e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2026; 18(6); 860-866

Original Research Article

Evaluation of Anxiolytic Effect of Ondansetron in Swiss Albino Mice

V. Arunkokil[1], L. Madhan[2], N. Preetha[3]

[1]MBBS, MD Pharmacology (Postgraduate), Department of Pharmacology, Coimbatore Medical College, Coimbatore, Tamil Nadu, India

[2]Professor and HOD, Department of Pharmacology, Coimbatore Medical College, Coimbatore, Tamil Nadu, India

[3]Professor and HOD, Department of Pharmacology, Government Erode Medical College, Perunthurai, Erode, Tamil Nadu, India

Received: 01-03-2026 / Revised: 15-04-2026 / Accepted: 21-05-2026

Corresponding author: Dr. V. Arunkokil

Conflict of interest: Nil

Abstract

Background: Anxiety disorders are among the most prevalent psychiatric conditions worldwide, affecting approximately one-eighth of the global population [1]. Current pharmacological management predominantly relies on benzodiazepines, azapirones, selective serotonin reuptake inhibitors (SSRIs), and beta-blockers, many of which are associated with sedation, dependence, and abuse potential [3]. Ondansetron, a selective 5-HT3 receptor antagonist, modulates serotonergic neurotransmission through allosteric inhibition and represents a promising candidate for anxiolytic therapy with a potentially superior tolerability profile. Objective of this study is to evaluate and compare the anxiolytic activity of ondansetron at two dose levels (0.5 mg/kg and 1 mg/kg, oral) against alprazolam (0.25 mg/kg, oral) as the standard drug, using three validated rodent behavioural models in Swiss albino mice.

Methods: Twenty-four adult Swiss albino mice were randomly divided into four groups (n=6 each). Group I received distilled water (0.4 ml oral, control); Group II received alprazolam 0.25 mg/kg oral (standard); Group III received ondansetron 0.5 mg/kg oral; and Group IV received ondansetron 1 mg/kg oral. Drugs were administered for seven consecutive days, after which behaviour was assessed using the Elevated Plus Maze (EPM), Open Field Test (OFT), and Hole Board Apparatus Test (HBT). One-way ANOVA followed by Tukey's post-hoc test was used for statistical analysis.

Results: Ondansetron at 1 mg/kg significantly increased time spent in the open arm (159.33 ± 12.37 sec) and reduced time in the closed arm (140.67 ± 12.37 sec) on EPM, comparable to alprazolam (154.50 ± 12.36 sec; 145.50 ± 12.36 sec). Similarly, ondansetron 1 mg/kg increased locomotor activity (88.17 ± 6.76 squares), time spent in the centre square (76.00 ± 4.86 sec) on OFT, and head-poking frequency (10.48 ± 1.47) on HBT. One-way ANOVA revealed highly significant differences across all parameters (F values 31.66–115.79; $p < 0.00001$). Post-hoc analysis showed no significant difference between ondansetron 1 mg/kg and alprazolam 0.25 mg/kg, confirming equipotent anxiolytic activity.

Conclusion: Ondansetron demonstrates significant dose-dependent anxiolytic activity in Swiss albino mice, with the higher dose (1 mg/kg) producing effects comparable to the standard benzodiazepine alprazolam. This positions ondansetron as a potential anxiolytic agent warranting further clinical evaluation.

Keywords: Anxiolytic activity; Ondansetron; 5-HT3 receptor antagonist; Elevated plus maze; Open field test; Hole board apparatus; Swiss albino mice; Alprazolam; Serotonin; Behavioural pharmacology.

