2**	209.8*	172.2*	165.2*	189.8**
Venlafaxine	31.3***	55.7**	214.1*	191***	169.6*	209.6**
PRZ + AMI	103.4	92.7	Not tested	Not tested	Not tested	Not tested
PRZ + LTN	88.2*	85.9*	186.9*	177*	191.3**	229.3**
PRZ + VNL	87.3*	83.2*	232.6**	184.5*	169.6*	199.4**
PRP + AMI	88.4*	80.7*	Not tested	Not tested	Not tested	Not tested
PRP + LTN	87.6*	80.3**	201.1*	173.3*	172.8*	209.6**
PRP + VNL	64.3***	63.6***	258.7**	200**	183.7**	219.8***

FST:Forced Swim Test, TST: Tail Suspension Test, EPM: Elevated Plus Maze, LDA: Light Dark Arena - VNL: Venlafaxine, PRZ: Prazosin, PRP:Propranolol, LTN: Losartan : ANOVA followed by Dunnet's posthoc test - *p<0.05, ** p<0.01, ***p<0.001

Light dark arena

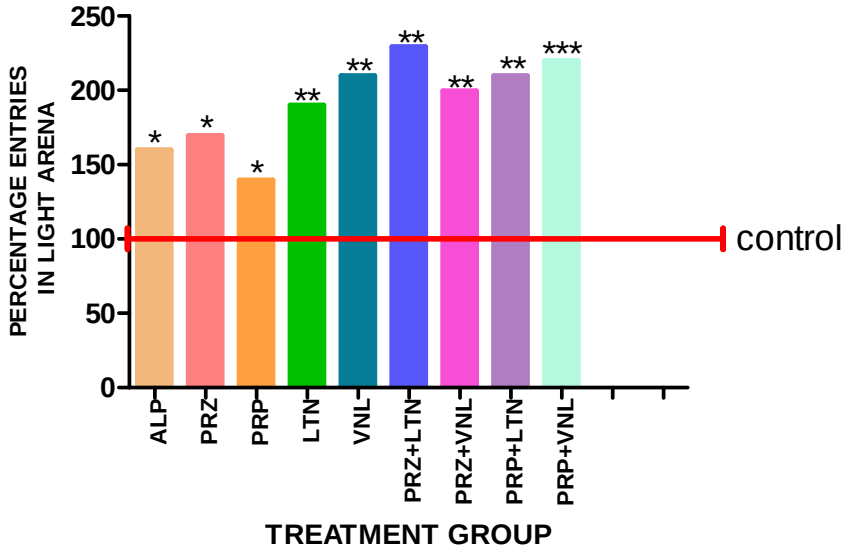
a) Entry in light arena

The mean number of entries in alprazolam, prazosin, propranolol, losartan and venlafaxine treated groups were 2.67± 0.33, 2.83± 0.40, 2.33± 0.21, 3.16± 0.40 and 3.5± 0.43 respectively, which were significantly ($p< 0.05$, $p< 0.01$) increased as compared to 1.67± 0.21 of control group. (Table 1, Fig 5)

In prazosin co administered with losartan or with venlafaxine separately, significantly ($p< 0.01$) increased number of entries with mean values of 3.83±0.31 and 3.33±0.42 respectively were observed as compared to that of control. (Table 1, Fig 5)

Propranolol co administered with losartan or venlafaxine separately, showed significant ($p< 0.05$, $p<0.01$) increase in mean number of entries with mean values of 3.5±0.43 and 3.67± 0.21 respectively as compared to that of control. (Table 1, Fig 5)

