

Antidepressant effect of Ziprasidone in *wistar albino* rat by forced swimming test model

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Abstract

Background: Major depressive disorder is a common psychiatric condition and response conventional antidepressant drugs are sometimes unpredictable. Atypical antipsychotics by virtue of their pharmacodynamic profile show potential antidepressant effect. Newer antidepressants as monotherapy or as augmenting agent for current therapy are need of the day. Ziprasidone is an atypical antidepressant drug possesses potential antidepressant activity by virtue of its 5HT_{1A} agonistic activity and 5HT_{1D}, 5HT_{2A} and D₂ receptors antagonistic activity.

Method: Since its introduction in 1977 the forced swimming test model is still being used for evaluation of potential antidepressant molecule. 30 healthy male Wistar albino rat of 150-200 grams weight were divided in 3 groups with 10 rats in each. Group A was treated with 0.9% Normal Saline, Group B with Fluoxetine and Group C with Ziprasidone for 42 days. Forced Swimming test was done on day 0, 7, 14, 21, 28, 35 and 42 days.

Result: After 42 days of treatment both fluoxetine and ziprasidone shows significant antidepressant activity. In comparison to Normal saline both the drugs shows significant antidepressant activity. There is significant deference in antidepressant activity between Fluoxetine and Ziprasidone. Antidepressant activity of Fluoxetine started to appear from day 7 with p vale of 0.000 and of Ziprasidone started to appear from 14 days with p value of 0.000.

Conclusion: Ziprasidone as virtue of its diverse pharmacodynamic effect can be suitable candidate for clinical trials of MDD as monotherapy or as an augmenting agent of standard antidepressant therapy.

Keywords: Atypical antipsychotics, Depression, Antidepressant, Ziprasidone

1. Introduction

Major depressive disorder (MDD) is common in psychiatric practice wherein a patient presents with at least one of the two major symptoms, constant sadness or anhedonia, accompanied by at least five of these nine secondary symptoms for at least two weeks. The secondary symptoms include worthlessness, concentration difficulties, changes in diet, disturbed sleep patterns, decrease interest or pleasure, irritability, and change in activity, fatigue and suicidal tendency. It is differentiated from bipolar disorder by the absence of a manic or hypomanic episode. [1]

Although depression can occur at any age, adults 18 to 29 years of age experience the highest rates of major depression during any given year. Women are at increased risk of depression from early adolescence until their mid-50s, with a lifetime rate that is 1.5 to 3 times greater than for men.[2] Depressive disorders are common during adolescence, with co-morbid substance abuse, suicide attempts, and deaths occurring frequently in these patients.[3]

Depressive disorders and suicides tend to occur within families. For example, approximately 8% to 18% of patients with major depression have at least one first-degree relative (father, mother, brother, or sister) with a history of depression. [4] Monozygotic twins have a higher concordance rate (46%) than dizygotic siblings (20%). [5] Biochemical factors include decrease in level of neurotransmitters like nor-epinephrine and serotonin in the brain.[6] Crucial life events, particularly the death or loss of a loved one or an emotional trauma can precede the onset of depression.[7]

The past 2 decades have seen improvements in the screening, diagnosis, and treatment of MDD. Despite a large increase in the number of antidepressants, the pharmacotherapy of depression remains inadequate.[8] Although meaningful therapeutic effects are observed only after several weeks of treatment with existing antidepressants,[9] at least 40% of patients do not respond to antidepressant therapy.[10] Additionally, most of the currently available agents are associated

with frequent and persistent side effects, such as sedation, apathy and fatigue, sleep disturbances, cognitive impairments and sexual dysfunctions.

Antidepressant drugs, including the serotonin selective reuptake inhibitors (SSRI) and serotonin norepinephrine reuptake inhibitors (SNRIs) have gained wide acceptance, primarily because of their relative safety. However, expectations with regard to efficacy may be higher than reality in clinical practice. Given the relatively modest response and remission rates seen during monotherapy of MDD with all contemporary, first line antidepressants; there is urgent need to develop treatments which are both safer and more effective than those currently available.

In the past few years, some antipsychotics have gained FDA approval for add-on treatment in MDD, such as Aripiprazole, Quetiapine and Olanzapine. Ziprasidone is an atypical antipsychotic, acts by binding in high affinity to 5HT1A receptors, while it is antagonist to 5HT1D, 5HT2A and D2 receptors. Its pharmacological profile makes it a potential candidate for antidepressant study.[11, 12]

Keeping this in mind the current study is designed to evaluate potential antidepressant activity of atypical antipsychotic drug Ziprasidone and compare its effectiveness with standard antidepressant Fluoxetine (SSRI) in depressive animal model.

