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AN EXPERIMENTAL STUDY TO EVALUATE THE EFFECT OF TRANDOLAPRIL AND NIMODIPINE IN ANXIETY, DEPRESSION AND MOTOR COORDINATION USING BEHAVIORAL MODELS IN SWISS ALBINO MICE

Sayed Shakita Fatima [*1], Rishi Pal [1], DA Rizvi [2], A. Singh [3], F. Asif [1], S. Hasan [1], R. Nath [1], A. K. Sachan [1] and R. K. Dixit [1]

Department of Pharmacology and Therapeutics [*1], King Georges Medical University, Lucknow - 226003, Uttar Pradesh, India.
Department of Pharmacology [2], Era's Lucknow Medical College and Hospital, Lucknow - 226001, Uttar Pradesh, India.
Department of Pharmacology [3], Dr Ram Manohar Lohia Institute of Medical Sciences, Lucknow - 226016, Uttar Pradesh, India.

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Correspondence to Author:
Dr. Sayed Shakita Fatima

Department of Pharmacology and Therapeutics, King Georges Medical University, Lucknow - 226003, Uttar Pradesh, India.

E-mail: shakitasayed@gmail.com

ABSTRACT: The present study aimed to assess the role of angiotensin-converting enzyme inhibitor (trandolapril) and calcium channel blocker (nimodipine) in anxiety, depression, and motor coordination using behavioral models in mice. This was an experimental study involving 72 swiss albino mice divided into 12 groups. Groups 1 to 4 were used to evaluate the anxiolytic effect using Y maze after 5 days of treatment. Groups 5 to 8 were used to evaluate the antidepressant effect using forced swim test on days 1, 10, 20, and 30. Groups 9 to 12 were used to evaluate the effect on motor coordination using the Rotarod apparatus at 0, 30, 60, 90, 120 min. Statistical evaluation was done by ANOVA. $P < 0.05$ was considered statistically significant. Fall-off time was significantly earlier in only the standard group at 30 and 60 min. The period of immobility was lower in both the test groups on day 30. The total number of visits significantly decreased in both the test groups and standard groups on day 5. The results showed the presence of antidepressant and anxiolytic effects in both the test groups without muscle relaxant property. Therefore it can be proposed that both trandolapril and nimodipine can be new possible targets for treating anxiety and depression without affecting motor coordination at presently used doses.

INTRODUCTION: Chronic non-communicable diseases are a major concern worldwide as it carries a significant load of morbidity and mortality.

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Risk factors that contribute are an unhealthy lifestyle, lack of physical activity, prolonged stress that may lead to raised blood pressure, obesity, and deranged blood glucose. Stress, which is an inevitable part of our life, has been linked to a variety of illnesses.

There is a stronger relation between stress and psychiatric illness [1]. As a response to stress, there occurs derangement in Renin-Angiotensin-Aldosterone System (RAAS) [2].

This affects the Hypothalamic-pituitary-adrenal axis (HPA), and sympathetic activity, which works in correlation with RAAS. There is a higher prevalence of depressive symptoms, approximately 30% in patients with HTN [3].

Another meta-analysis conducted amongst south Asian countries in 2019 suggested a pooled prevalence of depression in 38% population with hypertension a pooled prevalence of anxiety of about 29% amongst patients with non-communicable diseases [4]. Both anxiety and depression have been implicated as cause and result of acquiring chronic illnesses like hypertension and diabetes. Therefore discovering cardiovascular medications with the beneficial neuropsychiatric outcome is a need of an hour. There are findings that suggest that anti-depressant medications do antagonize the action of Angiotensin II (Ang II).

Therefore, drugs that antagonize RAAS or Ang II may prove as potential targets for depression. ACEI, namely captopril and perindopril, have shown beneficial effect in elevating mood in hypertensive patients [5, 6]. Ang II is an important bioactive molecule of RAAS formed from Ang I *via* the action of Angiotensin-Converting Enzyme I (ACE). Renin is produced by Juxtaglomerular cells of kidneys in response to hyponatremia, low blood pressure, and it converts Angiotensinogen to Ang I in the liver; this is further acted upon by ACE in plasma and to a larger extent by membrane-bound ACE in the vascular system, especially of pulmonary and renal endothelium to form Ang II,

