# Memantine as an Add-on Therapy in Alcohol Withdrawal Syndrome

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**ÖZET:**

## Alkol geri çekilme sendromunda ek tedavi olarak memantinin etkinliği

**Amaç:** NMDA reseptör antagonistlerinin alkol geri çekilme sendromunun tedavisinde, nöbetleri önlemede ve günlük alınan alkol miktarını azaltmada etkili olduğu yapılan preklinik çalışmalarda gösterilmiştir. Ancak insanlarda alkol yoksunluğu sendromunda NMDA reseptör antagonistlerinin etkinliği ile ilgili çok az sayıda çalışma vardır. Bu çalışmada bir NMDA reseptör antagonisti olan memantinin alkol geri çekilme sendromu tedavisinde etkinliğini ölçmeyi amaçladık.

**Metot:** Çalışma prospektif, randomize, çift kör bir çalışma olarak planlanmıştır. Çalışmaya toplam 32 hasta alındı. 16 hasta benzodiazepin ve memantin grubuna randomize edilirken, 16 hasta benzodiazepin ve plasebo grubuna randomize edildi. Hastalara ilk hafta 10mg/gün memantin verilirken, ikinci hafta doz 20 mg/gün memantine yükseltildi. Alkol geri çekilme belirtilerinin şiddeti Gözden Geçirilmiş Alkol Geri Çekilme Şiddeti Derecelendirme Formu (CIWA-AR) ile ölçüldü. Hastaları değerlendirmek için ayrıca Alkol Kullanım Bozuklukları Tarama Testi (AKBTT), Karbonhidrattan yoksun transferin (CDT), ortalama eritrosit hacmi (MCV) ve gama glutamil transferraz (GGT) testleri kullanıldı. Mann-Whitney-U testi kullanılarak1., 4., 7., 10. ve 15. günlerde iki grubun CIWA-AR skorları karşılaştırıldı. Çoklu testler için p değerleri düzeltildi.

**Bulgular:** Her iki grupta yaş, cinsiyet, evlilik hali, eğitim ve iş sahibi olma açısından benzer özellikler gösteriyordu. Ayrıca çalışmanın başlangıcında her iki grup arasında AUDIT, CDT, MCV ve GGT skorları açısından fark bulunmadı. Çalışmanın başlangıcında memantin grubunun CIWA-AR skoru ortalaması 23.63±7.24 iken plasebo grubunun CIWA-AR skoru ortalaması 22.94±7.47 olarak tespit edildi. Gruplar arasındaki fark istatistiksel olarak anlamlı değildi. 4., 7, 10. ve 15. ölçüm günlerinde memantin kullanan hastaların CIWA-AR skorları sırasıyla 7.88±4,37, 2.44±2.03, 0.94±0.99 ve 0.25±0.44'dü. Plasebo grubundaki hastaların 4., 7, 10. ve 15. ölçüm günlerindeki CIWA-AR skorları ise sırasıyla 8.63±4,79, 4.19±2.10, 2.50±1.82 ve 1.13±0.96 bulundu. Ek ilaç olarak memantin kullananlarda CIWA-AR skorlarında düzelme daha iyi olmasına karşın, aradaki fark istatistiksel olarak anlamlı değildi. Memantin kullananlarda ayrıca CIWA-AR ölçeğinin tremor ve terleme gibi alt ölçek puanlarında daha fazla düşüş bulundu. Yine de iki grup arasındaki fark istatistiksel olarak anlamlı değildi.

**Sonuç:** Memantinin alkol geri çekilme sendromu tedavisinde etkili olduğunu gösteren çalışmalara karşın çalışmamızda istatistiksel olarak anlamlı bir farklılık bulmadık. Bizim çalışmamızda memantinin plaseboya üstünlüğü yoktu. Buna rağmen daha fazla denek sayısıyla, ek ilaç verilmeden yapılacak randomize plasebo kontrollü çalışmalar, memantinin ve diğer antiglutamaterjik ajanların alkol geri çekilme sendromundaki etkinliğini göstermede yardımcı olabilir.

