Treatment of major depression co-morbid with alcohol dependence with memantine or escitalopram - randomized comparison

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Background

- The lifetime prevalence of alcohol dependence is 5.2 % in Finland and 5.4% in the USA over the age of 18 years
- Co-occurrence of alcohol dependence in those with depressive disorders is common: 24.3% in men and 48.5% in women

Background

- The treatment of major depressive disorder (MDD) comorbid with alcohol dependence is difficult and controversial
- The current attractive medications for MDD with alcohol dependence are selective serotonin re-uptake inhibitors (SSRI) for their tolerability, potential effectiveness and safety

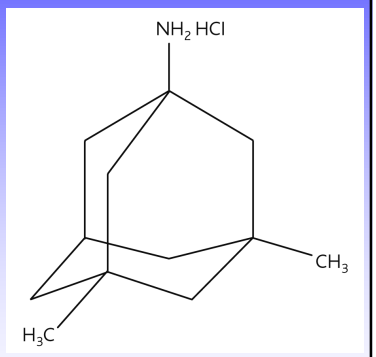
Why memantine?

Background

- Chronic ethanol administration up-regulates NMDA-receptor functions and contributes to ethanol tolerance
  - There is increasing evidence that NMDA-receptors have a significant role in mood disorders
- Acamprosate is a weak NMDA modulator which acts as an antagonist at the metabotropic glutamate receptor (mGluR5)
  - Acamprosate is approved in many countries for the treatment of alcohol dependence
  - However, recent studies report increasingly conflicting data on acamprosate

Memantine, chemistry & pharmaceutical information

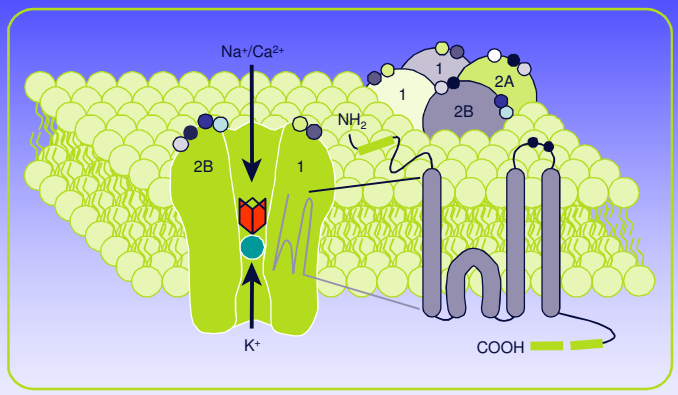
- **Memantine is a non-competitive ionotropic NMDA receptor antagonist**
- **Generic name (INN)**
  - Memantine hydrochloride
- **Trade names**
  - Ebixa® Axura® Namenda®
- **Chemical name (IUPAC)**
  - 1-amino-3,5-dimethyl-adamantane hydrochloride
- **Empirical formula**
  - $C_{12}H_{21}N.HCl$
- **Molecular weight**
  - 215.77 (memantine hydrochloride)
    179.31 (as base)



Memantine, mechanism of action

- Memantine is a voltage-dependent, moderate affinity, uncompetitive NMDA receptor antagonist
- Memantine blocks the effects of pathologically elevated tonic levels of glutamate that may lead to neuronal dysfunction
- Some animal studies have shown that memantine decreases alcohol drinking

Memantine at NMDA receptor



Agonists
- Glutamate NMDA

Coagonists
- Glycine
- D-serine

Channel Blockers
- Mg^{2+}
- **Memantine**

Antagonists
- APV
- Mrz 2/576
- Ifenprodil (2B)
- Zn^{2+}

Modulator
- Polyamines
- Alternative splicing
- Glycosylation site

Parsons et al 1998

Memantine, clinical research

- In clinical use for the treatment of moderate to severe Alzheimer's disease
- There are so far only few studies examining the effects of memantine on depression and alcohol consumption in humans
- Suppresses the craving for alcohol in moderate drinkers when deprived (Bisaga and Evans, 2004)
- In actively drinking alcohol-dependent non-depressive patients, memantine did not reduce craving or alcohol consumption (Evans et al., 2007) In recovering alcohol-dependent patients memantine reduced craving (Krupitsky et al., 2007)