Fig 5. LIGHT DARK ARENA (Entries)



p<0.05, ** p<0.01,p<0.001**

VNL: Venlafaxine, PRZ: Prazosin, PRP:Propranolol, LTN: Losartan, ALP: Alprazolam

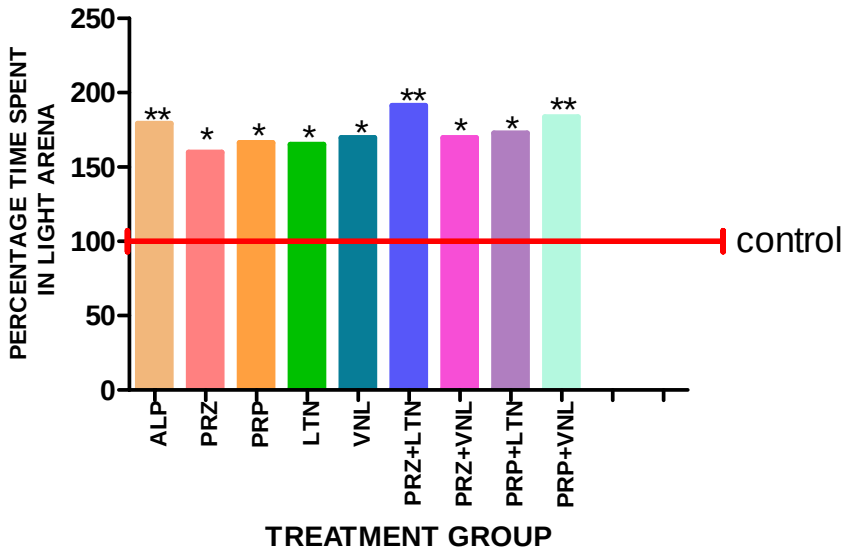
b) Percentage of time spent in light arena

The mean percentage of time spent in the light arena in alprazolam, prazosin, propranolol, losartan and venlafaxine were 16.5±1.7, 14.67± 0.87, 15.33±0.94, 15.22±0.74 and 15.61±1.28 respectively, which were significantly ($p< 0.05$, $p< 0.01$) increased as compared to 9.17± 2.06 of control. (Table 1, Fig 6)

In prazosin co administered with losartan or venlafaxine separately, significantly ($p<0.05$, $p< 0.01$) increased percentage of time spent in light arena with mean values of 17.61± 1.29 and 15.61± 0.57 respectively as compared to that of control was observed. (Table 1, Fig 6)

In groups receiving propranolol with losartan or venlafaxine separately, the mean percentage of time spent in light arena were 15.89± 1.04 and 16.89± 0.54 respectively which were significantly ($p< 05$, $p< 0.01$) increased as compared to that of control. (Table 1, Fig 6)

Fig 6. LIGHT DARK ARENA (Time spent)



p<0.05, ** p<0.01,p<0.001**

VNL: Venlafaxine, PRZ: Prazosin, PRP:Propranolol, LTN: Losartan, ALP: Alprazolam

Discussion

The objective of the present study, as mentioned earlier was to investigate prazosin, propranolol and losartan regarding their influence on behavior. The other objective being, study of their interactions with commonly used anti depressants *viz.* amitriptyline, venlafaxine and angiotensin receptor antagonist losartan.

Acute (single dose) studies

Results of the present study indicate that prazosin has significant anxiolytic activity (Fig 3-6), despite of its depressant action (Fig 1 &2). The anxiolytic activity observed in the present study agrees with earlier reports where in prazosin has been shown to exhibit significant anxiolytic activity[18] and to be beneficial in the treatment of PTSD[19], while its depressant activity resembles with findings of Al-Tubuly *et al.*[10]

Propranolol in contrast to prazosin showed significant anxiolytic and anti depressant activity in all the paradigms employed in the present study. Their findings corroborate earlier reports regarding its effect on anxiety[11] and on depression[12]. However the present finding of its anti-depressant activity differs from several earlier reports based on animal experiments[10] and clinical observations[20]. The discrepancy between the present finding and the earlier experimental study report could be explained on the basis of different species (albino mice) and lower dose (1mg/kg) used in the earlier study.

The significant anti-depressant and anxiolytic activity of losartan as observed in the present study confirms the earlier reports.[7,21,22] Similarly established anti-depressants, amitriptyline and venlafaxine both showed significant anti-depressant activity while alprazolam a commonly used anxiolytic showed significant anxiolytic activity in the present study. Venlafaxine in addition to its anti-depressant activity also exerted anxiolytic activity confirming the reports of several earlier experimental[23,24] and clinical[25,26] studies.