**Anahtar sözcükler:** Memantin, NMDA, alkol geri çekilmesi

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**ABSTRACT:**

## Memantine as an add-on therapy in alcohol withdrawal syndrome

**Objective:** NMDA receptor antagonists were found to be effective treating alcohol withdrawal syndrome, preventing seizures, and decreasing daily alcohol intake in preclinical studies. But there were only few studies on the efficacy of NMDA receptor antagonists in humans. In this current study, we evaluated the effects of memantine, an NMDA receptor antagonist on alcohol withdrawal syndrome.

**Methods:** The study was planned as a prospective, randomized; double-blind study. In total, 32 patients enrolled in study. 16 patients were randomized to benzodiazepine plus memantine group and 16 were randomized to benzodiazepine plus placebo group. Memantine was administered to patients as 10 mg/day in first week of study and 20 mg/day in second week of study. Severity of alcohol withdrawal was measured by Revised Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-AR). Mean Corpuscular Volume (MCV), Gama Glutamyl transferase (GGT), Carbohydrate Deficient Transferrine (CDT), and Alcohol Using Disorders Identity Test (AUDIT) tests were also administered to evaluate patients. CIWA-AR scores of the two groups were compared with Mann-Whitney U test at 1$^{st}$, 4$^{th}$, 7$^{th}$, 10$^{th}$, and 15$^{th}$ days of treatment. P values were corrected for multiple comparisons.

**Results:** Two groups were identical on age, sex, marital status, education and employment. There were also no differences in AUDIT, CDT, MCV, and GGT scores between two groups at the beginning of the study. Mean CIWA-AR score of the memantine group was 23.63±7.24 and mean CIWA-AR score of the placebo group was 22.94±7.47 at the beginning of the study. The difference between two groups was not statistically significant. CIWA-AR scores of the memantine group were 7.88±4,37, 2.44±2.03, 0.94±0.99, and 0.25±0.44 respectively on the 4$^{th}$, 7$^{th}$, 10$^{th}$ and 15$^{th}$ measurement days. CIWA-AR scores of the placebo group were 8.63±4,79, 4.19±2.10, 2.50±1.82, and 1.13±0.96 respectively on the 4$^{th}$, 7$^{th}$, 10$^{th}$ and 15$^{th}$ measurement days. Although the decline in CIWA-AR scores was higher in memantine group, there was no statistically significant difference between memantine and placebo group. Memantine group had better improvement in tremor and sweating subscales of CIWA-AR but this difference was not statistically significant.

**Discussion:** Despite the previous results that were mentioning that memantine was effective in alcohol withdrawal syndrome, we could not find statistically significant difference between two groups. Although memantine was not superior to placebo in our setting, randomized placebo controlled studies with more subjects and no extra medication might be helpful for showing efficacy of memantine and other antiglutamatergic agents in alcohol withdrawal syndrome.

**Key words:** Memantine, NMDA, alcohol withdrawal

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## INTRODUCTION

Alcohol acts in the brain by influencing several different systems such as dopaminergic, serotonergic, and glutamatergic systems (1). NMDA (N-methyl-d-aspartate) and glutamatergic systems have been the most frequently addressed pathways for alcohol dependency in recent years (2). Accumulating evidence suggests that prolonged ethanol exposure leads to a compensatory "upregulation" of NMDA mediated functions supposedly contributing to the occurrence of ethanol tolerance, dependence, as well as the acute and delayed signs of ethanol withdrawal (3). Most of the data revealing the role of glutamatergic system in alcohol addiction comes from experimental studies. Demonstration of efficacy of antiglutamatergic agents in animal studies has reinforced beliefs concerning a causative relationship between dependency and the glutamatergic system (4). The strongest evidence for the involvement of this system in humans as well, comes from acamprosate clinical trials. Being a homocystic acid derivative, acamprosate is a structural analog of glutamate. The ability of drugs acting on NMDA receptors, such as acamprosate and topiramate, to reduce both withdrawal and craving behavior have drawn attention to NMDA and glutamatergic system (5,6).

