*Research Article / Araştırma Makalesi*

# Are NMDA Antagonists or Venlafaxine More Effective in the Forced Swimming Test?

## NMDA Antagonistleri mi Venlafaksin mi Zorlu Yüzme Testinde Daha Etkili?

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**Abstract**

**Background:** The aim of this study is to compare the antidepressant-like effects of NMDA antagonists (zinc sulfate, amantadine, and folic acid) with venlafaxine.
**Materials and Methods:** Ninety-six male Swiss Albino mice were used in the experiments and divided into experimental groups. To assess depression-like behaviors in the animals, the forced swim test was performed. The effects of the drugs on locomotor activity were measured using the open field test.
**Results:** No differences were found between venlafaxine, folic acid, or zinc sulfate when administered alone in the experimental depression model. When administered in combination, the highest antidepressant-like effect was observed in the zinc-amantadine combination and the zinc sulfate-amantadine-folic acid combination. When venlafaxine and folic acid were administered together, the antidepressant-like effect was greater compared to other venlafaxine combinations.
**Conclusions:** The use of these combinations in the treatment of depression is important for the enhancement of antidepressant efficacy.

**Keywords:** Amantadine, folic acid, depression, NMDA, zinc sulfate, venlafaxine

**Öz**

**Amaç**: Bu çalışmada NMDA antagonistlerinin (çinko sülfat, amantadin ve folik asit) antidepresan benzeri etkilerinin venlafaksin ile karşılaştırılması amaçlanmıştır.
**Materyal ve Metod:** Deneylerde doksan altı Swiss Albino erkek fare kullanıldı ve deney gruplarına ayrıldı. Hayvanların depresyon benzeri davranışlarını test etmek amacıyla zorlu yüzme testi yapıldı. İlaçların lokomotor aktivite üzerindeki etkileri açık alan testi kullanılarak ölçüldü.
**Bulgular:** Venlafaksin, folik asit veya çinko sülfat tek başına uygulandığında aralarında deneysel depresyon modelinde fark bulunmadı. Kombinasyon halinde uygulandığında en yüksek antidepresan benzeri etki çinko sülfat-amantadin kombinasyonunda ve çinko sülfat-amantadin-folik asit kombinasyonunda gözlendi. Venlafaksin ve folik asit birlikte uygulandığında antidepresan benzeri etki diğer venlafaksin kombinasyonlarına göre daha fazlaydı.
**Sonuç:** Bu kombinasyonların depresyon tedavisinde kullanılması antidepresan etkinliğin artışı açısından önemlidir.

**Anahtar Kelimeler:** Amantadin, Folik asit, Depresyon, NMDA, Çinko sülfat, Venlafaksin

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## Introduction

Depression, a significant health issue, negatively affects patients' daily lives, reduces work productivity, and can lead to hospitalization in severe cases. Despite the availability of various treatments, the success rate in treating depression is often unsatisfactory (1). Depression, being a psychiatric disorder, carries significant morbidity and mortality rates (2). It is estimated that depression is responsible for 50-70% of suicides, making it a crucial public health concern (3).

Currently prescribed antidepressant medications mostly target monoamines, such as serotonin,
noradrenaline, or dopamine, by inhibiting their reuptake or metabolism (4). Recent preclinical research indicates that the glutamate N-methyl-D-aspartate (NMDA) receptor might play a role in the mechanism of action of antidepressant medications (5,6). Studies have shown that functional antagonists targeting the NMDA receptor complex exhibit antidepressan like effects in animal models of depression (7-8).

Zinc sulfate is essential for various enzymatic processes, including DNA replication, transcription, and protein synthesis and it regulates cell division and differentiation (9). Zinc sulfate is also essential for a number of metabolic activities and is a strong inhibitor of the NMDA receptor complex (10). Research has indicated that individuals with depression exhibit reduced levels of zinc sulfate in their blood, which return to normal following therapy (11,12).

Serum and red blood cell folic acid concentrations in patients with major depressive disorder were considerably lower than those in healthy controls. Depression severity is associated with lower serum folic acid concentrations (13). It has been previously shown that folic acid has an antidepressant effect via NMDA antagonism. (14).

Glutamatergic system research, and NMDA receptor antagonists have garnered more attention in recent years owing to their possible antidepressant benefits. Amantadine, a non-competitive NMDA receptor antagonist, has been shown to reduce the immobility time in rats during forced swimming tests. Amantadine has already been approved for clinical trials in conditions such as Parkinson's disease (15).

