Double-Blind, Randomized Comparison of Memantine and Escitalopram for the Treatment of Major Depressive Disorder Comorbid With Alcohol Dependence

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Objective: The aim of the study was to evaluate possible new treatments for major depressive disorder in patients with comorbid alcohol dependence in a municipal alcohol treatment unit. The efficacy of memantine, a noncompetitive glutamate *N*-methyl-D-aspartate (NMDA)-receptor blocker used for the treatment of moderate to severe Alzheimer's disease, was compared with that of escitalopram, a selective serotonin reuptake inhibitor antidepressant.

Method: Eighty alcohol-dependent outpatients with major depressive disorder (DSM-IV criteria) seeking treatment from municipal alcohol treatment clinics in Helsinki, Finland, were randomly assigned 1:1 to receive memantine 20 mg/day or escitalopram 20 mg/day. During the study period, patients continued their routine treatment at the clinics. Abstinence was not required. Concomitant interventions or imposed treatment goals were not offered by the study physician. The patients returned to the treatment clinics at weeks 1, 2, 4, 12, and 26 for data collection and for medication checking and dispensing. Outcome measures were the Montgomery-Asberg Depression Rating Scale (MADRS) and Beck Depression Inventory-II for depression, Hamilton Rating Scale for Anxiety (HAM-A) and Beck Anxiety Inventory for anxiety, Consortium to Establish a Registry for Alzheimer's Disease test battery for cognitive functions, and Social and Occupational Functioning Assessment Scale for social and occupational functions and quality-of-life measures. Twenty-nine patients in each group completed the study. All primary and secondary outcome statistical analyses were performed by an independent source for intent-to-treat populations, which included all patients randomly assigned to treatment. The study was conducted from December 2004 to May 2006.

Results: Both treatments significantly reduced the baseline level of depression and anxiety according to MADRS and HAM-A, which were the primary measures ($p < .0001$). There was no significant difference between the memantine and escitalopram groups. Assessed cognitive functioning scores were primarily within the normative range and were unchanged in both groups. Quality-of-life outcomes equally improved in both treatment groups.

Conclusions: These data provide new evidence for the safety and potential efficacy of memantine and escitalopram for major depressive disorder in patients with comorbid alcohol dependence.

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Alcohol dependence and alcohol abuse are significant public health problems all over the world.[1,2] The lifetime prevalence of alcohol dependence was 5.4% in the United States among those over the age of 18 years in the National Comorbidity Survey (NCS) Replication.[2] The lifetime prevalence of alcohol abuse was 14.1% (men 20.1%, women 8.2%) in the NCS[1] and 13.7% in men and 4.1% in women in the Cross-National Comparisons (CNC) in the Seven Surveys.[3] Co-occurrence of alcohol dependence in those with depressive disorders was common: 24.3% in men and 48.5% in women according to the NCS[1] and 18.1% in men and 41.2% in women according to the CNC.[3] In Finland, the 1-year prevalence of comorbid alcohol dependence and major depressive disorder

(MDD) according to the Finnish Health 2000 Survey[4] was 0.4% in the population over the age of 30 years in the year 2000.

Concurrent depression and alcoholism lead to greater disability than alcoholism alone.[5,6] The lifetime suicide rate is estimated to range from 2% to 18% in alcoholism[7,8] and from 2% to 15% in depression.[8] Comorbidity increases the risk of suicide among depressive patients 2.1 times.[8]

The medical treatment of MDD comorbid with alcohol dependence is difficult and controversial.[9] Clinical improvement in mood and alcohol dependence was shown with mirtazapine in a multicenter, open-label study.[10] A recent placebo-controlled trial with sertraline did not provide consistent support for the use of sertraline[11] or resulted in an improvement that was modest at best and seen mainly in women.[12] Nevertheless, the current attractive medications for MDD with alcohol dependence are selective serotonin reuptake inhibitors (SSRIs) for their tolerability, potential effectiveness,[9,13–15] and safety in overdose for a group of patients at known increased risk for attempting suicide.[8] Even when there is a risk of increased suicide attempts with SSRIs in depressive patients,[16] the mortality rate among these patients has been shown to decrease with SSRIs.[17]

The SSRI used in the present study is escitalopram, the *S*-enantiomer of citalopram. There is evidence from various controlled clinical trials[18] showing that citalopram is an effective antidepressant, but there are no studies in patients with comorbid alcohol dependency. Escitalopram has been reported to have better efficacy and rate of response than the racemic compound.[19,20]

