Leea Muhonen

Treatment of Patients Comorbid with Alcohol Dependence and Major Depressive Disorder with Memantine and Escitalopram - Outcome and Predictors

Publications of the National Public Health Institute A 29/2008

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

ACADEMIC DISSERTATION

To be presented with the permission of the Faculty of Medicine, University of Helsinki,
for public examination at the Christian Sibelius-auditorum,
Välskärinkatu 12, on December 19th, at 12 noon.

Helsinki 2008

Publications of the National Public Health Institute
KTL A29/2008

Julkaisija-Utgivare-Publisher

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ISBN 978-951-740-890-5
ISSN 0359-3584
ISBN 978-951-740-891-2 (pdf)
ISSN 1458-6290 (pdf)

Kannen kuva - cover graphic: Leea Muhonen: Kenkälaatikkopuu

Yliopistopaino
Helsinki 2008

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ISBN 978-951-740-890-5; 978-951-740-891-2 (pdf-versio)
ISSN 0359-3584; 1458-6290 (pdf-versio)
http://www.ktl.fi/portal/4043

TIIVISTELMÄ

Samanaikainen alkoholiriippuvuus ja vakava masennustila on haasteellista sekä lääketieteelliselle hoidolle että tutkimukselle. Tämä oireyhtymä on yksi yleisimmistä psykiatrisista häiriöistä niin Yhdysvalloissa kuin Suomessakin. Potilaiden ja heidän omaistensa inhimillisen kärsimyksen lisäksi myös kokonaistaloudelliset terveydenhoidolliset kustannukset ovat suuret tämän oireyhtymän hoidossa: niiden arvioidaan olevan yli neljäkymmentä prosenttia korkeammat kuin pelkän depression kohdalla.

Tässä tutkimuksessa pyrittiin löytämään uusia hoidollisia vaihtoehtoja alkoholiriippuvuudesta ja vakavasta masennuksesta yhtäaikaisesti kärsivien potilaiden hoidossa. Tutkimukseen osallistui 80 potilasta Helsingin kaupungin kolmelta A-klinikalta. Kyseessä oli kaksoissokko, randomisoitu, kahden eri tavalla vaikuttavan lääkkeen, essitalopraamin (selektiivinen serotoniinin takaisinoton estäjä) ja memantiinin (glutamaatin NMDA reseptorin ei-kilpaileva estäjä) vertaileva tutkimus. Potilaiden oireiden kulkua seurattiin 26 viikkoa depressioon, ahdistuneisuuteen, kognitioihin, elämänlaatuun ja alkoholin käyttöön liittyvillä mittareilla. Tämän jälkeen tarkasteltiin hoitovastetta alkutilanne- ja taustamuuttujien valossa. Pyrkimyksenä oli löytää joitakin ennustekijöitä, joiden pohjalta kliinikko voisi tehdä hoitoratkaisunsa näiden potilaiden hoidossa.

Molemmat lääkkeet vähensivät merkittävästi sekä masennusta että ahdistuneisuutta, eikä essitalopraami- ja memantiiniryhmien välillä ollut tilastollisesti merkitsevää eroa. Kognitiiviset toiminnot olivat lähtövaiheessa normatiivisella tasolla. Elämän laatu parani molemmissa hoitoryhmissä. Alkoholimittareilla AUDIT (alkoholihäiriöiden tunnistusmittari) ja OCDS (pakkomielteisen ja pakkotoimintoisen alkoholinkäytön mittari) paranivat molemmissa hoitoryhmissä.

Varhainen ensimmäisen vakavan masennuksen episodin alku näytti ennakoivan huonoa vastetta essitalopraamille, mutta ei memantiinille, mitattuna Montgomery-Åsberg depression rating scale -asteikolla. Toisaalta myöhäinen ensimmäisen masennuksen episodi näytti ennakoivan hyvää hoitovastetta essitalopraamille. Niinpä ensimmäisen masennuksen alkamisikä saattaisi olla käyttökelpoinen ennustekijä näille lääkkeille.

AUDIT-mittarilla mitattuna varhainen ensimmäisen masennuksen alkamisikä ennusti huonoa hoitovastetta essitalopraamille samoin kuin humalahakuisen juomisen alkamisikä. Aktiivinen alkoholinkäyttö tutkimuksen alkaessa ennakoi tutkimuksen keskeyttämistä.

HTTLPR-geenin L-alleeli näytti ennustavan parempaa hoitovastetta essitalopraamille kuin S-alleeli.

Avansanat: Alkoholismi; Sitalopraami; Glutamiinihappo; Vakava masennus; Serotoniinin takaisinoton estäjät; Serotoniinitransportterin geenivaihtelu; Ennustetekijät

ABBREVIATIONS

A-clinics	Alcohol-clinics
AE	Adverse event
ALT = ALAT	Alanine aminotransferase
ANOVA	Analysis of variance
AST = ASAT	Aspartate aminotransferase
AUDIT	Alcohol Use Disorders Identification Test
AUDIT 2	AUDIT quantity - frequency
AUDIT QF	AUDIT quantity - frequency
AUDIT 3	AUDIT heavy drinking days
BAI	Beck Anxiety Inventory
BDI-II	Beck Depression Inventory II
Ca	Calcium
CERAD	Consortium to Establish a Registry for Alzheimer's Disease cognitive test battery
CI	Confidence Interval
Cl	Chloride
CNC	Cross-National Comparison
COMBINE-study	Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence
Crea	Creatinine
DSM-IV TR	Diagnostical and Statistical Manual of Mental Disorders, Text Revision
CDT	Desialotransferrine
FDA	US Food and Drug Admistration
EQ-5	European Quality of life (5 items)
GABA	γ-aminobutyric acid
GGT	γ-glutamyl transferase
HAM-A	Hamilton Anxiety Scale
5-HIAA	5-hydroxy indole acetic acid
HPA	Hypothalamus-pituitary-adrenal
5-HT	5-hydroxy tryptamine = serotonin
5-HTT	5-hydroxy tryptamine transporter
5-HT 3-receptor	5-hydroxy tryptamine 3-receptor
5-*HTTLPR*	5-hydroxy tryptamine transporter linked polymorphic region
ICH	International Conference on Harmonisation
K	Kalium
L-variant	Long variant

MADRS	Montgomery-Åsberg Depression Rating Scale
MCV	Mean corpuscle volume
MDD	Major Depressive Disorder
MDE	Major Depressive Episode
Mg	Magnesium
MMSE	Mini Mental State Examination
Na	Natrium
NCS	National Comorbidity Survey
NCS-R	National Comorbidity Survey replication
NMDA	N-methyl-D-aspartate
NOS	Not otherwise specified
OCDS	Obsessive Compulsive Drinking Scale
SAE	Serious adverse event
SAS	Statistical Analysis Software
SCID (TR)	Structured Clinical Interview for DSM-IV (text revision)
SD	Standard deviation
SOFAS	Social and Occupational Functioning Assessment Scale of DSM-IV
SSRI	Selective Serotonin Reuptake Inhibitor
STAR*D	Sequenced Treatment Alternatives to Relieve Depression
S-variant	Short variant
TCA	Tricyclic antidepressant
TPQ	Tridimensional Personality Questionnaire
VAS	Visual Analogue Scale
WHO	World Health Organization

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ISSN 0359-3584; 1458-6290 (pdf-version)
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ABSTRACT

The treatment of comorbid alcohol dependence and major depression is a challenge to medical research and practice. This comorbidity is one of the most common psychiatric disorders in the United States and also in Finland. Besides the human suffering of both patients and their relatives, the economical costs of total medical care of this comorbidity are over forty percent higher than those of depression alone.

The aim of this research was to find out some new treatment options for these patients. There were 80 patients recruited from municipal alcohol-clinics in Helsinki, who were subjected to a double-blind, randomized trial with two differently acting medicines, escitalopram (selective serotonin transporter inhibitor) and memantine (glutamate N-methyl-D-aspartate receptor partial antagonist). The patients were followed 26 weeks for depression, anxiety, cognition, quality of life and drinking measures. After that phase, the treatment response was looked for from the baseline data to ascertain if there were any predictive signs which would be beneficial for clinicians when planning the treatment for these patients.

Both treatments reduced the baseline level of depression and anxiety and there was no significant difference between the memantine and the escitalopram groups. Assessed cognitive functioning scored primarily within the normative ranges. Quality of life improved in both treatment groups. Alcohol measures Alcohol Use Disorders Identification Test (AUDIT) and Obsessive Compulsive Drinking Scale (OCDS) improved in both treatment groups.

The early onset of the first major depressive episode seemed to predict poor response to escitalopram, but not to memantine, when measured with the Montgomery-Åsberg Depression Rating Scale. Vice versa, the late onset of the first depressive episode seemed to predict good response to escitalopram. So the age at the first depressive episode might be a relevant predictor to these treatments.

When measured drinking by AUDIT, the early onset of the first depressive episode and the early onset of intoxicative drinking seemed to predict poor response to escitalopram. The active drinking at the time of the beginning of the study, predicted early termination of the treatment with both medicines.

The long variant allele of the 5-hydroxy tryptamine transporter linked polymorphic region (5-*HTTLPR*) gene predicts better treatment response to escitalopram compared to the short variant allele.

Keywords: Alcoholism; Escitalopram; Memantine; Major Depressive Disorder; 5-*HTTLPR* ; Predictors

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles referred to in the text by their Roman numerals:

I. Muhonen LH, Lönnqvist J, Juva K, Alho H (2008): Double-blind, randomized comparison of memantine and escitalopram for the treatment of major depressive disorder comorbid with alcohol dependence. *J Clin Psychiatry 69:392-399.*

II. Muhonen LH, Lahti J, Sinclair D, Lönnqvist J, Alho H (2008a): Treatment of alcohol dependence in patients with co-morbid major depressive disorder - predictors for the outcomes with memantine and escitalopram medication. *Subst Abuse Treat Prev Policy 3:20.*

III. Muhonen LH, Lönnqvist J, Lahti J, Alho H (2008): Age at onset of first depressive episode as a predictor for escitalopram treatment of major depression comorbid with alcohol dependence. *Psychiatry Res, accepted for publication.*

IV. Muhonen LH, Alho H, Lahti J, Lönnqvist J, Haukka J, Saarikoski ST (2008): Serotonin transporter polymorphism as a predictor for escitalopram treatment of major depressive disorder comorbid with alcohol dependence. *Submitted.*

1 INTRODUCTION

Alcohol dependence and alcohol abuse are significant public health problems in Finland (Pirkola et al. 2005) and all over the world (Kessler et al. 2005; Kessler et al. 1997). The 12-month prevalence of alcohol dependence was 3.9% in Finnish Health 2000 survey in the population over the age of 30 years (Pirkola et al. 2005). The lifetime prevalence of alcohol dependence was 5.4% in the USA over the age of 18 years in the National Comorbidity Survey Replication (NCS-R) (Kessler et al. 2005). The lifetime prevalence of alcohol abuse was 14.1 % (men 20.1%; women 8.2%) in the National Comorbidity Survey (NCS) (Kessler et al. 1997); and 13.7% in men and 4.1% in women in the Cross-National Comparison (CNC) in the Seven Surveys (Kessler et al. 2003).

In the Finnish Health 2000 survey, the 12-month prevalence of Major Depressive Disorder (MDD) was in Finland 4.9%, and the prevalence of comorbidity with alcohol dependence in Finland in year 2000 was 0.4% (Pirkola et al. 2005). The lifetime prevalence of major depression was 16.6 % and co-occurrence of alcohol dependence with depressive disorders was common: 24.3% in men and 48.5% in women according to the NCS (Kessler et al. 1997) and 18.1% in men and 41.2% in women according to the CNC (Kessler et al. 2003). In research of major depressive outpatients, 11.9% had comorbid alcohol abuse/dependence (Rush et al. 2005). Both alcohol dependence and major depression pose a significant risk for the development of the other disorder at 1 year after onset (Gilman and Abraham 2001).

Concurrent depression and alcoholism lead to greater disability than alcoholism alone (Oslin et al. 1999; Thase et al. 2001). The lifetime suicide rate in alcoholism is estimated to range from 2% to 18% (Pirkola et al. 2004; Sher et al. 2005) and in depression from 2% to 15% (Sher et al. 2005). Comorbidity increased the risk of suicide among depressive patients 2.1 times (Sher et al. 2005). Major depression occurring before substance dependence predicted severity of suicidal intent, and major depression occurring during abstinence predicted number of suicidal attempts (Aharonovich et al. 2002). Besides human suffering, this comorbidity leads to higher total medical care expenditures, which are 44% higher than those for patients with depression alone (Mark 2003).

The medical treatment of MDD comorbid with alcohol dependence is difficult and controversial. Antidepressant medication exerts a modest beneficial effect for these patients and more research is warranted both to diagnostic field and treatment of this comorbidity (Nunes and Levin 2004). Sobriety has marked and early, globally averaged and regionally specific morphological, metabolic as well as functional benefits for convalescent alcoholics (Bartsch et al. 2007), and should be encouraged before treatment of depression (Nunes and Levin 2006). However, for many patiens the requirement of sobriety is too demanding (Baekeland and Lundwall 1975). The aim of this research was to find out some new treatment alternatives in the treatment of comorbid alcohol dependence

and major depression. In addition to this, another aim was to find out some predictive signs for clinicians when making decisions of medical treatment for this comorbidity. The exclusion of the division of patients to "primary depressive" or "secondary depressive" groups was made because the assumption was that it was unknown whether the depression was primary or secondary, even when it appeared after long-lasting alcohol dependence. The study was based on double-blind, randomized comparison of two differently acting compounds, memantine, a non-competitive antagonist of glutamate NMDA receptor, and escitalopram, a selective serotonin reuptake inhibitor. Memantine was choosen because its neuroprotective properties and similarity with acamprosate, a compound the US Food and Drug Administration (FDA) approved for the treatment of alcohol dependence.