This then acts on angiotensin II type1 and type 2 receptors. Ang II is unable to cross the blood-brain barrier and communicate via circumventricular organs. AT1R is present in the hypothalamic-pituitary-adrenal axis, amygdale, paraventricular nuclei, nucleus tractus solitaries. The actions of AT1R and AT2R are opposite to each other, where AT1R is responsible for the detrimental effects of Ang II [7]. Studies have shown neuroinflammation, oxidative stress, increased inflammatory cytokines, derangement in RAAS, sympathetic outflow, and altered calcium signaling as underlying pathology in anxiety and depression. The RAAS and its active peptide angiotensin II (Ang II) have been found to have major involvements in anxiety and depression, most probably *via* angiotensin II-linked (nicotinamide adenine dinucleotide phosphate oxidase) NADPH oxidase-derived oxidative stress in the central nervous system (CNS) [7]. Therefore, there is an evident potential of RAAS modulators in the prevention and treatment of anxiety and mood disorders. Trandolapril is an angiotensin-converting enzyme inhibitor (ACEI) with central action.

Being highly lipophilic it easily crosses the bloodbrain barrier and inhibits the angiotensin-converting enzyme (ACE) in the brain,, thereby decreasing the excess release of Ang II, which is implicated to have a causative role in anxiety and depression [8]. Calcium ions are important mediators of cell signaling as a result of their ability to induce changes in membrane potential of a cell and also through their roles as intracellular messengers, thereby been responsible for a wide spectrum of physiological processes, including neurotransmitter or hormone release, activation of gene transcription and muscle contraction.

The key mediators of calcium entry are voltage-gated calcium channels, especially in the brain, heart, and muscle. In the nervous system, calcium channel blockers are becoming potential therapeutic targets for pathologies such as parkinson's disease, pain, addiction, and anxiety [9]. Nimodipine is a short-acting calcium channel blocker having central action [10]. It affects voltage-gated calcium channels of L and T type, derangement of which are implicated in depression, anxiety.

Angiotensin II has a pro-inflammatory effect and has a modulatory role in apoptosis, inflammation. It causes increased degradation of protein and increased apoptosis in skeletal muscles, thereby leading to skeletal muscle wasting and atrophy. High levels of brain angiotensin II is related, therefore, to a disturbance in motor activity. This muscle injury in part is because of the increased level of reactive oxygen species and high levels of superoxides which are produced by NADPH oxidase [11]. There is also decreased oxidative phosphorylation and accumulation of abnormal mitochondria in skeletal muscles [12]. During an action potential, there occurs calcium influx in purkinje cells in the cerebellum.

The encoding of information from the cortical cerebellum to deep cerebellar areas then occurs as a result of the generation of impulse firing from these cells, which is very uniform and in tonic rhythm. However in many conditions such as neuro-degenerative disorders, sick purkinje cells fire in bursts leading to too much calcium in cells which can precipitate and worsen ataxia leading to poor motor coordination [13, 14]. Considering the role of the renin-angiotensin system and calcium in the above parameters, the present study was conducted with an objective to evaluate anti-anxiety, anti-depressant, properties as well as effect on motor co-ordination of angiotensin-converting enzyme inhibitor trandolapril and calcium channel blocker nimodipine in different mice models.

MATERIAL AND METHODS:

Animals: The study was conducted in the Department of Pharmacology & Therapeutics, King George's Medical University, Lucknow. 72 healthy female swiss albino mice, weighing 20-30 gm were utilized for this experimental study. Mice were obtained from CPSCEA - certified animal house [IITR, Lucknow]. They were housed in appropriate-sized cages in an institutional animal house under a controlled temperature environment [25 ± 2 °C], maintaining 12 h light / 12 h dark cycle. They were fed with a normal pellet diet and water *ad libitum*. They were allowed to acclimatize for 2 weeks to a new environment prior to the experiments. The care of animals was done as per CPCSEA guidelines. Ethical clearance was obtained from the Institutional Animal Ethics Committee (IAEC) with approval number-(no.118/IAEC/2019).

Drugs: Trandolapril was procured from Sigma Aldrich. It was solubilized in DMSO (Dimethyl Sulfoxide) and dissolved in normal saline, and administered per orally (p.o.) in a dose of 5 mg/kg [15]. nimodipine was given 2.5 mg/kg intraperitoneally (i.p.) [16,] imipramine (10 mg/kg i.p.) [17,] diazepam (1 mg /kg i.p.) [18] were purchased from an authorised medical store.