Ethanol influences several areas of the brain and various neurotransmitter pathways. The capacity to block *N*-methyl-D-aspartate (NMDA) glutamate receptors may be one of the most important influences of alcohol in the brain. Chronic ethanol administration up-regulates NMDA-receptor function and contributes to ethanol tolerance.[21] There is increasing evidence that NMDA-receptors have a significant role in mood disorders.[22] A recent study showed elevated glutamate levels in the occipital cortex in medication-free subjects with MDD compared with healthy controls.[23] A preliminary study reported that the NMDA modulator riluzole was effective for treatment-resistant depression[24] and for residual depressive symptoms in those already receiving antidepressant treatment.[25] Some NMDA modulators, such as D-cycloserine and amantadine, have been shown to possess antidepressant effects when used in the treatment of tuberculosis and Parkinson's disease.[26] Lamotrigine, a compound that is used to treat bipolar depression, decreases glutamate transmission.[27,28] Recently, it was shown that intravenous injection of the NMDA antagonist ketamine hydrochloride is effective for patients with treatment-resistant MDD.[29,30]

Memantine is a noncompetitive, voltage-dependent NMDA-receptor antagonist that is approved for the treatment of moderate to severe Alzheimer's dementia. Memantine may have neuroprotective properties that may be beneficial against the neurotoxic effects of alcohol use.[21] Some studies,[31] but not all,[32] have reported that memantine has positive effects on mood.

The aim of the present study was to assess the effect of memantine relative to escitalopram in the treatment of MDD in patients with comorbid alcohol dependence, in a heterogeneous patient sample from municipal alcohol treatment clinics.

In this report, we will describe the findings from a prospective, randomized, double-blind, 26-week clinical trial examining the efficacy of memantine or escitalopram with regard to depression, anxiety, quality of life, and cognitive functions in patients with MDD comorbid with alcohol dependence.

METHOD

Study Participants and Ethics

Men and women aged 26 to 65 years who were voluntarily seeking outpatient treatment for alcohol problems at 3 Helsinki municipal Alcohol-clinics (A-clinics; Annankatu, Malmi, and Töölö clinics) were screened. Helsinki, Finland, is a city of a half-million inhabitants, and municipal A-clinics provide various nonprofit medical and psychosocial options yearly for 6000 people with alcohol problems. Patients who had a history of heavy drinking (5 or more daily drinks for men and 4 or more daily drinks for women) for at least 10 years, had significant depression (defined by Beck Depression Inventory-II [BDI-II][33] score > 17), and were interested in voluntarily taking part in the study were recommended by their A-clinic doctor or social worker therapist to the study physician's interview and screening. For inclusion, the patients were interviewed by a psychiatrist (L.H.M.) using the Structured Clinical Interview for DSM-IV (SCID)[34] and were required to meet the criteria for both alcohol dependence and MDD according to DSM-IV-TR.[35] Abstinence was not required, but the time after possible prior inpatient detoxification had to be at least 4 weeks. The exclusion criteria included other substance use dependence screened by urine test (amphetamine, benzodiazepines, cocaine, tetrahydrocannabinol, and opiates; Olympus Diagnostica GmbH, Hamburg, Germany), schizophrenia or other psychotic disorder and bipolar I and II disorder, acute risk of suicide, pregnancy or breast-feeding, a severe untreated somatic problem or a serious liver dysfunction (aspartate aminotransferase [AST] and alanine aminotransferase [ALT] > 200 U/L), and mental disability. Other medications prescribed by the patient's physician were allowed, with the exception of other antidepressants.

The study was approved by the independent Hospital District of Helsinki and Uusimaa Ethical Committee and the Finnish National Agency of Medicine. The study was conducted according to the International Conference on Harmonisation guidelines for Good Clinical Practice and the 1964 Declaration of Helsinki. The study was registered on the National Public Health study registry in March 2005 (172–9) and on ClinicalTrials.gov (NCT00368862). All patients had to be able to read and understand the patient information sheet and sign the informed consent statement. All participants were free to stop study medication whenever they wanted. The patients were not paid or reimbursed for participation.

