

A Comparative Study of Anxiolytic Effect of Aprepitant and Fosaprepitant in Rodent Model

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ABSTRACT

Background: Anxiety disorders are common psychiatric conditions, while currently available anxiolytic drugs, particularly benzodiazepines, are associated with limitations such as sedation, cognitive impairment, tolerance, and dependence. The Substance P/neurokinin-1 (NK1) receptor system has been implicated in stress and anxiety. This study evaluated the anxiolytic-like effects of the NK1 receptor antagonists aprepitant and fosaprepitant in comparison with alprazolam.

Methods: A comparative experimental animal study was conducted using male albino mice. Animals were allocated into six groups receiving gum acacia, normal saline, alprazolam orally, aprepitant, or fosaprepitant. Anxiolytic-like activity was assessed using the Elevated Plus Maze (EPM) and Bright and Dark Arena (BDA) models on the 1st and 10th days following treatment. Behavioral parameters included time spent in open/bright areas, entries, and rearing activity. Data were analyzed using one-way ANOVA followed by Tukey's post-hoc test.

Results: Both aprepitant and fosaprepitant produced significant anxiolytic-like effects compared with placebo in both behavioral models. On day 1, both drugs increased EPM open-arm exploration and BDA bright-arena entries and time. These effects were more pronounced after 10 days of treatment. Aprepitant produced greater open-arm time than fosaprepitant on day 10, although both remained less effective than alprazolam. Alprazolam consistently demonstrated the strongest anxiolytic response. Increased or preserved rearing activity supported enhanced exploration rather than behavioral suppression.

Conclusion: Aprepitant and fosaprepitant demonstrated significant anxiolytic-like activity in mice, with greater effects following repeated administration. NK1 receptor antagonism may represent a potential non-benzodiazepine pathway for anxiolytic drug development.

Keywords: Aprepitant; Fosaprepitant; Alprazolam; Neurokinin-1 receptor; Substance P; Anxiety; Elevated Plus Maze; Bright and Dark Arena.

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INTRODUCTION

Anxiety disorders are among the most prevalent mental health conditions globally, exerting a substantial burden on individuals, families, and healthcare systems. The World Health Organization estimated that in 2025 nearly 359 million people were affected, including 58 million children and adolescents [1]. These disorders are characterized by excessive fear, worry, and behavioral disturbances that impair social, occupational, and academic functioning. Despite the availability of pharmacological and psychotherapeutic interventions, many patients experience incomplete remission, adverse effects, or treatment resistance,

underscoring the urgent need for novel therapeutic strategies [1].

The pathophysiology of anxiety is multifaceted, involving dysregulation of neurotransmitters, neuropeptides, and neural circuits. Substance P (SP) and its primary receptor, the neurokinin-1 receptor (NK1R), have emerged as important modulators of stress and affective responses. SP is widely distributed in the central and peripheral nervous systems, particularly within the limbic system, hypothalamus, and amygdala—regions intimately linked to emotional behavior [2]. Beyond its role in nociception, SP contributes to emesis, defensive behavior, cardiovascular regulation, salivary secretion, smooth muscle contraction, and

vasodilatation, highlighting its broad neuromodulatory functions [2].

In the spinal cord, SP facilitates nociceptive signaling, while NK1R disruption attenuates late-phase responses to injury. In the brainstem, SP modulates the emetic reflex, a mechanism exploited clinically through NK1R antagonists that reduce chemotherapy-induced nausea and vomiting [3]. Importantly, SP also participates in stress-related neural processing, producing either anxiogenic or anxiolytic responses depending on species and site of administration. This bidirectional effect complicates interpretation of preclinical findings, and species-specific differences in NK1R pharmacology further challenge translational relevance [4–6].