Groups: 72 female swiss albino mice were randomly divided into 12 groups (n = 6). Groups 1 to 4 were used to evaluate the anxiolytic effect as compared with diazepam using Y maze for 'total number of visits' on days 1 and 5. [Group 1 (normal saline), Group 2 (trandolapril), Group 3 (nimodipine), Group 4 (diazepam)]. Groups 5 to 8 were used to evaluate the antidepressant effect and compared with imipramine using forced swim test and 'period of immobility' was evaluated at days 1, 10, 20, 30 [Group 5 (normal saline), Group 6 (trandolapril), Group 7 (nimodipine), Group 8 (imipramine)]. Group 9 to 12 were used to evaluate the effect on motor coordination using Rotarod apparatus and compared with diazepam for 'fall off' time at 0, 30, 60, 90, 120 min. [Group 9 (normal saline), Group 10 (trandolapril), Group 11 (nimodipine), Group 12 (diazepam)].Statistical evaluation was done by ANOVA followed by a post hoc test. $P < 0.05$ was considered statistically significant.

Behavioral Test:

Y Maze: The apparatus consists of identical three arms. Each arm was 30 cm × 5 cm × 15 cm (length × width × height). Y maze has an equilateral triangular center; each arm is at an angle of 120°, forming the letter Y shape of the maze. The three arms needed to be made similar to prevent animal's predilection when placed into the maze. Mice were treated with test and standard drugs for consecutive 5 days once daily, and the last dose was given on the 5th day, 60 min before the experiment, and kept individually in one arm of the apparatus. No habituation session was given so as to maintain stress and anxiety. Each unhabituated mouse was placed at the end of one arm and allowed to move freely through the maze during a 10-min session. Mouse entering in the arm of the maze with all four feet was counted as a single entry [19].

Forced Swim Test: Forced swim test (FST) is the most widely employed behavioral model for assessing antidepressant activity [20]. The apparatus consisted of a transparent cylinder filled with water at room temperature. In this test, each mouse was placed in a cylinder with enough water (filled to 15 cm depth) so that it could not touch the bottom with its hind paws. Immediately after dropping the mouse in water, an immediate burst of activity was shown by the mouse; it tried to escape and then eventually adopted an ''immobile'' posture, where it will make only those movements necessary to keep its head above water. The session for mice was for 6 min consisting of a pretest (initial 2 min) and a test (the last 4 min).

The duration of immobility for baseline was recorded 1 day prior [21]. On the day of testing thirty minutes after i.p. and 1 hr after oral administration of drugs, mice were gently dropped individually into the cylinder for 6 min. Duration of immobility was recorded during the last 4 min swimming test. Mice were judged to be immobile when they floated in an upright position without movements or making minor movements of their limbs just necessary to keep their head above water. These three groups received the respective treatment for consecutive 30 days, and the duration of immobility was noted again on the 10th, 20th, and 30th day. The water was changed after testing each animal and mice were dried before returning to their respective home cages.

Rotarod Test: The apparatus consists of a rotating rod 3 cm in diameter divided into 5 sections by plastic discs. This rod is about 50 cm high from the base of the apparatus. The platform is equipped with sensors that allow the device to cease rotation and record the ending time of the test when mice contact the platform. The mice were given the training to acclimatize to stay on the revolving drums. Animals remaining on Rota-Rod (15 rpm) 1 min or more in three successive trials were selected 1 day before the actual day of testing [22, 23]. On the test day, the mice were placed again on the same rotating rod. The mean of three training runs was taken as a control performance time (Basal reading). The mice in the test, standard and control group were then treated with respective drugs and fall-off time was again assessed after a duration of 0, 30, 60, 90 and 120 min [24]. The fall-off time from the rotating rod was noted [25].

Statistical Analysis: Data were expressed as Mean ± Standard error. Results were analyzed using SPSS (Statistical Package for Social Sciences) Version 21.0 statistical analysis software by ANOVA single factor followed by post hoc Tukey's HSD test. An Intragroup comparison was done using the 'paired-t test'. $p<0.05$ was considered to be significant.

