International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 8, Issue 6, 2016

Original Article

# EVALUATION OF ANTIANXIETY, ANTIDEPRESSANT AND SEDATIVE EFFECTS OF NIMODIPINE IN SWISS ALBINO MICE

**HEMANT TANWANI*[1], PREM NYATI[2], SHUBHAM ATAL[1], RITESH CHURIHAR[1]**

[1]Department of Pharmacology, M. G. M. Medical College, A. B. Road. Indore (M. P), India, [2]Department of Pharmacology, Index Medical College, Khudel, Indore (M. P), India
Email: dr.riteshchurihar@gmail.com

*Received: 07 Mar 2016 Revised and Accepted: 20 Apr 2016*

**ABSTRACT**

**Objective**: Study of Nimodipine, a calcium channel blocker was done on experiments involving tail suspension test (TST), elevated plus maze (EPM) test and Phenobarbitone induced sleeping time in Swiss albino mice.

**Methods:** Nimodipine was given by intraperitoneal (i. p.) route in the dose of 2.5 & 5 mg/kg body wt respectively in albino mice of either sex (n=6) and effects were evaluated on (i) TST for antidepressant activity (ii) EPM for anti-anxiety and (iii) Loss of righting reflex for hypnotic activity and results were compared with the standard drugs like sertraline, diazepam and phenobarbitone respectively. Statistical analysis was done by ANOVA followed by Post hoc Tukey's test using SPSS v.20.0 software.

**Results**: Nimodipine at a dose of 2.5 mg/kg has shown moderate anti-anxiety and antidepressant activities compared to control with no changes in the activity of acute sertraline; however, the antidepressant activity of subacute sertraline (14 d treatment) was summed up by 2.5 mg/kg dose without any hypnosis. While at higher doses of 5 mg/kg depression, behavior (prolonged time of immobilization on TST) and sedation (prolonged phenobarbitone induced sleep time) were seen.

**Conclusion**: Nimodipine has shown moderate antidepressant and anti-anxiety activities at low doses and can be used as add-on therapy to routine drugs with least of peripheral side effects.

**Keywords**: Nimodipine, Diazepam, Sertraline, Elevated plus maze (EPM), Tail suspension test (TST) and righting reflex



## INTRODUCTION

Depression and morbid anxiety are the most common type of neurotic disorders which have affected the productivity of nations worldwide in terms of economic and manpower loss. Depression is characterized by severe negative and nihilistic thoughts (life is not worth living), the intense sadness of mood, loss of interest in routine work, low or high appetite, insomnia and severe suicidal tendency. Similarly, anxiety neurosis is accompanied by autonomic overactivity leading to tachycardia, tremors, sweating, and loss of confidence, etc. for work. These symptoms are dependent upon massive release of neurotransmitters like norepinephrine, dopamine, and glutamate. They possibly include neurotensin and neuro kinins too. The activity of most of above neurotransmitters is largely dependent upon release from the presynaptic terminals of neurons and ultimately intracellular calcium ion concentration built up through voltage-gated slow calcium channels [1]. Hence, calcium blockers in all probability must have a vital role to inhibit the release of the above neurotransmitters in the brain to control the symptoms [2].

Current therapy for the above disorders is by the use of antidepressants of different types most common of which include Tricyclic Antidepressants (TCADs), Selective Serotonin Reuptake Inhibitors (SSRI) and sedatives as add-on therapy. TCADs like imipramine are associated with anticholinergic side effects and drug dependence while SSRI ones are having side effects of initial anxiety, the long onset of action, nausea, dysorganesmia and the rarely serotonin syndrome. Hence, due to the side effect profile of current drugs search for a better drug will be worth trying which is relatively safe and free from major side effects.