Study Design

Study enrollment began on December 20, 2004, and the last patient completed the study on May 25, 2006. The same study physician (L.H.M.) screened, enrolled, and treated all patients. After an initial examination, patients underwent procedures including the recording of demographic and medical history, physical examination, and laboratory examinations (urine drug screen and serum AST, ALT, desialotransferrin, γ-glutamyltransferase [GGT], thyroid-stimulating hormone, creatine, sodium, and potassium). A screening interview (SCID)[34] was performed to ensure the diagnoses of MDD and alcohol dependence and to provide a detailed diagnostic characterization of the mental and alcohol problems of the patients. Interviews for the Montgomery-Asberg Depression Rating Scale (MADRS, the primary depression measure),[36] the Hamilton Rating Scale for Anxiety (HAM-A, the primary anxiety measure),[37] the Social and Occupational Functioning Assessment Scale (SOFAS),[38] and the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) cognitive test battery including the Mini-Mental State Examination (MMSE)[39] were performed. The CERAD test battery was chosen because it can easily be used by individuals other than psychologists and contains several parts assessing episodic memory, which can be impaired in alcoholics especially due to B_1-vitamin deficiency (Korsakoff's syndrome).[40] A set of questionnaires were filled in by the patients, including the BDI-II,[33] Beck Anxiety Inventory (BAI),[41] visual analog scale (VAS)[42] for quality of life (using the scale bad to excellent), and Alcohol Use Disorders Identification Test (AUDIT).[43]

All patients meeting the inclusion criteria were randomly assigned by an independent person (Sirpa Päivinen) to memantine or escitalopram groups using a 1:1 ratio (N = 40 + 40) and random permuted blocks (Vassar Statistic randomizing algorithm). The sample size was defined by dichotomous power analysis in which $\alpha = .05$, $\beta = 0.10$, $f(\alpha\beta) = 10.5$, $p_1 = 10$, $p_2 = 40$ and $N = p_1 \times (100 - p_1) + p_2 \times (100 - p_2)/(p_2 - p_1) \times 10.5 = 38$. The randomization was concealed until the study database was locked on June 6, 2006, by an independent clinical study monitor (Medikalla Oy, Medfiles; Turku, Finland). In an emergency or in case of a serious adverse event, an individual random number could be opened by the same person who performed the randomization. The study medication (provided by Lundbeck Oy Ab, Turku, Finland) was double-dummy packed: the patients took 2 pills every time, one of which was the active medicine and the other, identical placebo for the second medication. The medication was labeled and controlled by an independent supplier (Pharmia Ltd., Seinäjoki, Finland). Eligible patients received orally either 20 mg/day of escitalopram or 20 mg/day of memantine. The starting dose was 5 mg for both drugs and was increased at weekly intervals by 5 mg/day to 20 mg/day. After 4 weeks, the study physician was allowed to decrease the dose if a patient could not tolerate the medication. Patients were instructed to take the study medication in the morning. There were no additional psychosocial interventions by the study physician for alcohol consumption or other treatment goals. Patients were permitted to telephone the study physician at any time. If the patient did not appear at a scheduled visit, a new appointment was offered.

During the 26-week treatment period, the patients returned to the A-clinic at weeks 1, 2, 4, 12 ± 2, and 26 ± 2 for data collection and for medication checking and dispensing. At weeks 18 to 20, a 10- to 15-minute phone conversation with each patient was made by the study physician to ensure contact during the 3-month interval between the 2 visits. At each visit, the study medication intake since the previous visit was recorded using the medication diary. The study medication intake was measured with the pill count from the returned blisterpacks. Any possible adverse events were elicited by the study physician at each visit and recorded by the study participant to the diary for adverse events adverse events. Other measures were recorded on specific weeks: MADRS, HAM-A, SOFAS, BDI, BAI, and VAS (0, 4, 12, and 26 weeks) and CERAD (0 and 26 weeks). Clinical laboratory tests (mean corpuscular volume, carbohydrate-deficient transferrin [CDT], AST, ALT, and GGT) were taken at the beginning of research and were repeated at weeks 4, 12, and 26 to ensure the safety of test medication. Breath or blood testing for alcohol was not performed, but if the patient was obviously intoxicated, a new appointment was offered. The study was monitored by an independent organization.