The therapeutic potential of NK1R antagonists in psychiatric conditions has been explored with mixed results. Early clinical trials suggested antidepressant and anxiolytic effects independent of serotonergic and noradrenergic pathways [7]. However, subsequent studies failed to consistently replicate these findings, fueling debate about their efficacy [8–11]. Nevertheless, the mechanistic rationale remains compelling: blocking SP-mediated signaling may dampen hyperactive stress circuits and reduce pathological anxiety. This is particularly relevant given the limitations of current anxiolytics, such as benzodiazepines, which carry risks of dependence, sedation, and cognitive impairment [9]. Aprepitant, a selective centrally acting NK1R antagonist, is approved for prevention of chemotherapy-induced nausea and vomiting. It competitively inhibits SP binding at NK1Rs in brainstem regions critical for emesis, such as the nucleus tractus solitarius and area postrema [12]. Its ability to cross the blood-brain barrier and achieve central receptor occupancy makes it relevant for neuropsychiatric applications. Peripherally, aprepitant modulates NK1Rs in the gastrointestinal tract, attenuating vagal afferent signaling [13]. The same mechanism—antagonism of SP at NK1Rs—has been hypothesized to underlie potential anxiolytic effects [14,15]. Fosaprepitant, a water-soluble prodrug of aprepitant, is rapidly converted after intravenous administration. It shares the same pharmacodynamic profile but offers advantages in parenteral delivery, making it suitable when oral administration is impractical. Given their shared mechanism, both agents represent promising candidates for repurposing in anxiety disorders. However, comparative data on their anxiolytic efficacy, particularly in preclinical models, remain sparse. This study was therefore designed to investigate the anxiolytic effects of aprepitant and fosaprepitant in rodent models using validated behavioral paradigms. By directly comparing these agents, we aim to clarify differences in efficacy attributable to pharmacokinetic or pharmacodynamic factors. Such evidence is critical

for guiding translational research and optimizing therapeutic strategies for anxiety disorders.

MATERIALS & METHODS

This study was designed as a comparative and experimental animal-based investigation conducted over a period of 18 months at the Department of Pharmacology in a tertiary care hospital in eastern India. Ethical approval for the work was obtained from the Institutional Animal Ethics Committee prior to initiation, vide letter no. 55/IAEC/IGIMS/2024, ensuring compliance with established guidelines for animal research. The project was financially supported by the Multidisciplinary Research Unit (MRU), IGIMS, Patna, under sanction letter no: IGIMS/MRU/09/2024, thereby facilitating the systematic evaluation of the proposed objectives within a controlled institutional framework.

Procurement and Rearing of Animals

The study was conducted on male albino mice (weight 20–25 g). Mice were obtained from a CCSEA-registered breeder and were kept in the central animal house facility of the institution. Mice were maintained under standard conditions, as provided by the Committee for Control and Supervision of Experimental Animals (CCSEA), at a temperature of 18–24 °C, humidity of 50±5%, and a 12:12 hours light–dark cycle. Mice were housed in polypropylene cages, and food pellets and water were provided *ad libitum*. All experimental animals were acclimatized for 15 days prior to the initiation of the experiment.

Intervention

A total of 30 albino mice were used in this study. They were divided into 6 groups of 6 animals each. The test drugs were administered in doses based on previous studies [16, 17]. The tests were carried out 45 minutes after the last dose of the drugs on the 1st and 10th day [Table 1].

Methodology

In this study, two validated behavioral models were employed to assess anxiety in albino mice, namely the Elevated Plus Maze (EPM) and the Bright and Dark Arena. The Elevated Plus Maze (EPM) is a widely used test for assessing anxiety-like behavior in rodents, based on their natural aversion to open elevated spaces and tendency to explore novel environments. The apparatus consists of two open arms and two closed arms of equal dimensions, intersecting at a central square, allowing free movement between arms [Figure 1]. Anxiety levels are inferred from the number of entries, time spent, and rearing behavior in the open versus closed arms. Mice were placed in the central square facing a closed arm. The number of entries, time spent and the number of rears in each type of arm (open/closed) was recorded for 5 min. An entry was defined as the presence of all four paws in the arm [18].