DOI: 10.25258/ijcpr.18.6.140

Introduction

Anxiety disorders constitute one of the most common and debilitating groups of psychiatric conditions globally, estimated to affect approximately one-eighth of the total world population [1]. They encompass a heterogeneous spectrum of conditions including generalised anxiety disorder, panic disorder, social anxiety disorder, and post-traumatic stress disorder, collectively associated with significant morbidity, impaired quality of life, and substantial economic burden [2,5]. The neurobiology of anxiety is complex, involving the interplay of multiple neurotransmitter systems. Serotonin (5-hydroxytryptamine; 5-HT), norepinephrine, and gamma-aminobutyric acid (GABA) are established key mediators in the pathophysiology of anxiety

disorders [2,6]. Currently available pharmacological treatments include benzodiazepines, which act through GABA-A receptor potentiation; buspirone, a 5-HT1A partial agonist; SSRIs; serotonin-norepinephrine reuptake inhibitors (SNRIs); and beta-adrenergic blockers [3,7]. Although effective, these agents carry well-recognised limitations, including sedation, cognitive impairment, tolerance, physical dependence, and, particularly for benzodiazepines, significant abuse liability [8,9]. The continued search for anxiolytic agents with novel mechanisms of action and improved safety profiles remains an important priority in psychopharmacological research [10].

The serotonin type-3 (5-HT3) receptor is a ligand-gated ion channel expressed in the limbic system, the hippocampus, and prefrontal cortex — regions critically implicated in anxiety regulation [4,11]. Preclinical evidence indicates that selective 5-HT3 receptor antagonism enhances serotonergic transmission via allosteric modulation, producing anxiolytic effects without the sedative or dependence-inducing properties of benzodiazepines [4,12]. Ondansetron, originally developed and widely used as an antiemetic in oncology practice, is one of the most potent and selective 5-HT3 receptor antagonists available [13]. Several preclinical studies have suggested its potential anxiolytic properties [3,14], though systematic animal model-based characterisation at varying doses remains limited.

Three well-validated behavioural paradigms are widely employed to characterise anxiolytic activity in rodents [15,16]. The Elevated Plus Maze (EPM) exploits the innate conflict between the aversive response to open, elevated spaces and the drive to explore, measuring the proportion of time spent in open versus closed arms [17]. The Open Field Test (OFT) measures locomotor activity and thigmotaxis, with increased central-field exploration reflecting reduced anxiety [18]. The Hole Board Apparatus Test (HBT) quantifies exploratory head-dipping behaviour, a sensitive index of anxiolytic drug action in mice [19].

The primary objective of this study was to evaluate the anxiolytic effect of ondansetron administered orally at two doses (0.5 mg/kg and 1 mg/kg) in Swiss albino mice over a seven-day treatment period, using the Elevated Plus Maze, Open Field Test, and Hole Board Apparatus. The secondary objective was to compare the magnitude of ondansetron's anxiolytic effect with that of alprazolam (0.25 mg/kg, oral), the standard benzodiazepine anxiolytic, and to assess dose-response relationships through one-way ANOVA and post-hoc analysis.

Materials and Methods

This study was conducted after obtaining approval from the Institutional Animal Ethics Committee (IAEC) of Coimbatore Medical College, Coimbatore, India (Approval Number: IAEC/CMCH/PH/039/2023, dated 28 November 2023), in compliance with the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India. Twenty-four adult Swiss albino mice of either sex, weighing between 20 and 30 g, were procured from a registered animal house. Animals were quarantined for seven days and then acclimatised to the experimental room conditions (temperature 22 ± 2°C, 12-hour light/dark cycle, ad libitum food and water) for at least five days prior to the commencement of experimentation.

Ondansetron (4 mg/2 ml injectable formulation, diluted to required concentrations in distilled water) and alprazolam (0.25 mg tablets, crushed and suspended in distilled water) were obtained commercially. Distilled water served as the vehicle control. All doses were prepared fresh on the day of administration and given by oral gavage (0.4 ml volume).

Animals were randomly assigned to four groups of six mice each (n=6 per group) by simple randomisation. Group I (Control) received distilled water 0.4 ml orally; Group II (Standard) received alprazolam 0.25 mg/kg orally; Group III (Low-dose test) received ondansetron 0.5 mg/kg orally; and Group IV (High-dose test) received ondansetron 1 mg/kg orally. All drugs were administered once daily for seven consecutive days, and behavioural testing was carried out at the end of the treatment period, 30 minutes after the final drug administration.