2 REVIEW OF THE LITERATURE

2.1 Neurobiology of ethanol

Several neurotransmitter systems in different brain areas contribute to the neurobiological basis of alcoholism. Involvement of neurotransmitters and neuropeptides, as well as ligand-gated ion channels have not been fully examined and understood but they are under intensive research. Neuropharmacologic studies in animal models have provided evidence for specific neurochemical mechanisms in specific brain reward and stress circuits that become dysregulated during development of alcohol dependence (Koob 2003). Several neurotransmitters are involved in the different components of alcohol dependence. Glutamate and γ-aminobutyric acid (GABA) are considered to be the primary transmitters mediating alcohol effects (Zigmond et al. 1999).

Glutamate receptors regulate neuronal differentiation, synaptic plasticity and memory (McDonald and Johnston 1990). These receptors are linked to ligand-gated ion channels that are activated by the neurotransmitter glutamate and are critically involved in many forms of synaptic plasticity including those associated with learning and memory (Woodward et al. 2006). The capacity to block N-methyl-D-aspartate (NMDA) glutamate receptors may be one of the most important influences of alcohol in the brain (Krystal et al. 2003). Alcohol affects glutamatergic transmission in three ways: by interfering with fast excitatory neurotransmission, by promoting excitotoxity, and by impairing neurodevelopment (Tsai et al. 1995). Acutely, ethanol reduces excitatory glutamatergic synaptic neurotransmission (Lovinger et al. 1989). Chronic ethanol administration upregulates NMDA receptor function and contributes to ethanol tolerance (Krystal et al. 2003). Glutamatergic transmission belongs to mechanisms playing important roles in the process underlying the development and maintenance of addiction (Tzschentke and Schmidt 2003). Upregulation of NMDA receptors could contribute to development of alcohol deprivation effect (Sinclair and Senter 1967) that is expressed as increased craving for alcohol after an abstinence period (Sinclair 1980). Ethanol induced acute attenuation of NMDA receptor neurotransmission after chronic upregulation of NMDA receptors is supposed to be responsible for "black-out" related to alcohol intoxication (Tsai and Coyle 1998), which is assumed to arise from impaired long-term potentiation, a cellular analogue to recent memory (Kauer et al. 1988).

While glutamatergic neurotransmission is excitatory and mediates signals via Calcium, Natrium and Magnesium -ions, *GABAergic neurotransmission* is inhibitory and mediates signals via Cloride-ions (Zigmond et al. 1999). At concentrations that are present during acute intoxication, alcohol stimulates GABA receptor mediated chloride flux in rat cerebral cortex (Suzdak et al. 1986). GABA contributes to motor-impairing (Hellevuo et al.

1989), sedative and anxiolytic-like effects of ethanol (Liljequist and Engel 1984) and aggressive behavior caused by cortical disinhibition (Begleiter and Porjesz 1999; Miczek et al. 1997). After chronic use, the adaptative changes in this neurotransmitter system are thought to underlie partly the development of alcohol dependence (Grobin et al. 1998). One hypothesis is that GABAergic interaction with the brain stress neurotransmitter corticotrophin-releasing factor may be an important component for the transition from social drinking to addiction (Koob 2004).

In acute use, ethanol increases the level of *serotonin* in nucleus accumbens (Yoshimoto et al. 1992). Alcoholics that use large quantities of alcohol show evidence of differences in brain serotonin levels compared with non-alcoholics (Lovinger 1997). Type 2 alcoholism (Cloninger et al. 1981; Cloninger et al. 1988), e.g. early onset of alcohol abuse and antisocial, impulsive and violent behavior, has been found to be associated with low cerebrospinal fluid serotonin metabolite 5-hydroxy indole acetic acid (5-HIAA) concentration (Virkkunen and Linnoila 1993) and with low activity serotonin transporter promoter genotype (Hallikainen et al. 1999). The activation of serotonin receptors also modifies the activity of the neurotransmitter *dopamine*, which, like serotonin, modulates neuronal activity (Lovinger 1997).

Alcohol intake increases the level of *dopamine* in nucleus accumbens (Weiss et al. 1993). The activation of dopaminergic system produces euphoria (Wise and Bozarth 1985). Alcohol increases firing of dopamine neurons in the ventral tegmental area by activating GABAA receptors or by inhibiting NMDA receptors (Cami and Farre 2003). The ability of alcohol to produce reinforcing qualities on emotional contents and motivational status has been linked to alcohol's addiction potential (Chastain 2006). The present receptor data from animal and especially human studies are emphasizing the importance of Dopamine 2 receptors in alcohol dependence (Tupala and Tiihonen 2004).

Also other transmitter systems are emerging as mediators of alcohol reward. Acute ethanol exposure leads to an increase in extracellular *adenosine*, activating nucleus accumbens, which is supposed to play a significant role in reinforcement and reward, and mediation of voluntary alcohol consumption (Mailliard and Diamond 2004). *Neuropeptide Y* and the endogenous opioid peptide system have been hypothesized to be involved in reinforcing effects of alcohol (Reid and Hunter 1984). *Norepinephrine* has a significant role in modulating ethanol-related behaviors and psychological responses (Weinshenker et al. 2000). The activation of *cannabinoid CB 1 receptor* promotes alcohol reward (Basavarajappa and Hungund 2002) and cannabinoid CB 1 receptor antagonist is supposed to suppress various alcohol-related behaviors (Colombo et al. 2007). Active alcohol intake in chronic alcoholism may increase spontaneous production of *interleukines and other cytokines* (Laso et al. 2007), which may, interfering with serotonergic systems, cause depressive illness (Dunn et al. 2005).

2.2 Neurobiological connection between alcohol dependence, depression and cognition

Hippocampus is proposed to be an important site of alcohol influence in the brain in the development of alcohol dependence. Hippocampal dysfunction and neurodegeneration are common results from the neurotoxic effects of alcohol. Events related to hippocampal neurogenesis such as learning, memory, and mood are dysregulated in chronic alcoholism (Nixon 2006). Considering the importance of hippocampus in major depression (Mervaala et al. 2000) and cognition (Parsons 1994), chronic alcohol exposure reduces hippocampal neurogenesis and dendritic growth in newborn neurons (He et al. 2005). There is evidence that adult hippocampal neurogenesis may be regulated by NMDA receptors present in precursor cells (Nacher et al. 2007).

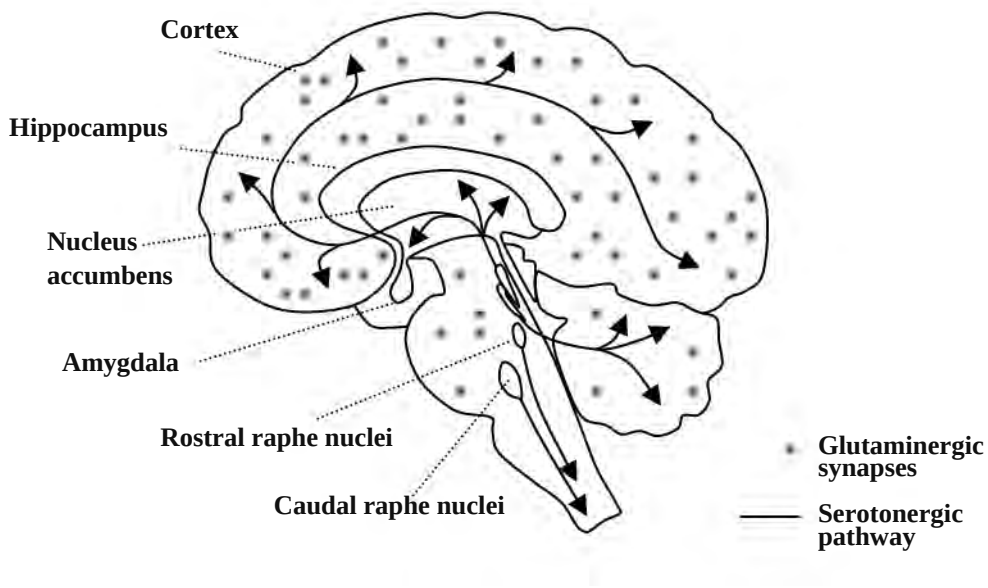
Alcoholism is associated with a range of memory and executive deficits leading to mild generalized dysfunction of the brain which results in a variable pattern of impairment in perceptual-motor skills, visual-spatial functions, learning, memory, and abstraction and problem solving (Parsons and Nixon 1993). As much as 10% of dementias are supposed to be alcohol related (Oslin and Cary 2003). Neurodegeneration is at present thought to be a consenquence of a failure in normal regeneration in brain regions that contain neurogenesis, such as the hippocampus. Some drugs interacting with glutamate receptors have shown to be neuroprotective, such as metabotrophic glutamate receptor antagonist acamprosate (De Witte et al. 2005) and the ionotropic glutamate receptor antagonist memantine (Parsons et al. 1999). Ethanol regulates proliferation of glia and a lower number of glia was found in the cortex in depression (Rajkowska and Miguel-Hidalgo 2007).

Depression as such is associated with memory and executive deficits (Veiel 1997), which are presumed to be related to reduced cerebral activation in medial and dorsolateral prefrontal cortex and correlate to severity of depression (Buchsbaum et al. 1997). Major depression is associated with a selective loss of hippocampal volume that persists long after the depression has resolved (Sapolsky 2000b). Serotonin has been shown to produce long-lasting facilitation of synaptic transmission in the amygdala, and to have a possible synaptic role in long-term memory for learned fear. This long-term effect of serotonin may be very important for the long-term storage of amygdala-based emotional behavior (Huang and Kandel 2007). Recently it was suggested that the intensity of past depression contributes to the impairment of memory due to toxic link between the burden of depression and cognition (Gorwood et al. 2008). The antidepressant treatment reverses the decreases in neurogenesis following chronic alcohol drinking (Malberg et al. 2000). The failure in normal neuroregeneration provides a new aspect for understanding psychiatric diseases related to chronic alcoholism (Nixon 2006). In a Finnish study, the volume of the left hippocampus was significantly smaller in the group of severe depressive patients compaired with the controls (Mervaala et al. 2000), which is associated with hypersecretion of glucocorticoids (Sapolsky 2000a) and imbalance in the activity of

hypothalamus-pituitary-adrenal (HPA) axis (McEwen 2005). In a study of cognition in remitted major depression patients, the deficits in executive functions in MDD worsened during chronic course of depression (Paelecke-Habermann et al. 2005). Chronic alcohol use leads to reduced brain levels of β-endorphin, which contribute to negative emotional states (Herz 1997) related to depression (Heinz et al. 2001). It is supposed that depression could contribute to the pattern of cognitive impairment in alcoholism (Penick et al. 1994). This hypothesis was investigated by evaluating depression and cognitive functioning of alcoholics, and the results suggested that the deficits were not generally exacerbated by comorbid depressive symptoms (Uekermann et al. 2003).The brain glutamatergic system, with its NMDA receptors, is suggested to be involved in toxic neuronal loss due to an increased glutamatergic neurotransmission during repeated alcohol withdrawal (Tsai et al. 1995).

Some NMDA-antagonists ameliorate cognitive deficits in adult rats withdrawn from chronic ingestion of alcohol (Lukoyanov and Paula-Barbosa 2001). In addition, the Selective Serotonin Reuptake Inhibitors (SSRI) were shown to be neuroprotective in a preclinical study, as long-term (2-4 weeks) administration resulted in upregulation of neurogenesis (Li et al. 2003). In a preliminary study, it was shown that one year treatment with SSRI led to significant increase in hippocampal volume and increase in memory functioning in posttraumatic stress disorder (Bremner 2006). Antidepressant therapy following stroke fostered long-term improvement of executive function (Narushima et al. 2007).

Figure 1. Serotonergic pathways and Distribution of Glutamate receptors.



2.3 Alcohol Dependence

2.3.1 Definition of alcohol dependence

The development of alcohol dependence requires both the use of alcohol and the vulnerability to dependence. Alcohol dependence is described in the Diagnostical and Statistical Manual of Mental Disorders, Text Revision (DSM-IV TR)(American Psychiatric Association 2000), as a subtype of Substance Dependence, as a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues use of alcohol despite significant alcohol-related problems (criteria in table 1).

Table 1. DSM-IV TR criteria for Alcohol Dependence.