Acute Interaction studies:

As prazosin was devoid of anti-depressant activity in the interaction studies it was used in effective dose with effective doses of losartan or amitriptyline or venlafaxine.

In the present study prazosin antagonized the anti-depressant activity of amitriptyline. Though there are no reports regarding such interaction studies prazosin has been shown to decrease the anti-depressant activity of desipramine[9], which resembles amitriptyline in its pharmacological profile. However prazosin also has been reported to potentiate anti-depressant activity of imipramine.[10] The discrepancy could be explained on

the basis of animal species (albino mice) and higher dose of prazosin (5 mg/kg) used in the earlier study.

Prazosin failed to significantly antagonize the antidepressant as well as anxiolytic activity of venlafaxine and losartan, though it decreased their antidepressant activity to some extent. However, no reports regarding such an interaction of prazosin with losartan and venlafaxine could be traced in literature.

These observations of the present study indicate that the anti-depressant activity of amitriptyline are mainly mediated through adrenergic α- receptors while additional mechanisms other than adrenergic system are involved in mediating anti-depressant activity of venlafaxine and losartan.

In the present interaction studies propranolol potentiated the anxiolytic activity of losartan and venlafaxine as well as anti-depressant activity of all the three drugs. Reports regarding such interactions are scanty. However selective β_1 –blockers such as practolol and atenolol have been reported to potentiate the anti-depressant activity of desipramine.[27] But the present finding about the interaction between propranolol and amitriptyline disagree with the earlier reports where in propranolol has been shown to significantly antagonize the anti-depressant activity of DMI.[28] The discrepancy could be due to use of different rat strain (CD-COBS) and lower dose of propranolol (5mg/kg) in earlier study.

The present findings indicate anti-depressant activity appears to be mediated partly by adrenergic α receptors, while anxiolytic activity is independent of both α_1- and β-adrenoceptors. And if the present results are extrapolated to clinical situation, propranolol and losartan could be the better anti-hypertensives combined with venlafaxine in comorbid conditions, which further needs to be confirmed by clinical studies.

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References

1. Stahl SM. Essential Psychopharmacology. 2nd ed. New Delhi : Foundation books, Cambridge University Press; 2000.
2. John MJ. Drug Therapy. The Medical Management of Depression (review). New Eng J Med 2005; 353: 1819-34.
3. Shrivastava S, Kochar MS. The dual risks of depression and hypertension. Postgraduate Medicine 2002; 111: 1-9.