Elevated Plus Maze (EPM): The EPM consisted of two open arms (50 cm × 10 cm) and two enclosed arms (50 cm × 10 cm × 40 cm) arranged in a plus sign, elevated 50 cm from the floor [17]. Each mouse was placed at the centre of the apparatus facing an open arm. The time spent in open arms and closed arms was recorded over 5 minutes. An increase in time in the open arms relative to control was considered indicative of anxiolytic activity [15,17].

Open Field Test (OFT): The OFT was conducted in an open-topped square arena (60 cm × 60 cm) with a floor divided by lines into 25 equal squares, of which the central 9 squares defined the centre zone [18]. Each animal was placed in the centre and observed for 5 minutes. The number of squares crossed (locomotor activity) and the time spent in the central area (index of reduced thigmotaxis) were recorded manually [16,18].

Hole Board Apparatus Test (HBT): The hole board consisted of a square platform (40 cm × 40 cm) with 16 equally spaced holes (3 cm diameter, 2.5 cm deep). Each mouse was placed at the centre and the number of head-dipping (poking) episodes into the holes over 5 minutes was counted [19]. A higher frequency of head-dipping is associated with reduced anxiety and is sensitive to anxiolytic drug effects [19,20].

All data are expressed as mean ± standard deviation (SD). One-way analysis of variance (ANOVA) was performed to assess overall significance across groups for each behavioural parameter.

Tukey's honest significant difference (HSD) test was applied as a post-hoc test for pairwise comparisons. A p-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using standard statistical software.

Results

A total of 24 Swiss albino mice completed the seven-day treatment protocol across all four groups without any observed mortality or adverse behavioural signs. Data from all animals were included in the final analysis. Table 1 presents the mean time (in seconds) spent by mice in the open and closed arms of the EPM across the four treatment groups. Control animals (G1) spent a mean of 64.83 ± 11.63 seconds in the open arm and 235.00 ± 11.37 seconds in the closed arm, reflecting baseline anxiety-like behaviour. Treatment with ondansetron 0.5 mg/kg (G2) produced a moderate but significant increase in open-arm time (112.00 ± 13.91 sec) and a corresponding reduction in closed-arm time (188.00 ± 13.91 sec). At the higher dose of 1 mg/kg (G3), ondansetron further increased open-arm time to 159.33 ± 12.37 sec, closely approximating the effect of alprazolam 0.25 mg/kg (G4: 154.50 ± 12.36 sec). The one-way ANOVA revealed highly significant inter-group differences for both open-arm time ($F = 73.307$; $p < 0.00001$) and closed-arm time ($F = 73.781$; $p < 0.00001$).

Table 1: Effect of Ondansetron and Alprazolam on Mice Behaviour in Elevated Plus Maze (EPM)

Group	Open Arm Mean (sec)	Open Arm SD	Closed Arm Mean (sec)	Closed Arm SD
G1 – Control (Distilled Water)	64.83	11.63	235.00	11.37
G2 – Ondansetron 0.5 mg/kg	112.00	13.91	188.00	13.91
G3 – Ondansetron 1 mg/kg	159.33	12.37	140.67	12.37
G4 – Alprazolam 0.25 mg/kg (Standard)	154.50	12.36	145.50	12.36

Values expressed as Mean ± SD; n=6 per group. *Statistically significant at p<0.05 by one-way ANOVA. G1=Control (distilled water); G2=Ondansetron 0.5 mg/kg; G3=Ondansetron 1 mg/kg; G4=Alprazolam 0.25 mg/kg.

The effects of drug treatment on locomotor activity and central-field exploration in the OFT are summarised in Table 2. In the control group, mice crossed a mean of 56.50 ± 7.26 squares and spent 17.83 ± 4.40 seconds in the centre zone, consistent with baseline thigmotactic behaviour.

