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Electroconvulsive Therapy in Major Depression

A Clinical and Genetic Approach

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ACADEMIC DISSERTATION

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List of original publications

This series of studies is based on the following publications, referred to in the text by their Roman numerals I-IV. Some additional data is also presented.

I. Huuhka M, Anttila S, Leinonen E, Huuhka K, Rontu R, Mattila KM, Huhtala H, Lehtimäki T (2005): The apolipoprotein E polymorphism is not associated with response to electroconvulsive therapy in major depressive disorder. J ECT 21:7-11.

II: Huuhka M, Korpisammal L, Haataja R, Leinonen E (2004): One-year outcome of elderly inpatients with major depressive disorder treated with ECT and antidepressants. J ECT 20:179-185.

III. Huuhka M, Haanpää M, Leinonen E (2004): Electroconvulsive therapy in patients with depression and fibromyalgia. Eur J Pain 8:371-376.

IV. Huuhka M, Seinelä L, Reinikainen P, Leinonen E (2003): Cardiac arrhythmias induced by ECT in elderly psychiatric patients: Experience with 48-hour Holter monitoring. J ECT 19:22-25.

Abbreviations

ACTH	Adrenocorticotropic hormone
ADL	Activities of Daily Living
ADT	Antidepressant drug treatment
APA	American Psychiatric Association
APOE	Apolipoprotein E
BDI	Beck Depression Inventory
BDNF	Brain derived neurotrophic factor
BF	Bifrontal
BiTri	Bigeminy/Trigeminy
BL	Bilateral
CBF	Cerebral blood flow
CGI	Clinical Global Impression
CMR	Cerebral metabolic rate for glucose
CNS	Central nervous system
CORT	Cortisol
CRPS	Complex regional pain syndrome
DA	Dopamine
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders; fourth edition
ECG	Electrocardiogram
ECS	Electroconvulsive shocks
ECT	Electroconvulsive therapy
EEG	Electroencephalography
FIQ	The Fibromyalgia Impact Questionnaire
FM	Fibromyalgia
GABA	Gamma-aminobutyric acid
HRV	Heart rate variability
5-HT	Serotonin
5-HTT	Serotonin transporter
5-HTTLPR	Serotonin transporter promoter gene region
IADL	Instrumental Activities of Daily Living
LSS-A	Life Satisfaction Scale A
MADRS	Montgomery and Åsberg Depression Rating Scale
MDD	Major depressive disorder
MDE	Major depressive episode
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
NE	Norepinephrine
NMS	Neuroleptic malignant syndrome
PET	Positron emission tomography
PRL	Prolactin
Q-Les-Q	Quality of Life Enjoyment and Satisfaction Questionnaire
RUL	Right unilateral
ST	Seizure threshold
SVES	Supraventricular extrasystoles
SVT	Supraventricular tachycardia
TPH	Tryptophan hydroxylase
TrkB	Tyrosine kinase B
TSH	Thyroid-stimulating hormone

VES	Ventricular extrasystoles
VT	Ventricular tachycardia

Abstract

Background: Electroconvulsive therapy (ECT) is the most effective treatment method in major depression. It is also effective in some other serious mental diseases, such as mania and some forms of schizophrenia, particularly with affective symptoms or catatonia. It has been reported that ECT also has benefical effects on some pain symptoms. ECT is considered to be a safe and effective treatment even in elderly patients and in somatically ill patients. It has been suggested that the response to ECT of elderly patients in major depression is even better than in younger patients. The most common side-effects of ECT are cognitive, including transient postictal confusional state and longer acting anterograde and retrograde memory dysfunction. However, the most serious complications of ECT are of a cardiovascular nature. Cardiovascular complications most often occur in elderly patients and in patients with pre-existing cardiovascular diseases. Despite the fact that ECT has been used over six decades its fundamental mechanism is still obscure. It may be connected to neurochemical, neuroendocrine, and neurophysiological effects. It has also been suggested that genetic factors may modulate the treatment response.

Aims: The purposes of the present series of studies were to investigate the association between the response of ECT and apolipoprotein E (APOE) gene polymorphism in major depressive disorder (MDD) (Study I). To study the acute efficacy and long-term outcome of ECT and antidepressant drug treatment (ADT) in elderly patients with MDD (Study II). To evaluate the effects of ECT on depression, pain and other physical symptoms in patients with concomitant MDD and fibromyalgia (FM) (Study III). To study if ECT induces cardiac arrhythmias in elderly patients with major depressive episode (MDE) (Study IV).

Subjects and methods: All the patients (except 10 in Study III) were hospitalized because of major depression. The study group in Study I consisted of 119 patients and 398 healthy blood donors as controls. Genomic DNA was extracted from peripheral blood leukocytes. The DNA samples were genotyped by employing the 5'exonuclease assay and fluorescent allele-specific TaqMan probes. In Study II 30 patients were treated with ECT and 21 patients with antidepressants. After discharge the patients were followed up for one year. The acute treatment effects were measured by standard depression rating scales and the relapse rate was evaluated during the follow-up. Study III consisted of 13 patients. The effects of ECT on depression, pain and other physical symptoms of FM were evaluated with standard measurements. After ECT the patients were followed up for three months. The follow-up assessments were carried out one week, one month and three months after the last ECT session. The study group in Study IV consisted of 31 patients. Automated Holter monitoring was performed for 48 hours, 24 hours before ECT and 24 hours after ECT.

Results: APOE polymorphism was not associated with the treatment response to ECT in major depression. Elderly patients with MDD had a good acute response to both ECT and ADT. Relapses were frequent in both groups; many of these occurred during the first month after discharge. ECT was effective in the treatment of the depressive symptoms of the patients with concomitant MDD and FM, but had no effect on the pain symptoms of the patients. ECT caused a significant increase in bigeminy/trigeminy and supraventricular tachycardia in elderly patients. Pre-ECT arrhythmias predicted post-ECT arrhythmias. ECT caused a high incidence of ST changes. Although arrhythmias were common, all the patients completed the ECT course.

Conclusions: APOE polymorphism may not be related to the response to ECT in MDD. In accordance with previous reports the present results indicate that ECT is an effective treatment

method in elderly patients with MDD. However, relapses were common and occurred in many patients soon after completion of treatment. This emphasizes the need for a careful follow-up and in some cases even consideration of the continuation or maintenance ECT. ECT is also an effective treatment in the depression of patients with concomitant MDD and FM, but it has no effect on their pain symptoms. ECT is a safe treatment even in elderly patients with a somatic illness, although it may increase some cardiac arrhythmias. These are usually clinically inconsequential and do not prevent the course of ECT.

Tiivistelmä

Tausta: Psykiatrinen sähköhoito (electroconvulsive therapy, ECT) on tehokkain hoitomuoto vaikeassa masennuksessa. Se on tehokas myös muissa vakavissa psykiatrisissa sairauksissa, kuten maniassa ja skitsofrenian mielialaoireissa sekä katatoniassa. Sähköhoidolla on havaittu olevan suotuisia vaikutuksia myös joidenkin kiputilojen hoidossa. Sitä pidetään turvallisena hoitomuotona myös vanhuksilla ja somaattisesti sairailla potilailla. Sen on havaittu olevan jopa tehokkaampi vanhusikäisillä kuin nuoremmilla depressiopotilailla. Yleisimmät sähköhoitoon liittyvät haittavaikutukset ovat kognitiivisia, kuten ohimenevä toimenpiteen jälkeinen sekavuus ja pidempikestoinen muistivaikeus. Vakavimmat sähköhoitoon liittyvät haittavaikutukset ovat sydänperäisiä. Sydänperäisiä haittavaikutuksia ilmenee useimmiten vanhuksilla ja potilailla, joilla on sydänsairauksia. Vaikka sähköhoitoa on käytetty jo yli kuusi vuosikymmentä, sen vaikutusmekanismia ei vieläkään täysin tunneta. Vaikutusmekanismi saattaa liittyä sähköhoidon aiheuttamiin neurokemiallisiin, neurohormonaalisiin ja neurofysiologisiin muutoksiin. On myös esitetty, että geneettiset tekijät saattavat vaikuttaa hoitovasteeseen.

Tavoitteet: Näiden tutkimusten tarkoituksena oli selvittää apolipoproteiini E (APOE) geenin polymorfismin yhteyttä sähköhoidon vasteeseen vaikean masennuksen (MDD) hoidossa (tutkimus I). Tarkoituksena oli myös verrata sähköhoidon ja masennuslääkehoidon välitöntä ja pitkäaikaista tehoa vaikeaa masennusta sairastavilla vanhuspotilailla (tutkimus II). Lisäksi arvioitiin sähköhoidon vaikutusta masentuneiden fibromyalgiapotilaiden (FM) masennus- ja kipu oireisiin (tutkimus III). Tarkoituksena oli myös selvittää, aiheuttaako sähköhoito sydänperäisiä rytmihäiriöitä masennusta sairastavilla vanhuspotilailla (tutkimus IV).

Potilaat ja menetelmät: Kaikki potilaat (lukuun ottamatta 10 potilasta tutkimuksessa III) olivat sairaalahoidossa vaikean masennuksen vuoksi. Tutkimuksessa I oli 119 potilasta ja verrokkeina

398 tervettä verenluovuttajaa. Genominen DNA eristettiin perifeerisen veren valkosoluista ja DNA näytteet genotyypitettiin. Tutkimuksessa II 30 potilasta hoidettiin sähköhoidolla ja 21 potilasta masennuslääkkeillä. Sairaalasta kotiutumisen jälkeen potilaita seurattiin vuoden ajan. Välitön hoitovaste arvioitiin vakiintuneilla masennusarviointiasteikoilla ja sairausjaksojen uusiutuminen laskettiin seurannan aikana. Tutkimuksessa III 13 fibromyalgiaa sairastavaa masennuspotilasta hoidettiin sähköhoidolla. Sen vaikutusta masenuusoireisiin, kipuun ja muihin fibromyalgian fyysisiin oireisiin arvioitiin standardoiduilla arviointiasteikoilla. Potilaita seurattiin hoitojakson jälkeen kolme kuukautta. Seurannan aikana arvioinnit tehtiin viikon, kuukauden ja kolmen kuukauden kuluttua viimeisestä hoitokerrasta. Tutkimuksessa IV tutkimusryhmä koostui 31 potilaasta. Automaattinen Holter-nauhoitus rekisteröitiin 48 tunnin ajan, 24 tuntia ennen ja 24 tuntia toimenpiteen jälkeen.