Objectives

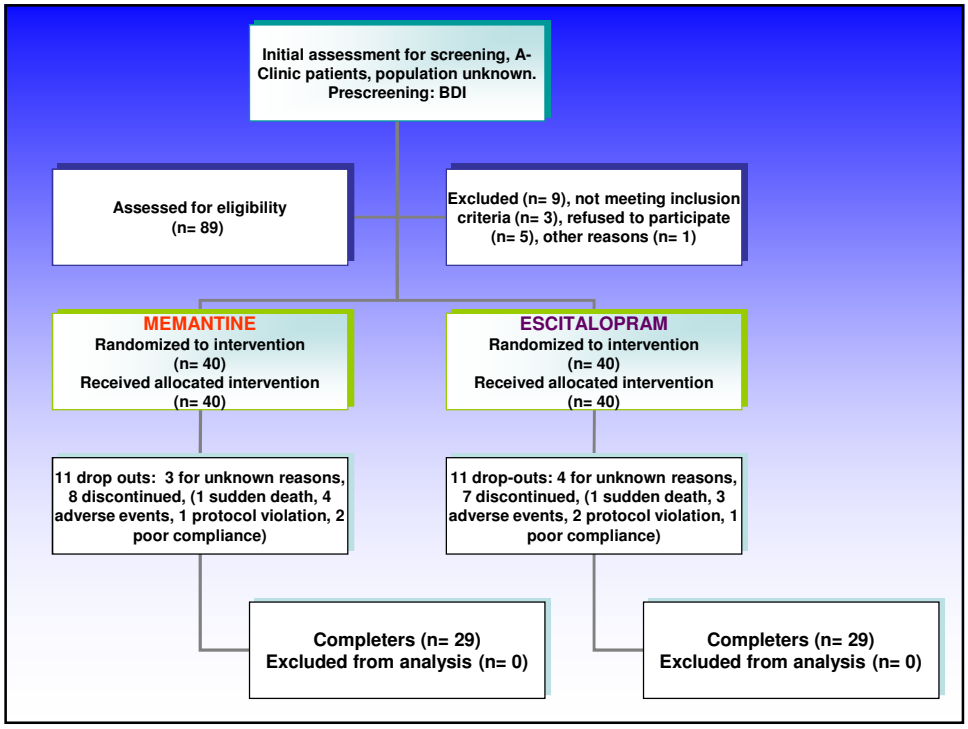
- The aim of the study was to evaluate possible new treatments for major depression in patients with comorbid alcohol dependence
- The efficacy of memantine was compared in a double-blind randomized manner with escitalopram (SSRI antidepressant)

Methods

- 80 alcohol dependent **treatment seeking** outpatients with major depressive disorder **from A-clinics** were randomized 1:1 to receive **memantine 20 mg** per day or **escitalopram 20 mg** per day
- Interviewed by a psychiatrist using the Structured Clinical Interview for DSM IV (SCID), and were required to **meet the criteria of both alcohol dependence and MDD according to DSM-IV**
- **No detoxification, abstinence was NOT required**
- Study visits at weeks 1, 2, 4, 12, and **26**

Methods

- **Primary outcome** measures: **Abstinence days** and heavy alcohol consumption by Drinking Diary, and **MADRS** for depression
- Secondary measures: AUDIT, OCDS for alcohol, BDI for depression, HAM-A and BAI for anxiety, CERAD for cognitive functions, and SOFAS for social functions and EQ-5 for quality of life
- All primary and secondary outcome statistical analyses were performed by an independent source for **intent-to-treat populations**, which included all randomized patients