The Bright and Dark Arena test was used to evaluate anxiety in albino mice, employing a wooden box with two distinct chambers—a dark chamber painted black and dimly lit with red light, and a bright chamber painted white and illuminated by a 100-watt light source positioned above. The chambers were connected by a small doorway at floor level, allowing free movement between them. Based on rodents' natural aversion to brightly lit spaces, anxiety was assessed through reduced entries, decreased time spent, and diminished exploratory behavior in the bright chamber, with the apparatus cleaned using 10% ethanol after each trial to eliminate odor bias [19].



Figure 1: Elevated Plus Maze

Statistical Analysis

Observed values were noted in a printed tabulated form at the time of the experiment and then represented in tabular form using Microsoft Excel 365, before being transferred to Jamovi version 2.4.1 for further statistical analysis. Continuous data such as time spent, entries, and rearing were expressed as mean $\pm$ standard error of mean (SEM), and one-way ANOVA was used to determine the statistical significance of differences between groups of albino mice. The Tukey HSD ("Honestly Significant Difference") post-hoc test was also performed to indicate which groups were significantly different from others. The chi-square test was used to evaluate the statistical significance of categorical data such as the arm of first entry in the elevated plus maze test.

Table 1: Drug treatment schedule for acute anxiolytic effect

Group	Number of Animals (Mice)	Drug	Brand Name	Manufacturer	Dose	Route of administration	Comments
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A	6	Control (1% Gum Accacia)	Neelkanth Minechem	10mg/kg	Oral- once for 10 days.	Control for oral drug
B	6	Normal Saline	NS 0.9% Injection	10 ml/kg	I.P. once for 10 days.	Control for I.P.
C	6	Alprazolam	Alprax Pharmaceuticals Ltd	0.08 mg/kg	Oral- once for 10 days.	Comparison with standard drug of proven anxiolytic activity (Oral)
D	6	Aprepitant	Prep Kit Laboratories Pvt Ltd	30 mg/kg	I.P. once for 10 days.	Assessment of anxiolytic effect in acute administration
E	6	Fosaprepitant	Fosaprepitant Pharmaceuticals Pvt. Ltd.	30 mg/kg	I.P. once for 10 days.	Assessment of anxiolytic effect in acute administration

RESULTS

Table 2: Comparison of Outcome Parameters in Elevated Plus Maze at 1st Day

Groups	Intervention	Time Spent in Seconds (Mean $\pm$ SEM)	Number of Rears (Mean $\pm$ SEM)	% of Open / Total
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		Open Arm	Closed Arm	Open Arm	Closed Arm	Arm Entries (Mean $\pm$ SEM)
A	Placebo (Gum acacia)	24.77 $\pm$ 0.424	275.5 $\pm$ 0.4931	1.833 $\pm$ 0.3073	3.667 $\pm$ 0.3333	27.5 $\pm$ 0.272
B	Placebo (NS)	25.92 $\pm$ 0.603	274.3 $\pm$ 0.5237	1.667 $\pm$ 0.2108	3.5 $\pm$ 0.2236	27.67 $\pm$ 0.4193
C	Alprazolam (Oral)	41.1 $\pm$ 0.6105	259.5 $\pm$ 0.5396	2.333 $\pm$ 0.3333	4.5 $\pm$ 0.4282	45.67 $\pm$ 0.7601
D	Aprepitant (Oral)	35.05 $\pm$ 0.4326	265 $\pm$ 0.4658	2.333 $\pm$ 0.3333	4.167 $\pm$ 0.3073	36 $\pm$ 0.4017
E	Fosaprepitant (IP)	35.22 $\pm$ 0.4949	265.2 $\pm$ 0.411	2.5 $\pm$ 0.4282	4.167 $\pm$ 0.4014	35.62 $\pm$ 0.5833
F-Value (One Way ANOVA)		177.0	194.6	1.199	1.389	210.6
p-Value (One Way ANOVA)		<0.0001 ^a	<0.0001 ^b	0.3358 ^c	0.2664 ^d	<0.0001 ^e

a: (P<0.0001 for all Tukey's Post-hoc comparison except A-B (0.5316) & D-E (0.9994))

b: (P<0.0001 for all Tukey's Post-hoc comparison except A-B (0.3912) & D-E (0.9984))

c: (p>0.05 for all Tukey's Post-hoc multiple comparison)

d: (p>0.05 for all Tukey's Post-hoc multiple comparison)

e: (P<0.0001 for all Tukey's Post-hoc comparison except A-B (0.9994) & D-E (0.9839))