Tulokset: APOE polymorfismi ei liittynyt sähköhoidon vasteeseen vaikean masennuksen hoidossa. Vaikeasta masennuksesta kärsivät vanhukset saivat hyvän välittömän vasteen sekä sähköhoidosta että lääkehoidosta. Masennusjaksojen uusiutuminen oli kuitenkin yleistä molemmissa ryhmissä ja tapahtui usein pian sairaalasta kotiutumisen jälkeen. Sähköhoito oli tehokas myös fibromyalgiapotilaiden masennusoireissa, mutta sillä ei ollut vaikutusta kipuoireisiin. Sähköhoito lisäsi vanhuspotilaiden bigeminiaa, trigeminiaa ja supraventrikulaarista takykardiaa. Rytmihäiriöt lisääntyivät erityisesti potilailla, joilla niitä esiintyi jo ennen hoitoa. Sähköhoito aiheutti myös paljon ST-tason muutoksia. Vaikka rytmihäiriöt olivat yleisiä, hoitosarjaa ei jouduttu kenelläkään niiden vuoksi keskeyttämään.

Johtopäätökset: APOE polymorfismi ei liity sähköhoidon vasteeseen vaikeassa masennuksessa. Kuten on aiemmin todettu, myös tämän tutkimuksen perusteella sähköhoito on tehokas hoitomuoto vaikeaa masennusta sairastavilla vanhuksilla. Masennusjakson uusiutuminen on kuitenkin yleistä ja se tapahtuu usein pian hoitojakson jälkeen. Tämä puoltaa tarkkaa seurantaa

hoitojakson jälkeen ja joissakin tapauksissa tulisi harkita myös jatko- tai ylläpitosähköhoitoa. Sähköhoito on myös tehokas hoitomuoto fibromyalgiapotilaiden masennusoireissa, mutta sillä ei ole vaikutusta heidän kipuoireisiinsa**.** Sähköhoito on yleensä turvallinen hoitomuoto myös vanhuspotilaille, joilla on somaattisia sairauksia, vaikkakin se voi lisätä sydämen rytmihäiriöitä. Ne ovat kuitenkin yleensä kliinisesti merkityksettömiä, eivätkä ole este sähköhoidolle.

Introduction

Major depressive disorder (MDD) is a very common disorder (Kessler et al. 2003) causing both individual suffering, and family and economic burden (Pincus and Pettit 2001, Katon et al. 2003). According to epidemiological studies most depressive persons in the general population receive inadequate treatment (Kessler et al. 2003). Unrecognized, undertreated and treatment resistant depression is a significant public health problem with profound effects on health care costs (Greenberg et al. 2004, Russell et al. 2004).

Electroconvulsive therapy (ECT) is the most effective treatment for patients with severe and treatment resistant depression [American Psychiatric Association (APA) 2001]. ECT is generally used as a second line treatment. It is a treatment of choice in patients who have not responded to antidepressant medication. The efficacy of ECT has also been well documented in mania and some forms of schizophrenia (APA 2001). ECT has been used successfully in treating the motor and psychiatric symptoms of Parkinson's disease (Rasmussen and Abrams 1991). Some studies have been published on the effectiveness of ECT in chronic pain (Bloomstein et al. 1996, Rasmussen and Rummans 2000). In recent years many technical improvements in the devices and the procedure for ECT have been introduced and the treatment is considered to be safe even in medically ill patients and in elderly ones (Gormley et al. 1998, Manly et al. 2000). The response of elderly patients to ECT has been reported to be as good as or even better than that of middle-aged patients (Tew et al. 1999, Brodaty et al. 2000, O'Connor et al. 2001).

ECT has been used for nearly seven decades, however, its mechanism of action is still largely unknown. Neurochemical, neuroendocrine, and neurophysiological effects may be involved. It has also been suggested that the genetic factors may modulate the treatment

response. Fisman et al. (2001) reported that apolipoprotein E (APOE) genotype was associated with the response to ECT in MDD.

In this dissertation the association between APOE gene polymorphism and response to ECT in MDD was studied. Moreover, the acute treatment response and long-term outcome of ECT was evaluated in elderly patients with MDD, likewise the efficacy of ECT in patients with concomitant MDD and fibromyalgia (FM). Moreover, the cardiac arrhythmias induced by ECT were studied.

1 Review of the literature

1.1 Major depressive disorder

Major Depressive Disorder (MDD) is characterized by one or more Major Depressive Episodes (MDEs). The DSM-IV (American Psychiatric Association 1994) criteria for MDE are following:

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. Symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations are not included.

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 of 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 ability 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 a 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., a 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 the 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.

1.1.1 *Epidemiology*

MDD is a common psychiatric illness. About 16% of population have been reported to have an MDE some time in their lives (Steffens et al. 2000, Kessler et al. 2003). The lifetime prevalence of major depression varies widely in different studies and perhaps across countries. In a cross-national study in 10 countries the prevalence rates of MDD varied between 1.5% and 19.0% (Weissman et al. 1996). Steffens et al. (2000) reported that the estimated lifetime prevalence of MDD in elderly population was 20.4% in women and 9.6% in men.

The 12-month prevalence rate of MDD has been reported to vary between 0.8% and 10.3% (Kessler et al. 1993, Weissman et al. 1996, Kessler et al. 2003). In two large population studies in Finland, the 12-month prevalence rate in the Finnish general population has been reported to be 4.9% (Pirkola et al. 2005) and 9.3% (Lindeman et al. 2000). Pirkola et al. (2005) reported that

the 12-month prevalence of MDD among elderly people (over 65 years of age) in Finland was 2.7% in women and 1.1% in men. A prevalence rate around 2:1 between females and males has been presented in several studies (Kessler et al. 1993, Weissman et al. 1996, Pirkola et al. 2005).

In a large population study by Steffens et al. (2000), the current prevalence of major depression in elderly nondemented individuals was reported to be 4.4% in women and 2.7% in men. In contrast to relatively low rates of major depression in the elderly in the community, estimations of point prevalence in hospitalized medically ill elderly patients have varied between 11% and 21% (Koenig et al. 1988, Koenig et al. 1997). Bruce et al. (2002) reported that the prevalence of major depression in elderly patients receiving home care was 13.5%. The prevalence rate of major depression among elderly nursing home patients has been estimated to vary between 8% and 13% (Rovner et al. 1991, Jongenelis et al. 2004).

Differences between countries in the rates of MDD suggest that there may be cultural differences or different risk factors, which may affect the expression of this disorder (Weissman et al. 1996). The differences in the prevalence rates may also be partly explained by the evaluation methods (Narrow et al. 2002).

1.1.2 *Etiology*

Major depression is an etiologically complex and multifactorial disorder resulting from an interaction of biological, environmental psychological and social factors (Kendler et al. 1999, Manji et al. 2001, Kendler et al. 2002, Kendler et al. 2004, Young et al. 2004) and genetic predisposition (Kendler et al. 1999, Sullivan et al. 2000, Lesch 2004, Hoefgen et al. 2005, Kendler et al. 2005).

1.1.2.1. *Monoamine hypothesis of depression*

The major hypothesis about the neurobiological etiology of depression is based on neurotransmitter depletion causing deficiency of monoamine neurotransmitters (Stahl 2001). The monoamine neurotransmitters in the brain are catecholamines norepinephrine (NE) and dopamine (DA) and indoliamine serotonin (5-HT). The diminished monoamine function is associated with clinical depression. This hypothesis is supported by the mechanism of action of antidepressant drugs (Delgado 2000). Antidepressants acutely increase the availability of neurotransmitters at the synapse, either inhibiting their intraneuronal reuptake or metabolism, or increasing their release by blocking the $alpha_2$ auto- and heteroreceptors in the monoaminergic neurons (Elhwuegi 2004).

On the other hand monoamine depletion does not exacerbate symptoms in unmedicated depressed patients, nor does it cause depression in healthy volunteers with no depressive illness (Delgado 2000, Berman et al. 2002). However, depletion of the serotonin precursor tryptophan induced a transient return of depressive symptoms in some patients with remitted MDD (Delgado et al. 1990, Neumeister et al. 2004).

Long-term tricyclic antidepressant drugs and electroconvulsive shocks enhance neurotransmission across 5-HT synapses by sensitizing postsynaptic 5-HT neurons (Blier et al. 1990). It has been suggested that there may be an altered 5-HT1A autoreceptor function in depression and that this may play a role in the mechanisms underlying treatment response to selective serotonin reuptake inhibitors (SSRI) especially in late-life depression (Meltzer et al. 2004). A decrease in the 5-HT1A mRNA in the dorsolateral prefrontal cortex and hippocampus in patients with MDD has been reported (Lopez-Figueroa et al. 2004). The hippocampal reduction of 5-HT2A receptor binding has also been reported in MDD patients (Mintun et al. 2004).

There may be alteration in serotonin transporter (5-HTT) in patients with mood disorders. Austin et al. (2002) found that depressed subjects who had committed suicide had a decrease in serotonin transporter-immunoreactive axons in the prefrontal cortex. In addition, reductions were found in the density of brain 5-HTT binding sites in depressed patients (Malison et al. 1998, Ichimiya et al. 2002). However, Meyer et al. (2004) did not find any difference in the regional 5-HTT binding potential between patients with MDE and healthy subjects except that severely negativistic patients had significantly higher 5-HTT binding potential in some brain regions. Laasonen-Balk et al. (2004) reported that recovery from depression was associated with increased 5-HTT (as well as dopamine) binding in the midbrain.

It has been suggested that an acute increase in the amount of the norepinephrine (and other monoamines) at the synapse during antidepressant treatment induces long-term adaptive changes ending in the desensitization of the inhibitory auto- and heteroreceptors (Elhwuegi 2004). The desensitization of these inhibitory receptors results in higher central monoaminergic activity that coincides with the appearance of a therapeutic response (Elhwuegi 2004). The norepinephrine transporter (NET) in the locus coeruleus (LC) in major depression may reflect a compensatory downregulation of this transporter protein in response to an insufficient availability of its substrate (norepinephrine) at the synapse (Klimek et al. 1997).

There are some studies suggesting the involvement of dopamine in unipolar depression. However, the results are contradictory. McTavish et al. (2005) reported that tyrosine depletion did not induce depressive symptoms in euthymic subjects with a past history of major depression. McLean et al. (2004) suggested that dopaminergic factors are involved in disrupted affect/reward-based processing characteristic of clinical depression. The mechanism of action of antidepressants may also be linked to altered dopamine function in depression (Brunswick et al.

2003). Dremencov et al. (2004) suggested that the fast-onset of action of antidepressant treatment also associated with the interaction of 5-HT and dopamine.