Results, Demographic and Clinical Background Variables

Variable	Memantine (n=40)	Escitalopram (n=40)
Age (years, mean ± SD)	47.5(±8.3)	47.9(±8.3)
Gender, male (n, %)	23 (57.5)	21 (52.5)
First alcohol intoxication, (age, mean)	15.3 (±3.8)	15.4 (±2.3)
Onset of regular use of alcohol (age, mean)	20.7(±6.7)	20.5 (±6.3)
Onset of alcohol abuse (age mean)	29.5(±8.1)	28.3(±8.3)
Onset of alcohol dependence (age, mean)	30.6 (±8.3)	29.1(±8.5)
Drinking at study initiation (n, %)	17 (42.5)	17 (42.5)
Alcohol problems among relatives (n, %)	31 (79.5)	30 (76.9)
Baseline AUDIT (mean)	27.4 (±7.1)	28.4 (±6.4)
First depressive episode (age, mean)	27.8(±12.3)	24.2 (±13.0)
Duration of current depression (months, mean)	23.2(±30.0)	46.6(±67.9)
Total number of depressive episodes (mean)	10.0(±7.1)	9.6(±9.0)
No difference on psychosocial counseling during the study period, mean visits in the memantine 7.7 ± 1.4 and in the escitalopram 7.1 ± 1.5		

Table 1. Baseline demographic and clinical background measures. No significant differences between the groups.

Alcohol Consumption

- The completion rate was high in both groups, especially among the patients who had been abstinent at the beginning of the study
  - However, among those patients who were not abstinent at baseline, 47% in both groups discontinued the study
- Numbers of abstinent days were high in both groups throughout the study
  - Alcohol consumption measured by the AUDIT QF (quantity-frequency) score was significantly reduced in both groups, as was the craving for alcohol measured by the OCDS
  - In the second half of the study, ($p < 0.06$) more abstinent days were found in the memantine group
  - Lower OCDS scores were observed with memantine, but not reaching significance
- Subst Abuse Treat Prev Policy. 2008 Oct 3;3(1):20.

Alcohol Consumption

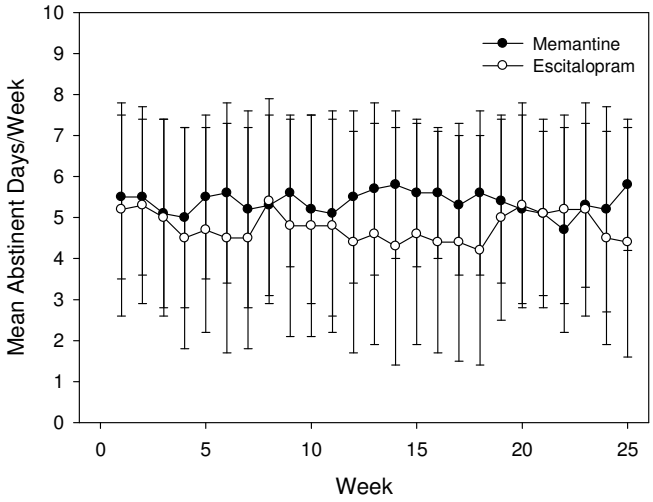
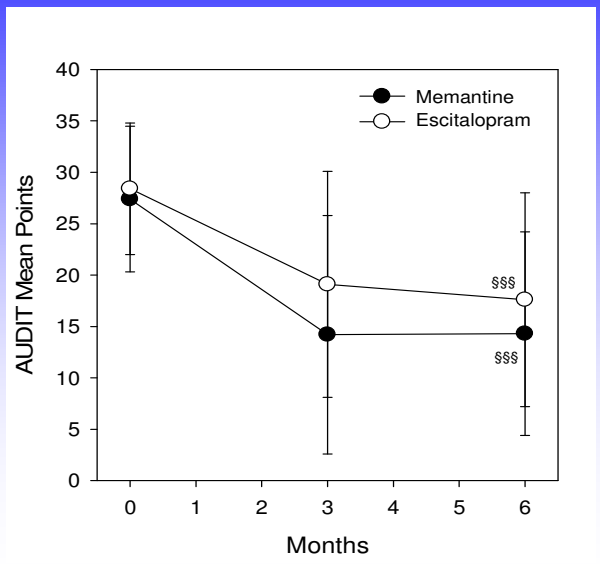


Fig. 2. Mean number of abstinent days per week.