Venlafaxine is a potent inhibitor of the reuptake of both norepinephrine and serotonin. The drug is used in the treatment of major depression, as well as in anxiety disorders and panic disorder. While all currently available antidepressants, including venlafaxine, demonstrate therapeutic effectiveness in about 60-70% of patients with depression, they often fall short in cases of treatment-resistant depression. As a result, ongoing research continues to explore new approaches and treatments for depression (16).

This study aimed to compare the effectiveness of zinc sulfate, folic acid, and amantadine, either separately or in combination, as NMDA receptor antagonists in treating depression, with venlafaxine, a commonly used antidepressant.

## Materials and Methods

This study was conducted with the required authorization and consent from the Erciyes University Faculty of Medicine Ethics Committee (No: 01/175, dated 02.05.2006). The Scientific Research Projects Unit of Erciyes University provided funding for the study's supplies and the laboratory animals under project code TT-06-35. This study was conducted in accordance with the Guide for the Care and Use of Laboratory Animals.

In the experiments, ninety-six male Swiss Albino mice weighing 25-30 g were used. The mice were kept in 40×28×17cm cages at a constant temperature of 23–24°C. They had full access to water and a normal laboratory diet, and their cages were light- and dark-cycled every 12 hours. The experiments were carried out at the Erciyes University Experimental Clinical Research Center (DEKAM).

### *Drugs*

All the medications were dissolved in physiological saline. The drugs were administered to the mice via intraperitoneal injection at the same volume (0.5 ml/Mouse), 24 hours, 1 hour, and 15 minutes before the experiment. The solutions were freshly prepared daily. The drugs used are listed shown in Table 1.

**Table 1.** Study drugs

| Drugs | Company | Dose |
|---|---|---|
| Folic acid | Sigma-Aldrich, Stenheim, Switzerland | 5 mg/kg |
| Amantadine HCL | Sigma-Aldrich, St. Louis, MO, USA | 20 mg/kg |
| Zinc sulfate | Merck KGaA, Darmstadt, Germany | 30 mg/kg |
| Venlafaxine | Wyeth, Pearl River, NY, USA | 30 mg/kg |

### *The forced swimming test*

The glass pool used was cylindrical and measured 25 cm in height and 10 cm in diameter. The water in the glass pool was maintained at 22-23°C and was added to a depth of 10 cm. Mice were placed in a water-filled glass pool, and their immobility times during the last 4 min of the 6 min duration they spent in the glass pool were recorded (very slight movements made by the mice to keep their heads above the water and their immobility on the water surface were considered as immobility) (17).

### *Locomotor activity test*

For the test, a transparent white non-transparent plexiglass box measuring 30×30×25 cm in size and in a square shape was used. The floor is divided into four equal parts with black lines (18). The experimental animals were gently introduced into the open field test apparatus, consistently in the same direction. During the thirty-minute test period, the frequency of line crossings by the animals was assessed. Line crossing was defined as the number of times the experimental animal moved from one square to another using all four limbs. An increase in locomotor activity was determined if the number of line crossings in the medication group exceeded that in the control group. Conversely, a

decrease in locomotor activity was inferred if the number of line crossings was lower than that of the control group.

***Statistics***

The Shapiro-Wilk test was used to determine if the data obtained from the groups had a normal distribution. One-way analysis of variance (ANOVA) was used to determine the significance of the differences between groups. When a significant difference was found, Tukey's test was used for multiple comparisons under the assumption that variances were homogeneous. For all tests, a significance level of $p<0.05$ was considered statistically significant.

## Results

Table 2 illustrates the impact of venlafaxine, amantadine, zinc sulfate, and folic acid treatment on the immobility scores of mice. Venlafaxine and zinc sulfate, administered at dose of 30 mg/kg, resulted in a significant reduction in immobility time, by approximately 50%. Similarly, amantadine at a dose of 20 mg/kg and folic acid at a dose of 5 mg/kg decreased in immobility time.

No significant difference ($p>0.05$) was observed between the groups that received venlafaxine and those receiving zinc sulfate and folic acid. Immobility time in the amantadine-treated group was significantly shorter than that in the control group ($p<0.01$). Conversely, the mean immobility time of the zinc sulfate + folic acid group was significantly longer than that of the folic acid + amantadine group ($p<0.01$). Similarly, the mean immobility time of the zinc sulfate + amantadine and zinc sulfate + folic acid + amantadine groups was significantly shorter than that of the folic acid + amantadine group ($p<0.05$). There was no noticeable difference in the mean immobility time between the zinc sulfate + amantadine and zinc sulfate + amantadine + folic acid groups ($p>0.05$). Additionally, the mean immobility time of the amantadine group alone was significantly shorter than that of the zinc sulfate + folic acid group ($p<0.05$) (Table 2).