A maladaptative pattern of alcohol use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

(1) tolerance, as defined by either of the following:

(a) a need for markedly increased amounts of the alcohol to achieve intoxication or desired effect

(b) markedly diminished effect with continued use of the same amount of the alcohol

(2) withdrawal, as manifested by either of the following:

(a) the characteristic withdrawal syndrome for the alcohol

(b) alcohol is taken to relieve or avoid withdrawal symptoms

(3) alcohol is often taken in larger amounts or over a longer period than was intended

(4) there is persistent desire or unsuccessful efforts to cut down or control alcohol use

(5) a great deal of time is spent in activities necessary to obtain the alcohol (e.g., driving long distances), use alcohol or recover from its effects

(6) important social, occupational, or recreational activities are given up or reduced because of alcohol use

(7) the alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g. continued drinking despite that an ulcer was made worse by alcohol consumption)

Diagnosis of substance dependence, to the appropriate extent, according Diagnostic and Statistical Manual of Mental disorders, Fourth Edition (DSM-IV), Text Revision (American Psychiatric Association, 2000)

2.3.2 Glutamate and alcohol dependence

Glutamate is the major excitatory amino acid in the central nervous system. It and related amino acids are thought to be utilized by 40 percent of synapses (Coyle and Puttfarcken 1993). Repeated bouts of high alcohol consumption induce an imbalance between inhibitory and excitatory neurotransmission within nucleus accumbens that may drive excessive drinking behavior (Szumlinski et al. 2007). Long term alcohol use increases the number of glutamate NMDA receptors (Nagy 2004), alters the function of NMDA receptors (Petrakis et al. 2004), and leads to ethanol tolerance (Nagy 2004). The glutamate antagonist treatment reduces ethanol-seeking and relapse behavior in rats (Backstrom et al. 2004). Animal studies have shown that memantine, an uncompetitive NMDA receptor antagonist, decreases alcohol drinking (Bachteler and Spanagel 2005; Holter et al. 1996). Memantine also reduced alcohol drinking in rats when the access to alcohol was limited to a short period daily (Piasecki et al. 1998), and in mice when alcohol drinking had been increased by schedule-induced polydipsia (Escher et al. 2006). Memantine has been shown to block ethanol-induced upregulation of NMDA receptors (Maler et al. 2005).

Similar effects on alcohol drinking in humans have been found with other NMDA receptor blockers (Bachteler et al. 2005; Holter et al. 2000; Vengeliene et al. 2005) including acamprosate (Bouza et al. 2004; Heyser et al. 1998; Spanagel et al. 1996). Acamprosate is a weak NMDA modulator, which acts on metabotrophic glutamate receptors. It is already in use for treating alcohol dependence (Kranzler and Van Kirk 2001). Although the results of the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE study) (Anton et al. 2006), found no superiority of acamprosate compared with placebo, it was found to significantly reduce relapse rates in alcohol dependence in several placebo-controlled double-blind trials (Soyka and Roesner 2006). In patients motivated to achieve abstinence, acamprosate seems to be an effective treatment (Pettinati and Rabinowitz 2006). Similar effects in alcohol dependent patients have been reported with oxcarbazepine, which reduces glutamatergic transmission at corticostriatal synapses (Croissant et al. 2006), and topiramate, that may partly act as an antagonist at some glutamate receptors (Johnson et al. 2007).

In a study examining the effects of memantine on alcohol use in humans, memantine suppressed the craving for alcohol in moderate drinkers, when they were deprived, but not later when they were drinking (Bisaga and Evans 2004). In a study reporting effects of memantine on cue-induced alcohol craving in recovering alcohol-dependent patients after detoxification, memantine did not stimulate alcohol craving before exposure to an alcohol cue, and it attenuated cue-induced craving for alcohol in a dose-related fashion (Krupitsky et al. 2007).

2.3.3 Serotonin and alcohol dependence

Serotonin plays a role in regulation of mood, appetite, arousal, sleep, pain and many other behaviors (Roth 1994). In animal studies, it was found that the levels of serotonin and its metabolites were lower in cerebrospinal fluid of alcohol preferring rats than in non-preferring rats (McBride et al. 1995) and alcohol preferring monkeys (Heinz et al. 2001). Alcohol preferring rats also had a lower number of serotonin neurons than the non-preferring rats (Zhou et al. 1994). Various animal studies have shown that voluntary alcohol drinking by rats was reduced by compounds that increase serotonergic actions (Amit et al. 1984; McBride et al. 1992; Naranjo et al. 1986), including zimilidine, viqualine and fluoxetine.

Preliminary clinical work supported the efficacy of zimilidine, one of the first SSRIs, in human alcoholics (Naranjo and Bremner 1992). A similar but safer compound, citalopram, was found to be effective in treating human alcohol dependence (Naranjo et al. 1986). In alcoholism without depression, SSRIs have shown positive results in reducing drinking, especially when the drinking has not initially been severe (Balldin et al. 1994; Hautzinger et al. 2005; Naranjo and Knoke 2001a; Pettinati et al. 2001; Tiihonen et al. 1996).

2.4 Major depressive disorder

2.4.1 Definition of major depressive disorder

Major depressive disorder (MDD) is described in the Diagnostical and Statistical Manual of Mental Disorders, Text Revision (DSM-IV TR)(American Psychiatric Association 2000) and characterized by one or more Major Depressive Episodes (MDE) (criteria in table 2).

Table 2. DSM-IV TR Criteria for Major Depressive Episode.

A. Five (or more of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure:

(1) depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful)

(2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)

(3) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day

(4) insomnia or hypersomnia nearly every day

(5) psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)

(6) fatigue or loss of energy nearly every day

(7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self reproach or guilt about being sick)

(8) diminished ablity to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)

(9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without specific plan, or a suicide attempt or a specific plan for committing suicide

B. The symptoms do not meet criteria for a Mixed Episode.

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to the direct physiological effects of a substance (e.g., drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

E. The symptoms are not better accounted for by Bereavement, i.e.., after loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

Diagnosis of bipolar disorder, to the appropriate extent, according Diagnostic and Statistical Manual of Mental disorders, Fourth Edition (DSM-IV), Text Revision (American Psychiatric Association, 2000)

2.4.2 Glutamate and major depression.

Glutamate NMDA receptors have been implicated in crucial physiological processes, such as synaptogenesis, learning and memory (Heresco-Levy and Javitt 1998). In addition to participation in synaptic transmission and neuronal plasticity, NMDA receptors also play a crucial role in the regulation of neuronal development and connectivity (Cline and Constantine-Paton 1990). Both competitive and non-competitive antagonists of NMDA receptors reduced the behavioral deficit in an animal model of depression comparable to imipramine (Papp and Moryl 1994). In a recent animal study, the compound ceftriaxone, a beta-lactam antibiotic that stimulates uptake of glutamate, demonstrated antidepressant-like effects in several mouse models (Mineur et al. 2007). In animal studies, memantine produced antidepressive-like activity (Ljungberg 1986; Moryl et al. 1993).

There is increasing evidence from neuroimaging studies that severe mood disorders are associated with impairments of structural plasticity and cellular resilience (Manji et al. 2003) and that NMDA-receptors have a significant role in mood disorders (Sanacora et al. 2003) by dysregulation of neurotransmission via NMDA receptors (Pittenger et al. 2007). These aspects are proposed to represent new ways to both understanding depressive symptomatology and developing more effective antidepressants (Paul and Skolnick 2003).

A recent study revealed elevated glutamate levels in the occipital cortex in medication-free subjects with major depressive disorder compared with healthy controls (Sanacora et al. 2004). In human suicide victims, selective alterations in the glutamate recognition site and its coupling to the co-transmitter glycine site were demonstrated (Nowak et al. 1995). In a study of refractory affective disorder, cerebrospinal fluid glutamate was reduced significantly in patients compared to controls (Frye et al. 2007) Some NMDA modulators, such as D-cycloserine and amantadine, have shown to possess antidepressant effect when used in the treatment of tuberculosis and Parkinson's disease (Kugaya and Sanacora 2005). A glutamate antagonist topiramate, a medication for seizure disorders, has been shown to be effective in the reduction of depressive symptoms and anger in depressive women (Nickel et al. 2005). Lamotrigine, a compound that is used to treat bipolar depression, decreases glutamate transmission (Hurley 2002; McElroy et al. 2004). It was shown that intravenous injection of the NMDA antagonist, ketamine, is effective for patients with treatment-resistant MDD (Krystal et al. 1998; Zarate et al. 2006a). The NMDA modulator riluzole was found to be effective in a preliminary study in treatment-resistant depression (Zarate et al. 2004) and in residual depressive symptoms with antidepressant treatment (Sanacora et al. 2006). A novel finding is that patients with major depressive disorder had reduced glutamate levels in both prefrontal region of interest (Hasler et al. 2007) and a link between an increase in glutamatergic metabolites in prefrontal brain areas and rapid antidepressive manipulations (Murck et al. 2008).

2.4.3 Serotonin and major depression

The diminished availability of serotonin is one of the crucial factors in depression (Meltzer 1989). Over thirty years ago, it was supposed that the concentration of serotonin in the cerebrospinal fluid correlates with the severity of depression in those patients, whose serotonin turnover is disturbed (Asberg et al. 1976). In a recent neuroimaging study, patients with MDD had significant lower serotonin transporter binding potential in the midbrain region than controls (Joensuu et al. 2007). The altered serotonin activity is one premise for the use of selective serotonin reuptake inhibitors (SSRIs) in the treatment of depressive disorders (Owens and Nemeroff 1994). SSRIs were developed for inhibition of the neuronal uptake pump for serotonin. The therapeutic mechanism of action of SSRIs involves alteration in the serotonin system. There are several studies and meta-analyses of SSRIs in the treatment of depressive disorders. The first SSRI approved as antidepressant was zimelidine. It was withdrawn from the market due to the report of Guillain-Barre syndrome in a few patients. Over a relatively short period occurred the development of five other SSRIs, namely fluoxetine, fluvoxamine, sertraline, paroxetine and citalopram (Vaswani et al. 2003). The more efficient compound escitalopram, the *S*-enantiomer of citalopram, is now widely used for the treatment of depression (Thase 2006). The treatment of major depression with SSRIs is widely accepted and recommended in Finnish recommendation for treatment of depression (Isometsä et al. 2005).

Even when there is a risk of increased suicide attempts in depressive patients treated with SSRIs (Jick et al. 2004), the mortality rate among these patients has shown to decrease (Tiihonen et al. 2006).

Figure 2. Treatment Studies of Alcohol- Related Disorders and Comorbid Depressive Disorder.

Outcomes of Treatments for Individuals with Alcohol-Related Disorder and Comorbid Depressive Disorder

Source		Interventions	Group N	Randomized Desing	Initial Abstinence	Alcohol-Related Criteria	Psychiatric Criteria
Psychosocial Interventions							
Brown et al. (1997)	(T)	Cognitive-Behavioral Therapy	19	No	Yes	DSM-III-R	BDI<9
	(C)	Relaxation training (RT)	16				
TCAs							
McGrath et al. (1996)	(T)	Imiprimine 300 mg/d + relapse prevention	36	Yes	No	DSM-III-R Alcohol dependence	DSM-III-R MDD, DD or depressive disorder NOS
	(C)	Placebo + relapse prevention	33				
Mason et al. (1996)	(T)	Desipramine 200 mg/d	15	Yes	Yes	DSM-III-R Alcohol dependence	DSM-III-R MDD
	(C)	Placebo	13				
Nunes et al. (1993)	(T)	Imiprimine	60	No	No	DSM-III-R Alcohol abuse or dependence	DSM-III-R Major MDD or Dysthymia
	(C)	No control					
SSRIs							
Roy (1998)	(T)	Sertraline 100 mg/d	18	Yes	Yes	DSM-III-R Alcohol dependence	DSM-III-R MDD
	(C)	Placebo	18				
Pettinati et al. (2001)	(T)	Sertraline 200 mg(d	12	Yes	Yes	DSM-III-R Alcohol Dependence	DSM-III-R MDD or DD
	(C)	Placebo	17				
Gual et al. (2003)	(T)	Sertraline 50-150 mg/d	39	Yes	Yes	DSM-IV Alcohol dependence	DSM-IV MDD, DD or both
	(C)	Plasebo	44				
Moak et al. (2003)	(T)	Sertraline 200 mg/d + CBT	38	Yes	Yes	DSM-III-R Alcohol dependence or Abuse	DSM-III-R MDD or Dysthymia
	(C)	CBT+ placebo	44				
Cornelius et al. (1997)	(T)	Fluoxetine 25 mg/d	25	Yes	Yes	DSM-III-R Alcohol dependence	DSM-III-R MDD
	(C)	Placebo	26				
Oslin (2005)	(T)	Naltrexone (50 mg/d) + sertraline (100 mg/d) + supportive Therapy	37	Yes	Yes	DSM-IV Alcohol dependence DSM IV Depressive Disorder	
	(C)	Placebo + sertaline (100 mg/d) + supportive therapy	37				
Atypical Antidepressants							
Roy-Byrne et al. (2000)	(T)	Nefazadone 500 mg/d + CBT	32	Yes	No	DSM-III-R Alcohol dependence	DSM-III-R MDD
	(C)	Placebo + CBT	32				
Hernandez-Avila et al. (2004)	(T)	Nefazadone 400 mg/d + supportive psychotherapy	21	Yes	Yes	DSM-IV Alcohol dependence	DSM-IV MDD
	(C)	Placebo + supportive psychotherapy	20				
Brown et al. (2003)	(T)	Nefazadone 600 mg/d	13	No	No	DSM-IV Alcohol dependence	DSM-IV MDD
	(C)	None					
Other Medications							
Dorus et al. (1989)	(T)	Lithium, 600 1,200 mg/d	89	Yes	Yes	DSM-III Alcohol dependence	DSM-III MDD or DD
	(C)	Placebo	82				
Salloum et al. (1998)		Naltrexone, 50 mg/d	18	No	Yes	DSM-III-R Alcohol dependence	DSM-III-R MDD
	(C)	No comparison condition	0				

T	Treatment Condition	C	Comparison Condition
MDD	Major Depressive Disorder	DD	Dysthymic Disorder
NC	Not calculabel	HAM-D	Hamilton Depression scale
HAM-A	Hamilton Anxiety scale	BDI	Beck Depressive Inventory