Statistical Analysis

All primary and secondary outcome statistical analyses were performed by an independent source (Medikalla Oy, MedFiles; Turku, Finland). All statistical evaluations utilized SAS Procedures in SAS system for Windows (Version 8.2), SAS Institute, Espoo, Finland. The intent-to-treat populations, which consisted of all patients randomly assigned to treatment, including 2 early terminat-

Table 1. Demographic and Clinical Background Variables at Baseline[a]

Variable	Memantine (N = 40)	Escitalopram (N = 40)
Age, mean (± SD), y	47.5 (8.3)	47.9 (8.3)
Gender, N (%) male	23 (57.5)	21 (52.5)
First alcohol intoxication, mean (± SD) age, y	15.3 (3.8)	15.4 (2.3)
Onset of regular use of alcohol, mean (± SD) age, y	20.7 (6.7)	20.5 (6.3)
Onset of alcohol abuse, mean (± SD) age, y	29.5 (8.1)	28.3 (8.3)
Onset of alcohol dependence, mean (± SD) age, y	30.6 (8.3)	29.1 (8.5)
Continued alcohol abuse at time of randomization, N (%)	17 (43.6)[b]	17 (42.5)
Alcohol problems among relatives, N (%)	31 (79.5)[b]	30 (76.9)[b]
Baseline AUDIT[43] score, mean (± SD)	27.4 (7.1)	28.4 (6.4)
First depressive episode, mean (± SD) age, y	27.8 (12.3)	24.2 (13.0)
Duration of current depression, mean (± SD), mo	23.2 (30.0)	46.6 (67.9)
Total no. of depressive episodes, mean (± SD)	10.0 (7.1)	9.6 (9.0)

[a]No significant differences between groups.
[b]Missing information on 1 subject.
Abbreviation: AUDIT = Alcohol Use Disorders Identification Test.

ing patients who reported taking no medication, were used in all tables and analyses. Descriptive statistics were calculated for all variables. Categorical variables were presented in frequencies tables (PROG FREQ in SAS) (number of cases and percentages) by treatment. The numerical variables were tabulated by treatment (PROG UNIVARIATE in SAS).

Baseline analyses were analyzed by logistic regression or analysis of variance (ANOVA). MADRS, BDI (depression), HAM-A, BAI (anxiety), and CERAD (cognitive performance) were all analyzed with ANOVA for repeated measures when treatment, time (0, 4, 12, and 26 weeks), and treatment-by-time interaction were in the model (PROC MIXED in SAS), and responses to the specific question "Has your depression declined during the study?" were analyzed by logistic regression (PROC LOGISTIC in SAS).

RESULTS

Eighty-nine patients were initially screened from patients of the Helsinki A-clinic; 3 were excluded because they did not meet inclusion criteria, 5 refused to participate, and 1 did not return after initial screening. Eighty patients were randomly assigned to either memantine (N = 40) or escitalopram (N = 40). Blinding was assured by a double-dummy design. Neither the study physician (L.H.M.), nor the patients, nor the data filer (Sirpa Päivinen) knew the medication group assignment. All patients were white, and 55% were men.

There were no significant differences between groups in demographic characteristics or in the initial alcohol and depressive measures (Table 1). The mean length of the present depressive period was 35 months. Current alcohol abuse was reported by 17 patients in both groups: 43.6% (17/39) in the memantine group and 42.5% (17/40) in the escitalopram group. Abstinence of 1 to 3 months was reported in the memantine group by 17 of 39 patients (43.6%) and in the escitalopram group by 18 of 40 patients (45.0%). Abstinence up to 1 year was reported in both groups by 5 patients: 12.1% (5/39) in the memantine group and 12.5% (5/40) in the escitalopram group. (Data are missing for 1 memantine-treated patient due to an interrupted interview.) The numbers of treatment visits in A-clinics during the study period were similar (in the memantine group, 7.7, SD ± 8.8 and in the escitalopram group, 7.1, SD ± 9.8).