Table 3 shows the effects of zinc sulfate, folic acid, and amantadine alone or in combination on spontaneous locomotor activity in mice. Compared to the control and other groups, the group that received venlafaxine had a considerably reduced mean number of line crossings($p<0.01$). There was no significant difference in the mean number of line crossings among the zinc sulfate, folic acid, and zinc sulfate + folic acid groups($p>0.05$). However, the mean number of line crossings in these groups was notably lower than that in the control group and all other groups except for the venlafaxine group ($p<0.01$).

When comparing the amantadine, folic acid + amantadine, zinc sulfate + amantadine, and zinc sulfate + folic acid + amantadine groups with the control group, the mean number of line crossings didn't significantly change ($p>0.05$). However, the mean number of line crossings in these groups was significantly higher than in the venlafaxine group ($p<0.01$) (Table 3).

**Table 2.** Mean ± SD values of immobility times obtained in the forced swimming test for each group

| Groups | *n* | Mean ± SD (sec) |
|---|---|---|
| Control | 8 | 167.3 ± 5.86* |
| Venlafaxine 30 mg/kg | 8 | 91.49 ± 2.51 |
| Zinc sulfate 30 mg/kg | 8 | 93.99 ± 2.8* |
| Folic acid 5 mg/kg | 8 | 93.20 ± 1.72 |
| Amantadine 20 mg/kg | 8 | 72.91 ± 3.38* |
| Zinc sulfate 30 mg/kg + Folic acid 5 mg/kg | 8 | 85.24 ± 3.88 **** |
| Folic acid 5 mg/kg with Amantadine 20 mg/kg | 8 | 67.54 ± 3.88**,*** |
| Zinc sulfate 30 mg/kg with Amantadine 20 mg/kg | 8 | 62.12 ± 2.29 |
| Zinc sulfate 30 mg/kg with Folic acid 5 mg/kg + Amantadine 20 mg/kg | 8 | 62.05 ± 0.95 |

** : The comparison of the venlafaxine, zinc sulfate and folic acid groups than that of the control group (p<0.01)*

***: The comparison of the zinc sulfate + folic acid group than that of the folic acid + amantadine group (p<0.01).*

****: The comparison of the zinc sulfate + amantadine and zinc sulfate + folic acid + amantadine groups than that of the folic acid + amantadine group (p<0.05)*

*****: The comparison of the amantadine group alone than that of the zinc sulfate + folic acid group (p<0.05)*

The effects of venlafaxine alone or in when combination with zinc sulfate, folic acid, and amantadine on immobility scores in mice are illustrated in Table 4. The mean immobility times of all groups (except control group) were significantly shorter than those of the venlafaxine group ($p<0.01$). The mean immobility time, the venlafaxine + folic acid group was significantly shorter than that of the other groups ($p<0.01$). The mean immobility time of the venlafaxine + amantadine group was significantly shorter than that of the venlafaxine + zinc sulfate group ($p<0.01$). The mean immobility time of the venlafaxine group was significantly shorter than that of the control group ($p<0.01$) (Table 4).

The effects of venlafaxine administration, both independently and in conjunction with other medications, on the spontaneous locomotor activity in mice are illustrated in Table 5. The mean number of line crossings in the venlafaxine group is significantly lower than in all other groups ($p<0.05$). There is no significant difference in the mean number of line crossings between the folic acid + venlafaxine group and the venlafaxine + zinc sulfate group ($p>0.05$). However, the mean number of line crossings in both of these groups is significantly lower than that in the venlafaxine + amantadine group ($p<0.01$). Except for the venlafaxine + amantadine group, the mean number of line crossings in all groups is significantly lower than that of the control group ($p<0.01$). There is no significant difference in the mean number of line crossings between the venlafaxine + amantadine group and the control group ($p>0.05$) (Table 5).