Length of Experimental Condition(s)	Psychiatric Outcomes Effect Sizes (Cohen's *d*)		Alcohol-Related Outcomes Effect Sizes (Cohen's *d*)		Source
					Psychosocial Interventions
8 sessions, 45 minutes each	(1) HAM-D*	0.69	(1) Percent days abstinent	0.59	**Brown et al. (1997)**
	(2) POMS Depression*	1.02			
	(3) POMS Anxiety	0.83	(2) Drinks per day*	0.71	
					TCAs
12 weeks	(1) HAM-D*	0.40	(1) % days drinking	0.08	**McGrath et al. (1996)**
			(2) % drinking heavily	-0.26	
			(3) Drinks per drinking day	0.26	
26 weeks	(1) HAM-D*	0.93	(1) Days to relapse	0.65	**Mason et al. (1996)**
12 weeks	Of all participants, 27 (45%) were deemed "responders". Mean post-treatment HAM-D=3(+/-3).		Of 27 responsers, 18 achieved abstinence and 9 had significant reduction in alcohol use		**Nunes et al. (1993)**
					SSRIs
6 weeks	(1) HAM-D*	1.06	Not Tested		**Roy (1998)**
	(2) BDI*	0.76			
14 weeks	(1) HAM-D	-0.21	(1) Percent Days Drinking	-0.36	**Pettinati et al. (2001)**
	(2) BDI*	-0.20	(2) Weeks to relapse	-0.10	
24 weeks	(1) HAM-D	NC	(1) Days to relapse	-0.17	**Gual et al. (2003)**
	(2) SF-36 Mental Health	0.48	(2) Cumulative Days of Abstinence	-0.04	
12 weeks	Females		(1) Time to first heavy drinking day	0.10	**Moak et al. (2003)**
	HAM-D*	0.76			
	BDI*	1.09	(2) Time to first drink	NC	
	Males		Drinks per Drinking Day*	0.50	
	HAM-D=3(+/-3).	0.01	(4) Percent Days Abstinent		
12 weeks	HAM-D*	0.57	(1) Cumulative Drinks*	0.76	**Cornelius et al. (1997)**
	BDI	0.45	(2) Cumulative drinking days*	0.57	
			(3) Drinks per drinking day*	0.68	
			(4) Cumulative days heavy drinking*	0.81	
			(5) # weeks to first heavy drinking*	0.73	
			(6) Weeks to first drink	0.38	
12 weeks	(1) Depression Remission (HAM-D<10)	-0.09	(1) Abstinence from heavy drinking*	-0.10	**Oslin (2005)**
					Atypical Antidepressants
12 weeks	HAM-D (<8)*	0.71	(1) Drinks per day	0.08	**Roy-Byrne et al. (2000)**
			(2) Alcohol Craiving	0.38	
10 weeks	(1) HAM-D	0.07	(1) Drinks per week*	0.82	**Hernandez-Avila et al. (2004)**
	(2) State Anxiety Inventory	0.52	(2) Heavy drinking days*	1.01	
12 weeks	(1) 45% reduction in HAM-D scores		(1) 27.5% reduction in Alcohol craving		**Brown et al. (2003)**
	(2) 40% reduction in HAM-A scores		(2) 87% reduction in drinks per week		
			(3) 68% reduction in days drinking per week		
					Other Medications
52 weeks	(1) BDI	0.24	(1) Days drinking past weeks	0.29	**Dorus et al. (1989)**
			(2) Addiction Severity Index Global	-0.11	
12 weeks	Trend in reduction of HAM-D scores (p=.078), BDI scores (p=.071), and GAF scores (p=.076)		Significant reduction in drinks per week and urge to drink		**Salloum et al. (1998)**

* Significant difference (p=<.05)

Initial Abstinence = Yes if patients were abstinent before beginning treatment.
Cohen's *d* represents effect of treatment condition (T) relative to condition (C), with small, medium, and large effects defined as 0.2, 0.5, and 0.8, respectively.

2.5 Current medical treatment of comorbid alcohol dependence and major depression

The number of efficacy studies among comorbid alcohol dependence and major depression is rather low, even when studies examining these separately are substantial. Studies with tricyclic antidepressants and atypical antidepressants in the treatment of this comorbidity have produced controversial outcomes as well as the studies with SSRIs, even when tricyclic antidepressants tend to show better results than SSRIs (Tiet and Mausbach 2007)(Figure 2).

The current attractive medications for MDD with alcohol dependence are, however, SSRIs for their tolerability and potential effectiveness (Cornelius et al. 1997; Cornelius et al. 2000; Nunes and Levin 2004; Roy 1998) even when some placebo controlled trials did not provide consistent support for the use of sertraline (Gual et al. 2003; Kranzler et al. 2006; Pettinati et al. 2001) or resulted in a modest improvement at best and mainly for women (Moak et al. 2003). The treatment of alcohol dependence comorbid with major depressive disorder (MDD) with SSRIs, however, has generally produced positive results (Berglund et al. 2003; Cornelius et al. 2003; Cornelius et al. 1997; Goldstein et al. 2006; Moak et al. 2003; Nunes and Levin 2004; Pettinati 2004). The treatment of this comorbidity with serotonin and noradrenalin transporter inhibitors has produced positive results (Hernandez-Avila et al. 2004; Yoon et al. 2006).

Nevertheless, SSRIs are safe compared to tricyclic antidepressants (TCA's) in the increased suicidality (Sher et al. 2005) that is comorbid with alcoholism (Pirkola et al. 2004).

2.6 Predictors for medical treatment of alcohol dependence comorbid with major depression

The treatment of comorbid major depression and alcohol dependence is difficult and controversial (Nunes and Levin 2006). Discontinuation of medical treatment is common (Kranzler et al. 1996b). Predictors to antidepressant medication in treatment of depression would be a challenge to clinicians among this group of patients (Bagby et al. 2002) The research on predictors for response to treatment in depression comorbid with alcohol dependence is exiguous. Comorbid cocaine abuse has shown to be associated with poorer response to antidepressant therapy for major depression comorbid with alcohol dependence (Cornelius et al. 1998). Additional research of predictive signs in major depression comorbid with alcohol dependence deals mainly with either one or the other disorder.

2.6.1 Predictors for treatment of depression

The research on the field of predictors in treatment of major depression is limited: substance abuse has been associated with poorer response to antidepressant therapy in depression as far as comorbidity with anxiety disorders and panic-agoraphobic spectrum (Bagby et al. 2002). In post-stroke depressed patients the anxiousness has predicted greater efficacy to citalopram and retarded depression to reboxetine (Rampello et al. 2004).

Early age of onset in major depression has been connected with more malignant course of depression (Klein et al. 1999; O'Leary et al. 2000), but not with response to medical treatment (Klein et al. 1999). Early onset of major depression has been a predictor for personality disorders (Ramklint and Ekselius 2003) and personality disorders as predictors has shown mainly poorer response to antidepressive treatment (Bagby et al. 2002). The personality traits using tridimensional personality questionnaire (TPQ) are found to be predictors to antidepressant: high harm avoidance scores have predicted lesser improvement to treatment with antidepressants in subjects with major depressive disorder (Abrams et al. 2004), harm avoidance scores and reward dependence scores, and their interaction were found to predict significantly poorer response to nefazodone (Nelson and Cloninger 1997; Nelson and Cloninger 1995).

Neurobiological factors such as dopamine impairments might have been distinguishing factor in treatment with SSRIs (Kampf-Sherf et al. 2004), which has been indicated by correlation on performances in neuropsychological functioning and neuromotor measures and treatment outcomes (Caligiuri et al. 2003; Taylor et al. 2006).

2.6.2 Predictors for treatment of alcohol dependence

The predictive signs in the treatment of alcoholism have been desired for years (Naranjo and Knoke 2001b; Pettinati and Rabinowitz 2006; Schaffer and Naranjo 1998). Prospective studies in non-human primates that underwent early separation stress have found an association between a low serotonin turnover rate and the disposition to excessive alcohol intake and impulsive aggression (Heinz et al. 2001). The comorbidity with depressive disorders, major depression (Rounsaville et al. 1987) and lifetime depression (Pettinati et al. 2001) worsen the results of treatment in alcoholism as far as comorbidity with anxiety disorder (Kushner et al. 2005; Willinger et al. 2002). However, comorbidity with major depression has predicted good outcome in some studies (Johnson 2003; Johnson 2004). In the Finnish Health 2000 study, social phobia and dysthymia were more common among actively alcohol dependent subjects than among subjects in remission (Pirkola et al. 2006).

Personality traits such as high novelty seeking and low harm avoidance covering exploratory excitability and impulsiveness predicted relapse (Willinger et al. 2002).

Since Cloninger's theory of type 1 and 2 alcoholism (Cloninger 1987), the investigation of different pathways to indicate optimal treatment and to understand the nature of craving has been active (Spanagel 2000; Verheul et al. 1999). Type 2 alcoholism is associated with early onset of alcohol abuse and low 5-HIAA concentrations in cerebrospinal fluid (Virkkunen and Linnoila 1990). This group of patients were suspected to have good response to SSRIs, but the results were contrary (Kranzler et al. 1996a). Early onset of alcohol problems predicted poor outcome in relapse prevention and the late onset of alcoholism predicted better outcome to SSRIs (Chick et al. 2004; Johnson 2004; Pitkänen et al. 2005).

In treatment with naltrexone, the high baseline depression was predictive for good treatment efficacy (Kiefer et al. 2003). Naltrexone seemed to be beneficial in the treatment of alcoholic patients with early onset of alcohol abuse, family history of alcoholism and comorbid use of other drugs of abuse (Rubio et al. 2005). Acamprosate was efficacious in patients with low baseline somatic distress (Kiefer et al. 2005) but from a pooled analysis of seven European trials, there were no predictive signs for acamprosate treatment (Verheul et al. 2005).

2.6.3 5-hydroxy tryptamine (serotonin) transporter linked polymorphic region *(5-HTTLPR)* as predictor

One of the most important genes related to major depression is 5-*HTTLPR*. Serotonergic neurotransmission is connected to both major depression and alcohol dependence (Kranzler and Anton 1994). Serotonin neurotransmission is regulated by 5-HTT gene and the gene expression is regulated by 5-*HTTLPR* polymorphism, in which the homozygosity for the long (L) allele results in threefold higher levels of presynaptic transport of 5-HT (Heils et al. 1996). Research to find predictive signs in serotonin transporter linked polymorphic region (5-*HTTLPR*) has consistently shown the short (S) allele association with depression but not with alcoholism (Dick et al. 2007; Marques et al. 2006; Nellissery et al. 2003). The burgeoning evidence connects S allele concurrent with early life stress on vulnerability to depression (Caspi et al. 2003; Dick et al. 2007; Wilhelm et al. 2006) and early alcohol use (Kaufman et al. 2007).

Association of 5-*HTTLPR* gene variations with the treatment response with SSRIs in depressed patients has shown conflicting data. Serretti found in a meta-analysis the significant association of the L-variant of 5-*HTTLPR* with a better response in depressed patients to SSRIs (Serretti et al. 2007) whereas in a recent analysis in a large clinical sample with careful patient characterization, such association was not found (Kraft et al. 2007). Remarkably, a supportive environment appeared to protect maltreated children with the S/S genotype from developing depression (Kaufman et al. 2004).

3 AIMS OF THE STUDY

The aim of this study was to evaluate new treatment compound, memantine, a non-competitive NMDA receptor blocker, for patients comorbid with major depression and alcohol dependence and compare the results with escitalopram, a selective serotonin reuptake inhibitor antidepressant, in a double-blind manner.

Specific aims of the study were:

1. To evaluate the influence on major depression, anxiety, cognitive functioning and quality of life.

2. To evaluate the influence on alcohol consumption and reward.

3. To determine for the treatment of major depression, clinical and genetical predictors of the response to both medicines.

4. To determine for the treatment of alcohol dependence, clinical and genetical predictors of the response to both medicines.

4 METHODS

4.1 Study participants and ethics

At three Helsinki Alcohol-clinics (A-clinics: Annankatu, Malmi and Töölö Clinics, covering a population of about 200 000 inhabitants), men and women aged 26 to 65 years who were voluntarily seeking outpatient treatment for alcohol problems were screened. Alcohol dependent patients with a history of heavy drinking (five or more daily drinks for men and four daily drinks for women) for at least ten years, and were considered to have significant depression by the therapist and the patient (defined by Beck Depression Inventory II (BDI-II) > 17), and who were interested in voluntarily taking part in the study were recommended by their A-clinic doctor or social therapist to the study physician's interview and screening. The recruiting lasted from Dec 20, 2004 to Dec 7, 2005. For inclusion, the patients were interviewed, by a psychiatrist LM, using the Structured Clinical Interview for DSM-IV TR (SCID), and were required to meet the criteria of both alcohol dependence and MDD according to DSM-IV TR. Abstinence was not required, but the time after possible prior inpatient detoxification had to be at least four weeks. The exclusion criteria were 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. Other medications prescribed by their physician were allowed, with the exception of other antidepressants.

The study was approved by the independent Hospital District of Helsinki and Uusimaa, Ethical Committee (permission 22/2004) and the Finnish National Agency of Medicine (KL# 87/2004). The study was conducted according the International Conference on Harmonisation (ICH) 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 the ClinicalTrials.gov Identifier (trial # NCT00368862). Separate informed consent for the DNA test for 5-*HTTLPR* allele variation was approved Hospital District of Helsinki and Uusimaa, Ethical Committee (permission to amendments 9.5.2006 and 29.4.2008). All patients had to be able to read and understand the patient information sheet and sign the informed consent. All participants were free to stop study medication whenever they wanted. The patients were not paid or reimbursed for participation.