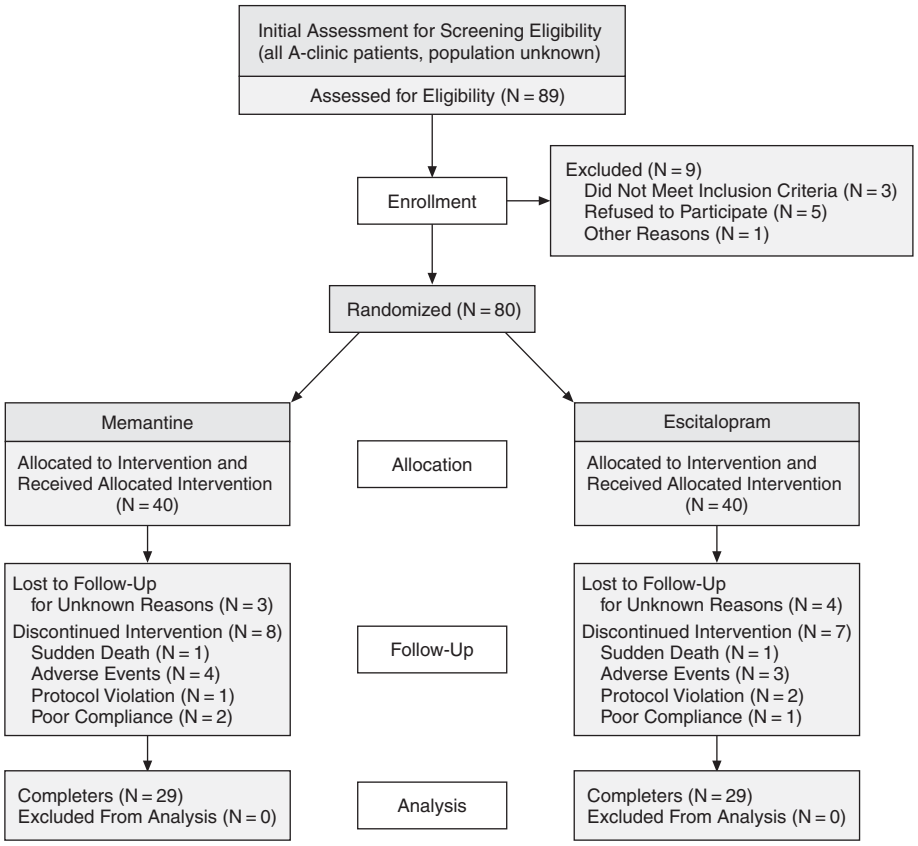
The study flow is shown in Figure 1. The completion rate of the 26-week study period was identical in both groups: 72.5% (N = 29) for memantine and 72.5% (N = 29) for escitalopram. The reasons for discontinuing the study were as follows: 1 sudden death in both treatment groups, adverse events (memantine 4, escitalopram 3), protocol violations (memantine 1, escitalopram 2), poor compliance (memantine 2, escitalopram 1), and loss to follow-up for unknown reasons (memantine 3, escitalopram 4). All 58 subjects who completed the study attended all appointments and showed at least 80% compliance based on tablet counts.

The average daily consumption of medication (mean ± SD) did not differ between the 2 medication groups: during the first 12 weeks, 17.4 ± 2.8 mg for memantine and 16.9 ± 3.6 mg for escitalopram, and for weeks 13 to 26, 17.4 ± 3.2 mg for memantine and 15.9 ± 4.4 mg for escitalopram.

Depression

During the 26-week study period, the depressive symptoms measured by MADRS score (reported as mean ± SD) decreased significantly from baseline in the memantine group from 25.8 ± 4.4 to 12.7 ± 7.0 and in the escitalopram group from 26.8 ± 4.1 to 11.5 ± 6.6 ($F = 138.04$, $df = 3$, $p < .0001$) (Figure 2), with no significant differences between the 2 treatment groups ($F = 1.13$, $df = 3$, $p = .94$). The self-rated depression scores (BDI) also decreased from baseline in both groups: in the memantine group from 27.7 ± 8.4 to 15.3 ± 11.1 and in the escitalopram group from 27.6 ± 6.8 to 14.3 ± 11.8

Figure 1. Study CONSORT Flowchart



(F = 25.77, df = 4, p < .0001); there was no difference between the 2 treatment groups (F = 0.92, df = 4, p = .68). When questioned at the end of the intervention, 75.9% of patients (22/29) in the memantine group and 72.4% of patients (21/29) in the escitalopram group reported their depression to be decreased.