**Table 3.** Values of line crossing numbers obtained in the open field test for each group

| Groups | *n* | Mean ± SD (sec) |
|---|---|---|
| Control | 8 | 78.25 ± 2.25 *,** |
| Venlafaxine 30 mg/kg | 8 | 60.50 ± 1.60 *** |
| Zinc sulfate 30 mg/kg | 8 | 69.37 ± 2.50 |
| Folic acid 5 mg/kg | 8 | 73.00 ± 2.72 |
| Amantadine 20 mg/kg | 8 | 78.00 ± 2.00 |
| Zinc sulfate 30 mg/kg with Folic acid 5 mg/kg | 8 | 72.25 ± 2.76 |
| Folic acid 5 mg/kg with Amantadine 20 mg/kg | 8 | 77.37 ± 3.24 |
| Zinc sulfate 30 mg/kg with Amantadine 20 mg/kg | 8 | 80.00 ± 2.00 |
| Zinc sulfate 30 mg/kg with Folic acid 5 mg/kg + Amantadine 20 mg/kg (Group 8) | 8 | 78.50 ± 1.41 |

**: The comparison of the venlafaxine than that of the control group (p<0.01)*
***: The comparison of the zinc sulfate, folic acid, and zinc sulfate + folic acid groups than that of the control group (p<0.01)*
****: The comparison of the amantadine, folic acid + amantadine, zinc sulfate + amantadine, and zinc sulfate + folic acid + amantadine groups than that of the venlafaxine group (p<0.01)*

**Table 4.** Values of immobility times in the forced swimming test for venlafaxine combined with other drugs and the venlafaxine group

| Groups | *n* | Mean ± SD (sec) |
|---|---|---|
| Control | 8 | 167.29 ± 5.86**** |
| Venlafaxine 30 mg/kg | 8 | 91.49 ± 2.51* |
| Venlafaxine 30 mg/kg + Folic acid 5 mg/kg | 8 | 62.76 ± 1.74** |
| Venlafaxine 30 mg/kg + Zinc sulfate 30 mg/kg | 8 | 82.25 ± 2.58*** |
| Venlafaxine 30 mg/kg + Amantadine 20 mg/kg | 8 | 70.64 ± 1.98 |

**: The comparison of the all groups(except control group) than of the venlafaxine group (p<0.01)*
***: The comparison of the all groups than that of the venlafaxine + folic acid group (p<0.01)*
****: The comparison of the venlafaxine + amantadine group than that of the venlafaxine + zinc sulfate group (p<0.01)*
*****: The comparison of the venlafaxine than that of the control group (p<0.01)*

**Table 5.** Values of line crossing numbers obtained in the open field test for venlafaxine combined with other drugs and the venlafaxine group

| Groups | *n* | Mean ± SD (sec) |
|---|---|---|
| Control | 8 | 78,25 ± 2,25*** |
| Venlafaxine 30 mg/kg | 8 | 60,50 ± 1,60* |
| Venlafaxine 30 mg/kg + Folic acid 5 mg/kg | 8 | 64,12 ± 2,53 |
| Venlafaxine 30 mg/kg + Zinc sulfate 30 mg/kg | 8 | 63,87 ± 2,53 |
| Venlafaxine 30 mg/kg + Amantadine 20 mg/kg) | 8 | 77,62 ± 2,66** |

**: The comparison of the all groups than that of the venlafaxine group (p<0.05)*
***: The comparison of the venlafaxine+folic acid and venlafaxine + zinc sulfate groups than that of the venlafaxine + amantadine group (p<0.01).*
****: The comparison of the venlafaxine, venlafaxine+folic acid and venlafaxine+zinc sulfate groups than that of the control group (p<0.01).*

## Discussion

Clinically effective antidepressant treatment includes pharmacological and non-pharmacological methods such as electroconvulsive therapy, encompassing a notable structural diversity of drugs, primarily targeting monoamine reuptake or metabolism. Only about 60-70% of patients respond to these treatments, and they have a range of undesirable side effects (19). Consequently, research has been ongoing for years in the quest for "better" antidepressants. Recently, functional glutamatergic-NMDA receptor antagonists have been shown to possess antidepressant-like properties (20).

Our findings revealed that non-competitive NMDA receptor antagonists, such as zinc sulfate, folic acid, and amantadine, reduced immobility time in the forced swimming test in mice to a degree comparable to that of venlafaxine. This is consistent with previous research indicating a dose-dependent decrease in the immobility duration in rats following treatment with amantadine and memantine (21). The antidepressant effects of the NMDA receptor antagonist ketamine and MK-801 were demonstrated in a study using the forced swimming test as a model of depression. (22). In the forced swimming test in mice, it was observed that the antidepressant like effects of both zinc sulfate hydroaspartate and citalopram were enhanced when administered in combination, and the locomotor activity of the animals decreased compared to the control group (23). Ketamine is an anesthetic drug used in dissociative anesthesia. The antidepressant effect of ketamine has been investigated for a long time. In addition clinical research has demonstrated the antidepressant benefits of ketamine, a potent NMDA antagonist, in depressive patients (24, 25).