Memantine is an NMDA receptor antagonist that has been approved for the treatment of Alzheimer's disease. It was synthesized in Lundbeck laboratories with the chemical name of 1-amino-3,5-dimethyladamantane hydrochloride. The NMDA receptor blocking effect of the agent was discovered in late 1980s (7,8). After demonstration of the roles of glutamate and NMDA receptors in the course of alcohol dependency, the molecule was initially tested in preclinical trials and then was used in a limited number of clinical trials. Lukoyanov et al. administered diclozipine, a non-selective NMDA antagonist, and memantine, a selective NMDA antagonist, to alcohol dependent mice after initiation of withdrawal symptoms and observed that although withdrawal symptoms did not respond to diclozapine, they were completely abolished by memantine (9). Kotlinska showed that memantine prevents the development of alcohol dependency in mice (10). Memantine was also as effective as diazepam in preventing withdrawal seizures in alcohol dependent mice (11,12). In their study on hypocampal cell cultures, Maler et al. have reported that NR1, NR2A, and NR2B subunits of NMDA receptors were induced by ethanol, however, this induction was not observed when memantine was co-administered with ethanol (13). Preclinical trials were suggesting that memantine reduces withdrawal symptoms resulting from hyperexcitability by inhibiting the stimulatory effects of alcohol on the NMDA receptor (11,13).

Efficacy of memantine humans was tested only in few studies. Bisaga and Evans administered 15 to 30 mg/day of memantine to 18 volunteers and found that memantine reduced craving if administered before alcohol intake (14). Later, when Evans et al. conducted a study in a double blind placebo-controlled design, memantine was not found to be significantly more effective than placebo in reducing alcohol intake (15). On the other hand, Krupitsky et al. showed that memantine reduced alcohol-related craving in a dose dependent manner (16).

In this current study, we investigated the effects of memantine, an NMDA antagonist, administered as an adjunctive medication in alcohol withdrawal syndrome.

## MATERIALS AND METHOD

Study Design and Instruments. This study was conducted in the Alcohol and Substance Abuse Center of Ankara Numune Hospital and was approved by the local Institutional Ethics Committee. Randomly selected 16 male patients between 18 and 65 years of age, who had a diagnosis of alcohol dependency according to DSM-IV criteria, were included in the study. An additional 16 male patients were included as the comparison group. All participants provided written informed consent. Those patients with comorbid chronic medical disorders such as diabetes mellitus, hepatic cirrhosis, anemia, hypertension etc. were excluded from the study. All patients were evaluated with SCID-I (Structured clinical Interview for DSM-IV) and patients with any axis I disorder other than nicotine dependency were also excluded from the study.

This study was designed as a prospective, randomized, double-blind, placebo-controlled trial. Patients were assessed for inclusion criteria on their first day of hospitalization. In addition to a semi-structured questionnaire form developed by the investigators consisting of items including sociodemographic data and detailed history of alcohol use, Alcohol Using Disorders Identity Test (AUDIT) and Revised Clinical Institute

Withdrawal Assessment for Alcohol scale (CIWA-AR) questionnaires were administered to each patient. AUDIT is a 10-item screening test providing information about drinking habits, alcohol consumption, and alcohol-related problems (17). Validity and reliability of Turkish form of AUDIT was made by Saatcioglu et al (18). CIWA-AR is a 10-item scale developed by Sullivan in 1989 to measure the severity of alcohol withdrawal syndrome (19). These 10 items are nausea, tremor, paroxysmal sweating, anxiety, agitation, tactile disturbances, auditory disturbances, visual disturbances, headache and orientation. A score of < 8 is defined as mild, 9 to 14 as moderate, and > 15 as severe withdrawal syndrome (19).

Routine investigations including a total blood count, serum biochemistry, hepatitis markers, thyroid markers, chest x-ray, and urinalysis were performed in all patients. Moreover, objective biological markers that are used in alcohol using disorders such as gamma glutamyl transferase (GGT), mean corpuscular volume (MCV) and carbohydrate deficient transferrin (CDT) were measured. For serum CDT level measurement, blood samples of all patients were obtained from their antecubital veins into anticoagulant-free test tubes at admission (prior to detoxification therapy was initiated). Serum samples were stored at -70°C after being centrifuged at 4000 rpm for 10 min. CDT% was assessed by Turbidimetric Immunoassay (TIA) method using Bio-Rad CDT% TIA kit in Behring Nephelometer BN-100. It was computed by using the following formula: CDT% = 7.8 x (CDT/Total Transferrin) - 0.2. For serum GGT level measurement, blood samples of all patients were obtained from their antecubital veins into anticoagulant-free test tubes at admission. After serum samples were centrifuged at 4000 rpm for 10 min, GGT levels were measured by Szasz-Persijn color test method in Roche Cobas Integra 400 plus (Roche Diagnostic GmbH, Deutschland) using L-gamma-glutamyl-3-carboxy-4-nitroanilide as substrate. For blood MCV level measurement, blood samples were obtained from antecubital veins to EDTA tubes. The MCV measurements were performed by using Sysmex KX-21N haemogram device.