1.1.2.2 *Neurotrophic hypothesis of depression*

In recent years there has been growing evidence that the neurotrophic mechanisms are important in the pathogenesis of depression as well as in the action of antidepressant medications (Gould et al. 2003). Brain derived neurotrophic factor (BDNF) is a small dimeric protein and is a member of the nerve growth factor family. It has been suggested that BDNF promotes neuronal survival, differentiation and neuroprotection (Hashimoto et al. 2004). The action of BDNF is mediated by its receptor, protein tyrosine kinase B (TrkB). It has been suggested that antidepressant drugs increase TrkB and BDNF signalling in cerebral cortex and this induces formation and stabilization of the synaptic connectivity (Saarelainen et al. 2003, Castren 2005). BDNF signalling appears to be necessary for the clinical antidepressive effects (Saarelainen et al. 2003, Castren 2004).

It has been reported that the serum level of BDNF is decreased in patients with MDD compared with healthy controls (Karege et al. 2002). Chronic antidepressant medication has been found to increase the serum BDNF levels in depressive patients (Chen et al. 2001, Aydemir et al. 2005). Neumeister et al. (2005) reported that tryptophan depletion increased the BDNF levels in healthy volunteers, but not in the patients with remitted MDD. They suggested that this is related to the complex interactions between serotonergic and neurotrophic systems.

1.1.3 *Genetics of depression*

The genetic influence of MDD has been shown in several adoption and twin studies (Wender et al. 1986, Kendler et al.1992, Lyons et al. 1998, Bierut et al. 1999, Kendler et al. 2005).

According to a comprehensive review by Sullivan et al. (2000) the share of genetic contribution is estimated to be about 31% to 42%. Compared with the general population, the first-degree relatives of depressed individuals have a nearly three-fold increase in their risk of developing a MDD (Lesch 2004).

1.1.3.1 *Candidate genes for MDD*

Some recently published linkage studies have suggested different candidate regions in different chromosomes for susceptibility to MDD: 2q33-34 (Zubenko et al. 2002), 12q22-23.2 (Abkevich et al. 2003) and 15q25.3-26.2 (Holmans et al. 2004). Gene association studies have reported a number of candidate genes to be involved in psychopathology and treatment response in MDD. However, the results are inconsistent and so far no susceptibility genes for MDD have been established (Fanous and Kendler 2004).

1.1.3.2 *Apolipoprotein E (APOE)*

Apolipoprotein E (APOE) is located on chromosome 19q13.2. Human APOE exists in three common isoforms, coded by different alleles: APOE ε2, ε3, and ε4. These result in different genotypes ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, and ε4/ε4 (Mahley and Rall 2000).

Most studies on the association between APOE ε4 and depression deal with geriatric depression. The results are still contradictory. In some studies an increase in APOE ε4 allele frequency in late-onset major depression has been found (Krishnan et al. 1996, Rigaud et al. 2001). However, most studies have failed to establish any such relationships (Zubenko et al. 1996, Schmand et al. 1998, Mauricio et al. 2000, Hickie et al. 2001, Steffens et al. 2003b, Cervilla et al. 2004). It has also been suggested that patients with ε4 allele had an earlier onset of depression (Lavretsky et al. 2000, Butters et al. 2003).

It has been suggested that APOE genotype may affect antidepressant treatment response and response to electroconvulsive therapy. Murphy et al. (2003) reported that patients with ε4 allele had a rapid onset of mirtazapine action, whereas paroxetine-treated ε4 carriers showed a slower onset of treatment response than non-carriers. Fisman et al. (2001) reported that ε4 allele carrying patients were more likely to respond to ECT in late-onset depression.

1.1.3.3 *Brain derived neurotrophic factor (BDNF)*

The human BDNF gene is located on chromosome 11p13 (Maisonpierre et al. 1991). G196A (val66met) polymorphism in the coding region of the BDNF gene is a functional polymorphism (met allele decreases BDNF secretion) (Egan et al. 2003). Even though BDNF has been connected with the pathophysiology of depression, two recent studies did not find any association between BDNF G196A (val66met) polymorphism and MDD (Hong et al. 2003, Tsai et al. 2003).

1.1.3.4 *Serotonin transporter gene (5-HTT)*

The 5-HTT gene is located on the long arm of chromosome 17. In a large population-based sample of 549 adult twins Kendler et al. (2005) found that individuals with 2 short (S) alleles at the 5-HTT locus were more sensitive to the depressogenic effects of stressful life events than those with 1 or 2 long (L) alleles.

The 5'-flanking promoter region of the 5-HTT gene has a biallelic insertion/deletion (5-HTTLPR). Hoefgen et al. (2005) reported that in a sample of 466 patients and 836 control subjects the short allele of 5-HTTLPR was significantly more frequent in patients with MDD than in control subjects.

Moreover, Caspi et al. (2003) reported that individuals with short allele of the 5-HTTLPR (homo- or heterozygote) exhibited more depressive symptoms, diagnosable depression, and suicidality in relation to stressful life events than individuals homozygous for the long allele. In a recent study by Gillespie et al. (2005) this finding was not replicated. In that sample of 1206 male and female twins no interaction between the 5-HTTLPR genotype and stressful life events predicting major depression was found. In one study an association between the homozygous long allele genotype of 5-HTTLPR and the depressive response to tryptophan depletion has been reported (Moreno et al. 2002). Steffens et al. (2002) found gender effects in 5-HTTLPR, with 23% of depressed men against only 5% of controls having two short alleles of 5-HTTLPR. The authors suggest the possibility that this genetic locus may exert differential effects based on gender, increasing the risk for depression in men.

1.1.3.5 *Other genes associated with MDD*

Research has been carried out on the association between several other genes and MDD. Sun et al. (2004) found a significant difference in tryptophan hydroxylase (TPH1) gene T27224C polymorphism C allele frequency between women with comorbid depression and anxiety and healthy controls. They suggested that C allele confers a protective effect. An association between tryptophan hydroxylase isoform (TPH2) gene and MDD has also been reported. Zill et al. (2004) detected a significant association between a single-nucleotide polymorphism of the TPH2 gene and MDD.

C825T polymorphism of the beta3 subunit of G protein (Gβ3) gene has been linked with depression and response to antidepressant treatment. It has been suggested that T allele is more frequent in MDD patients than in healthy controls (Zill et al. 2000, Serretti et al. 2003, Lee et al.

2004). Moreover, MDD patients bearing the T allele may show better response to antidepressant treatment than those without the T allele (Zill et al. 2000, Lee et al. 2004).

There are also reports on the association between other genes and depression. Polymorphisms on gamma-aminobutyric acid type A (GABA-A) receptor subunit genes α 1 and α *6* have been linked with mood disorders in female patients (Yamada et al. 2003). Heilig et al. (2004) found an association between depression and the T1128C and the T -399C polymorphisms in the promoter region of neuropeptide Y (NPY) gene. cAMP-responsive element-binding protein (CREB) is encoded by CREB1 gene. Zubenko et al. (2002) suggested that this gene may be associated with MDD in women.

1.1.4 *Depression in the elderly*

Major depression often goes unrecognized and untreated especially in elderly people (Bruce et al. 2002, Jongelis et al. 2004). The symptoms of depression in the elderly may differ from those in younger patients and this may be the reason why depression often goes undiagnosed in this age group (Glasser and Gravdal 1997). In addition to the usual depressive symptoms such as psychomotor retardation, loss of weight, fatigue and feeling of guilt, elderly patients often complain about symptoms such as neurocognitive impairment**,** somatic complaints and hypochondriasis**.** Agitated behaviour and verbal aggressiveness may also be related with depression (Fountoulakis et al. 2003). Neurocognitive impairment, ´pseudodementia´, refers to the manifestation of dementia symptomatology, which in fact is due to depression and disappears after antidepressant therapy (Plotkin et al. 1985, Koskinen 1991).

1.1.4.1 *Vascular depression*

It is suggested that late life depression can be divided into three subgroups with different etiological pathways: (1) early-onset depression with longstanding psychobiological vulnerability; (2) late-onset depression as a reaction to severe life stress; and (3) late-onset depression with vascular risk factors (van den Berg et al. 2001). There is growing evidence that cerebrovascular diseases are among the etiological factors in late-life depression (Alexopoulos 2005, Baldwin 2005). The term "vascular depression" describes depressive disorder in old age associated with cerebrovascular disease. It is related to deep ischemic subcortical brain lesions, particularly in frontal brain regions (O'Brien et al. 1998, Baldwin and O'Brien 2002, Camus et al. 2004, Kales et al. 2005). Such lesions, which typically occur in white matter, are seen as hyperintensities in the Magnetic Resonance Imaging (MRI) scan. Accordingly, possible loss of integrity in frontal and temporal white matter fiber tracts has been suggested in late life depression (Nobuhara et al. 2004). It is hypothesized that lesions may be associated with inflammatory processes (Baldwin 2005). Penninx et al. (2003) found that depressed patients had higher plasma levels of interleukin (IL)-6 than nondepressed subjects. Genetic factors may also be involved in vascular depression. Steffens et al. (2003c) reported an association between subcortical gray matter lesions and the presence of APOE ε4 allele.

Typical depressive features in vascular depression include reduced depressive ideation, greater psychomotor retardation, apathy and disturbance of executive function compared to ordinary MDD (Alexopoulos et al. 1997, Rapp et al. 2005, Vataja et al. 2005). Vascular depression is also associated with low depressive disorders in family history **(**Alexopoulos et al. 1997, Krishnan et al. 2004). Consequently, it has been suggested that recurrent early-onset MDD and late-onset MDD in elderly people may represent distinct phenomenological entities (Rapp et al. 2005).

Vascular depression is associated with poorer outcomes than nonvascular depression (O'Brien et al. 1998, Alexopoulos et al. 2002, Taylor et al. 2003, Kales et al. 2005) and it has been suggested that there is a bidirectional relationship between depression and vascular brain diseases (Baldwin 2005, Kales et al. 2005).

1.1.4.2 *Suicidality*

Depressive symptoms are strongly associated with suicidal ideations in later life and seem to be the most common risk factor for late-life suicide (Turvey et al. 2002, Pfaff and Almeida 2004). It has been estimated that about 83-87% of elderly people who committed suicide were suffering from a mood disorder and 65% of these from major depression (Conwell and Brent 1995, Wærn et al. 2002). Depression and suicidal ideation are not always easily recognized in elderly patients. Suominen et al. (2004) reported that in a sample of 81 elderly people who attempted suicide depression was diagnosed in only 4% of the cases before the attempt, but in 57% of the cases after the attempt, although the majority of the patients had an earlier health care contact. Pitkälä et al. (2000) found that 70% of old people who had committed suicide had been in contact with health care personal during the month before their death. However, depression and suicidal thoughts of the patients were not recognized in these communications and only 8% had received adequate antidepressive medication.