Table 3: Comparison of Outcome Parameters in Bright and Dark Arena at 1st Day

Groups	Intervention	Number of Rears (Mean $\pm$ SEM)		Number of Entries to Bright Arena (Mean $\pm$ SEM)	Time Spent in Bright Arena in Seconds (Mean $\pm$ SEM)
		Bright Arena	Dark Arena		
A	Placebo (Gum acacia)	0.5 $\pm$ 0.2236	12.5 $\pm$ 0.4282	1.667 $\pm$ 0.2108	11.33 $\pm$ 0.6667
B	Placebo (NS)	1 $\pm$ 0.2582	12.67 $\pm$ 0.4216	1.667 $\pm$ 0.2108	11.5 $\pm$ 0.4282
C	Alprazolam (Oral)	2.667 $\pm$ 0.3333	17.33 $\pm$ 0.4216	4.00 $\pm$ 0.5774	27.83 $\pm$ 0.7032
D	Aprepitant (Oral)	1.333 $\pm$ 0.2108	15 $\pm$ 0.3651	3.00 $\pm$ 0.3651	17.67 $\pm$ 0.8433
E	Fosaprepitant (IP)	1.667 $\pm$ 0.2108	15.17 $\pm$ 0.3073	3.33 $\pm$ 0.3333	19 $\pm$ 0.5774

F-Value (One Way ANOVA)	10.44	26.21	8.083	105.6
p-Value (One Way ANOVA)	<0.0001 ^a	<0.0001 ^b	0.0003 ^c	<0.0001 ^d

a: $p > 0.05$ for all Tukey's Post-hoc multiple comparison except A-C ($p < 0.0001$), A-E ($p = 0.0233$), B-C ($p = 0.0007$), and C-D ($p = 0.0077$).

b: $p > 0.05$ for all Tukey's Post-hoc multiple comparison except A-C ($p < 0.0001$), A-D ($p = 0.0011$), A-E ($p = 0.0005$), B-C ($p < 0.0001$), B-D ($p = 0.0024$), B-E ($p = 0.0011$), C-D ($p = 0.0024$), and C-E ($p = 0.0051$).

c: $p > 0.05$ for all Tukey's Post-hoc comparison except A-C ($p = 0.0011$), A-E ($p = 0.0262$), B-C ($p = 0.0011$), and B-E ($p = 0.0262$).

d: $p < 0.0001$ for all Tukey's Post-hoc comparison except A-B (0.9998) & D-E (0.6136)

Table 4: Comparison of Outcome Parameters in Elevated Plus Maze at 10th Day

Groups	Intervention	Time Spent in Seconds (Mean $\pm$ SEM)		Number of Rears (Mean $\pm$ SEM)		% of Open Entries (Mean $\pm$ SEM)
		Open Arm	Closed Arm	Open Arm	Closed Arm	
A	Placebo (Gum acacia)	26.8	274.	1.5	3.0	27.6
		3 $\pm$ 1.35	3 $\pm$ 1.68	$\pm$ 0.22	$\pm$ 0.36	2 $\pm$ 0.35
		2	7	36	51	91
B	Placebo (NS)	25.8	273.	1.66	3.0	27.4
		3 $\pm$ 0.94	5 $\pm$ 1.31	7 $\pm$ 0.21	$\pm$ 0.36	5 $\pm$ 0.32
		58		08	51	02
C	Alprazolam (Oral)	105.	190.	5 $\pm$ 0.25	6.5 $\pm$ 0.42	51.7
		5 $\pm$ 3.85	2 $\pm$ 3.26	$\pm$ 0.82	$\pm$ 0.82	8 $\pm$ 0.46
		4				15