RESULTS:

Assessment of Anti-Anxiety Activity: Anti-anxiety activity was assessed by a total number of visits performed on day 1 and day 5. Intergroup comparison on day 1 revealed comparable results between all four groups. But on Day 5, ANOVA revealed a significant difference in the number of visits on the Y-maze model in all four groups F= 38.16 ($p < 0.01$) **Table 1**. The percentage change in baseline was maximum for standard group diazepam (-41.18%) followed by nimodipine (-23.94%) and trandolapril group (-16.13%). The trend of decline in the period of immobility between the groups is shown in **Fig. 1**.

TABLE 1: INTERGROUP COMPARISON OF NUMBER OF VISITS ON Y MAZE

Groups	Day 1	Day 5
Normal saline (control)	35±0.85	40±1.46**
Trandolapril (test)	36.17±1.16	30.33±0.88**
Nimodipine (test)	35.50±0.67	27±1.41**
Diazepam (standard)	34±0.63	20±1.52**

Effect of test drugs on a number of visits on Y maze on day1 and after 5 days of treatment, each value is a mean of six observations, values are mean ± SEM of a number of visits, level of significance-** denotes $p < 0.01$.

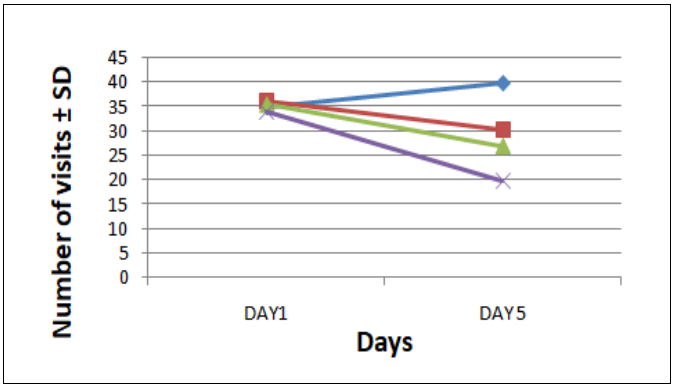

FIG. 1: TREND OF DECREASE IN NUMBER OF VISITS ON Y-MAZE. Values are mean ± SD of the number of visits. NS control; Trandolapril; Nimodipine; Diazepam standard.

Assessment of Anti-depressant Activity: Anti-depressant activity was assessed by a period of immobility in the forced swim test performed on days 1, 10, 20, and 30. ANOVA of the result on day 1 and day 10 was not statistically significant. ANOVA of results of day 20 yielded $F = 4.83$ ($p < 0.05$) and on day 30, yielded $F = 33.14$ ($p > 0.05$) which was significant statistically.

Between-group differences on day 20 by post hoc showed a significant difference only between the control and standard imipramine group. But on day 30, all the between-group differences were significant except between the trandolapril and nimodipine group **Table 2**. The intragroup comparison showed significant change from

baseline in the control group on day 20 (3.93%), day 30 (10.48%). The percentage change in the trandolapril group was found significant on day 30(-7.37%) and in the nimodipine group on day 30(-10.70). Imipramine group showed significant change on day 20(-10.17%) and day 30(-19.19%). The trend of decline in the period of immobility between the groups is shown in **Fig 2.**

TABLE 2: INTERGROUP COMPARISON OF PERIOD OF IMMOBILITY (SECONDS) IN FORCED SWIM TEST

Groups	Day 1	Day 10	Day 20	Day 30
Normal saline (control)	190.83 ± 6.62	191.83 ± 7.82	198.33 ± 6.09	210.83 ± 5.43**
Trandolapril (test)	194.50 ± 4.12	192.00 ± 3.20	190.00 ± 2.67	180.17 ± 2.66**
Nimodipine (test)	191.67±4.19	192.33±4.24	189.33±3.87	171.17±3.34**
Imipramine(standard)	188.50 ± 8.36	184.17 ± 7.05	169.33 ± 8.12*	152.33 ± 6.39**

Effect of test drugs on period of immobility after start of treatment as compared to control and standard, each value is a mean of six observations, values are mean ± SEM of a period of immobility(seconds), level of significance-* denotes $p < 0.05$, ** denotes $p < 0.01$