Further, the neurotransmitter theory [3] for most of above neurotic disorders involves either excess release of excitatory neuro-transmitters for an episode of morbid anxiety while same when depleted will cause up-regulation of adrenergic receptors in CNS with depression features. Sudden desensitization of beta receptors or role of some unknown inhibitory neurotransmitters (yet an unexplored area) can also be proposed for the sudden intense sadness or extreme low fee. Similarly, depression periods are associated with low levels of serotonin or norepinephrine with high levels of dopamine [4] which may be responsible for the impulsive behavior in the form of aggression and self-harm, even to the extent of suicidal attempts. Further, there may also be an imbalance of excitatory and inhibitory transmitters as evidenced by the use of benzodiazepine which act by enhanced activity of GABA (a major inhibitory neurotransmitter in brain [5-7]. Buspirone due to its presynaptic $5HT_{1A}$ agonistic actions inhibits the release of above neurotransmitters, but it is a slow acting drug, requiring about 6-8 wks to produce beneficial effects. Propranolol is mainly used for the control of peripheral manifestations of anxiety like tachycardia and tremors, but on the long term it itself produces depression. All above drugs are associated with marked side effects.

Examples of neurotic disorders include anxiety neurosis, obsessive compulsive disorder (O. C. D), hysteria, social phobias, post-traumatic stress disorder (P. T. S. D) and endogenous depression, etc.

Currently, used calcium channel blockers include nifedipine, amlodipine, nicardipine, diltiazem, verapamil, nimodipine, and nicardipine, etc. Calcium channel blockers have been used for various cardiovascular disorders like hypertension, myocardial ischemia, cardiac arrhythmias and peripheral vascular disease, etc [8]. Out of these nimodipine has shown beneficial effects in neurological disorders like cerebral stroke and migraine without any significant adverse effects on the cardiovascular system. Due to the high lipid solubility and relative safety profile, it created our interest to explore its potential use in neurotic disorders [8, 9].

Calcium channel blockers are working via voltage-gated calcium channels of various types [10, 11] which mainly include L, N, P/Q, R and T-subtypes. Out of these L-type of channels is mainly working in blood vessels and heart. N-type is working in neurons and is also responsible for the release of few endocrine hormones while T-type is mainly involved in neuronal activity. The functions of P/Q and R

subtypes are still undefined. However blockers are nonspecific in relation to the type of channel being involved. If calcium is responsible for the release of multiple neurotransmitters such as norepinephrine, glutamate, dopamine, etc. in the CNS, then blockers in all possibilities must have a vital role in prevention and treatment of various diseases associated with an excess of these transmitters like morbid anxiety and other psychiatric depression [12]. Nimodipine due to high lipid solubility, cerebral penetration and blocking action on slow calcium channels can be a potential target to treat neurotic disorders. At low doses, it has been shown to inhibit release of norepinephrine and dopamine. This may explain its anti-anxiety effects. Only very limited studies have been performed to evaluate above activities and prove its utility. Hence, more research work is worth doing [13].

## MATERIALS AND METHODS

### Drugs

Tab Serta (Sertraline 50 mg Intas pharma India), Tab Compose (Diazepam 10 mg Ranbaxy Pharmaceuticals, India) and Tab Nimodip (Nimodipine 30 mg-SUV Pharmaceuticals, India). In all the experiments drugs were given by intraperitoneal route except subacute intervention where sertraline was given by oral route. Drugs were purchased from the market through their authorized representatives.

### Animals

Swiss albino mice (20-30 g) of either sex were procured from the central animal house, M. G. M. Medical College, Indore and acclimatized for a period of 7 d at room temperature (25±2 °C) and 50±15% relative humidity. They were housed in a standard cage and maintained on standard pellets and water ad libitum. The animals were used as per standard animal handling guidelines. The study was carried out in the Department of Pharmacology, M. G. M. Medical College, Indore (M. P.) India. The study protocol was approved by the Institutional Animal Ethics Committee (IAEC) registered with CPCSEA (Reg. No. 709) on 26-8-2014.