Since subjects with alcohol withdrawal syndrome demonstrating evident symptoms were included in the study, a standard dose of 30 mg/day diazepam was initiated in all patients and fluid-electrolyte balance was maintained. Diazepam dose was given as mentioned in the literature for patients with severe alcohol withdrawal syndrome (20). Diazepam dose was reduced daily by 5 mg and discontinued at the end of the sixth day. Memantine 10 mg/day was started in patients who were previously randomized to the active drug group. The dose was increased to 20 mg/day at the eight day and stopped at the fifteenth day. Dose of memantine was given as its dose in Alzheimer Disease. Currently the recommended daily dose of memantine in Alzheimer Disease is 20mg (10mg twice daily) (21). Corresponding amounts of placebo were administered to patients in the control group. Oral solution form of memantine was given to study group and a colorless, clear, alcohol and sugar free liquid was used as placebo. All medicines and placebo were provided by researchers. Randomization procedures and dose setting, administration of treatment and questionnaires were performed by different investigators. CIWA-AR was administered to all patients at the same time of the day for each patient.

Statistics. SPSS 13.0 software was used for statistical

**Table 1: Demographic characteristics of the participants**

| | Memantine Group (16 patients) (n) (%) | Placebo Group (16 patients) (n) (%) | Mann Whitney-U test P value |
|---|---|---|---|
| Age | 45.8±8.7 | 43.6±7.3 | 0.76 |
| Education (years) | 8.5±3.5 | 9.1±3.4 | 0.51 |
| Employment (fulltime) | 12 (%75) | 14 (%87,5) | 0.65 |
| Age of first alcohol use | 18.2±4.8 | 19.7±5.4 | 0.82 |
| Age of regular alcohol use | 15.9±9.0 | 11.5±5.7 | 0.99 |
| Drinks per day | 22.2±7.8 | 19.6±6.1 | 0.347 |
| History of epileptic seizures | 5 (%31,3) | 3 (%18,8) | 0.41 |
| History of delirium tremens | 2 (%12,5) | 2 (%12,5) | 1 |
| Alcohol Using Disorders Identity Test | 37±3.4 | 35.1±4.6 | 0.17 |
| Carbohydrate Deficient Transferrine | 5.82 | 4.81 | 0.64 |
| Mean Corpuscular Volume | 96.7 | 98.4 | 0.36 |
| Gama Glutamyl Transferase | 138.8 | 193.2 | 0.69 |

**Table 2: Average of CIWA-AR scores in measurement days**

| Day | Memantine Group | Placebo Group | P value | Z |
|---|---|---|---|---|
| 1 | 23.63±7.24 | 22.94±7.47 | .696 | -0.32 |
| 4 | 7.88±4,37 | 8.63±4.79 | .423 | -1.08 |
| 7 | 2.44±2.03 | 4.19±2.10 | .017 | -2,27 |
| 10 | 0.94±0.99 | 2.50±1.82 | .019 | -2.69 |
| 15 | 0.25±0.44 | 1.13±0.96 | .023 | -0.11 |

analysis. Descriptive analysis was performed for sociodemographic data. CIWA-AR scores comparisons of groups were made by the Mann Whitney-U test. Bonferroni correction was made for multiple testing. (Bonferroni-adjusted $p<0.01$)

## RESULTS

There were no significant differences between the study and control groups in terms of age, educational status, occupation, age at starting alcohol, mean duration of alcohol use, and daily amount of alcohol consumption ($p>0.05$). The mean baseline AUDIT score reflecting drinking habits, alcohol consumption, and alcohol-related problems was 37.0±3.4 for the study group and 35.1±4.6 for the control group. No statistically significant difference was found between the groups for baseline AUDIT score ($p>0.05$). The baseline mean CDT, MCV and GGT values, that are objective biological markers used in the assessment of alcohol dependency, were not statistically different between the two groups ($p>0.05$). Baseline characteristics of the study groups are presented in Table 1.