No statistically significant difference between the treatment groups in a-days ± SD

AUDIT



- **Change in alcohol use measured by the AUDIT scores, §§§ significant reduction from base values prior to treatment, p<.0001, ± SD**

Craving

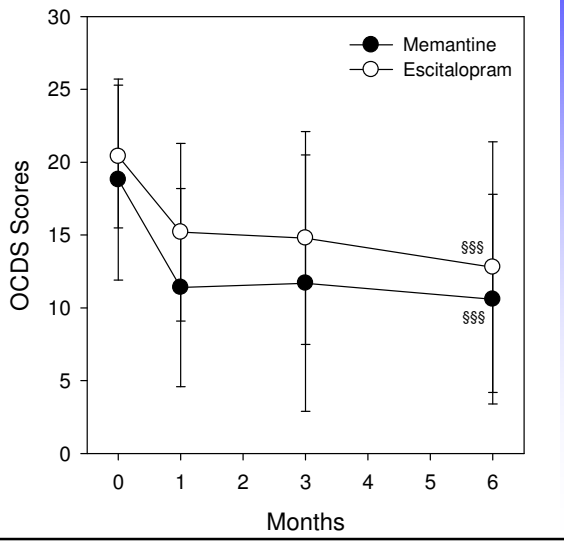


Fig. 3. OCDS scores
The total nean (±SEM) OCDS values were significantly reduced in both groups, §§§ p<0.001

Depression and Anxiety

- Both treatments significantly reduced the baseline level of depression and anxiety (p< 0.0001)
- There was no significant difference between the memantine and escitalopram groups
- J Clin Psychiatry. 2008 Mar;69(3):392-9

Depression and Anxiety

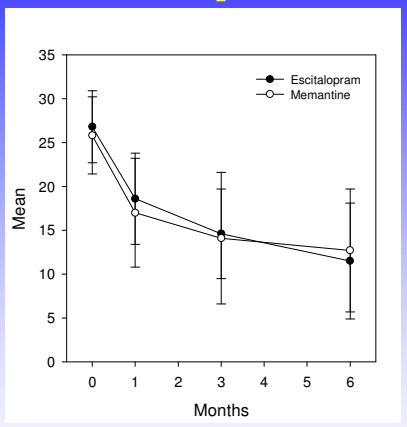


Figure 4. Mean MADRS scores. Significant change from baseline, p< 0.0001. No significant difference or interaction between the groups

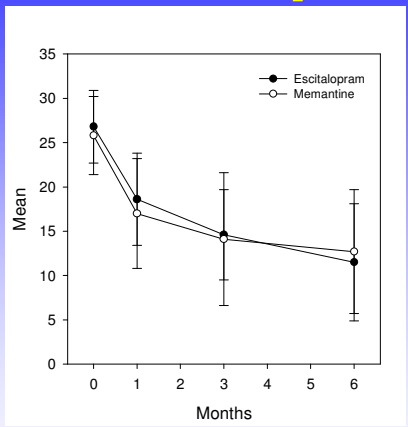


Figure 5. Mean HAM-A scores. Significant change from baseline p< 0.0001. No significant difference or interaction between the treatment groups

Others

- Quality of life, significant improvement but no difference between the groups
- Social and occupational functioning, SOFAS scores increased significantly in both treatment groups, no difference between the groups
- CDT, ASAT, ALAT, CDT, and GGT, no reduction, group no difference
- Assessed cognitive functioning (CERAD) scored primarily within the normative range and were not changed in either group
- No group difference in reporting adverse events