### Methodology

### Anti-anxiety activity on EPM

### Principle

EPM [14, 15] is the simplest method to evaluate the anti-anxiety property of various drugs. Exposure of the animals to novel maze alley evokes an approach-avoidance conflict which is stronger in the open arms as compared to enclosed space. Rodents have a version for high and open space and prefer enclosed arms and therefore spend a greater period of time in enclosed arms [16, 17]. When the animals enter open arm, they freeze, become immobile, defecate and show fear like movements. The plasma cortisol level is also reported to be increased, as a true reflection of anxiety.

### Equipment

The elevated plus-maze was introduced by Pellow [18] for rats and by Listetil for mice respectively. The EPM apparatus consisted of two open arms (30 x 5 cm) and two closed arms (30 x 5 x 20 cm) emanating from a common central platform (5 x 5 cm). The two parts of identical arms are opposite (at a right angle) to each other. The entire apparatus is elevated to a height of 50 cm above the floor level. The latest y-maze apparatus consists of three arms where all the arms are closed; one arm is illuminated while two arms are non-illuminated, but the current is passed at the floor. Each arm entry is compared before and after giving the test drug. Entries in each arm are counted by electronic counters.

### Method

Total no of animals 24 were divided into four groups (n=6). Group I-Distilled water (0.2 ml), Group II-Diazepam 2 mg/kg, Group III-Nimodipine 2.5 mg/kg, Group IV-Nimodipine 2.5 mg/kg and diazepam 2 mg/kg combination. The animals were exposed to house caging for ten days with adequate food, water, with proper day and night 12 hourly cycles. Proper acclimatization of the animals was done for the place and handlers where the experiment was to be performed. On the eleventh day after the adequate adaptation, mice received the treatment at 11.30 am a half hour before the start of the session between 12 noon-1pm. At the beginning of the session, a mouse was placed at the center of the maze, its head facing the closed arms and total entries in different arms was recorded. An entry was defined as the presence of all four paws in the arm. The EPM was carefully wiped, with 10 % of ethanol after each trial, to eliminate the possible bias due to the order of the previous animal. The entries were recorded automatically by the electronic recorder in different arms for ten minutes.

### Antidepressant activity

### Method

TST is also a simple apparatus to study the antidepressant activity of different drugs. Animals are suspended inverted on the wire by adhesive tape fixed to the tail. The height of the wire is 50 cm above the study table. Mobility is recorded for 300 s. There are periods of alternate mobility and immobility. Antidepressant activity is reflected by a decrease in the time of immobilization when the rodents are suspended inverted from their tail. Both acute and sub-acute (15 d treatment) studies were carried out. Here 24 mice were divided into four groups of (n=6) and treated as follows-Group I-Distilled water (0.2 ml). Group II-Sertraline 2 mg/kg. Group III-Nimodipine 2.5 mg/kg Group IV-Nimodipine 5 mg/kg and Group V-Nimodipine 2.5 mg/kg and Sertraline 2 mg/kg. Groups were similar in both the acute and subacute studies (sertraline which was given orally for 15 d).

### Effects on duration of sleep

### Method

The hypnotic effect is seen on phenobarbitone induced sleeping time**.** The loss of writing reflex is considered as a time of onset of sleep while the recovery is calculated by regaining and maintaining of the correct posture. Total animals 24 were divided into four groups of (n=6) each and treated as follows. Group I-Distilled water 0.2 ml. Group-II-Phenobarbitone 35 mg/kg, Group III-Nimodipine 5 mg/kg and Group IV-combination of Nimodipine and Phenobarbitone in above doses.

## RESULTS

(1) Nimodipine at a dose of 2.5 mg/kg body wt has shown a moderate anti-anxiety effect. The percentage ratio of entry into open arms/closed arms was significantly higher as compared to the control even after acclimatization for 10 d implying moderate anti-anxiety effects. The ratio was further increased when it was combined with diazepam, having nearly addictive actions. However same cannot be said with confidence about anti-anxiety activity at 5 mg/kg since (i) total entries were reduced (ii) animals were sluggish on plus-maze due to CNS depression and (iii) TST has shown depression due to prolongation time of immobilization (still anti-anxiety effects can be expected due to calming property). (table 1).