In the present study, the antidepressant like effects of venlafaxine were compared when administered alone and in combination with zinc sulfate, folic acid, and amantadine, as well as when these three drugs were administered separately.

Zinc sulfate has an antidepressant like effect that has been shown in the literature in prior research as well as in our study. NMDA receptor antagonism has been shown to play a role in the antidepressant like effect of zinc sulfate (26). This study also compared the antidepressant like effects of zinc sulfate with those of amantadine and folic acid. Similar to previous studies, zinc sulfate did not enhance locomotor activity in the present study. When zinc sulfate was administered alone, it showed a similar effect to venlafaxine and folic acid, but was found to be less effective than amantadine. However, when zinc sulfate was combined with amantadine, the resulting antidepressant like effect was greater than that of the combination with folic acid. The effect of the zinc sulfate + amantadine combination was similar to that of the zinc sulfate + amantadine + folic acid combination. In terms of locomotor activity, zinc sulfate did not increase locomotor activity when administered alone or in combination with other drugs. When administered with

venlafaxine, the combination of zinc sulfate showed a greater antidepressant like effect than venlafaxine alone, but showed less antidepressant like effects than the combinations of venlafaxine + folic acid and venlafaxine + amantadine. The zinc sulfate + venlafaxine combination reduced locomotor activity compared to that in the control group.

Imipramine, citalopram, tianeptine and zinc sulfate hydroaspartate were administered repeatedly for 7, 14 and 21 days in rats. In most rats, treatments resulted in a decrease in the amplitude of pharmacologically isolated NMDA and AMPA/kainate receptor-mediated field potential components. The effects of zinc sulfate and tianeptine were evident even after 7 days of treatment (27). Folic acid has been shown to contribute to the recovery and improvement of individuals with depression. According to studies conducted on patients with depression, there is a relationship between depressive conditions (especially severe depression) and low levels of folic acid (28). When combined with zinc sulfate, folic acid exhibit a higher antidepressant like effect than venlafaxine alone. In our study, we observed that when amantadine was administered, the antidepressant like effect increased when combined with zinc sulfate. When applied in a triple combination of folic acid, zinc sulfate, and amantadine, the antidepressant like effect was higher than when administered in binary combinations or alone. Folic acid enhanced the effect of venlafaxine and was found to be more effective than the venlafaxine-zinc sulfate and venlafaxine-amantadine combinations. Patients who did not respond adequately to antidepressant treatment had low levels of folic acid in their blood. It was observed that the effectiveness of the treatment increased when patients were given folic acid treatment before the treatment (29). In a study involving 110 outpatient patients with severe depression during an 8-week fluoxetine treatment period, serum folic acid, B12 vitamin, and homocysteine levels were monitored. The clinical response to improvement initially showed a 30% reduction in the Hamilton Depression Rating Scale (HDRS) score and subsequently a 50% reduction after eight weeks. Low serum folic acid levels were observed at the beginning of clinical improvement. Serum folic acid levels increased over time (30). Similar to our study, when venlafaxine was combined with folic acid and administered for 14 and 21 days, an increase in antidepressant like effect was observed in both the forced swim test and the tail suspension test (31). In this study, amantadine alone exhibited a higher antidepressant like effect than venlafaxine, zinc sulfate, and folic acid. When venlafaxine and amantadine were administered together, they showed a lower antidepressant like effect than venlafaxine alone and venlafaxine + folic acid, but a higher antidepressant like effect than venlafaxine + zinc sulfate. In another study, imipramine, venlafaxine, fluoxetine, and non-competitive NMDA antagonists, amantadine, memantine, and neramexane were used in a forced swimming test in mice to demonstrate synergistic interactions (32).

In our study, it was observed that the antidepressant like effect increased when folic acid and zinc sulfate were administered. Similarly, magnesium and copper deficiencies have been thought to contribute to depression. It is suggested that both minerals exert antidepressant like effects through NMDA antagonism (33).

## Conclusion

When comparing the antidepressant like effects of zinc sulfate, folic acid, and amantadine, the highest antidepressant like effect was observed with amantadine. If these drugs are administered in binary combination form, the highest antidepressant like effect is observed with the zinc sulfate + amantadine combination. When these drugs were combined with venlafaxine, the highest antidepressant like effect was observed with the combination of venlafaxine and folic acid. The use of these combinations in the treatment of depression is important in terms of efficacy. Further research is needed on the use of these combinations for the treatment of depression.

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