1.1.5 *Depression and physical illness*

Comorbid physical illnesses are common in patients with MDD (Proctor et al. 2003, Mueller et al. 2004). Silverstone (1996) found that 5.1% of medically ill inpatients had a comorbid MDD. Kisely and Goldberg (1996) reported that in general practice the prevalence of current psychiatric morbidity was 25% and major depression was the most common diagnosis (17%). On the other hand a significant percentage of patients with MDD suffer from concurrent general

medical conditions. Yates et al. (2004) found that 52.8% of outpatients with MDD suffered from significant medical comorbidity.

Depression is associated with a variety of physical illnesses such as cardiovascular disease (Hance et al. 1996, Lesperance et al. 1996, Musselman et al. 1998, Dam 2001, Ziegelstein 2001), cancer (Spiegel and Giese-Davis 2003), endocrine disturbances (Anderson et al. 2001) and Parkinson's disease (Nuti et al. 2004). Chronic painful physical conditions (joint/articular, limb, or back pain, headaches, or gastrointestinal diseases) (Ohayon and Schatzberg 2003) and especially fibromyalgia also have connections to depression (Goldenberg et al. 2004).

1.1.5.1 *Depression and fibromyalgia*

Fibromyalgia (FM) is a chronic pain syndrome. Its estimated prevalence is around 2% in the general population, and up to 20% among rheumatology outpatients (White et al. 1999, White and Harth 2001). FM is more common in women than in men (White et al. 1999). Besides musculoskeletal pain, characteristic symptoms include fatigue and sleep disturbance. The diagnosis of FM is based on a history of widespread pain and the presence of excessive tenderness on applying pressure to 11 out of 18 specific muscle-tendon sites (Wolfe et al. 1990). It has been suggested that patients with FM and control subjects generally detect sensory stimulation at the same levels, but the level at which these stimuli become unpleasant or felt as pain is lower in FM patients (Gibson et al. 1994, Kosek et al. 1996). The diagnosis and existence of FM has been criticised, because it is based only on subjective symptoms without specific pathophysiological characteristics (Croft 2003, Ehrlich 2003, Hadler 2003, van Houdenhove 2003). There are difficulties in distinguishing FM from other functional somatic syndromes such as chronic fatigue syndrome, irritable bowel syndrome and from psychiatric disorders such as depression and anxiety (Cathebras et al. 1998).

The etiology of FM is still poorly understood. FM has been associated with certain infections (Buskila et al. 1997, Goldenberg 1999, Thomson and Barkhuizen 2003), neuroendocrine system disturbance (Adler et al. 2002), biochemical and immunological abnormalities (Richards and Cleare 2000, Panerai et al. 2002) and autonomic dysfunction (Cohen et al. 2000, Rai et al. 2000). A recent functional MRI study supports the hypothesis that FM is characterised by cortical and subcortical augmentation of pain processing (Gracely et al. 2002). Psychological and psychosocial factors have also been suggested to influence the occurrence and persistence of this disorder (Walker et al. 1997, Barsky and Borus 1999).

Several studies report that FM is comorbid with MDD (Hudson et al. 1985, Epstein et al. 1999, Okifuji et al. 2000). Hawley and Wolfe (1993) analysed more than 6000 consecutive ambulatory patients with rheumatic disease and found that patients with FM were more depressed than other patients. Okifuji et al. (2000) found that 30 out of 69 patients with FM had concurrent depression and 18 of these met the diagnostic criteria for MDD. Rahinantti (1998) studied the psychological factors related to FM in a sample of 61female FM patients and found that 67% of them had depression. The lifetime prevalence of severe depression is reported to be around 70% in FM patients compared to 13% in patients with arthritis (Hudson et al. 1985, Epstein et al. 1999).

It has been hypothesised that FM is a disorder of affective spectrum, in which FM and MDD are characterized by shared, familiarly mediated risk factors (Hudson et al. 2004, Raphael et al. 2004). According to community-based family studies there is familial co-aggregation of FM and major mood disorder **(**Arnold et al. 2004a, Hudson et al. 2004, Raphael et al. 2004). Arnold et al. (2004a) reported that FM and reduced pressure pain thresholds aggregate in

families. They suggested that genetic factors may be involved in the etiology and pain sensitivity of FM and that mood disorder and FM share some of these inherited factors.

The strongest evidence in pharmacological pain relief in FM is shown by amitriptyline and other tricyclic antidepressants (Arnold et al. 2000, O' Malley et al. 2000, Goldenberg et al. 2004). The pain relieving effect of tricyclic antidepressants is independent of their action on depressive symptoms. The doses of tricyclic antidepressants used in pain alleviation in randomised controlled studies were lower than those used in depression. Some positive therapeutic effects in FM have been reported even with citalopram (Anderberg et al. 2000), fluoxetine (Arnold et al. 2002) and mirtazapine (Samborski et al. 2004). Samborski et al. (2004) reported that reduction of FM symptoms with mirtazapine significantly correlated with the reduction of depressive symptoms. In a recent study by Arnold et al. (2004b) duloxetine (serotonin and norepinephrine reuptake inhibitor) was found to be effective for fibromyalgia symptoms in patients with or without major depressive disorder. The mode of action of antidepressants in FM is unclear, but it has been assumed to be related to potassium channel modulation and NMDA (N-methyl-D-aspartate) receptor antagonism, and in addition to the modulation of monoamine neurotransmitters (Lawson 2002). However, it has been suggested that the treatment of fibromyalgia with pharmacotherapy as well as with other therapies is of little efficacy (Cathebras et al. 1998) and of modest long-term prognosability (Henriksson 1994, Wolfe et al. 1997).

1.1.6 *Treatment of MDD*

The treatment of MDD includes pharmacotherapy, psychotherapy (cognitive, behavioural, interpersonal, psychodynamic), combined pharmacotherapy and psychotherapy and ECT (APA 2000, Suomen Psykiatriyhdistys 2004). The choice of the acute phase treatment depends on clinical and other factors such as the severity of symptoms of MDD and the preference of the

patient (APA 2000). Psychosocial treatment combined with antidepressant medication may be considered as an initial treatment modality in patients with mild to severe MDD (APA 2000). Combined psychological and antidepressant therapy has been associated with a higher improvement rate than antidepressant treatment alone (Pampallona et al. 2004). In patients with psychotic features combined antidepressant and antipsychotic medication should be used (APA 2000). ECT should be considered in moderate and severe MDD, especially in patients with psychotic features, catatonic stupor or suicidality and in cases when a rapid response is required. ECT should also be considered in patients who have not responded to antidepressant medication. It is reported that 50-60% of medication resistant patients respond to ECT (Devanand et al. 1991, Prudic et al. 1996).

1.2 Electroconvulsive therapy (ECT)

1.2.1 *History of ECT*

The origins of convulsive therapy go back to the observation that the psychotic symptoms of patients with schizophrenia are sometimes alleviated after a spontaneous epileptic seizure. The Hungarian neuropsychiatrist von Meduna hypothesized that induced seizure in patients reduced their schizophrenic symptoms. Thus convulsive therapy has been clinically used since 1934. Meduna induced seizures first with camphor and later with pentylenetetrazol (Meduna 1936). The insulin coma was also introduced in 1933 by a Swiss psychiatrist Sakel (Fink 1984, Kalinowski 1986).

ECT was a modification of chemically induced seizures. The first electrically induced seizure was administered by the Italians Cerletti and Bini in 1938 to a patient with catanonic schizophrenia (Cerletti and Bini 1938). The introduction of ECT was a remarkable turning-point in the history of clinical psychiatry.

After its introduction, the use of ECT spread within a few years throughout the western world (Fink 1984). Owing to its simplicity in utilization and its safety, it gradually replaced pharmacoconvulsive therapies to become a first-line somatic therapy for schizophrenia and affective disorders (Kolb and Vogel 1942, Gralnick 1946). Within a few years it became apparent that ECT was even more effective in depression than in schizophrenia (Smith et al. 1943).

In the early 1940s a combination therapy with ECT and insulin or pentylenetetrazol was commonly used (Sadler 1945, Kalpa 1947). ECT in combination with insulin coma treatment was used in Finland as late as in the 1960s (Achte 1967). It was suggested that this combination would increase the efficacy of the treatment (Sadler 1945).

The most important improvement in ECT treatment was the introduction of muscle relaxation by succinyl choline and general anesthesia in the early 1950's (Kalinowski 1986). As late as the 1980s ECT was generally used in Finland without oxygenation, anesthetics, and muscle-relaxants. Since the 1970s treatment without anesthesia has been considered unacceptable (McCleave and Blakemore 1975).

The introduction of effective psychopharmacological agents for the treatment of schizophrenia and affective disorders in the 1950s and 1960s caused a decrease in the use of ECT (Weiner 1979). The negative public opinion associated with ECT contributed to a reduction in the use of this treatment (Fink 1991). In recent decades, however, there has been a reawakened interest in ECT (Fink 1993, Thomson et al. 1994). The small amount of research carried out in Finland on the utility of ECT seems to suggest a relatively low rate of use (Strömgren 1991, Isometsä et al. 1994, Suominen et al. 1998, Huuhka et al. 2000, Isometsä et al. 2000, Heikman

2002). In Pitkäniemi Hospital (District Mental Hospital / University Clinic of Psychiatry) 14% of all inpatients were treated with ECT in both 1944 and 1964 and 2% in 1997 (Huuhka et al. 2000). The limited availability of ECT may be one of the reasons for its low rate of use. The modern practice of ECT requires a high-level facility, such as special treatment unit with a highly trained medical staff including a psychiatrist, an anesthetist and a treatment nurse. In the last few decades this treatment method has received minimal education and training resources in the psychiatric hospitals and medical shools of Finland.

1.2.2 *Mechanism of action of ECT*

The mechanism of action of ECT is not fully understood. A generalized epileptic seizure is necessary but not sufficient for a therapeutic response. Traditionally, seizure duration of at least 20 seconds for the motor response and/or 25 seconds for the ictal electroencephalographic (EEG) response are considered adequate (Beyer et al. 1998). However, slightly suprathreshold right unilateral ECT (RUL ECT) seizure particularly, although adequate in duration may be therapeutically insufficient **(**McCall et al. 2000, Sackeim et al. 2000). The clinical efficacy of ECT is influenced by the electrical dose exceeding the seizure threshold (ST) (Sackeim et al. 2000). ST is higher in bilateral ECT (BL ECT) than RUL ECT (McCall et al. 1993), with sine wave than with brief pulse stimulation (Weiner 1980a), with men than with women and with elderly than with young persons (McCall et al. 1993, Boylan et al. 2000). Seizure duration is related to patient characteristics and treatment factors. A brief seizure may occur with insufficient or markedly suprathreshold stimulus doses (Sackeim et al. 1991). During the course of ECT there is an increase in ST and decrease in seizure duration (Coffey et al. 1995, Kales et al. 1997).