Predictors for better treatment outcomes

Depression

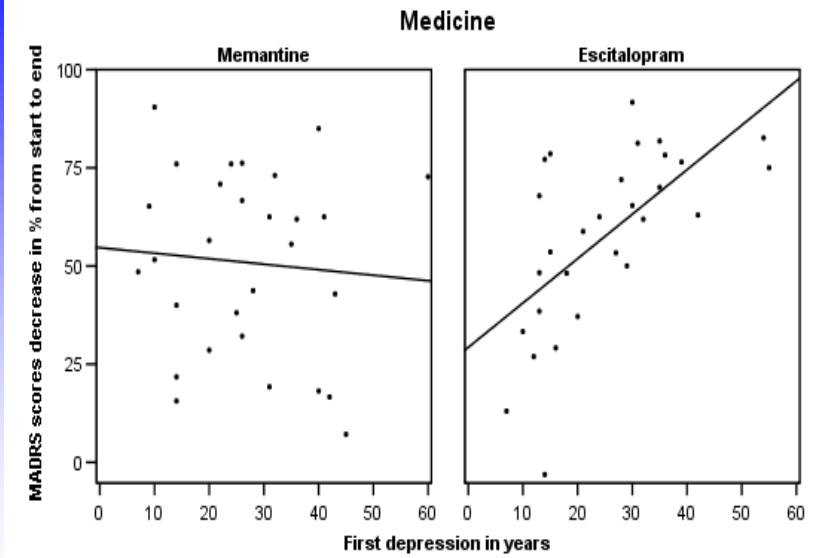
- Comparisons were made between patients in remission (final MADRS ≤ 12) and non-responding patients (MADRS decrease <50%)
- The age at onset of the first major depressive episode significantly correlated with the treatment response in the escitalopram group; the mean age at onset of depression among patients on the non-responders group was 13.7 ±4.0 years and 31.9± 11.9 years in remission ($p < .0001$)
  - These results are significantly different than those with memantine

Predictors for better treatment outcomes

Alcohol

- Those patients who were abstinent at the beginning of treatment were significantly more likely to complete the treatment than those who were still drinking at the beginning
- Comparisons were made by multiple linear regression analyses whether age at first alcohol intoxication predicted change during the six month treatment in the OCDS and the AUDIT scores
  - Early age at first alcohol intoxication predicted poor treatment outcomes in patients treated with escitalopram which was not found in patients treated with memantine

- Psychiatry Research, in press 2008



- A significant correlation ($p < 0.0001$) was found with escitalopram but not with memantine. The difference between the two correlations was significant ($Z = 3.7254$, $p = 0.0002$)

Study Limitations

- A comparative study, no placebo group
- Relatively small study (n = 80, compliers 58)
- The placebo-effect may be considerable in this population
  - It is possible that a part of the improvement of depression was due to the placebo-effect or the natural episodic course of depression
  - However, the mean prior duration of depression in our sample was 35 months, and the patients suffered of chronic major depression

Conclusions

- These data provide new evidence for the safety and potential efficacy of memantine and escitalopram for major depression in patients with comorbid alcohol dependence
- Our results indicate that both memantine and escitalopram are useful adjunct medications for the treatment of alcohol dependence co-morbid with major depression
  - Memantine was at least as effective with regard to drinking as escitalopram
- Our study provides evidence that the onset of the first major depressive episode might be a clinically relevant predictor of a response to escitalopram treatment in patients with major depression and comorbid alcohol

TREATMENT OF PATIENTS COMORBID WITH ALCOHOL DEPENDENCE AND MAJOR DEPRESSIVE DISORDER WITH MEMANTINE AND ESCITALOPRAM –OUTCOME AND PREDICTORS

- **Leea H. Muhonen MD; ACADEMIC DISSERTATION**
  - ***To be presented with the permission of University of Helsinki, for public examination at 19.12.2008***

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Inclusion/exclusion

- Inclusion: treatment seeking, alcoholism, major depression (DSM-IV)
- Exclusion: other substance use dependence (screened by urine test), other unstable severe mental illness (screened with the SCID), risk of suicide, pregnancy or breastfeeding, a severe untreated somatic problem, or a serious dysfunction of liver (aspartate aminotransferase [AST] and alanine aminotransferase [ALT] > 200), mental disability and incarceration
- Limits: Other medications prescribed by their physician were allowed, with the exception of other antidepressants

All adverse clinical events with an incidence of ≥ 10% : all patients

Adverse clinical event	Memantine N(%)	Escitalopram N(%)
Total number of patients evaluated	39 (100 %)	38 (100 %)
Total number of patients with an ACE	35 (89.7 %)	37 (97.4 %)
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%)