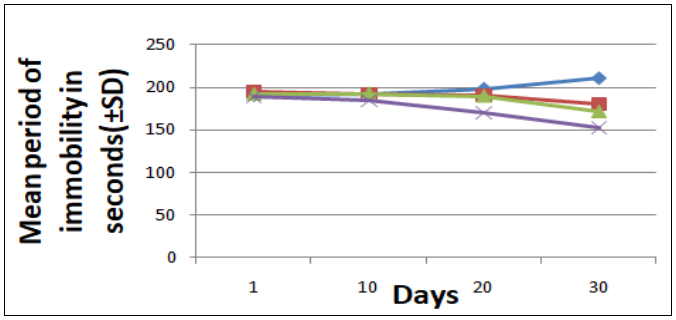

FIG. 2: TREND OF DECREASE IN 'PERIOD OF IMMOBILITY' (SECONDS) IN FORCED SWIM TESTS. Values are mean ± SD of period of immobility (seconds), NS (control); Trandolapril; Nimodipine; Imipramine (standard)

Assessment of Motor Coordination Activity: Motor coordination was assessed by duration of stay on rotating rod and measuring 'fall-off time'. At baseline 0 min, 90 min and at 120 min fall-off time of mice in all the above 4 groups were comparable upon intergroup comparison. Fall-off time was significantly earlier in

TABLE 3: INTERGROUP COMPARISON OF 'FALL-OFF' TIME (SECONDS) ON ROTAROD

Groups	0 min(s)	30 min(s)	60 min(s)	90 min(sec)	120 min(s)
NS (control)	270.50±2.75	270.67±2.95	268.5±2.81	269.17±3.55	270.33±2.55
Trandolapril (test)	271.17±2.67	272.33±2.07	271±2.33	272.50±1.97	272.17±2.32
Nimodipine (test)	273.67±2.70	271.50±3.58	272±3.01	272.67±3.29	274.17±3.17
Diazepam (standard)	269.83±3.38	222.50±3.01**	243±2.72**	269.17±3.59	268.17±3.33

Diazepam group as compared to the other three groups at 30 min ($F = 68.67$) and 60 min ($F = 25.62$), **Table 3**. Percentage change in baseline was maximum at 30 min (-17.54) followed by 60min (-9.94) in diazepam group as seen in **Fig. 3**.

Effect of test drugs on fall off time at various time period after test dose as compared to control and standard, each value is a mean of six observations, values are mean ± SEM of fall-off time (seconds), level of significance-* denotes $p < 0.05$, ** denotes $p < 0.01$

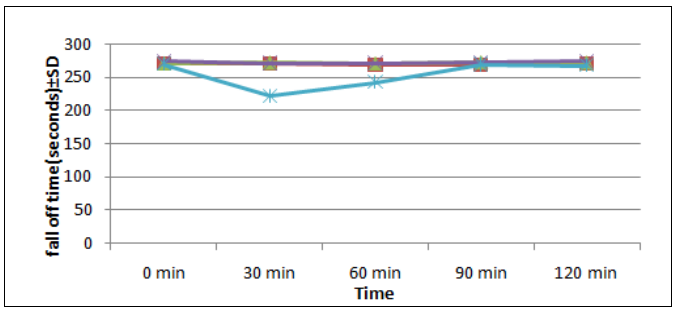

FIG 3: TREND OF 'FALL-OFF' (SECONDS) TIME IN TEST GROUPS AS COMPARED TO CONTROL AND STANDARD ON ROTAROD. Values are mean ± SD of fall-off time (seconds). NS (control); Trandolapril; Nimodipine; Diazepam.

DISCUSSION: The number of visits decreased in both the test groups showing an anxiolytic effect for trandolapril and nimodipine, but the effect was lower than the standard drug diazepam. It is already well known that diazepam produces GABA facilitatory effect on GABA receptors, thereby producing anxiolysis [26]. There are various proposed mechanisms through which ACEI and CCB could produce anxiolysis. There are receptors for binding to angiotensin II present in the amygdala which is considered to mediate fear and anxiety. ACE antagonist trandolapril crosses the blood-brain barrier and block the formation of angiotensin II and thus prevent excess output from the amygdala circuits.

The other reason for the anti-anxiety effect may also be due to the role of ACE antagonist over the benzodiazepine/GABA system. Previous studies showed that there occurs higher angiotensin release and decreased benzodiazepine/GABA release in an anxiety state [27]. Some evidence suggests the role of paraventricular nuclei (PVN) in the brain to regulate autonomic functions through Ang II and attenuation of the GABA system leads to a higher concentration of angiotensin II which further excites PVN and augments sympathetic outflow. Therefore, it can be concluded that conditions like stress and hypertension up-regulate RAAS in PVN responsible for autonomic hyperactivity [27]. ACEI prevents the excess release of angiotensin II and decreased NOX-derived oxidative stress in the CNS [7].