2. Material and Methods

Healthy male Wistar albino rats weighing between 150-200 grams were taken for the present study. The animals were kept in clean and dry cages, with 12 h: 12 h light-dark cycle at room temperature and humidity. They were acclimatized to the available housing condition and were fed with standard laboratory diet consisting of soaked black gram (Kala Chana) and water was given ad libitum. Arrangements were made to ensure regular cleaning of cages and disposal of excreta and urine. The whole experiment was conducted in accordance with ethical norms approved by Institutional Animal Ethics Committee (IAEC) Guidelines. Tab. fluoxetine: - (Floxin 20 mg tab) D.D. pharmaceuticals (P) Ltd. Jaipur and Tab. ziprasidone: - (Zipsydon 20 mg tab) Sun pharma Laboratories Ltd. East Sikkim were used. Control groups were treated with 0.9% Normal saline and 1% gum acacia. Dose of the drugs was calculated from the standard clinical human dose on the basis of surface area.^[13] Surface area ratio of 200g rat for 70 kg man is 0.018. Thus human dose of drug (for a 70 kg person) multiplied by 0.018 gives the value of that drug for 200g of rat.^[14] The entire experiment was carried out in postgraduate laboratory "Department of Pharmacology and therapeutics Rajendra Institute of Medical Sciences, Ranchi" and test was done between 9:00 am to 2:00 pm.

2.1 Inclusion criteria:

1. All the animals used for the study were healthy and active in their cage.
2. Animals were male Wistar albino rats.
3. Weight of the animal used was 150-200grams.

2.2 Exclusion criteria

1. Diseased and inactive rats were excluded from study.
2. Female rats were excluded.
3. Rats with weight less than 150grams and above 200grams were excluded.

Experimental animals were divided into three groups with ten animals in each group. The rats were kept in three adequately roomed animal cages. All the cages were appropriately labelled. Animals in each cage were also labelled separately and colour coded with the help of permanent marker. They were evaluated for antidepressant activity using Forced swimming test (FST) animal model. Animals were brought to the experiment room 1 hour before beginning of the experiment. The food and water was removed for the duration of test. Animals were weighed and appropriate dose of drug was given orally to different groups. The experiment was conducted 1 hour after oral administration of the drug. Sufficient gap was maintained for giving the drug so that all the animals are tested after 1 hour of the oral administration of the drug.

2.3 Details of groups were as follows

| Groups | No of rats | Drugs |
|--------|------------|-------------|
| A | 10 | 0.9% NS |
| B | 10 | Fluoxetine |
| C | 10 | Ziprasidone |

2.4 Forced swimming test:

The forced swimming model to test for antidepressant activity was developed by Porsolt *et al* during 1977 - 1978.[15, 16] The model used in the present study was similar to the original method described. The animals were forced to swim in a plastic cylinder measuring 30 X 30 cm containing water at room temperature to a depth of 20 cm. After an initial 2 minute period of vigorous activity, each animal assumed a typical immobile posture. The rat was considered

immobile when it remained floating in the water without struggling, making only minimum movements of its limbs necessary to keep its head above water. The rats were subjected to a 15-min training session under similar conditions, 24 hour before the test. The total duration of immobility was recorded during next 4 minutes of total 6 minute test. The changes in immobility duration were studied after administering drugs in separate group of animals. Following swimming sessions, the rats were dried with towel and placed in a cylinder heated under 60 W bulb. The animals were dried under heated cylinder for 15 minutes before returning to the home cages.

2.5 Statistical analysis: -

Statistical analysis of data was carried out by employing analysis of variance (ANOVA) test followed by Tukey's HSD (honestly significant difference) test for post-hoc analysis of significant overall differences. Confidence interval 95% and p - value < 0.05 was taken significant.

3. Results

The following data were obtained in all groups of Rat after administering them respective drugs for a period of 42 days. The immobility time (in seconds) were recorded on 0, 7th, 14th, 21st, 28th, 35th and 42nd day of treatment by Forced swimming test (FST) models.