4.2 Study medication

4.2.1 Memantine

Memantine is a non-competitive N-methyl-D-aspartate (NMDA) ionotropic glutamate receptor blocker. In addition, it inhibits 5-Hydroxy tryptamine 3-receptors, which may contribute to its therapeutic efficacy (Johnson and Kotermanski 2006). It has also some antagonism on nicotinic acetylcholine receptors (Parsons et al. 1999). It is approved for the treatment of moderate to severe Alzheimer disease (Gortelmeyer and Erbler 1992; Johnson and Kotermanski 2006), with no clear benefit to date for mild stages of Alzheimer's disease or for vascular dementia (Muir 2006). It may have some effect on alcohol related dementia (Cheon et al. 2008). In a preclinical study, memantine seems to have anxiolytic response (Minkeviciene et al. 2008).

A research with memantine in the field of neurodegenerative diseases like glaucoma (Levin and Peeples 2008), amyotrophic lateral sclerososis (Lou Gehrig's disease), Parkinson's disease and neuropathic pain (Planells-Cases et al. 2006) is in progress.

It is efficient in treatment of Huntington's disease (Beister et al. 2004). An additional finding is that memantine may have therapeutic potential for tinnitus (Figueiredo et al. 2008; Lobarinas et al. 2006), migraine (Charles et al. 2007; Peeters et al. 2007) and binge eating disorder (Brennan et al. 2008).

Memantine seems not to have abuse liability in cocaine dependent rats (Hyytiä et al. 1999) or humans (Vosburg et al. 2005).

4.2.2 Escitalopram

The SSRI used in the present study is escitalopram, the active *S*-enantiomer of the racemic selective serotonin reuptake inhibitor citalopram. It is a highly selective inhibitor of the serotonin transporter protein (Murdoch and Keam 2005). There is evidence that citalopram is an effective antidepressant in various controlled clinical trials (Pollock 2001). The escitalopram shows better efficacy and higher rates of response than the racemic compound (Owens et al. 2001; Sanchez et al. 2004).

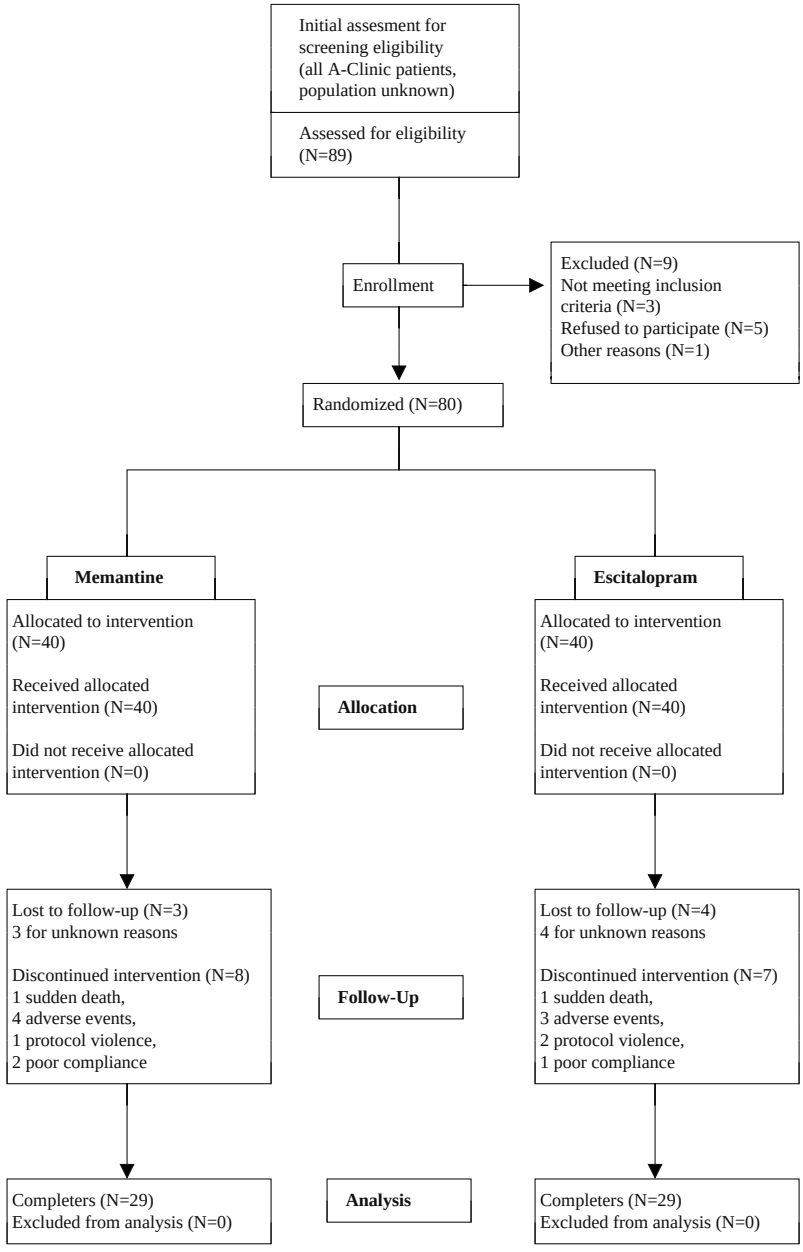
In addition, escitalopram is indicated in generalized anxiety disorder (Varia and Rauscher 2002), social anxiety (Varia et al. 2002), panic disorder (Stahl et al. 2003) and obsessive-compulsive disorder (Stein et al. 2007).

Escitalopram has been investigated in posttraumatic stress disorder with good results (Robert et al. 2006) as well as gambling (Grant et al. 2006).

4.3 Study design

Study enrollment began on December 20, 2004, and the last patient completed the study on May 25, 2006. The same study physician (LM) screened, enrolled, and treated all patients. After providing initial examination, patients underwent procedures including the recording of demographic and medical history, physical examination, laboratory examinations (urine drug screen, serum AST, ALT, desialotransferrine (CDT), gamma-glutamyltransferase (GGT), tyreotropine, creatine, sodium and potassium) with the analysis performed by the independent accredited VITA-terveyspalvelut Ltd, Helsinki, Finland, a screening interview (SCID (First et al. 1995)) to provide a detailed diagnostic characterization of mental and alcohol problems of the patients, and interviews for the Montgomery-Åsberg Depression Rating Scale (MADRS (Montgomery and Asberg 1979)), the Hamilton Anxiety Scale (HAM-A (Hamilton 1959)), the Social and Occupational Functioning Assessment Scale (SOFAS (Goldman et al. 1992)) and the Consortium to Establish a Registry for Alzheimer Disease cognitive test battery (CERAD (Fillenbaum et al. 1997)). A set of questionnaires were filled in by the patients, including: Tridimensional Personality Questionnaire (TPQ (Cloninger 1987)), Beck Depression Inventory II (BDI-II (Beck et al. 1996)), Beck Anxiety Inventory (BAI (Beck et al. 1988)), Alcohol Use Disorders Identification Test (AUDIT (Saunders et al. 1993)), Obsessive Compulsive Drinking Scale (OCDS (Anton 2000)) and Visual Analogue Scale (VAS (Nord 1991; Scott and Huskisson 1976)). In addition, The European Quality of life, 5 items (EQ5) (EuroQol Group 1990) and Koskenvuo items for quality of life (Koskenvuo 1979) were permitted. The quantification of alcohol consumption and study medication during the 26 week treatment period was assessed by Drinking Diary (Poikolainen and Kärkkäinen 1983), AUDIT QF (Aalto et al. 2006) and AUDIT 3 (Gual et al. 2002).

Figure 3. Study CONSORT Flowchart.



All patients meeting the inclusion criteria were randomly assigned by an independent person (S. Päivinen) to memantine or escitalopram groups using 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 α=0. 05, β=0. 10, f($\alpha\beta$)=10,5 , p_1=10, p_2=40 and n=p_1 x (100-p1) + p_2 x (100-p_2) / (p_2-p_1) x 10.5=38, to control the dropouts the sample size in each group is 40. The randomization was concealed until the study database was locked (MedFiles Ltd, June 6, 2006). In an emergency or in a case of Serious adverse event (SAE) an individual random number could be opened by an independent person. The study medication (kindly provided by Lundbeck Oy Ab, Turku, Finland) was double-dummy packed: the patients took two 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 were randomly allocated to receive either 20 mg /day escitalopram or 20 mg/day 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 four 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. Other than antidepressive drugs, concomitant medication was allowed during the study. There were no additional psychosocial interventions by the study physician. Concomitant intervention on alcohol consumption was not done, and no treatment goals were imposed. 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 18-20, a 10-15 minute phone conversation with each patient was made. At each visit, the study medication intake since the previous visit was recorded using the drinking diary. The study medication was ensured with the pill count from the returned baggage. Any possible adverse events were elicited by the study physician at each visit and recorded by the patient to drinking diary. Other measures were recorded on specific weeks: MADRS, HAM-A, SOFAS, BDI-II, BAI, OCDS, EQ-5, Koskenvuo life scale and VAS (0, 4, 12 and 26 week); AUDIT (0 week) and AUDIT 2 (12 and 26 week) modified to report events in the previous month; TPQ and CERAD (0 and 26 week). Clinical laboratory tests (Mean corpuscle volume [MCV], CDT, Blood ASAT, ALAT, CDT, and GGT) were taken in the beginning of research and were repeated at weeks 4, 12 and 26 to ensure the safety of medication. The study was monitored by an independent organization Medikalla Oy, Medfiles, Turku.

For the outcome association analysis the patients in both medication groups that completed the study were divided twice in two subgroups. The first division was for predictors in treatment of depression: remitted patients were those who had at the end of study MADRS scores ≤12 and non-responders were those of the rest who had reduction of MADRS scores <50% (Montgomery et al. 1993). MADRS was analyzed in total score and in dimensions of a

three-factor analytic model (Parker et al. 2003). The second division was for predictors in treatment of alcohol dependence: those who received AUDIT-points <8 constituted the group of remission and those with AUDIT-points ≥20 constituted the group of non-responders, according to World Health Organization (WHO) distribution (Babor and World Health Organization. Dept. of Mental Health and Substance Dependence. 2001). All baseline and demographic data was analyzed with these distributions.

All primary and secondary outcome statistical analysis was performed by independent source (Medikalla Oy, MedFiles, Turku).

Figure 4. Study Investigation Flowchart.

	*			**			
-1	0	1 wk	2 wk	1 mo	3 mo	4.5 mo	6 mo
R	D LAB +TSH, Na, K, S, SCID M+Cerad, TPQ	D	D	D Lab M (not AUDIT)	D LAB M	PC BDI BAI	D LAB M, Cerad, TPQ

R	=	Recruiting patients, patient information, inclusion/exclusion criteria
D	=	Doctor's visit
PC	=	Phone contact
LAB	=	Blood Count, CDT, ASAT, ALAT, GGT, Crea
Lab	=	Crea, ASAT, ALAT, GGT, Na, K
S	=	Status and demographic data
SCID	=	Check the criteria for alcohol dependence and major depression with SCID
M	=	Study outcome measures: AUDIT, BDI-II, BAI, MADRS, HAM-A (Hamilton Anxiety), EQ-5, Koskenvuo life scale, VAS, drinking diary
BDI	=	BDI-II (Beck depression inventory, sent to patients)
BAI	=	(Beck Anxiety Inventory, sent to patients)
*	=	informed consent, randomization, start of the medication (25% of the final dose)
**	=	medication 100 %

4.4 Statistical analysis

Statistical evaluation utilized Statistical Analysis Software (SAS) Procedures in SAS® system for Windows (Version 8.2), SAS-institute, Finland. The intent-to-treat population, which included all randomized patients including two early terminating 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 measures were analyzed by logistics regression or analysis of variance. MADRS, BDI-II, HAM-A, BAI, CERAD, AUDIT and OCDS were all analyzed with analysis of variance (ANOVA) for repeated measures when treatment, time (0,4,12 and 26 weeks) and treatment*time interaction were in the model (PROG MIXED in SAS®) and responses to specific question ("Has your depression or drinking declined during the study?") were analyzed by logistic regression (PROG LOGISTIC in SAS®). The modeling of associations between genotype and MADRS score decrease and genotype and AUDIT score decrease was carried out with linear regression separately in both medication groups. First "LL" genotype was compared to other genotypes, then linear trend in respect to number of "L" alleles (0, 1, or 2) was checked. Linear trend was tested with likelihood ratio statistics.

Differences in baseline characteristics for the four groups (memantine in remission / non-responders and escitalopram in remission / non-responders) were analyzed with analysis of variance, analysis of covariance and multiple linear regression analyses. Moreover, Spearman’s correlations were calculated between variables by treatment group. Differences between correlations in memantine and escitalopram groups when measured with MADRS, were analyzed with Z statistics (Hays 1963).

5 RESULTS

Out of those eighty-nine patients, who were initially screened from patients of the Helsinki A-clinic, three were excluded because they did not meet inclusion criteria, five refused to participate and one did not return after pre-screening. Eighty patients were randomized to either memantine or escitalopram (N=40 + 40). Blinding was assured by a double-dummy design. The patients were aged 26 to 65 years, and 55% were men. There were no significant differences between groups in their demographic characteristics in the initial alcohol and depressive measures. The mean length of the present depressive period was 35 months. Active alcohol abuse was reported by seventeen patients in both groups. Abstinence of one to three months was reported in the memantine group by 17 patients and in the escitalopram group by 18 patients. Abstinence up to one year was reported by five patients in both groups. (Data is missing for one memantine-randomized patient due to an interrupted interview.) The number of study patients' treatment visits in A-clinics during the study period was similar (in memantine group 7.7, Standard Deviation (SD)±8.8 and in escitalopram group 7.1, SD±9.8).