A higher electrical dosage (stimulus intensity) produces more intense ictal EEG expression and greater postictal suppression (Luber et al. 2000, Nobler et al. 2000) and BL ECT produces more intense ictal EEG expression and greater postictal suppression than RUL ECT (Perera et al. 2004). In a recent study by Perera et al. (2004) greater ictal power and coherence and postictal suppression in EEG were found to correlate with a good outcome. It is assumed that inhibitory processes during and immediately following seizures are involved in the mechanism of action of ECT (Sackeim 1983, Perera et al. 2004). ECT produced a marked short-term increase in delta and theta power activity in prefrontal cortex and this increase of slow-wave activity is linked to the efficacy of ECT (Sackeim et al.1996, Heikman et al. 2001). Sackeim et al. (1996) reported that interictally increased delta power in prefrontal regions was associated with the magnitude of symptomatic improvement. Accordingly, Heikman et al. (2001) found in magnetoencephalographic (MEG) recordings, that the increase of the theta activity in the left frontal cortex correlated with the efficacy of the ECT treatment. In that study the change of the ratio of left and right frontal theta activity to occipital theta activity had a positive correlation with the therapeutic effect.

Electroconvulsive shocks (ECS) have been shown to regulate gene expression of distinct neurotrophic signalling pathways particularly in the hippocampus of rats (Altar et al. 2004, Sun et al. 2005). According to Altar et al. (2004) neurogenesis, neurite outgrowth, and neuronal plasticity associated with BDNF, glutamate and cAMP-protein kinase A signalling pathways may mediate the antidepressant effects of ECT in humans. ECT has been found to have various acute effects on neurotansmitter, neuroendocrine and neurochemical systems. However, it has been suggested that none of these acute biochemical changes has consistent associations with the efficacy of ECT (Sackeim et al. 1995).

1.2.2.1 *Neurotransmitters*

Hofmann et al. (1996) reported that ECT increases the 5-hydroksyindoleacetic acid (5-HIAA) serum level and they suggested that ECT improves serotonergic responsiveness and neurotransmission. Markianos et al. (2002) studied the changes in the serotonergic and in dopaminergic systems' responsivity before and after a therapeutic course of ECT. According to them, the therapeutic effect of ECT in depression is not a result of considerable modifications in the responsivity of these neurotransmitters although there may be a moderate increase in 5-HT1A receptor responsivity. Repeated ECSs in the rat enhance 5-HT synaptic transmission by increasing the sensitivity of postsynaptic 5-HT1A receptors (Chaput et al. 1991).

After a single ECT there is an acute increase in the blood levels of epinephrine and norepinephrine (NE) (Weinger et al. 1991) correlating positively with the ECT dosage (Mann et al. 1990). Werstiuk et al. (1996) found that ECT results in a reduction in platelet $alpha_2$-adrenoceptor numbers and increases leukocyte $beta_2$-adrenoceptor densities in depressed patients. Kelly and Cooper (1997) reported that, compared to baseline during a course of ECT, there was a significant decrease in plasma NE in those patients with melancholic/psychotic depression but an increase in those with a non-melancholic depressive illness. These authors suggested that melancholic/psychotic depression involves disturbances in noradrenergic systems and that this is not evident in non-melancholic depressions.

It has been suggested that the function of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) is involved in mechanism of anticonvulsant and antidepressant actions of ECT (Sackeim et al. 1983, Perera et al. 2004). Devanand et al. (1995) reported a significant reduction in the free plasma GABA for up to 1 h after seizure termination. However, Sanacora et al. (2003) reported a two-fold increase in occipital cortex GABA concentrations after

a course of ECT. Clinically successful ECT has been associated with increased vascular perfusion and GABAergic neurotransmission in the right temporal and bilateral parietal cortices (Mervaala et al. 2001).

Reduced cortical glutamate/glutamine levels in patients with MDD have been found to be normalized after a successful ECT (Michael et al. 2003, Pfleiderer et al. 2003). Ende et al. (2000) found in Proton Magnetic Resonance Spectroscopic Imaging of the hippocampal region that compared with an age-matched control group, the choline-containing compounds signal in patients with a MDE was significantly lower than normal before ECT and normalized during ECT.

1.2.2.2 *Neurohormones*

After a single ECT there is an acute increase in the plasma thyroid-stimulating hormone (TSH) (Esel et al. 2002), adrenocorticotropic hormone (ACTH) (Whalley et al. 1987, Kronfol et al. 1991), prolactin (PRL) (Lisanby et al. 1998), cortisol (CORT) (Kronfol et al. 1991) and vasopressin (VP) (Weinger et al. 1991). According to Kronfol et al. (1991) there were significant increases in post-ECT plasma ACTH, PRL and CORT levels. Compared to the first ECT, repeated treatments were associated with a significant decrease in the magnitude of hormone surge. These hormonal changes induced by ECT may reflect changes at the neurotransmitter level. Esel et al. (2002) reported a significant increase in TSH levels 30 minutes after ECT compared to the pre-ECT values and decrease in thyroxine values respectively.

1.2.2.3 *Brain derived neurotrophic factor (BDNF)*

It has been shown in animal experiments that repeated ECSs cause an increase in the BDNF mRNA expression in the rat hippocampus and a corresponding increase in the proliferation and

survival of neurons, particularly serotonergic axon. (Zetterstrom et al. 1998, Vaidya et al. 1999, Madhav et al. 2000, Malberg et al. 2000, Altar et al. 2004).

1.2.2.4 *Cerebral blood flow (CBF) and glucose metabolism*

There are contradictory results from studies concerning the effects of ECT on cerebral blood flow (CBF) and the cerebral metabolic rate (CMR) for glucose. Bonne et al. (1996) reported an increase in CBF in patients responding to ECT whereas CBF remained unchanged in patients not responding to the treatment. Fukui et al. (2002) found an increase in the decreased thalamic CBF in those pain patients obtaining pain relief from ECT. In contrast Nobler et al. (1994) reported that, particularly in responders, ECT resulted in additional perfusion reductions of CBF and CMR for glucose. In that study blood flow reductions in the anterior cortical regions were strongly associated with a positive clinical response in both depression and mania. In a Positron Emission Tomography (PET) study Henry et al. (2001) also found that a decrease in global CMR for glucose correlated with the response to ECT. However, they also reported relative increases in CMR for glucose in regions with known dopaminergic innervations (caudate and upper brainstem). Nobler et al. (2001) found in PET a decreased regional cerebral glucose metabolism after ECT especially in the frontal and parietal cortex, anterior and posterior cingulate gyrus, and left temporal cortex. Similar evolution of frontal perfusion has been reported in a 12-month study of elderly patients with MDD treated either with ECT or antidepressants (Navarro et al. 2004).

1.2.3 *Indications for use of ECT*

The main indications for clinical use of ECT are acute episodes of affective disorders and some forms of schizophrenia (APA 2001).

1.2.3.1 *Major depressive episode*

Generally ECT is regarded as a second line treatment even in MDE if antidepressant treatment has proved ineffective. ECT may be used as a first line treatment in cases in which a rapid response is necessary because of psychiatric or medical condition. It may be used as a first line treatment if the patient is severely suicidal, stuporous or has had a poor response to medication or a good response to ECT in earlier MDEs (APA 2001, McCall 2005).

1.2.3.2 *Mania*

In mania ECT is generally used in patients with acute mania who have not responded to pharmacological treatment (APA 2001). ECT has a rapid onset of action (Small et al. 1988) and it is associated with remission or marked clinical improvement in 80% of manic patients (Mukherjee et al. 1994). Volpe and Tavares (2004) reported that the use of ECT in mania reduced the risk of readmission of the patients.

1.2.3.3 *Schizophrenia*

ECT is particularly appropriate in patients with an acute onset of symptoms, with a short episode duration and with positive or affective symptoms or catatonia (Salzman 1980, Fink and Sackeim 1996, Chanpattana and Chakrabhand 2001, Suzuki et al. 2004). Reports exist that ECT in combination with antipsychotic drugs is effective in some cases of treatment-resistant schizophrenia (Sajatovic and Meltzer 1993, Tang and Ungvari 2003). In negative symptoms ECT has a poor response (Sajatovic and Meltzer 1993, Chanpattana and Chakrabhand 2001).

In the 1950s the use of ECT for schizophrenia declined after the introduction of effective antipsychotic agents. In USA about 11-20% of patients receiving ECT in 1970 and 1980 had schizophrenia as a primary diagnosis (Thomson et al. 1994). In Scotland between the years 1997

and 1999 this rate was about 6% (Fergusson et al. 2004). In Hong Kong between the years 1997 and 2002 of patients receiving ECT 23% had schizophrenia as a primary diagnosis (Chung 2003). In some countries schizophrenia still constitutes the main indication for ECT. In Thailand as many as 74% of patients treated with ECT in the years 2001-2002 (Chanpattana and Kramer 2004) and in Hungary 56% of patients in 2002 had schizophrenia as their primary diagnosis (Gazdag et al. 2004).

1.2.3.4 *Other indications*

There are several reports of the efficacy of ECT in Parkinson's disease (PD) especially with comorbid depression (Rasmussen and Abrams 1991, Friedman and Gordon 1992, Aarsland et al. 1997, Wengel et al. 1998, Kennedy et al. 2003). ECT has been shown to improve both depression and motor function and an improvement in motor function seems to be independent of depression (Friedman and Gordon 1992, Aarsland et al. 1997, Kennedy et al. 2003). There is also some evidence that continuation ECT may maintain the beneficial effects achieved during the initial course of ECT (Aarsland et al. 1997, Wengel et al. 1998).

Neuroleptic malignant syndrome (NMS) is an unpredictable and rare, but potentially fatal complication of antipsychotic medications. There are several reports that NMS has been successfully treated with ECT (Davis et al. 1991, Scheftner and Shulman 1992, Nisijima and Ishiguro 1999).

Because of the remarkable anticonvulsant effect of ECT it could be a useful treatment in patients with intractable epilepsy or status epilepticus unresponsive to pharmacological treatment (APA 2001). In practice, however, its use in this indication is limited.