In order to assess the severity of withdrawal symptoms, the CIWA-AR scale was administered to all patients by the same, blinded investigator on the 1st, 4th 7th, 10th and 15th days at the same time of the day. CIWA-AR scores of the first six days were not significantly different between the groups when compared using the Mann-Whitney U test ($p>0.05$). At the seventh day, CIWA-AR scores of the memantine group were significantly different than the control group. But when we made corrections for multiple comparisons this significance disappeared. CIWA-AR scores are presented in Table 2.

In this study we also compared the two groups according to CIWA-AR item subscores on the 1st, 4th 7th, 10th and 15th days. Difference between the groups in tremor (memantine 1,51±0,82, control 2,12±0,71) and paroxysmal sweating (memantine 0,81±0,75, control 1,43±0,72) subscale scores on the fourth day were significant. But this significance did not exist after corrections for multiple comparisons ($p>0.01$). The decrease in other subscale scores in the memantine group were also higher but the differences were not statistically significant ($p>0.01$).

## DISCUSSION

In general, substances having cross-tolerance with alcohol are used in the treatment of alcohol-related withdrawal symptoms, and benzodiazepines are frequently the first drug of choice all around the world (22). Apart from benzodiazepines, many pharmacological agents have been used in the management of alcohol withdrawal syndrome. Although they are not used alone in the treatment of alcohol withdrawal syndrome, these agents may increase efficacy and decrease treatment duration when used as supplementary drugs (23).

We used a NMDA receptor antagonist, memantine, as an adjunctive drug in the treatment of alcohol withdrawal syndrome in this study. We found that memantine group had lower CIWA-AR scores during study periods. We also found that CIWA-AR subscale scores such as tremor and paroxysmal sweating were lower in memantine group on measurement days. But when we compared groups statistically, we found that addition of memantine to standard alcohol withdrawal treatment did not cause any statistically significant difference between these two groups. There were a few studies in literature mentioning the efficacy of memantine in alcohol withdrawal syndrome and these studies differentiated from our study with the study design and memantine doses. In one of these studies Bisaga and Evans used memantine as a pharmacological probe to look at the processes involved in the effects of alcohol in moderate drinkers and reported that memantine reduced the daily amount of alcohol intake (14). In another study Evans et al. used memantine

in treatment seeking alcohol dependent individuals (15). They looked whether it would reduce craving in a dependent population in a 16 week treatment trial and did not find a statistically significant difference between memantine and placebo groups (15). In a study similar to our study design, Krupitsky et al. found that memantine 30mg/day was effective in alcohol detoxification (16). In the same study, they also found that lamotrigine and topiramate were effective in alcohol detoxification and suggested that antiglutamatergic approaches might be useful in alcohol withdrawal syndrome (16). In this study, different from ours, researchers used higher doses of memantine without an additional medication. We might speculate that if the study was designed in a way that memantine would be used as a single therapeutic agent; it might be possible to find statistically significant differences between the memantine and placebo groups starting from the first day. The combined use of memantine and diazepam has probably concealed observation of this finding.

Despite the advantages of this current study such as the study population being chosen from hospitalized patients and frequently performed assessments, our study has some potential limitations. The main limitation is the small sample size, 16 patients in study and control groups, which precluded the use of parametric tests that would provide more reliable statistical results. Secondly, since memantine has not been approved to be used in the management of alcohol withdrawal, doses that have been approved for the treatment of dementia were used in our study. Krupitsky et al. who used higher doses of memantine, (30mg/day) found that it was effective in alcohol withdrawal symptoms (15). This finding suggests us that the required dose in alcohol withdrawal might be higher. Controlled studies with flexible-dosing are needed to address this issue.

In conclusion, preclinical and clinical studies mention that anti glutamatergic medications are effective in alcohol withdrawal syndrome. Despite the previous reports that were mentioning that memantine was effective in alcohol withdrawal syndrome; we did not find statistically significant difference between these two groups. Although memantine was not superior to placebo in our study setting, randomized placebo controlled studies with larger sample size and no additional medication might be helpful for providing insights on the efficacy of memantine and other antiglutamatergic agents in alcohol withdrawal syndrome.

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