D	Aprepitant (Oral)	90.6	210	4.66	5.33	43.5
		7 ±	±	7 ±	3 ±	2 ±
		2.12	1.41	0.21	0.33	0.49
		4	4	08	33	22
E	Fosaprepitant (IP)	68.6	224.	4.5	5.66	43.8
		7 ±	7 ±	±	7 ±	5 ±
		12.3	9.74	0.42	0.33	0.18
			6	82	33	03
F-Value (One Way ANOVA)		38.1	64.3	38.4	19.2	210.
		6	0	6	6	6
p-Value (One Way ANOVA)		<0.0001 ^a	<0.0001 ^b	<0.0001 ^c	<0.0001 ^d	<0.0001 ^e

a: Tukey's post-hoc analysis showed significant differences for A-C ($p < 0.0001$), A-D ($p < 0.0001$), A-E ($p = 0.0003$), B-C ($p < 0.0001$), B-D ($p < 0.0001$), B-E ($p = 0.0002$), and C-E ($p = 0.0014$). All other pairwise comparisons were non-significant.

b: Tukey's post-hoc analysis showed significant differences for A-C, A-D, A-E, B-C, B-D, and B-E (all $p < 0.0001$), as well as C-D ($p = 0.0475$) and C-E ($p = 0.0002$). All other pairwise comparisons were non-significant.

c: $p > 0.05$ for all Tukey's Post-hoc multiple comparison except A-C, A-D, A-E, B-C, B-D, and B-E ($p < 0.0001$).

d: Tukey's post-hoc analysis showed significant differences for A-C ($p < 0.0001$), A-D ($p = 0.0012$), A-E ($p = 0.0002$), B-C ($p < 0.0001$), B-D ($p = 0.0012$), and B-E ($p = 0.0002$). All other pairwise comparisons were non-significant.

e: Tukey's post-hoc analysis showed significant differences for A-C, A-D, A-E, B-C, B-D, B-E, C-D, and C-E (all $p < 0.0001$). All other pairwise comparisons were non-significant.

Table 5: Comparison of Outcome Parameters in Bright and Dark Arena at 10th Day

Groups	Intervention	Number of Rears (Mean $\pm$ SEM)		Number of Entries to Bright Arena (Mean $\pm$ SEM)	Time Spent in Bright Arena (Mean $\pm$ SEM)
		Bright Arena	Dark Arena		
A	Placebo (Gum acacia)	10.6	21.0	4.66	5.33
		7 $\pm$ 2.12	$\pm$ 1.41	7 $\pm$ 0.21	3 $\pm$ 0.33
		4	4	08	33
B	Placebo (NS)	68.6	224.	4.5	5.66
		7 $\pm$ 12.3	7 $\pm$ 9.74	$\pm$ 0.42	7 $\pm$ 0.33
			6	82	33
C	Alprazolam (Oral)	105.	190.	5 $\pm$ 0.25	6.5 $\pm$ 0.42
		5 $\pm$ 3.85	2 $\pm$ 3.26	$\pm$ 0.82	$\pm$ 0.82
		4			

				n ± SEM)	n ± SEM)
A	Placebo (Gum acacia)	0.833 3 ± 0.307 3	12.83 ± 0.477 3	1.5 ± 0.223 6	12.5 ± 0.428 2
B	Placebo (NS)	1.667 ± 0.210 8	12.67 ± 0.557 8	1.833 ± 0.307 3	12.83 ± 0.307 3
C	Alprazo lam (Oral)	5 ± 0.365 1	23.67 ± 0.421 6	5.333 ± 0.333 3	32.0 ± 0.730 3
D	Aprepit ant (Oral)	3.833 ± 0.307 3	17.67 ± 0.557 8	4 ± 0.365 1	23.5 ± 0.428 2
E	Fosapre pitant (IP)	4.5 ± 0.428 2	18 ± 0.856 3	4.667 ± 0.210 8	23.33 ± 0.666 7
F-Value (One Way ANOVA)		30.18	58.22	33.88	235.9
p-Value (One Way ANOVA)		<0.0 001 ^a	<0.0 001 ^b	<0.0 001 ^c	<0.0 001 ^d