The completion rate of the 26 week study period was identical in both groups: 72.5% (29) for memantine and 72.5 % (29) for escitalopram (Table 2). The reasons for discontinuing the study were: adverse events (memantine 5, escitalopram 4), 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 of the 58 subjects who completed the study attended all appointments and showed at least 80 % compliance based on tablet counts.

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

5.1 Major depression, anxiety, cognition and quality of life

5.1.1 Major depression

The depressive symptoms measured by MADRS 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 ($F[3,77]=138.04$, $p<.0001$), with no significant differences between the two treatment groups ($F[3,77]=1.13$, $p=0.94$). In memantine group, 17/29 patients reached remission and 11/29 were non-responders. In escitalopram group, 17/29 patients reached

remission (MADRS ≤12) and 9/29 patients were non-responders (MADRS decrease <50%). One patient in escitalopram group and three patients in memantine group received MADRS decrease > 50 % but remained still >12 scores. On the baseline demographic data there were no differences between the age and gender in these four groups.

The self-rated depression scores (BDI-II) 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) ($F[4,77]=25.77$, $p<.0001$); there was no difference between the two treatment groups ($F[4,77]=0.92$, $p=0.68$). In memantine group, 17 patients reached BDI scores ≤ 15 and 12 of them ≤10. In escitalopram group, 21 patients reached BDI scores ≤15 and 17 of them ≤10.

When questioned at the end of the intervention, 75.9 % of patients in the memantine group and 72.4 % of patients in the escitalopram group reported their depression to be decreased.

5.1.2 Anxiety

Anxiety symptoms, measured by HAM-A, 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. ($F[3,77]=132.14$, $p<.0001$) with no significant difference between the two treatment groups ($F[3,77]=0.38$, $p=0.5$). 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 ($F[4,77]=6.45$, $p=0.0002$). There was no significant difference or interaction between the two treatment groups ($F[4,77]=1.31$, $p=0.27$) (Fig.3).

5.1.3 Cognitive functioning

The cognitive performance scores (CERAD) did not change significantly during the study period in either treatment group. They were already at baseline in the range of the reference values. The mean Mini Mental State Examination (MMSE) score at baseline was in memantine group 28.1±1.4 and in escitalopram group 28.0±1.7, and at the end of the study in memantine group 27.9±1.5 and in escitalopram group 27.4±1.5. ($F[1,77]=3.1$, $p=0.08$). The average retrieval percentage of wordlist at baseline was in memantine group 89.2±16.8 and in escitalopram group 83.9±19.5 ,and at the end of the study in memantine group 88.1 ±16.5 and in escitalopram group 89.9±13.5 ($F[1,77]=1.21$, $p=0.28$).

5.1.4 Quality of life

The quality of life, estimated using the Visual Analogue Scale (VAS) score, increased in both treatment groups. 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 ($F[3,77]=10.27$, $p<.0001$). There was no statistical difference between the two groups ($F[3,77]=0.25$, $p=0.9$). Scores on the social and occupational functioning scale, SOFAS, increased significantly 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 ($F[3,77]=39.75$, $p<.0001$)). There was no significant difference between the groups ($F[3,77]=1.7$, $p=0.86$).

5.2 Alcohol consumption and craving

5.2.1 Alcohol consumption

The AUDIT scores decreased from baseline in both groups, from 27.4±7.1 to 14.3±9.9 in the memantine group and from 28.4±1.0 to 17.6±1.9 in the escitalopram group. The overall reduction was highly significant ($F[2,77]=48.42$, $p<.0001$). There was a non-significant tendency for lower AUDIT scores in the memantine group than in escitalopram group ($F[1,77]=2.82$, $p=0.10$). The treatment by time interaction was not significant ($F[2,77]=1.19$, $p=0.31$).

Alcohol consumption measured by the AUDIT QF (quantity-frequency) score was significantly reduced in both groups: in the memantine group from 6.2±1.7 to 4.1±2.5 and in the escitalopram group from 6.1±1.7 to 4.3±2.3 ($F[2,77]=23.53$, $p<.0001$. The number of heavy drinking days measured by the AUDIT 3 score was also diminished significantly in both groups: for memantine from 2.9±1.1 to 1.8±1.3 and for escitalopram from 3.1±1.0 to 2.4 ±1.3; ($F[2,77]=20.29$, $p<.0001$. The difference between the groups approached significance with the memantine group doing slightly better ($F[2,77]=1,37$, $p=0.067$).

The number of abstinent days per week was high for both groups throughout the study. In weeks 14, 16, 18, and 25, the memantine group had significantly more abstinent days than the escitalopram group ($p<0.05$). The treatment by time interaction throughout the study was not significant ($F[2,74]=0.07$, $p=0.92$). The mean alcohol intake was 15.0±2.6g per day for the memantine group and 21.1±3.6g per day for the patients on escitalopram, with no significant difference between the groups ($F[1,74]=1.94$, $p=0.17$).

When questioned at the end of the intervention, 68.9% of patients in the memantine group and 62.1% of patients in the escitalopram group reported their alcohol use had decreased.

5.2.2 Alcohol craving

The OCDS total scores decreased in the memantine group 18.8±6.9 to 10.6±7.2 and in the escitalopram group from 20.4±4.9 to 12.8±8.6. The overall reduction was highly significant overall ($F[3,77]=25.76$, $p<.0001$). The interaction was not significant ($F[3,77]=0.69$, $p=0.56$). There was a trend for the memantine scores to be lower than those for escitalopram ($F[1,77]=3.30$, $p=0.073$). The scores were significantly lower in the memantine group than the escitalopram group at the 1 month visit ($F[1,72]=6.53$, $p=0.013$. The final scores were below 5 in 51% of the memantine patients but only 27% of the escitalopram patients.

The OCDS subscale scores related to the Obsessive Thoughts of Drinking decreased significantly ($F[3,77]=23.11$, $p <.0001$) in both groups: in the memantine group from 7.9 ±3.4 to 4.2±3.2 and in the escitalopram group from 8.9±2.4 to 5.3±4.2. These subscale values were significantly lower in the memantine than escitalopram subjects at the 1 month visit ($F[1, 72]=5.85$, $p=0.018$.

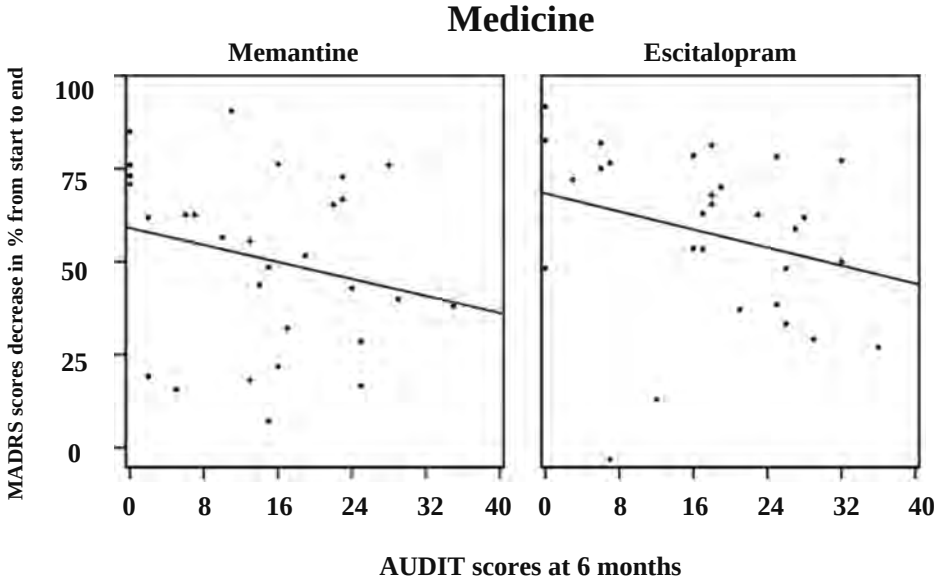
The OCDS Compulsive Drinking subscale also decreased significantly ($F[3,77=18.19$, $p<.0001$) in both groups: the decrease was from 10.9±4.0 to 6.4±4.6 in memantine group and it was 11.5±3.3 to 7.5±4.9 in escitalopram group. The score in the memantine group was significantly lower than that in the escitalopram group at 1 month ($F[1,72]=4.62$, $p=0.035$).

In both groups the mean serum concentration of ASAT, ALAT, GGT and CDT were within normal limits. There were no significant changes during the treatment period nor any significant difference between groups.

5.3 The comparison between recovery in depression and alcohol use

The analysis between the MADRS scores decrease and the AUDIT scores decrease showed difference in correlations : in memantine group there was a non-significant correlation ($p=0.12$), whereas in escitalopram group the correlation was significant ($p=0.025$). The data is based on an article containing the decrease in alcohol use (Muhonen et al. 2008a) and an article containing the decrease in depression and anxiety scores (Muhonen et al. 2008b).

Figure 5. Correlation between MADRS scores decrease and AUDIT scores at the end of the study, significant correlation in escitalopram group (p=0.025) unpublished.



5.4 Predictors for treatment of depression

Twenty-nine patients of forty (72.5%) completed the 26 weeks study period in both treatment group with either escitalopram or memantine.

5.4.1 Escitalopram group

In the escitalopram group the mean age at onset of major depression was significantly different between remitted and non-responding patients, 31.9±11.9 years (mean±SD) for remitted and 13.7±4.0 years for the non-responders ($t[24]=4.42$, $p=0.00018$). However, there was no difference in duration of current actual depressive episode 51.0±57.7 months in remission group and 65.3±110.6 months in non-responders group. The onset of the first depressive episode over the age of 20 years was associated to good treatment outcome ($p<0.005$): all of these patients reached remission in escitalopram group. All non-responding patients in escitalopram group had the first episode of depression before the alcohol dependency.

It was further tested with multiple linear regression whether age of onset of depression predicted change in MADRS when the scores were treated as continuous variables. Indeed, after controlling for the MADRS score in the baseline, earlier age of onset predicted higher MADRS score at six months in the escitalopram group (B=-0.30, 95% CI=-0.47 to -0.13, p=0.001). Further adjusting for gender and age did not alter the significance level. The family history of alcoholism did not correlate to the treatment outcomes, among the patients without family history of alcoholism three were in non-responder group and four in responder group.

In the three-factor analytic model of MADRS, the mean values of "psychic anxiety" dimension (questions 3, 9 and 10 of inner tension, pessimistic thoughts and suicidal thought) were more frequent in non-responders (9.1±2.4) than in remitted patients (7.2 ±1.6) ($p<0.05$).

The analysis of the Tridimensional Personality Questionnaire (TPQ), the signs of pessimism (p=0.05) and impulsiveness (p=0.09) were associated with poor outcome.

5.4.2 Memantine group

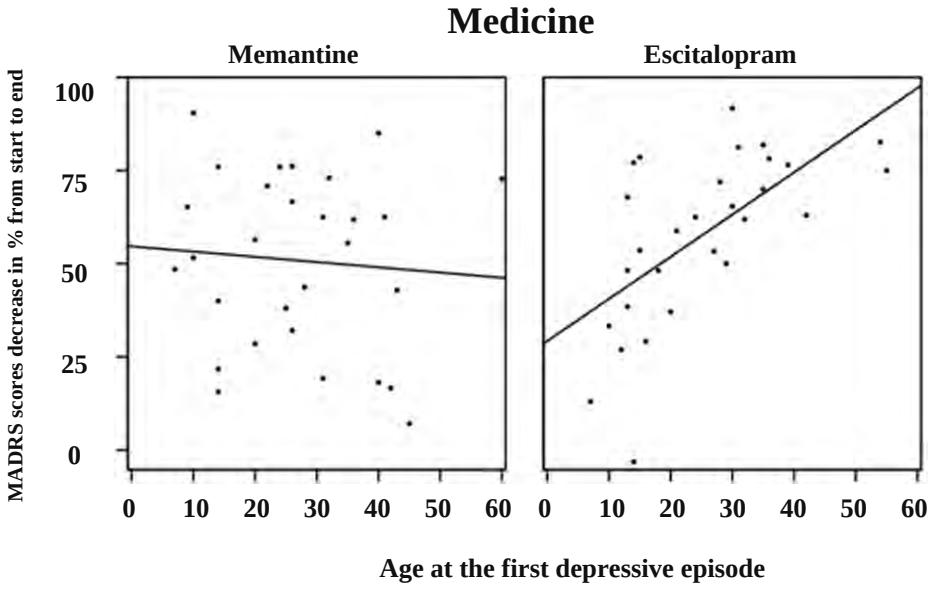
In memantine group, there were no differences in the age at onset of depression between remission group (28.4±13.5 months) and non-responders group (26.5±12.3 months). Among those of memantine group who had their first depressive episode under the age 20, six of ten patients received remission. The actual depressive episode had lasted in memantine remission group 16.1±25.3 years and non-responders group 21.6±33.4 years with no difference between the outcome groups. The onset of the first depressive episode was not associated to treatment outcome (t[26]=0.37, p=0.71). All patients without family history of alcoholism received remission and were associated to good treatment outcome ($p<0.05$).

In baseline MADRS value, in remitted patients group the mean was 23.5±3.2 and in non-responders 27.4±4.7 (p=0.02) predicting better outcome in lower baseline values. In the three-factor analytic model of MADRS, there were no differences between the mean values of non-responders and remitted patients in any dimensions.