1.2.4 *ECT and pain*

Beneficial effects of ECT in various pain states have been reported. Most of these studies are case series or reports of severe and intractable pain syndromes of a single or a few patients **(**Mandel 1975, Bloomstein et al. 1996, Hoshino et al. 1999). These include phantom limb pain (Pisetsky 1946, Bornstein 1949, Gillis 1969, Rasmussen and Rummans 2000), reflex sympathetic dystrophy (King and Nuss 1993), complex regional pain syndrome (CRPS) (Fukui et al. 2002, McDaniel 2003), atypical facial pain (Hampf et al. 1992), postherpetic neuralgia (Sameshima et al. 1999), and central post stroke pain (Doi et al. 1999). On the other hand, there are reports that some patients did not benefit from ECT (Salmon et al. 1988, McCance et al. 1996).

There are several reports of the efficacy of ECT in chronic pain syndromes associated with mood disorders **(**Mandel 1975, Bloomstein et al. 1996, Rasmussen and Rummans 2000, McDaniel 2003). Bloomstein and others (1996) reported that 20 out of 21 patients with chronic pain had experienced pain relief after ECT. Wasan et al. (2004) studied patients with concomitant chronic pain and MDD. Patients were treated with ECT and antidepressants and the controls were treated with antidepressant medications only. The authors suggested that ECT seemed to have an analgesic action of its own, which was independent of the improvement of MDD. It has been suggested that normalization of the balance of regional cerebral blood flow in the thalamus may be related to the analgesic efficacy of ECT (Fukui et al. 2002).

Schreiber et al. (2003) researched the effect of bilateral ECT on the pressure pain threshold and pressure pain tolerance. They evaluated deep bone-periosteal pain in 19 patients with MDD and found that both the pain threshold and pain tolerance increased after alleviation of depression by ECT. In contrast Gormsen et al. (2004) found no change in the pain threshold in MDD

patients treated with unilateral ECT even if the depression was improved. They compared 17 ECT treated MDD patients with 17 age and gender matched healthy controls (without ECT) in pain detection and tolerance thresholds to pain.

1.2.5 *Efficacy of ECT in MDD*

ECT has been considered to be the most effective treatment in MDD. Some recently published meta-analytic reviews of randomised and non-randomised controlled trials have indicated that the efficacy of ECT is superior compared with simulated ECT or placebo or antidepressant drugs (Kho et al. 2003, UK ECT Review Group 2003, Pagnin et al. 2004). Flint and Rifat (1998) reported that elderly patients with psychotic depression had a significantly higher response rate to ECT than to a combination of nortriptylene and perphenazine.

1.2.5.1 *Acute efficacy*

In patients to whom ECT has been given as a first line treatment as well as in those who have not received adequate antidepressant drug treatment (ADT) during the present MDE, the response rate is estimated to be 80-90% (APA 2001). In the clinical trials, however, the response rate has been reported to vary between 65% and 90% (Flint and Rifat 1998, Stoudemire et al. 1998, Sackeim et al. 2000, APA 2001, O'Connor et al. 2001, Petrides et al. 2001, Birkenhager et al. 2003, Husain et al. 2004).

1.2.5.2 *Long-term outcome*

There is a high rate of relapse after response to ECT. Birkenhager et al. (2004) reported the 6-month relapse rate to be 28% and 12 months relapse rate to be 41%. Sackeim et al. (2000) reported that 53% of patients relapsed within one year and 94% of the relapses occurred during the first 6 months. Stoudemire et al. (1998) reported that 29% of elderly patients relapsed during

an 18-month follow-up period after ECT. Prudic et al. (2004) reported that 64.3% of the patients who had remitted after ECT given in a community setting had relapsed within 24 weeks after ECT.

After a successful acute response to ECT the long-term outcome depends on the post-ECT continuation pharmacotherapy. In a study by McCall et al. (2002) where the one-month relapse rate was 37%, the authors suggested that this might be connected to inadequate post-ECT pharmacotherapy prophylaxis. In a study by Sackeim et al. (2001) MDD patients who remitted after ECT were treated with combination of nortriptyline and lithium, nortriptyline alone or placebo. The 6-month relapse rates of patients were 39%, 60%, and 84% respectively.

1.2.5.3 *Predictors of efficacy*

There is little evidence about biological and physiological factors predicting the response of ECT. APOE polymorphism may affect treatment response. Fisman et al. (2001) reported that patients carrying the ε4 allele were more likely to respond to ECT in late-onset depression. Old age has been associated with better outcome (O'Connor et al. 2001). Of the physiological markers, heart rate variability (HRV) has been suggested to predict the outcome. Nahshoni et al. (2004) reported that elderly patients with MDD who respond to ECT, might show increased vagal modulation. Low baseline HRV is associated with rapid relapse. Both high baseline HRV and increasing HRV during ECT may predict a sustained outcome (Karpyak et al. 2004). The clinical characteristics of patients and the technique of ECT may also predict the response of ECT. These include severity and subtype of depression **(**Petrides et al. 2001, Birkenhager et al. 2003), duration of depressive episode (Prudic et al. 2004), medical and psychiatric comorbidity (Heikman et al. 2002a, Feske et al. 2004), use of medications during ECT (Pettinati et al. 1990,

Klapheke 1993), medication resistance (Prudic et al. 1996), and electrode placement and stimulus dose (UK ECT Review Group 2003).

There is evidence that the subtype of depression may play a role in the therapeutic response to ECT. In most of the studies comparing psychotic and nonpsychotic depression a superior response rate has been found in patients with psychotic depression (Mulsant et al. 1991, Black et al. 1993, Petrides et al. 2001, Birkenhager et al. 2003, Kho et al. 2003). Birkenhager et al. (2003) reported a response rate of 92% in patients with delusional depression compared to 55% in patients with non-delusional depression. Petrides et al. (2001) reported an 87% overall remission rate of 253 depressive patients given bilateral ECT; patients with psychotic depression had a remission rate of 95% and those with nonpsychotic depression 83%. They also found that psychotic patients achieve quicker antidepressant response to ECT compared with nonpsychotic patients. It has been also suggested that psychomotor retardation predicts a good response (Hickie et al. 1996). Longer episode duration has been associated with poorer outcome (Prudic et al. 2004).

Black et al. (1993) reported that patients who responded to ECT were less likely to have secondary depression. Comorbid somatic or psychiatric conditions have been shown to lower the response to ECT (Sareen et al. 2000, DeBattista and Mueller 2001, Heikman et al. 2002a, Feske et al. 2004, Prudic et al. 2004). In a study by Heikman et al. (2002a) it was found that the response rate of patients with a pure moderate or severe depression was 63%, whereas only 8% of patients with a variety of somatic or psychiatric comorbidities and milder depression responded to ECT.

The benefits of using antidepressants in the course of ECT are poorly documented. There is some evidence that antidepressants during ECT may improve the acute clinical outcome. Nelson and Benjamin (1989) and Lauritzen et al. (1996) reported that tricyclic antidepressants improved the clinical outcome whereas Mayur et al. (2000) found no advantage with continuation of antidepressant during an ECT course in MDD. According to the APA ECT guideline, concurrent use of antidepressant medication and ECT should be considered particularly for patients with medication resistance (APA 2001). Starting the antidepressant during the course of ECT may prevent relapse after ECT (Sackeim et al. 2001).

Combined use of antipsychotics and ECT may have synergistic effects in psychotic depression (Klapheke 1993, APA 2001). However, anticonvulsant agents prescribed for mood stabilization should be discontinued before ECT, because they increase the ST and interfere with seizure expression (APA 2001). Using benzodiazepines during unilateral ECT, the maximum therapeutic response may be compromised (Pettinati et al. 1990). Concurrent use of lithium and ECT is suspected to increase neurotoxicity (Weiner et al. 1980b, Rudorfer et al. 1987). However, in a retrospective case-control study by Jha et al. (1996) the use of lithium together with ECT was not associated with a higher frequency of adverse effects. The APA Task Force Report (APA 2001) warns of the potential toxic effects of the concurrent use of lithium and ECT. However, for patients with severe and recurrent mood disorder complete discontinuation may not be advisable.

It has been reported that the response to ECT is weaker in patients who have not responded to previous antidepressant trials (Prudic et al. 1990, Devanand et al. 1991, Prudic et al. 1996, Sackeim et al. 2000). Prudic et al. (1996) studied 100 patients who received ECT for primary, unipolar, nonpsychotic subtype of MDE and found that only 63% of medication-resistant

patients responded, whereas the response rate of patients with inadequate pharmacotherapy before ECT was 91%. However, in some recent studies no association between antidepressant resistance and response to subsequent ECT was found (Pluijms et al. 2002, Husain et al. 2004, van den Broek et al. 2004).

Bilateral ECT has been considered to be more effective than unilateral ECT and a high dose ECT more effective than a low dose ECT (Abrams et al. 1983, UK ECT Review Group 2003). It is considered that an efficient stimulus dose in BL ECT is moderately suprathreshold, i.e. between 50% and 150% above ST (APA 2001). The efficacy of RUL ECT administered just above the ST is relatively poor when compared to BL ECT (Abrams et al. 1983, Sackeim et al. 1987, Tandon et al. 1988, McCall et al. 2000, Sackeim et al. 2000). Moreover, ST will rise during the course of ECT (Coffey et al. 1995). Decreases in relative stimulus intensity over the ECT course may affect the therapeutic potency. Ictal EEG indices may have considerable potential for predicting such stimulus intensity changes and their effect on therapeutic outcome in RUL ECT (Krystal et al. 1998).

RUL ECT has to be administered with a markedly suprathreshold stimulus dose to achieve an antidepressant efficacy similar to BL ECT (McCall et al. 2000, Sackeim et al. 2000). In a study by Sackeim et al. (2000) patients were given RUL ECT, with electrical dosages 50%, 150%, or 500% above the seizure threshold or BL ECT with an electrical dosage 150% above it. The authors concluded that high-dosage RUL and BL ECT were equivalent in response rate (65%) and approximately twice as effective as low-dosage (response rate 35%) or moderate-dosage (response rate 30%) unilateral ECT. Tew et al. (2002) also found that in elderly patients there were no significant differences in clinical response between RUL ECT 450% above ST and BL ECT.

McCall et al. (2000) suggested that the dose-response relationship in RUL ECT is up to 8 or 12 times ST. However, an increase in the stimulus dose will result in a corresponding increase in adverse effects. McCall et al. (2002) found no differences in the antidepressant efficacy or in the memory adverse effects between RUL ECT at eight times and BL ECT at 1.5 times ST.

It has been suggested that bifrontal (BF) electrode placement induces fewer cognitive side effects than does BL or RUL electrode placement (Lawson et al. 1990, Letemendia et al. 1993, Bailine et al. 2000, Bakewell et al. 2004). However, considering efficacy, the results of these studies are inconsistent. Bakewell et al. (2004) reported that BF ECT was not as effective as BL ECT. In contrast, Letemendia et al. (1993) reported that the BF ECT had better efficacy than BL or RUL ECT. Bailine et al. (2000) reported that BF ECT was as effective as BL ECT.