**Table 1: Effects of nimodipine on elevated plus maze test**

| Groups | Dose (i. p.) mg/kg | Mean ratio of open/closed arms in %±SEM | Inference |
|---|---|---|---|
| Control | 0.2 ml Distilled water | 32.49±2.02 | |
| Diazepam | 2 | 51.50±1.240[a,b,] | Known anxiolytic. |
| Nimodipine | 2.5 | 44.9±1.029[a,b,c,] | May have anti-anxiety property. |
| Nimodipine+diazepam | 2.5+2 | 58.60±0.97[a,c] | Improved anti anxiety effect of diazepam. |

Result-ANOVA with multiple tukey's tests. df = 3,12, n=5, [a]p<0.05 as compared to control, [b]p<0.05as compared combination of diazepam and nimodipine, [c]p<0.05as compared to diazepam, (2) Antidepressant activity was also seen at a dose of 2.5 mg/kg, which was changed to depressive behavior at high dose of 5 mg/kg as indicated by prolonged time of immobilization on TST (table2-3).

**Table 2: Effects of single dose of nimodipine on tail suspension test**

| Gross up | Dose (i. p) mg/kg | Time of immobilization (out of 300 s) (mean±SEM) | Inference |
|---|---|---|---|
| Control Distilled water | 0.2 ml | 209.2±3.11 | Control |
| Sertraline | 5 | 204.6±6.161 | No change on acute doses. |
| Nimodipine | 2.5 | 188.00±2.23[a] | Anti-depressant activity. |
| Nimodipine | 5 | 228.80±5.82[a.] | Significant depressant activity. |
| Nimodipine+sertraline | 2.5+5 | 200.80±3.00 | The antidepressant action of acute nimodipine, but no antidepressant activity of acute sertraline. |
| Nimodipine+sertraline | 5+5 | 224.40±4.45[a] | The depressant activity of higher dose of nimodipine having opposing effects on those of acute sertraline. |

Results-ANOVA with multiple Tukey's tests, d f= 4, 24, [a]p<0.05as compared to control.

**Table 3: Effects of nimodipine on subacute (14 d) sertraline on tail suspension test**

| Group | Dose (i. p) mg/kg | Time of Immobilization (out of 300 s) (mean±SEM) | Inference |
|---|---|---|---|
| Control Distilled water. | 0.2 ml | 209±7.88 | - |
| Sertraline | 5 | 98.4±8.95[a] | Antidepressant |
| Nimodipine | 2.5 | 180.8±8.79 [a,b] | Antidepressant but less than sertraline. |
| Nimodipine+sertraline | 2.5+5 | 84.8±3.49 [a,c] | Slight improvement in anti-depressant activity of sertraline. |

Result-ANOVA test was applied. p-value of the study= 0.000 (among different groups) d f=3,17., [a]p<0.05 as compared to control. [b]p<0.05 as compared to sertraline, [c]p<0.05 as compared to nimodipine 2.5 mg/kg.

Effect of nimodipine on subacute sertraline administration is of potentiation of the antidepressant activity of sertraline. Nimodipine itself has antidepressant activity at a dose of 2.5 mg/kg though it is inferior to that of sertraline.

(3) There was no effect of 2.5 mg/kg of nimodipine, but at 5 mg/kg it significantly increased the duration of sleep produced by phenobarbitone (table-4). Similarly, nimodipine itself could not induce sleep in mice.