In TPQ, the signs of pessimism and impulsiveness were not associated with treatment outcome in memantine group.

In both treatment groups, there was no difference between the baseline alcohol consumption and dependence measures (AUDIT, OCDS) abstinent days, onset of drinking and alcohol dependency.

Figure 6. Correlation between the age at onset of the first depressive episode of major depression and the efficacy of memantine and escitalopram.



Efficacy was measured as the decrease in MADRS from baseline to the end of the study (26 weeks). A highly significant correlation ($p < 0.0001$) was found with escitalopram but not with memantine. The difference between the two correlations was significant ($Z=3.7254$, $p=0.0002$).

5.5 Predictors for treatment of alcohol dependence

5.5.1 Escitalopram

In escitalopram group, 9 patients reached AUDIT <8 scores and 12 patients AUDIT scores >20. In memantine group, 9 patients reached AUDIT scores <8 and 9 patients over 20.

In escitalopram group, there was significant difference in demographic backgrounds on the age of the first alcohol intoxication, the mean age of the first intoxication was in non-responders group 14.6±1.4 years and in responders group 17.3±3.4 years (p=0.04). The similar difference was in the age of the first depressive episode: the mean age was in non-responders 20.4±8.3 years and in responders group 33.5±15.8 years (p=0.03). In multivariant analysis, the age in the first depressive episode explained the first intoxicative drinking significantly (p<0.05) but not vice versa.

5.5.2 Memantine

In memantine group, the mean age at the time of the first alcohol intoxication was in non-responders group 15.0±3.6 years and in responders group 16.1±2.5 years (p=0.39).The mean age in the time of the onset of first depressive episode was in non-responders group 28.1±16.9 years and in responders group 31.1±8.8 years (p=0.74).

5.5.3 Baseline alcohol use

In either group, there were no differences in mean ages in times of regular use of alcohol or alcohol dependence. The previous time of abstinence was not predictive, but those patients who were abstinent at the beginning of treatment were more likely to complete the treatment than those who were still drinking at the beginning (χ^2=6.51, df=1, p=0.011). This relationship was highly significant in the patients treated with memantine (χ^2=7.25, df=1, p=0.007): 8 of the 10 who dropped out were among the 17 (47.1 %) who were active drinkers at the baseline. The relationship was in the same direction in the escitalopram group but failed to reach statistical significance (χ^2=0.901, df=1, p=0.343). There was no significant difference between the memantine and escitalopram groups in this relationship between abstinence or drinking at the onset of treatment and the likelihood of dropping out (χ^2=1.864, df=3, p=0.601).

The baseline scores in AUDIT, OCDS and its subgroups were not predictive nor the baseline scores in other psychiatric measures.

5.6 Comparison between predictors in depression and alcohol use

In MADRS decrease, when compaired to onset of the first depressive episode and the first intoxicative drinking, there was no correlation in non-responders group with either medicines, whereas in responders group there were slight correlation with escitalopram (p=0.05) and remarkable correlation in memantine group (p=0.004).

In AUDIT decrease, when compaired to the onset of the first depressive episode and the first intoxicative drinking, there was no correlation in escitalopram non-responders group and a slight correlation (p=0.03) in memantine non-responders group. In responders group there were correlation between the age in the first depressive episode and the first alcohol intoxication in escitalopram group (p=0.013) but no correlation in memantine group.

5.7 5-*HTTLPR* polymorphism as a predictor

Of the 40 patients receiving escitalopram treatment, 11 dropped out. Of the patients finishing the trial, 20 patients received MADRS decrease ≥50% and 9 patients <50%. In the group responding to escitalopram treatment (N=20), 11 patients carried the LL genotype, 6 patients had the SL genotype and only one the SS genotype. Two patients did not sign the informed consent. The prevalence of the L-allele was consequently 78% and the prevalence of the S-allele 22%. In contrast, in the group of non-responders (N=9), there were only two patients with the LL genotype, six individuals carried the SL genotype and one the SS genotype. The frequencies of the L- and S-alleles were thus 55% and 45%, respectively.

When the response to the treatment was compared to the genotype by using linear regression, it was observed that the decrease in MADRS scores was significantly associated with LL genotype (F=5.46, p=0.028), the decrease was higher, mean difference being 20%, (95% CI: 2.2 to 37) in LL group compared to other genotypes. Also detected was linear trend in respect to number of L-alleles (F=4.64, p=0.04); having one L-allele more predicted 15% (95% CI: 0.6 to 29) unit decrease in MADRS score. In similar analysis no association between AUDIT and genotype was detected (F=0.23, p=0.64).

Of the 40 patients receiving memantine treatment, 11 dropped out. Of the patients finishing the trial, 16 patients received MADRS decrease ≥50% and 13 patients <50%. In the group responding to memantine treatment, 2 patients carried the LL genotype, 7 patients had the SL genotype and 2 the SS genotype. Five patients did not sign the

informed consent. The frequencies for both alleles were 50%. In the group of non-responders, 2 patients carried the LL genotype, 5 patients had the SL genotype and 3 the SS genotype. Three patients did not sign the informed consent. The frequencies for L- and S-alleles were 55% and 45%, respectively.

Using linear regression, there was no association with MADRS scores (F=0.02, p=0.90) and AUDIT scores (F=0.01, p=0.91) decreases and genotype in memantine group.

5.8 Safety and tolerability

During the half year study period, seven patients discontinued treatment due to adverse events, four in the memantine group and three in the escitalopram group.

In the memantine group, one patient was withdrawn due to eczema and three because of labile mood and depression. In the escitalopram group, one patient was withdrawn due to disorientation after the first day on medication, and two 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 one adverse event (AE) during the 26-week study period. The most common adverse event was 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 two treatment groups. Values for the clinical laboratory tests were in the normal range at the beginning and the end of the study.

Serious adverse events were reported by three patients (two memantine and one escitalopram), one suicide attempt in the memantine group and two sudden deaths (one due to hyperglycemia in the memantine group and one due to intoxication of street drugs in the escitalopram group).

6 DISCUSSION

6.1 Purposes of the study

The most eager aim of the study was to find out some new alternatives in the treatment of comorbid alcohol dependence and major depression. The importance of treatment studies in this comorbidity is in agreement with a novel finding of high level of childhood depressed mood association with earlier onset of alcohol problems (Crum et al. 2008).

Another aim was to detect some predictive signs for clinician when making decisions of medical treatment for this comorbidity. This study of treatment on alcohol dependence comorbid with major depression was a randomized comparison of two differently acting compounds, memantine, a non-competitive antagonist of glutamate NMDA receptor, and escitalopram, a selective serotonin reuptake inhibitor, in a double-blind manner. The patients for this study were recruited from three municipal A-clinics in Helsinki. The trial lasted 26 weeks.

6.2 Diagnostical considerations

The patients for this study were sent by nursing staff from communal alcohol-clinics. Out of the total sample of alcohol dependent patients, those patients who were noticed to have comorbid long-lasting severe depression were asked to meet study physician for detailed diagnostical interview by SCID (TR). The problem in this study was the definition of MDD comorbid with alcohol dependence. It is often assumed that MDD after alcohol dependence is secondary and caused by drinking, but there are several factors contributing to the confusion between alcoholism and affective disorders (Schuckit 1986). The truth is that we cannot be sure of the connection between these. Even when the mood is depressive in the time of withdrawal symptoms, we cannot know if the later depression is caused by alcoholism. They may have a relationship to each other or they may be independent diseases with some overlap in clinical symptoms. They may be originally consequences of the same origin, e.g. chronic stress or glucocorticoid exposure (Board et al. 1956; Jezova 2005; Wong et al. 2008). Distinguishing between primary and secondary depression among patients, and questions about whether alcoholism causes depression or depression causes alcoholism, or are they independent of each other, remain unanswered. The interaction between alcoholism and major depression needs further investigation.

6.3 Methodological considerations

6.3.1 Rating scales

In addition to recording of demographic and medical history, several different questionnaires and rating scales validated in Finland were fulfilled by the patients (BDI-II, BAI, VAS, EQ-5, Koskenvuo items for quality of life, AUDIT, OCDS, Drinking Diary and TPQ) and the study physician (MADRS, HAM-A; SOFAS and CERAD).

Almost all the scales proved to be useful in the study. The BDI-II scales reduction was analogous with those of MADRS and the BAI scales reduction was similar to those of HAM-A. Of quality of life scales, the VAS and the SOFAS scales gave the most valuable information. The EQ scale did not confront the study patients' problems and the Koskenvuo life chart did not add new information.

The measurement of alcohol dependence was problematic. The AUDIT and OCDS tests gave similar results for patients. Whereas the focus of AUDIT was in drinking patterns, the focus of OCDS was both in drinking patterns and in thoughts of drinking and gave more valuable information. The rating of this OCDS questionnaire, however, is too complicated to use in a normal clinical setting.

Conclusions from the drinking diary results were limited by the lack of baseline data before treatment for abstinent days, heavy drinking days and alcohol consumption, so whether the relative high number of abstinence days throughout the treatment period is actually different from those before treatment, remains unproved.

The TPQ test was useful, but it is not suitable for a normal clinical appraisal. It would be beneficial to establish a simple questionnaire for a clinician to detect personal styles of a patient.

CERAD test battery was chosen because it can easily be used by others rather than just psychologists and contains several parts assessing episodic memory. This can be impaired in alcoholics especially due to B1-vitamin deficiency (Korsakoff's syndrome), but also milder memory deficits can be seen in heavy drinkers (Parsons 1998). CERAD test battery seemed not to be sensitive enough to recognize cognitive impairment in this group of patients.

6.3.2 Cohort sample

The sample size of study patients was defined by dichotomous power analysis. The dropout ratio was somewhat lower than expected, only 27.5% compaired to nearly 40% described in literature (Kranzler et al. 1996b). The naturalistic character of the study (random sample of A-clinic outpatients) increases the applicability to clinical practice. The sociodemographic indicators correspond well to those generally found among patients treated at Finnish A-Clinics (Heinälä et al. 2001), suggesting the present material represents a relatively unbiased sample. The only difference observed was the higher percentage of women that can probably be attributed to the inclusion criteria of major depression.

6.3.3 Medicines

One basis for the study was the different transmitter action in brains between the study medicines. The other was a SSRI, escitalopram, as an active comparator and another was an uncompetitive glutamate antagonist, memantine, as an investigated medicine. There are, however, some pharmacological differences between individual SSRIs, citalopram and escitalopram being the most selective 5-HT reuptake inhibitors within this class of drugs (Carrasco and Sandner 2005) and, in addition, the differences between effects on dopamine D2 receptors (Penttila et al. 2004). In addition, it is possible that the action of both medicines, esitalopram and memantine, is based on the Hypothalamus-Pituitary-Adrenal (HPA) axis dysregulation, which is assumed to be a link between serotonin deficiency and increased glutamate activity in depression (Muller and Schwarz 2007). In addition, HPA is connected with both transmitters with alcoholism (Jezova 2005; Sher 2007). Concomitant medication, exept antidepressants, was allowed during the study. One third of the patients reported to use other psychiatric medication in the beginning of the study. The medication was asked with a self-rating questionnaire, so as not to separate tranquilizers and anti-psychotics. The definition of policy to bentzodiatsepines in A-clinics is, however, rather critical, and the use of them in this study was presumably insignificant.

6.3.4 Safety and tolerability

The amount of adverse events were somewhat higher in this study than they have been in producer’s information. The mortality is equal with the average mortality in this group of patients in Finland (Mäkelä and Saarnio 1997). These events were considered by the study coordinator (HA) not to be related to the study treatment based on clinical evaluation and forensic autopsy reports for each case.

6.4 Main findings

6.4.1 Depression and anxiety

Symptoms of depression and anxiety outcomes significantly improved in both treatment groups. The decrease in depressive symptoms in the escitalopram group in this study was consistent with conclusions from a recent review supporting SSRI treatment in depression with comorbid substance use disorders (Nunes and Levin 2004). The assumption that memantine, a non-competitive glutamate NMDA receptor blocker, reduces major depression, is in agreement with earlier findings of other glutamate antagonists (Hurley 2002; Kugaya and Sanacora 2005; McElroy et al. 2004; Zarate et al. 2004; Zarate et al. 2006a). However, few studies have addressed the effects of memantine on depression, and no previous studies have examined its efficacy on alcohol dependence related depression. A study by Zarate et al (Zarate et al. 2006b) on patients suffering severe depression did not find positive effects with memantine at a mean dosage 19.4 mg/day compared to placebo. The difference in the efficacy of memantine could be due to the different patient selection criteria which included therapy-resistant depressive patients and substance abuse as an exclusion criterion, while in this study all patients suffered from major depression comorbid with alcohol dependence.

6.4.2 Cognition

The CERAD cognitive test battery was within normal ranges at baseline and there were no significant differences in the follow-up in either of the treatment groups. The good cognitive performance among these depressive alcoholics was surprising. One reason for this is probably that these 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 was met. Although depression in itself can cause memory problems (Paelecke-Habermann et al. 2005), it seems that CERAD is not sensitive to this impairment (Collie et al. 1999).Thus it was not surprising that the performance in CERAD did not change during this trial. The cognitive impairment among alcoholics needs further investigation with a more sensitive test. It is important to determine, whether the impairment is due to alcohol or its metabolites, or it is caused by increased accidents and violence.

6.4.3 Quality of life

Quality of life improved in both groups significantly. The results are quite analogous to depression scale results as noticed recently (Saarni et al. 2007) and are otherwise difficult to explain. Quality of life scales reduced in both groups, with no difference between groups.