a: Tukey's post-hoc analysis showed significant differences for A–C, A–D, A–E, and B–C (all $p < 0.0001$), B–D ($p = 0.0009$), and B–E ($p < 0.0001$). All other pairwise comparisons were non-significant.

b: Tukey's post-hoc analysis showed significant differences for A–C, A–D, A–E, B–C, B–D, B–E, C–D, and C–E (all $p < 0.0001$). All other pairwise comparisons were non-significant.

c: Tukey's post-hoc analysis showed significant differences for A–C, A–D, A–E, and B–C (all $p < 0.0001$), B–D ($p = 0.0002$), B–E ($p < 0.0001$), and C–D ($p = 0.0277$). All other pairwise comparisons were non-significant.

d: Tukey's post-hoc analysis showed significant differences for A–C, A–D, A–E, B–C, B–D, B–E, C–D, and C–E (all $p < 0.0001$). All other pairwise comparisons were non-significant.

Both alprazolam groups showed greater time spent in the open arms and a higher percentage of open/total arm entries compared with the placebo groups, while aprepitant and fosaprepitant also increased open-arm exploration. These findings indicate that the major differences on the 1st day were reflected in open-arm exploration and time spent in the open arms rather than rearing behavior [Table 2].

In the bright/dark arena on the 1st day, alprazolam produced the greatest exploratory response, followed by fosaprepitant and aprepitant, compared with placebo groups. Bright-arena and dark-arena rearing, number of bright-arena entries, and time spent in the bright arena differed significantly among groups. These findings demonstrate increased exploration of the bright compartment following treatment, with alprazolam showing the highest numerical response [Table 3].

By the 10th day, repeated administration was associated with a marked increase in open-arm exploration. Overall, the 10th-day findings showed greater open-arm exploration with repeated treatment, with alprazolam producing the highest numerical response, followed by aprepitant and fosaprepitant for several parameters [Table 4].

On the 10th day, bright-arena exploration was also greater in the active-treatment groups than in the placebo groups. Thus, repeated treatment was associated with increased bright-arena exploration, with alprazolam showing the greatest numerical response and aprepitant and fosaprepitant showing broadly similar responses [Table 5].

DISCUSSION

The present study evaluated the anxiolytic-like effects of aprepitant and fosaprepitant in comparison with alprazolam and placebo using two established behavioral paradigms, the Elevated Plus Maze (EPM) and Bright and Dark Arena (BDA). The findings demonstrated that both aprepitant and fosaprepitant produced significant anxiolytic-like behavioral effects in mice, although the magnitude of these effects was consistently lower than that produced by alprazolam. These findings suggest that blockade of the Substance P/neurokinin-1 (NK1) receptor pathway can reduce anxiety-like behavior in experimental animals and that the behavioral response may become more evident following repeated administration.

Alprazolam demonstrated the strongest anxiolytic effect throughout the study and served as an appropriate positive control. These findings are consistent with the established anxiolytic action of benzodiazepines, which act through positive modulation of GABA-A receptors and enhancement of inhibitory neurotransmission [20]. Previous studies have similarly demonstrated that alprazolam increases open-arm exploration in the EPM and exploratory behavior in the BDA [21–23]. Thus, the present results provide expected evidence that the

experimental behavioral models were responsive to a recognized anxiolytic agent.

