Psychotic depression is a condition in which the individual manifests with primary mood symptoms found in major depression and also demonstrates secondary psychotic features such as delusions (fixed, false beliefs) and hallucinations (generally auditory). Although patients with psychotic depression have a greater risk of suicide, their chance of recovery is also better than other types of depression (1-4). Etiological studies revealed that family history, elevated plasma cortisol levels, are mainly responsible in these patients (5).

Till now, patients with psychotic depression are treated along two lines of treatment i.e. combination of antipsychotic – antidepressant and electroconvulsive therapy (ECT) (6-8). ECT is considered as a second line therapy to the drug treatment. Though both treatments are effective, they are slow to act and leave residual symptoms that last for months.

Literature revealed that some atypical antipsychotics such as risperidone and olanzapine possess antidepressant like properties (9, 10). At present, evidence supporting their use in psychotic depression is limited to case reports and small open label trials. Substantial weight gain and sedation are major problems, which restrict their use in treating mood disorder (11-14). Amisulpride has also demonstrated antidepressant like property (15). Effect of the two drugs on locomotor activity have been summarized by Perrault et al. and Ninan et al. (16, 17).

Amisulpride is superior to other atypical antipsychotics in having less incidence of weight gain and sedation due to its affinity for D2 and D3 receptors only (18).

Porsolt et al. in 1977 proposed the forced swimming test as a model to test antidepressant activity (19-21). In this initial model, emphasis was given on immobility of rats when they were forced to swim in a restricted space from which they were unable to escape.

The forced swimming test is considered as a reliable and sensitive method to test the effects of all major classes of antidepressants. But it was Detke et al. (22) who showed that including swimming and
climbing along with immobility, as active behavior is more appropriate. The reason behind this was that few antidepressants produced characteristic active behavior during forced swimming test and the method described by Porsolt, which focused on immobility only, may fail to detect the response.

This study was done to evaluate antidepressant like potential of amisulpride in experimental model of depression. The effect produced by amisulpride was compared with the standard antidepressant fluoxetine, a selective serotonin reuptake inhibitor (SSRI) and one of the first choice drugs in depression (23) and an atypical antipsychotic drug, olanzapine, claimed to have antidepressant like property (9).

MATERIALS AND METHODS

Drugs
Fluoxetine hydrochloride, amisulpride and olanzapine were obtained from Sun Pharma, Mumbai. All the treatments were prepared in distilled water and administered per oral (p.o.) with the help of oral gauge.

Animals
A total of 64 male Swiss albino mice weighing between 20-30 g were used. They were kept under standard conditions of temperature and humidity with a 12:12 light : dark cycle. The animals were fed with standard pellet diet and water ad libitum. Animal handling was performed in accordance to Good Laboratory Practice (GLP) guidelines and study was carried out according to the guidelines of IAEC [Institutional Animal Ethical Committee, MGM Medical College, Indore (M.P.), India.]

Protocol for drug intervention
Acute study
The mice were divided in four groups (n = 8 in each group) and drug administration was done as follows:

- **Group 1 (control)** – distilled water (1 ml/kg) 23.5, 5 and 1 h before the test.
- **Group 2 (fluoxetine)** – fluoxetine hydrochloride (10 mg/kg) 23.5, 5 and 1 h before the test (24).
- **Group 3 (amisulpride)** – amisulpride (70 mg/kg) 23.5, 5 and 1 h before the test (25, 26).
- **Group 4 (olanzapine)** – olanzapine (2 mg/kg) 23.5, 5 and 1 h before the test (27).

Chronic study
Drug administration protocol was kept similarly as in acute study except that in chronic study drugs were continued 28 days with last dose being given 2 h prior to the test.

The forced swimming test
Naive mice were forced to swim in a vertical Plexiglass cylinder (height 40 cm; diameter 20 cm) filled with 30 cm of water maintained at temperature of 25 ± 2°C. Swim periods were divided into a pre-test swim period of 15 min duration and a test swim period of 5 min duration on the next day. Both sessions were conducted between 10.00-16.00 h. After each session, mice were removed from water, dried with towels and housed in a warm place for 15 min before returning them to their cages. After testing of each mouse, the cylinders were emptied and thoroughly washed. In the initial pre-test period, mice were initially highly active and vigorously swimming in entire cylinder. After 2-3 min of enthusiastic swimming, a characteristic behavior called immobility, in which only the movements necessary to keep the head above water level were made, was achieved. In the test session performed 24 h later, this behavior of immobility was increased. Antidepressant drugs are known to attenuate this ‘facilitated immobility’. In the test session, time sampling technique was used to score several behaviors during a single viewing. Blocks of 5 s were used to judge animal behavior under the following three headings:

![Figure 1. Chemical structure of drugs: A. amisulpride, B. olanzapine, C. fluoxetine](image-url)
Evaluation of antidepressant like property of amisulpride per se...

1) Swimming — mouse was judged to be swimming if it was making active movements more than necessary to keep the head above water. 2) Immobility — mouse was said to be immobile when it was floating without struggling and making only those movements necessary to keep head above the water. 3) Climbing — mouse was judged to be climbing when it was making active movements with its forepaws in and out of water usually directed against the walls.

A rater who was blinded to the treatment groups did scoring. The entire test session was recorded using Canon power shot A75 digital video camera.