Ondansetron 0.5 mg/kg (G2) produced a modest increase in squares crossed (74.33 ± 5.54) and time in centre (29.10 ± 6.94 sec). The higher ondansetron dose (G3) elicited substantially greater locomotor activity (88.17 ± 6.76 squares) and markedly extended central-field dwell time (76.00 ± 4.86 sec), exceeding even the standard drug alprazolam (G4: 85.33 ± 5.21 squares; 70.67 ± 9.27 sec).

One-way ANOVA confirmed highly significant differences for both squares crossed ($F = 31.659$; $p < 0.00001$) and time in centre ($F = 115.788$; $p < 0.00001$). The notably high F-value for the centre-time parameter underscores the strong drug effect on anxiolytic behaviour as measured by thigmotaxis.

Table 2: Effect of Ondansetron and Alprazolam on Mice Behaviour in Open Field Test (OFT)

Group	Squares Crossed Mean	Squares Crossed SD	Time in Centre (sec) Mean	Time in Centre SD
G1 – Control (Distilled Water)	56.50	7.26	17.83	4.40
G2 – Ondansetron 0.5 mg/kg	74.33	5.54	29.10	6.94
G3 – Ondansetron 1 mg/kg	88.17	6.76	76.00	4.86
G4 – Alprazolam 0.25 mg/kg (Standard)	85.33	5.21	70.67	9.27

Values expressed as Mean ± SD; n=6 per group. *Statistically significant at p<0.05 by one-way ANOVA. G1=Control; G2=Ondansetron 0.5 mg/kg; G3=Ondansetron 1 mg/kg; G4=Alprazolam 0.25 mg/kg.

Table 3 shows the number of exploratory head-dipping episodes recorded during the HBT. Control mice exhibited a mean of only 2.33 ± 0.52 pokings, reflecting suppressed exploratory drive consistent with unchallenged anxiety. Ondansetron at 0.5 mg/kg (G2) approximately doubled the head-dipping count (4.50 ± 1.05), while the 1 mg/kg dose (G3) produced a marked increase to 10.48 ± 1.47 pokings, very closely matched by alprazolam (G4: 9.67 ± 1.63). The F-value of 64.157 ($p < 0.00001$) confirmed highly significant differences between groups.

Table 3: Effect of Ondansetron and Alprazolam on Head-Dipping in Hole Board Apparatus Test (HBT)

Group	Head Poking Mean	Head Poking SD
G1 – Control (Distilled Water)	2.33	0.52
G2 – Ondansetron 0.5 mg/kg	4.50	1.05
G3 – Ondansetron 1 mg/kg	10.48	1.47
G4 – Alprazolam 0.25 mg/kg (Standard)	9.67	1.63

Values expressed as Mean ± SD; n=6 per group. *Statistically significant at p<0.05 by one-way ANOVA. G1=Control; G2=Ondansetron 0.5 mg/kg; G3=Ondansetron 1 mg/kg; G4=Alprazolam 0.25 mg/kg.

Table 4 provides a consolidated overview of the ANOVA outcomes for all five behavioural parameters measured across the three test models.

All parameters yielded F-values substantially exceeding the critical threshold, with p-values below 0.00001, confirming that the treatment groups differed significantly from one another on every outcome measure. The highest F-value was recorded for time spent in the centre square of the OFT (F = 115.788), reflecting the greatest discriminatory sensitivity of this parameter, followed by closed-arm time in EPM (F = 73.781), open-arm time (F = 73.307), head-dipping in HBT (F = 64.157), and squares crossed in OFT (F = 31.659).