Table 1: showing change of immobility time (in seconds) by FST on 0, 7th, 14th, 21st, 28th, 35th and 42nd day in all groups. Data are as expressed mean \pm standard deviation

| | 0 day | 7 day | 14 day | 21 day | 28 day | 35 day | 42 day |
|-------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Gr. A | 48.0 \pm 3.97 | 48.1 \pm 2.02 | 47.8 \pm 2.97 | 47.7 \pm 4.85 | 47.8 \pm 3.93 | 46.9 \pm 3.07 | 47.3 \pm 3.09 |
| Gr. B | 48.3 \pm 2.67 | 46.3 \pm 2.40 | 43.4 \pm 2.67 | 40.3 \pm 2.31 | 36.7 \pm 3.09 | 33.1 \pm 2.76 | 32.1 \pm 2.64 |
| Gr. C | 48.2 \pm 1.93 | 46.4 \pm 1.77 | 44.1 \pm 2.13 | 42.7 \pm 1.95 | 40.6 \pm 1.84 | 39.1 \pm 1.93 | 37.0 \pm 2.00 |

Table 2: Showing the statistical analysis among all the groups

| Day | 0 | 7 | 14 | 21 | 28 | 35 | 42 |
|--------------------------|-------|--------|--------|--------|--------|--------|--------|
| Mean difference (Gr A-B) | 0.300 | 5.600 | 7.700 | 9.600 | 12.900 | 14.200 | 16.100 |
| p value | 0.995 | 0.000* | 0.000* | 0.000* | 0.000* | 0.000* | 0.000* |
| Mean difference (Gr A-C) | 0.200 | 1.700 | 4.200 | 5.000 | 7.200 | 7.800 | 10.300 |
| p value | 0.988 | 0.173 | 0.000* | 0.003* | 0.000* | 0.000* | 0.000* |
| Mean difference (Gr B-C) | 0.100 | 3.900 | 3.500 | 4.600 | 5.700 | 6.400 | 5.000 |
| p value | 0.997 | 0.000* | 0.004* | 0.006* | 0.000* | 0.000* | 0.000* |

Figure 1: Showing sequential change in Immobility time (in sec.) by Forced Swimming Test in All the Groups throughout the study period.

Comparison of Forced Swimming Test between all groups Throughout the study period

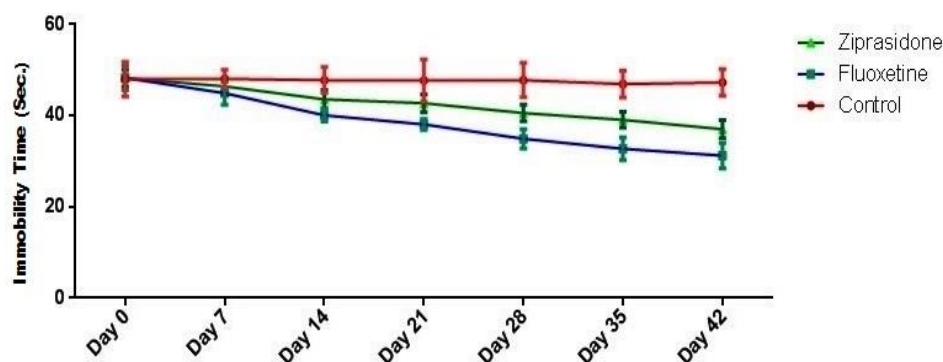
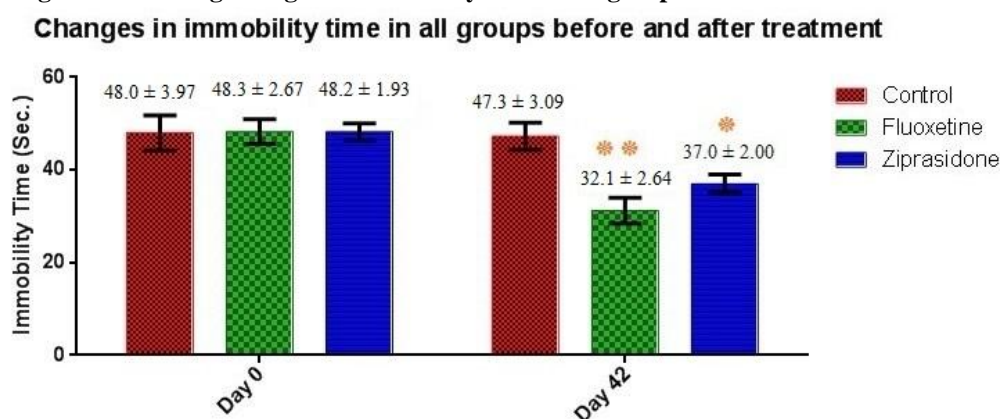


Figure 2: Showing changes in immobility time in all groups before and after treatment.