Heikman et al. (2002b) studied the treatment responses of a high dose (400% above the ST) RUL ECT, a moderate dose (150% above the ST) RUL ECT and the low dose (just above the ST) BF ECT. A high dose RUL ECT was associated with faster response than a low dose BF ECT. Moreover, there was a tendency for a higher response rate with a high dose RUL ECT when compared to either a moderate dose RUL ECT or BF ECT.

1.2.6 *Use of ECT in elderly patients*

ECT is proportionally more often used in elderly patients than in young or middle-aged ones (Thomson et al. 1994, Olfson et al. 1998, Reid et al. 1998, Glen and Scott 1999, Prudic et al. 2001, Breakey and Dunn 2004). Old age seems to be one of the predisposing factors for receiving ECT treatment for affective disorders. Thomson et al. (1994) reported that one third of people receiving ECT in USA in 1986 were more than 65 years old. Reid et al. (1998) found that 48 % of patients treated with ECT in Texas 1993-1995 during a 19-month period were over 65

years of age. Olfson et al. (1998) reported that patients aged 65 years and older had an estimated 6.7 times greater likelihood of receiving ECT than younger adults (18-34 years). Glen and Scott (1999) studied the use of ECT in Edinburgh in Britain between the years 1992 and 1997. The rate of ECT use among the elderly population (65 years or older) was three times higher than that in younger adults.

1.2.6.1 *Efficacy of ECT in elderly patients*

Several prospective studies have shown that ECT is highly effective in MDD in elderly patients (Godber et al. 1987, Tew et al. 1999, Brodaty et al. 2000). The acute response of elderly patients to ECT has been estimated to be as good as or even better than that of younger patients (Black et al. 1993, Tew et al. 1999, Brodaty et al. 2001, O'Connor et al. 2001). A Consortium for Research (C.O.R.E) in ECT reports the remission rates of 253 patients in three age-groups >65 years, 46-64 years and <45 years to be 90%, 89.8% and 70% respectively (O'Connor et al. 2001). It has been suggested that the better response to ECT in the elderly patients compared to younger patients may be associated with a lower rate of comorbid Axis II pathology (APA 2001). Psychotically depressed elderly patients treated with ECT have been reported to survive at least as well as those treated with pharmacotherapy (Flint and Rifat 1998).

1.2.7 *Adverse effects of ECT*

1.2.7.1 *Mortality*

The rate of mortality in ECT has been estimated to be up to 1 death per 80,000 treatments (APA 2001). Shiwach et al. (2001) analysed mortality associated with ECT in all patients treated in Texas between 1993 and 1998. Over this period, 8,148 patients received a total of 49,048 ECT treatments. No deaths occurred during ECT over the five-year period. Thirty patients died within 14 days of ECT. Only one death, which occurred on the same day as the ECT, could be

specifically linked to the anesthesia associated with ECT. Nuttall et al. (2004) reported that there were no ECT-related deaths among 2,279 patients given 17,394 treatments between the years 1988 and 2001 in Minnesota. Reid et al. (1998) reported that 2 patients died from possible anesthesia complications in 15,240 treatments in Texas between September 1993 and April 1995.

1.2.7.2 *Cognitive adverse effects*

The most common adverse effects associated with ECT are transient memory loss and related cognitive dysfunction. ECT induces acute postictal disorientation and anterograde and retrograde amnesia (Calev et al. 1991a, Calev et al. 1991b, Sackeim et al. 2000). Anterograde amnesia means difficulty in remembering learned materials after termination of a treatment course. Retrograde amnesia means difficulty in retrieving materials learned before the ECT course commenced. However, it has been shown that cognitive dysfunction induced by ECT is largely reversible (Calev et al.1991b, Sackeim et al. 1993, McCall et al. 2002). Calev et al. (1991b) reported that only one month after ECT both the anterograde and retrograde memory functions of the patients were restored to the pre-ECT levels and after six months exceeded these levels. In some cases retrograde amnesia may be long-lasting (Sobin et al. 1995, Lisanby et al. 2000). It has been suggested that patients who have had cognitive impairment before ECT and patients who have experienced prolonged disorientation in the acute postictal period after treatment may be the most prone to persistent retrograde amnesia for autobiographical information (Sobin et al. 1995)**.** However, most patients report subjective improvement in the memory after an ECT course relative to baseline (Coleman et al. 1996, Sackeim et al. 2000). It has been suggested that the subjective reports of cognitive functions are strongly influenced by the mood state and patients with a poor response are more likely to report persistent memory deficit than patients with a good response (Prudic et al. 2000).

Cognitive side effects correlate with the parameters of the treatment, e.g. duration of the seizure, electrical stimulus intensity, electrode placement, number of treatments and electrical waveform. Longer seizure duration and higher stimulus dosage above the seizure threshold increase the risk of cognitive side-effects (Sackeim et al. 1987, Calev et al. 1991a, Sackeim et al. 1993, McCall et al. 2000). Brief-pulse ECT produces less memory impairment than sine-wave ECT (Squire and Zouzounis 1986). BL ECT is associated with longer postictal disorientation and greater anterograde and retrograde amnesia than RUL ECT (Sackeim et al. 1993, Lisanby et al. 2000, Sackeim et al. 2000). However, RUL ECT with markedly suprathreshold intensity has no advantages in memory side-effects compared to BL (McCall et al. 2002). A twice weekly schedule causes less severe cognitive impairment than a thrice weekly schedule (Shapira et al. 2000).

1.2.7.3 *Cardiovascular adverse effects*

The most serious complications of ECT are cardiovascular (Welch and Drop 1989, Zielinski et al. 1993, Nuttall et al. 2004). The majority of cardiac events are transient arrhythmias and myocardial ischemia (Zielinski et al. 1993, Nuttall et al. 2004), but even asystole may occur (Burd and Kettl 1998, Robinson and Lighthall 2004). There is an increased risk of cardiac complications in patients with pre-existing cardiac diseases and in the elderly. In a study by Zielinski et al. (1993) 55% of the patients with cardiac disease had at least one complication such as transitory arrhythmias and ST-segment changes in the electrocardiogram (ECG) during ECT in contrast to 7.5% of those without a cardiovascular disease. In contrast, in a retrospective study by Manly et al. (2000) cardiac complications were not reported in a sample of 39 patients aged 75 years or older despite the fact that 24 patients had a history of cardiac disease. ECT has even been given to patients with cardiac pacemakers and patients with implantable cardioverter defibrillators (Dolenc et al. 2004, Giltay et al. 2005). Dolenc et al. (2004) reported that only one

serious cardiac event occurred, a case of supraventricular tachycardia (SVT), in 26 patients with cardiac pacemakers and 3 patients with implantable cardioverter defibrillators treated with ECT.

1.2.7.4 *Other adverse effects*

Prolonged seizure: The APA Task Force Report (2001) on ECT presents a cut-off of 180 seconds for a prolonged EEG seizure. In a large retrospective study by Nuttall et al. (2004) the prolonged seizure was reported as a complication in 0.31% of the 2,279 patients receiving ECT in the United States. The usual practice in the United Kingdom is to define a prolonged seizure as one lasting 120 seconds or more in EEG (Lock 1995, Benbow et al. 2003). According to this definition Benbow et al. (2003) and Mayur et al. (1999) reported that prolonged seizure occurred in between 16% and 19% of courses of ECT. A prolonged seizure is more likely to occur in patients having medical conditions such as electrolyte imbalance or medications that lower ST or prolong the seizure such as teophylline (APA 2001).

There are reports of cases with a nonconvulsive status epilepticus as a very rare complication of ECT (Smith and Keepers 2000, Povlsen et al. 2003). This is important in differential diagnosis in patients who develop prolonged confusion after ECT. Moreover, spontaneous rare tardive seizures occurring within hours of treatments have been reported (APA 2001). In addition, prolonged apnea is a rare complication that occurs primarily in patients who have slow metabolism of succinylcholine. Usually prolonged apnea resolves spontaneously within 30-60 minutes (Kramer and Afrasiabi 1991, APA 2001).

Cerebrovascular complications of ECT are also rare. The APA Task Force on ECT (APA 2001) recommends that patients with elevated intracranial pressure should be considered on a case-by-case risk-to-benefit ratio. There are case reports of successful use of ECT in patients

with idiopathic intracranial hypertension (Adam and Crowe 2003), with a brain tumor and increased intracranial pressure (Patkar et al. 2000), with intracranial vascular masses (Salaris et al. 2000) and with intracranial aneurysms (Bader et al. 1995).

Mania is a relatively uncommon complication of ECT. It develops in most cases in patients with bipolar disorder (Devanand et al. 1988, APA 2001). There is no established strategy for the management of manic symptoms emerging during the course of ECT. It could either be discontinued or continued depending on clinical judgement (APA 2001).

1.2.8 *Continuation ECT*

Continuation ECT refers the continuation of the treatment after a successful ECT course. Usually continuation treatment is started once a week and the period is gradually extended to a month depending on clinical response. Continuation treatment exceeding 6 months is termed maintenance ECT. Most of the patients referred to ECT are likely to be resistant to antidepressant therapy. That is why the risk of relapse after successful ECT in these patients is particularly high (Sackeim et al. 2001). Continuation and maintenance ECT have been shown to be an effective treatment strategy to prevent relapses after successful ECT in patients with a high relapse risk (Gagne et al. 2000, Andrade and Kurinji 2002). Gagne et al. (2000) reported that after successful ECT the cumulative probability of surviving without relapse or recurrence at 2 years was 93% for patients treated with continuation ECT and 52% for patients treated with antidepressants alone. At 5 years this declined to 73% for patients treated with continuation ECT and to 18% for patients treated with antidepressant-alone. Continuation ECT should be considered if pharmacotherapy alone has not been effective in the prevention of relapse, or if pharmacotherapy cannot be safely administered, or if the patient prefers treatment with ECT (APA 2001).

1.3 Conclusions based on the literature

The mechanism of the action of ECT is unknown. It may be connected to various neurotransmitters, neurohormones, BDNF and cerebral blood flow and glucose metabolism. It has also been suggested that genetic factors may be involved in the treatment response in MDD. However, there is only one earlier study examining the influence of genetic polymorphism and the treatment response of ECT. Fisman et al. (2001) reported that the APOE polymorphism was associated with ECT response in MDD.

ECT is proportionally more often used in elderly patients than in young or middle-aged ones. The acute response of elderly patients to ECT has been shown to be as good as or even better than that of younger patients (Black et al. 1993, Tew et al. 1999, Brodaty et al. 2001, O'Connor et al. 2001). The relapse rate in geriatric depression has been found to be high in patients treated with both ECT and antidepressants (Stoudemire et al. 1998).