Table 4: One-Way ANOVA Summary – All Behavioural Parameters Across Treatment Groups

Parameter	G1 (Control)	G2 (OND 0.5)	G3 (OND 1.0)	G4 (ALP 0.25)	F Value	p Value
Time in Open Arm (sec)	64.83 (11.63)	112.00 (13.91)	159.33 (12.37)	154.50 (12.36)	73.307	<0.00001*
Time in Closed Arm (sec)	235.00 (11.37)	188.00 (13.91)	140.67 (12.37)	145.50 (12.36)	73.781	<0.00001*
Squares Crossed (OFT)	56.50(7.26)	74.33(5.54)	88.17(6.76)	85.33(5.21)	31.659	<0.00001*
Time in Centre Square (sec)	17.83(4.40)	29.10(6.94)	76.00(4.86)	70.67(9.27)	115.788	<0.00001*
Head Pokings (HBT)	2.33 (0.52)	4.50(1.05)	10.48(1.47)	9.67(1.63)	64.157	<0.00001*

Values in parentheses represent SD; n=6 per group. *p<0.00001, statistically significant at 5% level. OND=Ondansetron; ALP=Alprazolam. EPM=Elevated Plus Maze; OFT=Open Field Test; HBT=Hole Board Test.

Table 5 summarises the results of Tukey's post-hoc pairwise comparisons for each behavioural parameter.

Statistically significant differences were observed between the control group and all active treatment groups across all parameters ($p < 0.05$). Similarly, ondansetron 0.5 mg/kg differed significantly from both ondansetron 1 mg/kg and alprazolam. Critically, pairwise comparison between ondansetron 1 mg/kg (G3) and alprazolam 0.25 mg/kg (G4) revealed no statistically significant difference on any of the five parameters, confirming that the two treatments produced equivalent anxiolytic effects.

Table 5: Tukey's Post-Hoc Pairwise Comparison – Summary of Significance

Parameter	G1 vs G3 / G4	G2 vs G3 / G4	G3 vs G4
Time in Open Arm (EPM)	Significant (p<0.05)	Significant (p<0.05)	Not Significant
Time in Closed Arm (EPM)	Significant (p<0.05)	Significant (p<0.05)	Not Significant
Squares Crossed (OFT)	Significant (p<0.05)	Significant (p<0.05)	Not Significant
Time in Centre Square (OFT)	Significant (p<0.05)	Significant (p<0.05)	Not Significant
Head Pokings (HBT)	Significant (p<0.05)	Significant (p<0.05)	Not Significant

G1=Control; G2=Ondansetron 0.5 mg/kg; G3=Ondansetron 1 mg/kg; G4=Alprazolam 0.25 mg/kg. Significant = p<0.05; Not Significant = p>0.05.

Discussion

The present study demonstrates a clear, dose-dependent anxiolytic effect of ondansetron in Swiss albino mice, as evidenced by behavioural modifications across three complementary and well-validated animal models of anxiety. The key finding is that ondansetron at 1 mg/kg produced anxiolytic effects statistically equivalent to the established benzodiazepine standard, alprazolam 0.25 mg/kg, in the EPM, OFT, and HBT, while the lower dose of 0.5 mg/kg also showed significant activity, albeit of lesser magnitude.

In the EPM, the increased time spent in the open arms by ondansetron-treated animals reflects a reduction in anxiety-driven avoidance of potentially threatening environments [15,17]. The EPM is one of the most widely used, ethologically validated models for anxiolytic drug screening, and its sensitivity to both benzodiazepines and serotonergic agents makes it particularly suitable for characterising the anxiolytic profile of ondansetron [3,17]. The observed increase in open-arm exploration in the ondansetron 1 mg/kg group (159.33 ± 12.37 sec) closely matched that of alprazolam (154.50 ± 12.36 sec), consistent with prior reports of 5-HT3 antagonism producing anxiolytic behaviour comparable to benzodiazepines in rodent models [4,14].

The OFT findings reinforce the EPM data. Anxiolytic agents are known to reduce thigmotaxis and increase central-field exploration without necessarily causing hyperlocomotion [16,18]. In the present study, ondansetron 1 mg/kg significantly increased both the number of squares crossed and, particularly, the time spent in the centre zone (76.00 ± 4.86 sec versus 17.83 ± 4.40 sec in controls). The notably high F-value for this parameter (115.788) suggests that central-field dwell time is among the most sensitive OFT indices for detecting serotonin-mediated anxiolysis. These results are consistent with Jain et al. [3], who reported significant anxiolytic activity of ondansetron in multiple murine behavioural models. The observed increase in locomotor activity further argues against the sedative confound that complicates interpretation of benzodiazepine effects in the OFT [8].