Anxiety

Anxiety symptom scores, measured by HAM-A mean score, decreased significantly from baseline in the memantine group from 17.1 ± 4.7 to 7.8 ± 4.3 and in the escitalopram group from 18.1 ± 4.4 to 7.9 ± 5.5 (F = 132.14, df = 3, p < .0001), with no significant difference between the 2 treatment groups (F = 0.38, df = 3, p = .4). The self-rated anxiety scores (BAI) decreased in the memantine group from 21.5 ± 11.7 to 12.6 ± 10.2 and in the escitalopram group from 20.2 ± 9.3 to 13.6 ± 14.9 (F = 6.45, df = 4, p = .0002). There was no significant difference or interaction between the 2 treatment groups (F = 1.31, df = 4, p = .27) (Figure 3).

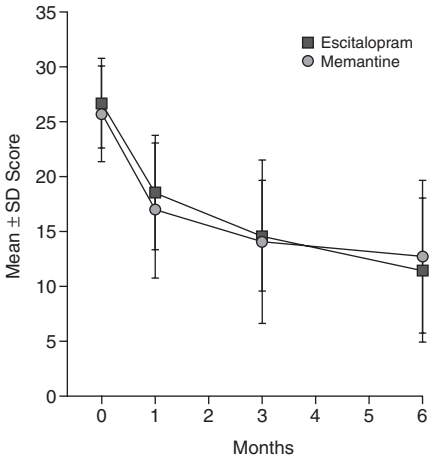
Cognitive Functioning

The cognitive performance scores (CERAD) at baseline were in the range of the reference values and did not change significantly during the study period in either treatment group. The mean MMSE score at baseline was 28.1 ± 1.4 in the memantine group and 28.0 ± 1.7 in the escitalopram group and at the end of the study was 27.9 ± 1.5 in the memantine group and 27.4 ± 1.5 in the escitalopram group (F = 3.1, df = 1, p = .08). The average retrieval percentage of wordlist at baseline was 89.2 ± 16.8 in the memantine group and 83.9 ± 19.5 in the escitalopram group and at the end of the study was 88.1 ± 16.5 in the memantine group and 89.9 ± 13.5 in the escitalopram group (F = 1.21, df = 1, p = .28).

Other Outcomes

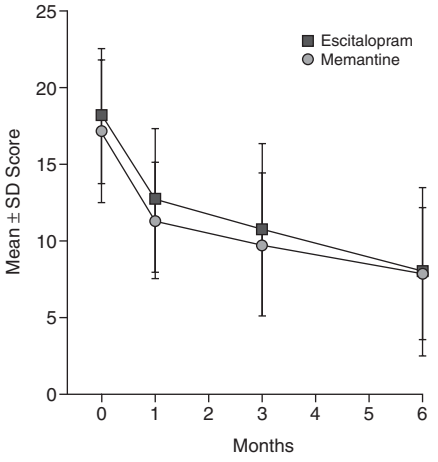
The quality of life was estimated using the VAS mm score. In the memantine group, it increased from 39.7 ± 19.3 to 54.6 ± 20.8 and in the escitalopram group from 40.5 ± 16.5 to 56.6 ± 23.2 (F = 10.27, df = 3, p < .0001). There was no statistical difference between the 2 groups (F = 0.25, df = 3, p = .9). Scores on the SOFAS increased significantly in both treatment groups: in the memantine group from 52.7 ± 9.2 to 67.2 ± 11.7 and in the escitalopram group from 53.2 ± 9.9 to 63.8 ± 11.4 (F = 39.75, df = 3, p < .0001). There was no significant difference between the groups (F = 1.7, df = 3, p = .86).

Figure 2. Change in Depression as Measured by the Montgomery-Asberg Depression Rating Scale[a]



[a]Significant change from baseline ($p < .0001$). No statistically significant difference or interaction between the treatment groups.

Figure 3. Change in Anxiety as Measured by the Hamilton Rating Scale for Anxiety[a]



[a]Significant change from baseline ($p < .0001$). No statistically significant difference or interaction between the treatment groups.

Safety and Tolerability

During the 26-week study period, 7 patients discontinued treatment due to adverse events, 4 in the memantine group and 3 in the escitalopram group.

In the memantine group, 1 patient was withdrawn due to eczema, and 3 were withdrawn because of labile mood and depression. In the escitalopram group, 1 patient was withdrawn due to disorientation after the first day of medication treatment, and 2 were withdrawn because of labile mood and/or depression. The majority of the patients (90% in the memantine group and 97% in the escitalopram group) reported at least 1 adverse event during the 26-week study period (Table 2). The most common adverse events were somnolence (memantine 36% and escitalopram 34%) and headache (memantine 36% and escitalopram 29%). There was no significant difference in the incidence of adverse events between the 2 treatment groups. Values for the clinical laboratory tests were in the normal range at the beginning and the end of the study.