In contrast, aprepitant and fosaprepitant produced moderate but statistically significant anxiolytic-like effects. These findings indicate that NK1 receptor antagonism was associated with reduced avoidance of the exposed arms, an established behavioral indicator of reduced anxiety-like behavior in the EPM [24]. The BDA findings further supported the observations obtained from the EPM. Since rodents naturally avoid brightly illuminated environments, increased entry into and time spent in the bright compartment is interpreted as reduced anxiety-like behavior [24]. The consistency of the findings across two different behavioral models strengthens the evidence that the observed effects were related to anxiolytic-like activity rather than being specific to a single test. The anxiolytic effects of aprepitant and fosaprepitant may be explained by their antagonism of the NK1 receptor, which is activated by Substance P, a neuropeptide involved in stress and emotional processing. NK1 receptors are expressed in several brain regions involved in anxiety, including the amygdala and hypothalamus [25]. Blocking this receptor may therefore attenuate stress-related neuronal signaling and reduce anxiety-like responses. Unlike alprazolam, which enhances the principal inhibitory GABAergic system, NK1 antagonists appear to exert a more modulatory effect on stress-related signaling [25]. This mechanistic difference may explain why their behavioral effects in the present study were significant but less pronounced than those produced by alprazolam.

An important finding was the increase in anxiolytic-like responses after repeated treatment. The difference between day 1 and day 10 was particularly apparent in the EPM, where aprepitant and fosaprepitant showed substantially greater open-arm exploration after 10 days than after the initial administration. Similar improvement was observed in the BDA, with increased bright-arena entries and time spent in the bright compartment after repeated treatment. This pattern suggests that sustained NK1 receptor blockade may produce behavioral effects that are more apparent after repeated exposure. Previous discussion of NK1 antagonists has proposed that sustained receptor blockade may induce neuroadaptive changes within pro-anxiety pathways [9]. The present findings therefore provide preclinical support for further investigation of repeated NK1 receptor antagonism rather than relying solely on acute drug administration.

The rearing behavior provides additional context for interpreting the results. On day 1 in the EPM, no significant differences were observed in either open- or closed-arm rearing among the groups. This suggests that the increased open-arm exploration produced by the active treatments was not accompanied by a major nonspecific alteration in rearing activity. By day 10, however, treatment

groups showed increased rearing, particularly those receiving alprazolam and the NK1 antagonists. Increased exploratory activity alongside increased open-arm and bright-arena exploration supports the interpretation that the behavioral changes were related to reduced anxiety rather than simple suppression of locomotor activity. Rearing is therefore useful for distinguishing anxiolytic effects from behavioral impairment or excessive sedation [26].

The results obtained from both EPM and BDA were concordant, and the greater response following repeated treatment suggests that NK1 receptor antagonism may have potential as an alternative pharmacological approach to anxiety. These observations are in agreement with previous preclinical evidence supporting the involvement of the Substance P/NK1 system in anxiety-related behavior [27, 28]. However, the findings should be interpreted as preclinical evidence, and their translation to human anxiety disorders requires further investigation. Nevertheless, the present results provide a useful experimental basis for further evaluation of aprepitant and fosaprepitant as potential non-benzodiazepine anxiolytic candidates.

CONCLUSION

The present experimental study demonstrates that the NK1 receptor antagonists aprepitant and fosaprepitant possess significant anxiolytic-like activity in albino mice, as evidenced by increased open-arm exploration in the Elevated Plus Maze and increased entry into and time spent in the bright compartment of the Bright and Dark Arena compared with placebo controls. The anxiolytic effects became more pronounced following repeated administration, suggesting that sustained NK1 receptor blockade may enhance the behavioral response. However, alprazolam consistently produced a greater anxiolytic effect than either aprepitant or fosaprepitant, confirming its established efficacy as a standard anxiolytic agent. The preservation or increase in exploratory rearing behavior further supports that the observed effects were not primarily attributable to motor suppression. Overall, these findings provide preclinical evidence that modulation of the Substance P/NK1 receptor system may represent a potential alternative pathway for the development of non-benzodiazepine anxiolytic therapies, although further studies are required to establish its translational relevance in human anxiety disorders.

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