**Table 4: The effects of nimodipine on phenobarbitone induced sleeping time**

| Groups | Dose (n=6) mg/kg | Mean Duration of sleep in min.±SEM | Inference |
|---|---|---|---|
| Control Distilled water | 0.2 ml | _ | |
| Phenobarbitone | 35 | 70.8±1.77 [a,b] | Known sedative |
| Nimodipine | 2.5 | _ | No sedative action |
| Nimodipine+phenobarbitone | 35+2.5 | 76.4±2.315[a,b,c] | Nimodipine prolonged the action |

ANOVA with post hoc multiple Tukey's test applied. df= 3,16., [a]p-value<0.05 as compared to control., [b]p-value<0.05 as compared to nimodipine 2.5 mg/kg.

## DISCUSSION

### Antianxiety and antidepressant activity

Nimodipine may be an example of a drug having selective inhibition of release of multiple neurotransmitters at different doses. At a dose of 2.5 mg/kg, there may be net lowering of few excitatory neurotransmitters like norepinephrine, glutamate and tachykinins, etc. without modulation (inhibition) of serotonin to produce anti-anxiety and antidepressant behavior as compared to control group. There was no change on the activity of acute sertraline group, however on subacute intervention; it potentiated the antidepressant activity of sertraline. This could be due to the down-regulation of adrenergic receptors brought by standard drug over a period of 14 d. Further, we have to hypothesize about the role of multiple inhibitory transmitters (area to be yet explored and searched) which bring about sudden depression or down feeling of mood. There may be a block of above unknown neurotransmitters to show antidepressant activity.

The basis of anxiety and depression is currently believed to be due to a nice interaction between excitatory neurotransmitters like norepinephrine (NE) and glutamate v/s inhibitory transmitters like gamma amino butyric acid (GABA). A very good explanation has been given about anxiety [3]. During attacks of sudden anger either there is the excessive release of norepinephrine or probably dopamine too at the synaptic junction from presynaptic vesicles or there is up-regulation of beta receptors at postsynaptic neurons. Nimodipine by decreasing intracellular calcium load may be able to reduce the firing of neurons and thus may control the release of different involved transmitters to control symptoms. TCADs are working on pre and postsynaptic neurons, and they prevent reuptake of serotonin and norepinephrine with consequent down-regulation of beta and serotonin receptors over a period of time. SSRI drugs inhibit uptake of serotonin only. On long-term changes in the form of modifications on genes [19-21] and neuroplasticity [3] too have been postulated. Depression too is presently considered a neurodegenerative disorder due to constant release of glutamate during episodes of anxiety with associated neuronal toxicity. While an antidepressant group of drugs by lowering anxiety may reduce degeneration and improve gene related neuroplasticity over the course of therapy. We propose that nimodipine by lowering neurotransmitter turnover may prevent or reduce the rate of neuronal degeneration to some extent to help the patients in the long term. In addition to treatment of depression, low dose of antidepressant drugs are often required for treatment of anxiety symptoms too. The mechanism for the actions of antidepressants in anxiety possibly involves the presynaptic autoreceptors which by inhibitory actions decrease the release during episodes of severe anxiety or by postsynaptic actions cause down-regulation of adrenergic receptors.

The depression has been suggested due to up-regulation of adrenergic receptors with consequent secondary changes in neurons [3]. The clinical evidence for above observations has been depression caused due to constant use of beta blockers and adrenergic neuron blockers with up-regulation of adrenergic receptors leading to sadness and depressive mood. Though propranolol is used for acute treatment of anxiety tremors, it is mainly used for lowering the peripheral manifestations in acute morbid anxiety only.

Hence as soon as the severity of anxiety is controlled, propranolol is stopped, and the patient is shifted to various antidepressant drugs.