The anxiolytic effect of nimodipine may be probably due to its ability to cross the blood-brain barrier and getting concentrated in the limbic system of the brain, which is formed by the hippocampus and amygdala. Some studies have revealed the presence of dihydropyridine binding sites in the amygdala, which makes it responsive to nimodipine and other dihydropyridines [28]. Another important mechanism attributed may be that calcium ion is involved in the release of many neurotransmitters like serotonin, acetylcholine, noradrenaline, and dopamine. However, excess release of these is implicated in the diseased state, which is effectively controlled by using calcium channel blocker [29]. Thus both trandolapril and nimodipine have shown significant anxiolytic activity, but this effect was without impairing motor coordination as both the test drugs did not impair fall-off time on the rotarod test. This was in contrast to diazepam, which also has shown skeletal muscle relaxant property and motor incoordination at anxiolytic dose **Fig. 3**.

Trandolapril has shown a decline in the period of immobility and percentage change from baseline on days 10, 20, 30 as compared with baseline (day 1), with the significant effect seen on day 30 ($p < 0.01$), while this decline was significant on both days 20 and 30 ($p < 0.01$) for the standard drug imipramine. The decrease in the period of immobility holds good predictive value for drugs having antidepressant activity. The findings in our study indicate that trandolapril, an angiotensin-converting enzyme inhibitor, possesses anti-depressant activity. There are various factors involved in the pathophysiology of depression. The deficiency of neurotransmitters such as serotonin and noradrenaline has been implicated as one of the important factors. Other factors are inflammation, changes in the HPA axis, alteration in neuroplasticity and neurogenesis, and oxidative stress [30, 31].

The mechanism of antidepressant activity of imipramine is proposed to be due to the prevention of reuptake of noradrenaline and serotonin [32]. Therefore, the decrease in the period of immobility in the forced swim test seems to be due to an increase in the availability of these neurotransmitters in the synapse. Experimental data from previous studies also revealed that antidepressant drugs via post-receptor action, show antagonism to the action of angiotensin II. Therefore drugs that antagonize Angiotensin II namely ACEI and ARB's may potentially show antidepressant action [33]. The possible mechanism of action of trandolapril could be by being highly lipophilic has good penetration through blood-brain barrier thereby blocking excess activation of RAAS especially in the brain, leading to the prevention of oxidative stress thereby maintaining the balance between scavenging system and reactive oxygen species and prevention neuroinflammation 7. Angiotensin II is suggested to have anti-opioid action as the action of captopril has been found to be reversed with naloxone [33,] thus strengthening this notion. There is evidence found that reveals dysregulation of the endogenous opioid system in

major depressive disorders [34]. Therefore the antidepressant action of trandolapril may be due to an increase in the level of endogenous opioids. Hyperactivity of the hypothalamic-pituitary-adrenal axis and increased cortisol levels owing to impaired feedback mechanism has been attributed as a cause of depression. Restoration of these derangements has been found with captopril in hypertensive patients and quadrated with its anti-depressant property. Trandolapril may also, by a similar mechanism considered to have produced anti-depressant effect [35]. Similarly, the probable mechanism for the action of nimodipine could also be by prevention of neuroinflammation [36]. A study by Kamasak and Adnan (2019) had revealed that nimodipine has an antioxidant property that may have contributed in reducing oxidative stress [37].

CONCLUSION: Therefore, it can be concluded that trandolapril and nimodipine have a beneficial role in treating anxiety and depression without affecting motor coordination at presently used doses. However, more studies are required by using trandolapril and nimodipine in more numbers of animal models and using more number of animals. There is also a need of further confirmation and strengthening of these results by measuring various biochemical parameters at various time intervals. If the above findings are extrapolated in humans and prove efficacious, trandolapril can be a good option for treatment of depression in hypertensive patients owing to its dual property with the advantage of the decrease in pill load and avoiding the need of anti-depressants which has serious side effects, thus improving adherence and preventing polypharmacy.

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CONFLICTS OF INTEREST: None declared

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