6.4.4 Alcohol consumption and craving

Both escitalopram and memantine groups had highly significant decreases from baseline in craving for alcohol as measured with the OCDS test, on both OCDS subscales, and on AUDIT and the AUDIT measures of alcohol consumption and of heavy drinking days. When comparing these two compounds, memantine was at least as effective as escitalopram for reducing alcohol craving, obsessive thoughts of drinking, compulsive drinking, alcohol consumption and maintaining abstinence. There was a general trend for memantine to produce better results than escitalopram, particularly in the latter half of the 26-week study period. The trend only occasionally reached significance and never for the entire treatment period. The efficacy for memantine is consistent with that usually found for acamprosate, another glutaminergic compound (Croissant et al. 2006; Kiefer et al. 2005; Krystal et al. 2003; Nagy 2004). The patient compliance was good. This study corroborates a recent study by Krupitsky et al. (Krupitsky et al. 2007), who reported that memantine reduced alcohol cue-induced craving in recovering alcoholics. Evans et al. (Evans et al. 2007) found no effect of memantine in patients who were actively drinking at the beginning of treatment. This is analogous with our findings that such patients have a higher drop out rate than those who were abstinent at the start of the treatment. This may be due to the severity of alcohol problems but, in addition, it also could reflect the characteristics of the possible anti-craving property of memantine (Holter et al. 1996). However, one wish for this study was to find out a new treatment alternative for those alcoholics who cannot stop drinking, and here it failed.

6.4.5 Comparison of decrease in depression and alcohol use

The association between decreases in depression and alcohol use has been debated for years. The clinicians working primarily in psychiatric settings tended to see depression as an independent entity or even as the causal factor driving the addiction. according to that opinion, the treatment should be focused on depression. The clinicians working in the treatment of alcohol problems, on the contrary, tended to view depression as a symptom of addiction, which would resolve if the addiction were properly treated (Nunes and Levin 2006). The research in the field of the treatment of this comorbidity has been meagre, and the treatment studies with SSRI still rare. Comparing to the earlier finding that the change in drinking does not correlate significantly with the change in depression (Cornelius et al. 1997), in this study, there was some correlation in a group of patients in the escitalopram group.

6.4.6 Predictors in treatment of major depression comorbid with alcohol dependency

The finding that escitalopram, in reducing depression in patients with depression comorbid with alcohol dependence increased greatly with the age of onset of depression, is a novel one. It is consistent, however, with a previous finding that adolescent patients with

major depression and alcohol dependence did not show up a favorable clinical course regarding depression when treated with another SSRI, fluoxetine (Cornelius et al. 2005). In our study, favorable escitalopram response was also predicted by low psychic anxiety and low pessimism, and good memantine response by lack of family history of alcoholism and depression at the baseline.

The research findings on the relationship between age of onset and antidepressant efficacy has been inconsistent. It is supposed that later onset of depression is a predictor of a positive response to antidepressant treatment (Bagby et al. 2002) and has been connected to a less malignant course of depression (Klein et al. 1999; O'Leary et al. 2000). In a European multicenter study, the early age at onset of MDD was associated with treatment-resistant depression (Souery et al. 2007). Such connection was not found in the recent STAR*D study with the response to citalopram (Zisook et al. 2007). In contrast to the situation in the STAR*D study, where the patients came from primary care or psychiatric care practices, our patients were treatment seeking for their alcohol dependence. In the STAR*D study, 24% of patients had dual diagnoses, but separate analysis of those patients was not performed.

In our study the relationship between age of onset and efficacy is completely different for the two medicines. Both reduced depression equally well, but only the efficacy with escitalopram was related to age of onset. There was a highly significant interaction between the two medicines with respect to the relationship to onset.

The reason why the patients with early onset of MDD had an inferior treatment response in the escitalopram group is unclear. One explanation could be the manifestation of bipolar depression. In a study of prevalence, correlates, disability and comorbidity of DSM-IV Alcohol Abuse and Dependence in the United States, the association between bipolar I and II disorders and alcohol dependence were almost twice as prevalent as comorbidity with major depressive disorder and alcohol dependence (Hasin et al. 2007). In addition, adults with early onset MDD are suggested to be at high risk of progression to bipolar disorder (Smith et al. 2005). According to that finding, it should be expected that more patients would have suffered from bipolar disorder. Although the patients in this study did not fulfill the criteria of bipolar I and II disorders using SCID-interview, the possibility that cannot be excluded that in this study, the bipolar diagnosis was missed because the possible manic or hypomanic episodes were masked by periods of alcohol intoxication. Perhaps some bipolar II or bipolar NOS diagnoses were missed. Therefore, it is possible that the association of the early onset of the first depressive episode with the unfavorable treatment response with escitalopram is related to depression in the bipolar spectrum (Angst et al. 2006; Benazzi and Akiskal 2007). Another explanation could be the impact of early childhood traumas resulting in increased vulnerability to depression, instead of slowly acting serotonin transporter (Caspi et al. 2003) where the serotonin reuptake inhibitor does not help. In addition, the depression in immature brains can induce such dysfunction, e.g. in HPA-axel, that increases the vulnerability to therapy-resistant depression (Rao 2006). The negative and hostile self-concept during a

major depressive episode in childhood or adolescence may as well produce depression comorbid with personality disorders, that weakens the influence of SSRIs (Bagby et al. 2002).

Although pessimism may predict suicidality in depressed patients (Oquendo et al. 2004) very little is known whether pessimism could indicate poor treatment prognosis as well. This study's finding that escitalopram-treated non-responders showed more pronounced pessimism at the baseline is in line with a recent study that showed that hopelessness is associated with poorer response of treatment with fluoxetine in MDD (Papakostas et al. 2007),

6.4.7 Predictors in treatment of alcohol dependence comorbid with major depression

Few possible specific predictive elements for the treatment of alcohol dependence comorbid with major depressive disorder with either escitalopram or memantine were observed. One predictor observed was the early age at onset of intoxicative alcohol consumption, which leads to poor treatment outcome with escitalopram but not with memantine. The poor outcome with escitalopram in alcohol abuse is in agreement with a previous finding that early onset of alcohol use is a predictor for poor treatment outcome with SSRI fluvoxamine (Chick et al. 2004). This study's finding may suggest that memantine could be useful treatment for type 2 alcoholics (early onset) comorbid with depression.

6.4.8 Comparison of predictors in depression and alcohol use

The finding that the early onset of the first depressive episode is a negative predictor for escitalopram treatment in alcohol dependence confirms this study's previous finding on treatment of this comorbidity regarding major depressive disorder in patients with this dual diagnoses (Muhonen et al. 2008c).

6.4.9 Serotonin transporter gene as a predictor

Serotonin transporter gene (5-hydroxy tryptamine linked polymorphic region, 5-*HTTLPR*) is one of the most important genes related to major depression. Serotonergic neurotransmission is connected to both major depression and alcohol dependence (Kranzler and Anton 1994). Serotonin neurotransmission is regulated by 5-HTT gene and the gene expression is regulated by 5-*HTTLPR* polymorphism. The research on association of 5-*HTTLPR* gene polymorphism and treatment response with SSRIs has been inconsistent (Kraft et al. 2007; Serretti et al. 2007). In both those studies, the patient selection consists of primary depressive patients. There seems to be no former studies of treatment response to SSRI with (5-*HTTLPR*) variations in a group of alcohol dependent patients comorbid with major depressive disorder. The treatment response was studied of escitalopram comparing with the 5-*HTTLPR* polymorphism versus those of memantine, a glutamate NMDA receptor modulator, which is not associated with serotonergic pathways. In this study,

the L-allele correlates with the positive treatment response measured with MADRS in escitalopram group, but not in memantine group. The finding is presumably connected to the limited patient selection in comorbidity with alcohol dependence. This study limits in depressive patients comorbid with alcohol dependence; the patients are collected from alcohol treatment units and may thus represent a genetical subgroup of MDD.

This finding may give some hope, that more detailed diagnostical patient selections and gene tests could give better treatment options to different patient groups, who suffer from depressive disorders.

However, decrease in alcohol use, measured with AUDIT, was not connected to L-allele in either treatment group.

6.5 Limitations

One limitation of the study includes the fact that there was no placebo group (Koponen and Lepola 2005). In prior studies the placebo-effect is considered to be remarkable in this population (Nunes and Levin 2004). 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, the mean prior duration of depression in this study's sample was 35 months, and most of the patients suffered mainly from chronic major depression.

The drinking results were limited by the lack of baseline data before treatment for alcohol consumption, abstinent days and heavy drinking days. Even when the AUDIT and OCDS scores decreased throughout the treatment period, whether the relative high number of abstinence days throughout the treatment period is actually different from those before treatment, remains unproved. In addition, one limitation is that neither of these medicines were accepted for treatment of alcoholism. So the results according to alcohol treatments are preliminary and need further investigation.

Another limitation is that the total number of patients may have been too low to detect a significant difference between two active treatments. In addition, the late gathering of blood samples for 5-*HTTLPR* polymorphism posed a reduction of DNA-samples of patients, and the significance of results. Also in addition, the patients were gathered from municipal A-clinics, and represent group of treatment-seeking patients, who are aware of their problems, and the results are not to be generalized to the total group of alcohol dependent patients comorbid with major depression.

One possible limitation is that all study patients were Caucasians and do not represent a multicultural and multiracial groups of patients comorbid with major depressive disorder comorbid with alcohol dependence.

7 CONCLUSIONS AND FUTURE IMPLICATIONS

The glutamate NMDA receptor modulator memantine and a SSRI escitalopram seem to be potentially effective and safe for the treatment of major depression comorbid with alcohol dependence.

Among this group of patients, the abstinence should be required before medication with antidepressant drugs to avoid the early termination of the medical treatment.

According to this study, the diagnosis of comorbid Alcohol Dependence with Major Depression, consists of different etiology, both genetically and environmentally, subgroups. This comorbidity seems to consist of heterogenic diagnostical subgroups of patients, and their treatment requires good diagnostical and clinical professional skills. It is not impending that there could be one treatment option for all patients with comorbid alcohol dependence and major depressive disorder, but different treatment alternatives for different subgroups should be investigated to detect an individual treatment for each patient. New treatment studies should be based on careful patient selection inside of this comorbidity. Genetic research would be of greatest importance to diagnostical accuracy and to understand the response to different medicines in groups of alcohol dependent patients suffering from major depressive disorder.

The finding of the age at the first depressive episode as a predictor for escitalopram treatment emphasizes the importance of a clinician to make a good anamnestic and clinical exploration of the patient before beginning the treatment.

The treatment of children with depressive features should be devised to recognize those who are at an increased risk of developing addictive disorders.

8 ACKNOWLEDGEMENTS

This study was carried out at the Unit on Prevention and Treatment of Addictions, Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki. I thank Professor Pekka Puska, the Director General of the National Public Health Institute, for facilities provided for the study.

I wish to express my greatest gratitude to Professor Jouko Lönnqvist, Head of the Department of Mental Health and Alcohol Research, for providing me the opportunity to fulfill my long-lasting dream of research, and for supervising me throughout this study. My most profound gratitude goes to Professor Hannu Alho, who has patiently guided and supervised me during this research.

I wish to thank the reviewers of my thesis, Professor (emeritus) Erkka Syvälahti and Professor Hannu Koponen, for their valuable comments and advice.

I wish to express my highest appreciation for my co-authors' contribution to this work. Kati Juva, M.D., Ph.D, David Sinclair, Ph.D., Sirkku Saarikoski, Ph.D., Jari Haukka, Ph.D., and Jari Lahti, M.A. Besides the writing of the articles, I have enjoyed the conversations and the new perspectives you have taught to me.

Several persons from the Unit of Prevention and Treatment of Addictions have been of greatest value to me: especially Sirpa Päivinen, who has helped me in many practical challenges, and Jukka Halme, who shared the room with me and helped me in many technical problems. Mauri Aalto has given important advice in estimating alcohol use disorders and the others of our unit have supported me with their interest.

The whole personnell of Alcohol Research Centre in Auratalo has made my years unforgetable and enjoyable. I specially want to express my gratitude to Docent Petri Hyytiä, who helped me to get acquainted with the neurobiological perspective of this study. I also want to thank Arja Mikkelinen, who helped me in many different ways. In addition, Professor Kalervo Kiianmaa and all other researchers in Auratalo, as well as Docent Iiris Hovatta in Biomedicum, have helped me with their conversations and advice.

Jukka Lindeman, you have been invaluable for me, with your unstinting help with the EndNote program use and other technical help in literature. I also thank Henna Ahtinen for statistical analysis of my many different wishes.

My thanks go to Matthew Grainger for his expert language editing and Marjut Grainger for the layout of this thesis, and Tapani Ihalainen for editing it.

I am deeply grateful to the personnell of Annakatu, Töölö and Malmi A-clinics for their help in recruiting the patients for this study, and to the patients, who helped me to learn of the complexity of alcohol dependence comorbid with depression.

I wish to thank the Finnish Foundation for Alcohol Research, the Helsinki Health Center Research Fund and the Finnish Psychiatric Association for supporting financially this study.

My warmest thanks go to my family: my sons Joonas and Jussi with their families; my parents and siblings with their families, and all other relatives and friends, who have encouraged me to continue with this thesis. Jussi and his cousin Juho have been of greatest help in the beginning of the data analysis, and my cousin Maria has encouragingly tutored me throughout the study.

My husband Heikki, who has encouraged and supported me throughout these years, deserves my hearty thanks.

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