Nimodipine by slightly lowering blood pressure will also take care of peripheral manifestations of anxiety and depression. Further, the advantage of nimodipine over propranolol may be due to its additional antidepressant property even at sub-therapeutic doses. Similarly, an advantage over diazepam may be in the form of no addiction and drowsiness. Similarly, the edge over buspirone may be due to its immediate onset. The biological sites in the brain for anxiety are organs like the hippocampus and prefrontal cortex (PFC) [22, 23]. Electroconvulsive therapy (ECT) has been shown to cause a massive release of amine transmitters with concomitant downregulation of receptors. This can explain ECT treatment for major depression. Like beta blockers, which are the only antagonist to catecholamines in the periphery, our investigational drug nimodipine in low doses can probably decrease the release of norepinephrine, glutamate and yet unknown multiple excitatory neurotransmitters in CNS to relieve anxiety. They have simply calming effect without the drowsiness which may be very advantageous in heavy machinery workers or heavy motor drivers on the road. Later expected depression will also be less since neurotransmitters will be stored in adequate amount in vesicles and constantly released in the synaptic cleft to elevate mood and also secondary to downregulation of serotonin and adrenergic receptors. Thus, our suggestions may favor for nimodipine for treating morbid anxiety with the advantage of no sedation in highly skilled persons, though it has been shown to prolong the sleeping time induced by phenobarbital. Our findings are matched to those of French study who have shown the anti-anxiety potential of nimodipine [24].

**Sedative property**

Further the animals were fully awake indicating no sedative effect (no calming property), but at higher dose of 5 mg/kg of nimodipine it was found to produce moderate CNS sedation shown by lower spontaneous motor activity, significantly reduced total entries in all the arms (though the proportion of entries in open arms was still higher as compared to closed arms-still doubtful antianxiety effects maintained) and also by prolonging sleep time. This could be a calming effect due to further inhibition of the release of some more excitatory neurotransmitters. At the same dose of 5 mg/kg, it showed depression activity by prolonged time of immobilization. This could be due to the simultaneous inhibition of serotonin release too from nerve endings. The depression was also seen with the certain group combination, and it was able to reverse the antidepressant activity of certain. The effect may be due to complete block of serotonin, in spite of down-regulation of adrenergic receptors. The Same dose probably also inhibits dopamine, which can further explain the antipsychotic activity (along with inhibition of serotonin release too) which is seen at doses of 5 mg-10 mg/kg dose in mice [25].

## CONCLUSION

The drug nimodipine has shown promising results for its antidepressant, anti-anxiety and calming activities in preclinical studies in albino mice. The drug can be tried as adding on therapy with routine drugs for the above disorders without significant side effects on the human system. However, further clinical trials have to be conducted to establish its utility. The half-life of nimodipine given by intraperitoneal route is 1.51 h while oral bioavailability is only10 % which may explain the inconstant results obtained till date in previous studies. If sustained release preparation is formulated for use by an oral/parenteral route which can maintain desired concentrations, it may be an additional tool for the treatment of neurotic disorders.

## ACKNOWLEDGEMENT

We are thankful to the dean and staff of the department of pharmacology for the co-operation and help required during the experimental work.