4. Meyer CM, Armenian HK, Eaton WW, Ford DE. Incident hypertension associated with depression in the Baltimore Epidemiologic Catchment area follow-up study. J Affect Dis. 2004;83(2-3):127-33.
5. Simonsick EM, Wallace RB, Blazer DG, Berkman LF. Depressive symptomatology and hypertension-associated morbidity and mortality in older adults. Psychosom Med. 1995;57(5):427-35.
6. Thase ME. Effects of venlafaxine on blood pressure; a meta-analysis of original data from 3744 depressed patients. J Clin Psychiatry 1998 Oct; 59(10):502-508.
7. Veena Nayak, Patil PA. Antidepressant activity of fosinopril, ramipril and losartan, but not of lisinopril in depressive paradigms of albino rats and mice. Indian Journal of Experimental Biology 2008; 46: 180-184.
8. Rubalcava CL, Guasti AF. Noradrenaline-serotonin interactions in the anxiolytic effects of 5-HT(1A) agonists. Behav Pharmacol. 1994 Feb ;5 (1):42-51
9. Kostowski W. Possible relationship of the locus coeruleus – hippocampal noradrenergic neurons to depression and mode of action of anti-depressant drugs. Pol J Pharmacol Pharm, 1985 Nov-Dec;37(6):727-743.
10. Al-Tubuly RA, Aburawi SM, Alghzewi EA, Gorash ZM, Errwami S. The effect of sympathetic antagonists on the antidepressant action of alprazolam. Libyan J med, AOP: 080101.
11. Angrini M, Leslie JC, Shephard RA. Effects of propranolol, buspirone, pCPA, reserpine, and chlordiazepoxide on open-field behavior. Pharmacol Biochem Behav Feb 1998; 59(2): 387-97.
12. Kinney GG, Griffith JCW and Hutzik DJ. Antidepressant like effects of 5-hydroxytryptamine$_{1A}$ receptor agonists on operant responding under a response duration differentiation schedule. Behavioural Pharmacology 1998; 9: 309-318.
13. Porsolt RD, Pichon ML, Jalfre M. Depression : a new animal model sensitive to antidepressant treatments. Nature 1977; 266: 730-2.
14. Steru L, Chermat R, Thierry B, Siman P. The tail suspension test : A new method for screening antidepressants in mice. Psychopharmacology 1985; 85: 367-70.
15. Pillow S, Chopin P, Fil SE and Briely B. Validation of open-closed arm entries in elevated plus maze as a measure of anxiety in rat. J Neurosci Methods 1985; 14: 149.
16. Costall B, Domeney AM, Gerrad PA, Kelly ME and Naylor R. Zacopride: anxiolytic profile in rodents and primate models of anxiety. J Pharm Pharmacol 1988; 40:302.
17. Ghosh MN. Fundamentals of Experimental Pharmacology. 3rd ed. Kolkota: Hilton and company; 2005.
18. Rubalcava CL, Guasti AF. Noradrenaline-serotonin interactions in the anxiolytic effects of 5-HT(1A) agonists. Behav Pharmacol. 1994 Feb ;5 (1):42-51.
19. Taylor FB, Lowe K, Thompson C, Mc-Fall MM, Peskind ER, Kanter ER, *et al.* Daytime Prazosin Reduces Psychological Distress to Trauma Specific Cues in Civilian Trauma Posttraumatic Stress Disorder. Biological Psychiatry 2006; 59(7): 577-581.

20. Stoudemire A, Brown JT, Harris RT, Blessing-Feussner C, Roberts JH, Nichols JC, Houpt JL. Propranolol and depression: a reevaluation based on a pilot clinical trial. Psychiatr Med. 1984 Jun; 2(2): 211-8.
21. Srinivasan J, Suresh B, Ramanathan M. Differential anxiolytic effect of enalapril and losartan in normotensive and renal hypertensive rats. J Physiol Behav 2003; 78: 585-91.
22. Braszko JJ, Kulakowska A, Winnicka MM. Effects of Angiotensin II and its receptor antagonists on motor activity and anxiety in rats. J Physiol Pharmacol 2003; 54: 271-81.
23. Andrews JM, Ninan PT, Nemeroff CF. Venlafaxine: a novel antidepressant that has a dual mechanism of action. Depression 1996; 4(2): 48-56.
24. Oliveira RA, Cunha GMA, Borges KDM, Bruin GS, Santos-Filho EA,Glauce SB, *et al.* The effect of venlafaxine on behaviour, body weight and striatal monoamine levels on sleep-deprived female rats. Pharmacology Biochemistry and Behavior 2004; 79(3): 499-506.
25. Lenox-Smith A, Conway P, Knight C. Cost effectiveness of representatives of three classes of antidepressants used in major depression in the UK. PharmacoEconomics 2004; 22(5): 311-319.
26. Montgomery SA, Tobias K, Zornberg GL Pregabalin and venlafaxine improve symptoms of generalised anxiety disorder. *Evidence-Based Mental Health* 2007; 10: 23.
27. Kitada Y, Miyauchi T, Kanazawa Y, Nakamichi H, Satoh H. Involvement of α- and β- adrenergic mechanisms in the immobility reducing action of desipramine in the forced swimming test. Neuropharmacology 1983; 22(9): 1055-1060.
28. Borsini F, Bendotti C, Velkov V, Rech R, Samanin R. Immobility test: effects of 5-hydroxytryptaminergic drugs and role of catecholamines in the activity of some antidepressants. J Pharm Pharmacol 1981; 33: 33-37.