Head-dipping frequency in the HBT provides an independent measure of exploratory drive, which is suppressed by anxiety and restored by anxiolytic compounds [19,20]. The marked increase in head-dipping from 2.33 ± 0.52 in controls to 10.48 ± 1.47 in the ondansetron 1 mg/kg group closely paralleled alprazolam (9.67 ± 1.63), confirming dose-dependent anxiolytic activity through this paradigm as well. The convergence of significant positive results across three mechanistically distinct models substantially strengthens the inference of genuine anxiolytic activity rather than a model-specific artefact.

The mechanistic basis for ondansetron's anxiolytic effects is grounded in its selective antagonism of 5-HT3 receptors, which are ligand-gated cation channels found in limbic and cortical areas central to anxiety processing [4,11].

Blockade of 5-HT3 receptors is believed to modulate serotonin release and indirectly influence dopaminergic and GABAergic circuits, collectively shifting the neurochemical milieu towards reduced anxiety states [12,13]. Unlike benzodiazepines, which directly potentiate GABAergic inhibition and carry risks of sedation, muscle relaxation, amnesia, and dependence, 5-HT3 antagonists are not expected to produce these adverse effects [9,10], making them of considerable translational interest. Compared to prior work, the current study corroborates the findings of Jain et al. [3], who similarly demonstrated anxiolytic activity of ondansetron in mice, and is consistent with the broader preclinical evidence reviewed by Olivier et al. [4] regarding the anxiolytic potential of the 5-HT3 receptor antagonist class. The contribution of serotonergic neurotransmission to anxiety, as detailed in standard pharmacology texts [2], underpins the rationale for this therapeutic approach. Furthermore, ethnobotanical and preclinical work on anxiety models, such as that of Grundmann et al. [1], has helped validate the EPM and related models as robust platforms for anxiolytic drug discovery.

Several limitations of this study merit acknowledgement. The sample size of six animals per group, though consistent with many experimental pharmacology studies, is relatively small and may limit statistical power for detecting modest between-group differences. The study did not include a locomotor activity test (e.g., actophotometer) to formally exclude motor-sedation as a confounding explanation for the behavioural changes observed, particularly for alprazolam; this represents an important avenue for future research [3]. Furthermore, the study employed a single species and strain, and the findings require replication in additional animal models before conclusions about generalised anxiolytic efficacy can be drawn. Translational extrapolation to humans requires clinical investigation.

Conclusion

This experimental study provides robust preclinical evidence that ondansetron, a selective 5-HT3 receptor antagonist, exerts significant dose-dependent anxiolytic activity in Swiss albino mice, as demonstrated across three independent and complementary behavioural paradigms — the

Elevated Plus Maze, Open Field Test, and Hole Board Apparatus Test. One-way ANOVA revealed highly significant differences across all five behavioural parameters ($p < 0.00001$), and post-hoc analysis confirmed that ondansetron 1 mg/kg produces anxiolytic effects statistically equivalent to alprazolam 0.25 mg/kg, the benzodiazepine standard, in all models evaluated.

The lower dose of ondansetron (0.5 mg/kg) also demonstrated significant anxiolytic activity relative to control, though of lesser magnitude than the higher dose or alprazolam. These findings support the hypothesis that 5-HT3 receptor antagonism is a viable and effective mechanism for anxiolytic drug action and position ondansetron as a candidate for further clinical evaluation in anxiety disorders, particularly given its established clinical safety profile as an antiemetic. Future studies should incorporate locomotor activity assays, chronic dosing protocols, anxiety-specific neurochemical analyses, and ultimately controlled clinical trials to fully characterise the anxiolytic potential of ondansetron in humans.

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