## CONFLICT OF INTERESTS

Declared none

## REFERENCES

1. Rang HP, Dale MM. Textbook of pharmacology. 7thEdition. Churchill Livingstone Elsevier, London [UK]; 2012. p. 265-85.
2. Sharma HL, Sharma KK. Principles of pharmacology. 2ndEdition. Paras Publications, Hyderabad India; 2012.
3. Gulley LR, Nemeroff CB. Biological basis of anxiety depression. J Clin Psychiatry 1993;54 Suppl I:16-9.
4. Dongju. http://www.ncbi.nlm.nih.gov/pubmed/?term=Seo%20D%5Bauth%5D S Patrick CJ, Kennealy PJ. http:// www.ncbi.nlm.nih.gov/ pubmed/?term=Kennealy% 20PJ%5Bauth%5D>Role of Serotonin and Dopamine System Interactions in the Neurobiology of Impulsive Aggression and its comorbidity with other clinical disorders. Aggress Violent Behav 2008;13:383-95.
5. Baldessarani RJ, Tarzai FI. The pharmacological basis of therapeutics. 12thEdition. McGraw-Hill New York; 2011. p. 461-80.
6. James BJ, Sadock VA. Schizophrenia in the synopsis of psychiatry. 10thedition. Behavioral Sciences/clinical psychiatry. Lippincott Williams and Wilkins [Philadelphia]; 2007.
7. Nyati P. Pharmacology SEED. 2nd edition. Global media, India; 2011.
8. Shrivastava SK. A complete textbook of medical pharmacology. 1st edition. The avichal publishing company, India; 2012.
9. Lacinova L. http://www.ncbi.nlm.nih.gov/Pubmed/? term= Lacinov%C3%A1%20L%5BAuthor%5D&cauthor=true&cauthor_uid=16096350>. Voltage-dependent calcium channels. Gen Physiol Biophys 2005;24 Suppl 1:1-78.
10. Schwatz A. Molecular and cellular effects of calcium channel blockers. Am J Cardiol 1992;70:6F-8F.
11. Tsien RW, Lipscombe D, Madison, Bley DV. Multiple types of neuronal calcium channels & their selective modulation. Trends Neurosci 1988;24 Suppl 1:431-8.
12. Goodnick PJ. The use of nimodipine in the treatment of mood disorders. Bipolar Disord 2000;2:165-73.
13. Rataboli P, Garg A, Muchandi K. Antidepressant effect of low dose nimodipine in the mouse behavior despair model. Internet J Pharmacol 2009;8:1.
14. Vogel HG. Antidepressant activity on the elevated plus maze in drug discovery and evaluation pharmacological assays. 2nd Edition. Springer-Verlag, Berlin [Heidelberg]; 2002.
15. Kaul PN, Kulkarni SK. New drug metabolism inhibitor of marine origin. J Pharm Sci 1979;67:1293-6.
16. Pellow S, Johnston AL, File SE. Selective agonists and antagonists for 5-hydroxytryptamine receptor subtypes and interaction with yohimbine and FG 7142 using the elevated plus-maze test in the rat. J Pharmacol 1987;39:917-28.
17. Sharma AC, Kulkarni SK. Evaluation of learning and memory mechanisms employing elevated plus-maze in rats and mice. Prog Neuro-Psychopharmacol Biol Psychiatry 1992;16:117-25.
18. Pellow S, Chopin P, File SE, Briley M. Validation of open: closed arm entries in an elevated plus-maze as a measure of anxiety in the rat. J Neurosci Methods 1985;14:149-67.
19. Ongür D, Heckers<http://www.pubfacts.com/author/ Stephan+ Heckers>S: "A role for glia in the action of electroconvulsive therapy". Harv Rev Psychiatry 2004;12 Suppl 5:253-62.
20. Duman RS. Depression: a case of neuronal life and death? Biol Psychiatry 2004;56 Suppl 3:140-5.
21. Duman CH<http://www.ncbi.nlm.nih.gov/Pubmed/? term= Duman%20CH%5BAuthor%5D&cauthor=true&cauthor_uid=16594263>, Duman RS<http://www. ncbi.nlm. nih.gov/ Pubmed/?term=Duman%20RS%5BAuthor%5D&cauthor=true&cauthor_uid=16594263>: Neurobiology and treatment of anxiety. Signal transduction and neural plasticity. Handy Exp Pharmacol 2005;169:305-34.
22. Warner-Schmidt JL, Duman RS. Hippocampal neurogenesis opposing effects of stress and antidepressant treatment. Hippocampus 2006;16 Suppl 3:239-49.
23. Less S. The relationship of anxiety to depression. Am J Psychother 1982;36:332-49.
24. Biala Gryzyna, Kruk Marta. Polish academy of sciences. Pologne 2007;59:636-44.
25. Tanwani H, Pandey SP, Atal S, Nyati P. Evaluation of the anti-psychotic effect of nimodipine using methylphenidate as a model to induce psychosis in albino mice. Int J Basic Clin Pharmacol 2015;4:1047-53.