4. Discussion

The results following these tests have been compared with that of standard antidepressant drug fluoxetine, and with 0.9% Normal Saline taken as control. A forced Swimming Test model is widely used to screen newer and potential antidepressant drugs. There is a significant correlation between the efficacy of antidepressants in forced swimming tests and clinical effectiveness of the drugs.[17] The test is quite sensitive and relatively specific to all major classes of antidepressants like tricyclics, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors and atypical antidepressants. [18]

The results in the forced swimming test were assessed by duration of immobility in last 4 minutes of total 6 minute test duration. Antidepressant activity is indicated by the reduction in the duration of immobility i.e. lesser the duration more the efficacy. The results have been expressed as mean \pm standard deviation of duration of immobility in seconds during 6 minute period. Table 1 shows the results of Forced Swimming test (FST) over time in Group A (Control, treated with 0.9% Normal Saline), Group B (treated with standard antidepressant Fluoxetine) and Group C (treated with Ziprasidone). Table 2 shows the results of ANOVA followed by post hoc Tukey's test among the groups and within the groups for FST. Figure 1 shows the group wise changes in immobility time (in seconds) by FST for the entire duration of the study and results from table 2 concludes that all the drugs, i.e. – fluoxetine and ziprasidone have significant antidepressant activity. Figure 2 shows Fluoxetine showed significantly superior antidepressant activity in comparison to ziprasidone.

A rapidly growing body of data indicates that dysfunction in serotonergic activity may be involved in the pathophysiology of depression [19].

Fluoxetine is a known antidepressant acts by inhibiting the uptake of serotonin by the neurons in the brain and enhances the serotonin neurotransmission through action on 5HT_{2A} and 5HT_{2C} receptors. [20] There is persuasive evidence for the antidepressant efficacy of some second generation antipsychotics (SGA) / atypical antipsychotics in clinical trials [21], as well as for the increase of their prescription in the treatment of patients with major depressive disorders (MDD). [22] Moreover, the use of SGAs in MDD is anticipated to grow and continue to be one of the leading augmentation strategies. [21] In the past few years, US FDA has given approval to some antipsychotics as add-on treatment in MDD, such as Aripiprazole, Quetiapine and Olanzapine.

In the case of the 5HT_{1D} terminal autoreceptors, occupancy of this receptor causes a blockade of serotonin release. On the other hand, drugs that block the 5HT_{1D} autoreceptors can promote serotonin release, and this could hypothetically result in antidepressant actions. At the same time stimulation of 5HT_{1A} receptors and blocking of 5HT_{2A} receptors, both causes increase release dopamine in the frontal cortex. This has led to speculation that those atypical antipsychotics with 5HT_{1A} partial agonist actions that are proven antidepressants (such as quetiapine and aripiprazole) may be working in part through this mechanism, and that other atypical antipsychotics with 5HT_{1A} partial agonist actions are also potential antidepressants (such as ziprasidone, lurasidone, iloperidone, and others). [23]

All known first generation antipsychotics are blockers of dopamine D₂ receptors, although at different degree of affinity. Increased levels of D₂ receptor occupancy for tight dopamine D₂ receptor blockers haloperidol and risperidone were associated with negative emotional experience, in contrast with loose D₂ receptor blocker olanzapine, based on theoretical prediction of D₂ occupancy. [24] Given its effects of low D₂ receptor occupancy, antidepressant efficacy might be expected in ziprasidone. [25, 26]

Pharmacological profile of Ziprasidone has high affinity towards 5HT_{1A} receptors and shows agonistic property along with, low affinity and antagonist action on 5HT_{1D}, 5HT_{2A} and D₂ receptors. [27, 28]

Study by R. Rajkumar *et al* in 2009 showed that Ziprasidone has antidepressant efficacy in a 1-m – chlorophenyl piperazine induced animal model of depression. [29]

Results of our study also show that ziprasidone has potential antidepressant activity in terms of improvement in the immobility time in depressive model of forced swimming test in rats.

Antidepressants are first-line treatment for patients with major depressive disorder (MDD). Commonly used antidepressants directly inhibit the reuptake of at least one monoamine neurotransmitter in the brain (serotonin, dopamine or noradrenalin), or block their degradation. Despite the availability of large number of antidepressants of different classes, significant portion of patients do not achieve remission [30] and treatment resistance is also common. [31] Augmentation of standard antidepressants with atypical antipsychotics as adjuvant therapy in MDD lies in their affinity for a number of serotonergic structures, including the 5HT1 and 5HT2 receptor subtypes. Atypical antipsychotics may be helpful for MDD, both as monotherapy and as antidepressant augmenting agents. [32, 33]

5. Conclusion

To the best of our knowledge this is the first animal study to evaluate the antidepressant effects of ziprasidone comparing with standard drug fluoxetine. Ziprasidone as virtue of its diverse pharmacodynamic effect can be suitable candidate for clinical trials of MDD as monotherapy or as an augmenting agent of standard antidepressant therapy. Well controlled clinical trials are needed to translate the result of our animal study in actual clinical setting.

6. Grants

The study was not supported by any grants or funding agencies.

7. Conflict of interest: -

The authors declare no conflict of interest.

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