**Statistical analysis**

Results were expressed as the mean ± SEM. One way analysis of variance (ANOVA) was used to analyze means of behavioral scores for each of the three behaviors that is immobility, swimming and climbing, followed by Tukey’s multiple comparison test in both acute and chronic studies. p < 0.05 was taken as significant value.

**RESULTS**

In both acute study (Table 1), fluoxetine (10 mg/kg, p.o.), amisulpride (70 mg/kg, p.o.) and olanzapine (2 mg/kg, p.o.) significantly increased the duration of swimming behavior [F (3,28) = 45.90, p < 0.01]. Similarly, all the three drugs decreased the duration of immobility in albino mice significantly [F (3,28) = 38.10, p < 0.01]. However, none of the drugs affected climbing behavior significantly [F (3,28) = 24.60, p < 0.01]. Furthermore, Tukey’s multiple comparison test showed that fluoxetine decreased immobility and increased swimming duration of mice significantly (p < 0.01) when compared to other three groups. Amisulpride affected the behaviors in a similar manner as that of fluoxetine but it was significant only when compared to control (p < 0.01) and equivalent when compared to olanzapine (p > 0.05).

In chronic study (Table 2), results followed the pattern of acute study with all the three drugs...
increasing swimming behavior \( [F (3,28) = 46.89, p < 0.01] \) and decreasing immobility phase \( [F (3,28) = 54.67, p < 0.01] \) significantly without affecting climbing behavior \( [F (3,28) = 1.131, p = 0.117] \). The Tukey’s test also showed the same results as acute study with fluoxetine’s effects more significant than other groups and amisulpride significant only when compared to control and equivalent to olanzapine in increasing swimming phase along with decreasing immobility phase.

**DISCUSSION**

It has been shown by Gessa et al. that the functions that are controlled by the mesocorticolimbic dopaminergic system are impaired in depressive disorders of a different nature, and whenever symptoms of depression can be mimicked in experimental animals they appear to be sustained by a deficit in mesocorticolimbic dopaminergic transmission. Thus, a deficit in mesocorticolimbic dopaminergic transmission may represent the common neurobiological substrate of the core symptomatology in different depressive conditions independently of their nosological classification, including dysthymic disorder, major depressive disorder, drug-induced depression and, possibly, negative symptoms of schizophrenia (28). The cornerstone of the treatment of depressive disorders has been antidepressant drugs, but in case of psychotic depression there is a psychotic component in addition to depression. So, while treating psychotic depression, antidepressants are combined with antipsychotics. Literature has showed some of the antipsychotics like olanzapine (9) are known to possess antidepressant like activity in addition to antipsychotic activity. Muller et al., Niskanen et al., and Pelc et al. have proposed the dopaminergic antidepressant like action of compounds belonging to the substituted benzamides family such as sulpiride and amisulpride (29-31). Papp has also shown similar antidepressant like activity of amisulpride in two animal models of depression, which included forced swimming test (26). In the present study, amisulpride was evaluated for antidepressant like activity in forced swimming test in albino mice. Activity of amisulpride was compared with olanzapine, an atypical antipsychotic and fluoxetine, a standard antidepressant.

In this study, fluoxetine, when compared to other groups, showed significant antidepressant activity \( (p < 0.01) \) by increasing the duration of swimming of albino mice along with reducing the duration of immobility. Both amisulpride and olanzapine, when compared to control, showed significant antidepressant like activity \( (p < 0.01) \). Antidepressant like activity of amisulpride and olanzapine was similar \( (p > 0.05) \).

None of the drugs affected the climbing behavior significantly. This finding is in accordance with the study of Detke et al. (22), which showed that the climbing behavior is typically affected by norepinephrine reuptake inhibitors, while other classes of antidepressants affected the behaviors of immobility and swimming.

The proposed mechanism of action of substituted benzamides implies a selective modulation of the dopaminergic system in the mesocorticolimbic area, which has been called forth to explain the antidepressive effect (32, 33) in small to moderate doses, including patients suffering from endogenous depression (34), or autism (35) and, in moderate to medium doses, a reported efficacy on negative symptoms of schizophrenia (36-38), with relatively few extrapyramidal side effects (39). On the other hand, olanzapine has also shown considerable antidepressant activity (9) and is being used in treatment of psychotic depression (11). But olanzapine has been reported to cause significant weight gain, sedation and unfavorably affect lipid profile (11-14). It has also been related to increased insulin levels in patients treated with olanzapine (40). These side effects of olanzapine may affect patient compliance whereas amisulpride is claimed to be free from these side effects (41, 42). This experiment shows that amisulpride has a significant antidepressant like activity equivalent to that of olanzapine in forced swimming test in albino mice. This finding is significant as amisulpride, if used in the treatment of psychotic depression alone or in combination with lesser doses of SSRIs, may result in lesser serotonergic side effects such as anxiety, insomnia, sexual dysfunction, serotonin syndrome etc. (43). Further, amisulpride is more efficacious and relatively safer with a less incidence of side effects like weight gain as compared to olanzapine which can improve patient adherence to treatment. Further clinical research is needed to confirm these experimental findings.

**CONCLUSION**

The results of the present study suggest that amisulpride, with better safety profile, has potential to reduce FST induced depressive behavior. This potential is comparable to that of olanzapine though less than fluoxetine.
REFERENCES