Table 2. All Adverse Clinical Events With an Incidence of ≥ 10% in Either Medication Group[a]

Adverse Clinical Event	Memantine, N (%)	Escitalopram, N (%)
Insomnia	9 (23.1)	6 (15.8)
Sexual dysfunction	8 (20.5)	9 (23.7)
Gastrointestinal problems	10 (25.6)	10 (26.3)
Dizziness	11 (28.2)	7 (18.4)
Increased sweating	4 (10.3)	8 (21.1)
Somnolence	14 (35.9)	13 (34.2)
Headache	14 (35.9)	11 (28.9)
Aggressiveness	4 (10.3)	2 (5.3)
Instability in mood	11 (28.2)	9 (23.7)
Dry mouth	1 (2.6)	4 (10.6)

[a]No significant differences between groups concerning the reporting of adverse events. Thirty-five (89.7%) of the 39 patients evaluated in the memantine group and 37 (97.4%) of the 38 patients evaluated in the escitalopram group had an adverse clinical event.

Serious adverse events were reported by 3 patients (2 memantine, 1 escitalopram): 1 suicide attempt in the memantine group and 2 sudden deaths (1 due to hyperglycemia in the memantine group and 1 due to intoxication with street drugs in the escitalopram group). The mortality is equal with the average mortality in this group of patients in Finland.[44] These events were considered by the study coordinator (H.A.) not to be related to the study treatment on the basis of clinical evaluation and forensic autopsy reports for each case.

DISCUSSION

The primary aim of the study was to compare the response to treatment with memantine and escitalopram on MDD and cognition in depressive alcohol-dependent patients in a common treatment setting (A-clinics). Abstinence was not required. In both treatment groups, depression and anxiety symptoms and quality-of-life outcomes all significantly improved. The decrease in depressive symptoms in the escitalopram group in our study was consistent with conclusions from a recent review supporting SSRI treatment in depression with comorbid substance use disorders.[9]

Our assumption that memantine, a noncompetitive glutamate NMDA-receptor blocker, reduces MDD is in agreement with earlier findings of other glutamate antagonists.[24,26–28,30] However, very few studies have addressed the effects of memantine on depression, and no previous studies have examined its efficacy on depression comorbid with alcoholism. A recent study by Zarate

et al.[32] of patients suffering severe depression did not find significant effects with memantine at a mean dosage of 19.4 mg/day compared to placebo. The difference in the efficacy of memantine could be mainly due to the different patient selection criteria. The sample studied by Zarate et al. included therapy-resistant depressive patients and used substance abuse as an exclusion criterion, while in our study all patients suffered from MDD comorbid with alcohol dependence.

All parts of the CERAD cognitive test battery were within normal ranges at baseline, and there were no significant differences at follow-up in either of the treatment groups. The good cognitive performance among these depressive alcoholics was somewhat surprising. One probable reason for this is that the patients were still a selected population of people seeking help and already within the social care system. Their basic needs for nutrition and medical care were met. Although depression in itself can cause memory problems,[45] it seems that CERAD is not sensitive to this impairment.[46] Thus, it was not surprising that the performance on CERAD did not change during this trial.

The limitations of the study include the lack of a placebo group. In prior studies, the placebo effect is considered to be remarkable in this population.[9] It is possible that a part of the improvement of depression was due to the placebo effect or the natural episodic course of depression. Nevertheless, it should be noted that the mean prior duration of depression in our sample was 35 months, and most of the patients suffered mainly from chronic MDD. Another limitation is that the total number of patients may have been too low to detect a significant difference between 2 active treatments.

We conclude from this study that memantine and escitalopram seem to be safe and potentially effective for the treatment of MDD comorbid with alcohol dependence. Further research and placebo-controlled studies are yet needed.

Drug names: amantadine (Symmetrel and others), citalopram (Celexa and others), escitalopram (Lexapro and others), ketamine (Ketalar and others), lamotrigine (Lamictal and others), memantine (Namenda), mirtazapine (Remeron and others), riluzole (Rilutek and others), sertraline (Zoloft and others).

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