Fibromyalgia is a chronic pain syndrome with high comorbidity with depression. There are several reports about the influence of ECT in chronic pain syndromes associated with mood disorders (Mandel 1975, Bloomstein et al. 1996, Rasmussen and Rummans 2000, McDaniel 2003). However, no previous studies exist investigating the effect of ECT on the pain and other symptoms in patients with FM.

ECT is usually considered to be a safe treatment even in elderly and somatically ill patients. Serious complications are rare, but when they occur, they are generally cardiovascular in nature (Welch and Drop 1989, Zielinski et al. 1993, Nuttall et al. 2004). The majority of cardiac events are transient arrhythmias and ST-segment changes. The risk of cardiac complications is increased in patients with pre-existing cardiac diseases and in the elderly. There

are only a few earlier studies using Holter monitoring to investigate the cardiac effects of ECT and in most of these studies the recordings were taken only for a short time period during and/or after the ECT (Dec et al. 1985, Zvara et al. 1997, Rasmussen et al. 2004).

2 Aims of the study

The overall aim of this study was to investigate the effect of genetic modulation on the outcome of ECT in MDD patients and the outcome of this treatment in elderly patients as well as in patients with concomitant somatic complaints.

The specific aims of this study were:

1. To study the relationships between the APOE polymorphism and response to ECT in MDD (Study I).

2. To evaluate the acute efficacy and long-term outcome of ECT vs. antidepressants treatment in elderly patients with MDD (Study II).

3. To evaluate the effects of ECT on depression, pain and other physical symptoms in patients with concomitant MDD and fibromyalgia (Study III).

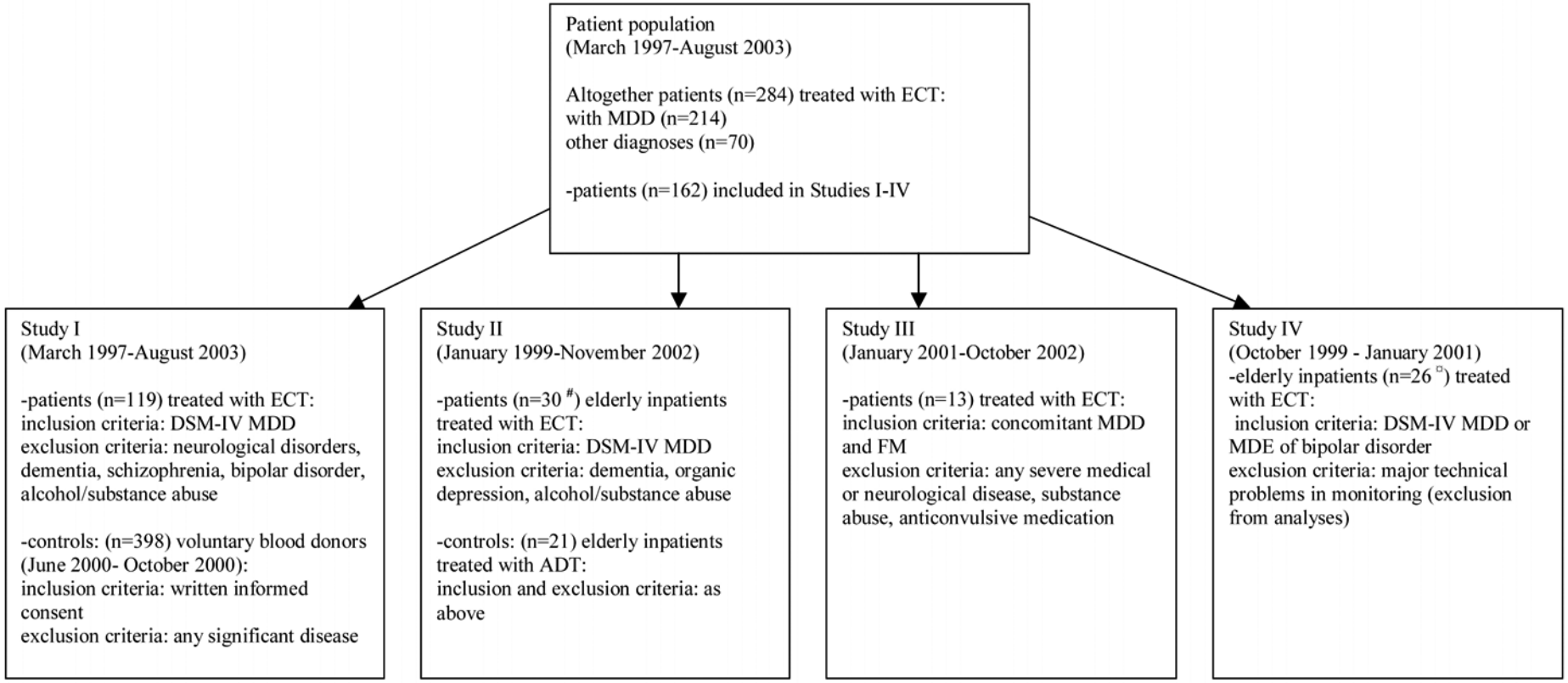
4. To evaluate the cardiac arrhythmias induced by ECT in patients with major depressive episode (MDE) (Study IV).

3 Patients and methods

3.1 Patients

This prospective study was carried out between March 1997 and August 2003 at the Pitkäniemi Hospital of the Department of Psychiatry, Tampere University Hospital. The selection of patients for the various studies is shown in Figure 1.

Figure 1. Flowchart of patient selection to Studies I - IV



n; Number of patients (controls)
MDD; Major Depressive Episode
ECT; Electroconvulsive therapy
ADT; Antidepressant drug treatment
FM; Fibromyalgia
16 of the patients were also included study I
¤ 10 of the patients were also included study I

All the study patients were referred for ECT because of treatment-refractory depression. Treatment-resistance to antidepressants was defined as 2 or more unsuccessful trials of antidepressant medication at an adequate dose for at least 4 weeks (6 weeks in the Study II) (Russell et al. 2004). All patients had MDD except for five patients in Study lV, who had major depressive episode (MDE) of bipolar disorder. These five patients with MDE were included in Study IV because the aim of that study was only to evaluate ECT-induced cardiac arrhythmias. Diagnoses based on semi-structured clinical interviews were made by an experienced psychiatrist (MH). All patients (except those five in the Study IV) fulfilled the diagnostic criteria for MDD according to DSM-IV with or without psychotic features. The sociodemographic and clinical data of the patients are given in Table 1.

Table 1. Sociodemographic and clinical and ECT data of patients and controls (studies I-IV)

	Study I	Study II	Study III	Study IV
Patients (n)	119	30	13	26
Gender, female, n (%)	65 (55)	22 (73)	9 (69)	18 (69)
Age (mean±SD)	57.7±14.0	69.6±6.2	49±7.9	69.3±6.0
Patients with physical illness of clinicacal importance, n (%) #	55 (46)	17 (57)	5 (38) *	21 (81)
Psychotic depression, n (%)	51 (43)	10 (33)	0 (0)	3 (12)
MADRS baseline (mean±SD)	32.5±8.2	31.6±8.5	26.2±5.0	
MADRS after ECT (mean±SD)	11.3±8.8	8.1±6.0	13.2±10.5	
BDI baseline (mean±SD)		29.4±10.3		
BDI after ECT (mean±SD)		10.6±9.9		
CGI change, n (%) ¤		26 (87)	6 (46)	
MMSE baseline (mean±SD)	27.0±3.6	27.2±2.0		
MMSE after ECT (mean±SD)	26.9±2.9	26.3±3.6		
Controls (n)	398	21		
Gender, female, n (%)	182 (46)	20 (95)		
Age (mean±SD)	44.7±11.3	73.1±7.5		
Patients with physical illness of clinicacal importance, n (%)#		17 (81)		
Psychotic depression, n (%)		3 (14)		
MADRS baseline (mean±SD)		28.5±5.4		
MADRS after ECT (mean±SD)		13.4±10.6		
BDI baseline (mean±SD)		28.9±6.6		
BDI after ECT (mean±SD)		17.1±14.1		
CGI change, n (%) ¤		11 (52)		
MMSE baseline (mean±SD)		27.7±1.8		
MMSE after ECT (mean±SD)		28.7±1.5		

n; Number of patients (controls)
Other than exclusion criteria
* Except fibromyalgia
MADRS; Montgomery and Åsberg Depression Rating Scale (Montgomery and Åsberg 1979))
BDI; Beck Depression Inventory (Beck et al. 1961)
CGI; Clinical Global Impression Change Scale (Guy 1976)
¤ much or very much improved
MMSE; Mini-Mental State Examination (Folstein et al. 1975)

3.1.1 *Patients in the APOE study (Study I)*

The samples of analysis of APOE polymorphism were drawn from 119 patients (54 males and 65 females) with MDD, who were consecutively admitted for ECT (Table I). The sociodemographic and clinical data of these patients are given in Table 1. Patients with neurological disorders, dementia, schizophrenia, bipolar disorder and alcohol or other substance abuse were excluded from the study. Three out of the 122 patients who met the inclusion criteria and were invited to participate in the study declined. The controls were 398 (216 males and 182 females) healthy blood donors (Table I).

3.1.2 *Elderly patients in the follow-up study (Study II)*

The study group consisted of 51 elderly (≥ 60 years) patients (9 males, 42 females) with MDD (Table 1). Exclusion criteria were as follows: dementia, alcohol or other substance abuse, and depression caused by organic factors.

According to clinical judgement, the patients were initially divided into 2 treatment groups, the first one (n=30) receiving ECT and the second (n=21) antidepressant (ADT) drug treatment (Table I). The criteria for choosing ECT were as follows: a rapid response was needed due to severe psychotic or suicidal symptoms, a history of a poor response to antidepressants, and/or a good previous response to ECT. Response to drug treatment was considered poor if at least 2 antidepressant trials (drugs of different classes, duration ≥6 weeks, the highest recommended dose for the elderly) had failed. After discharge from hospital, the patients were followed up until a new hospitalisation or until 1 year had passed. Antidepressants were chosen according to clinical considerations such as history of previous response and side effects with ADTs, type of depressive symptoms, possible concomitant physical illnesses, and somatic drug treatments

regarding interactions. The serum levels of the antidepressants used were measured when available and when clinically needed.

3.1.3 *Patients with concomitant MDD and fibromyalgia (Study III)*

The study group consisted of 13 patients, four men and nine women, aged 36-61 years (Table 1). The inclusion criteria were therapy refractory (at least two unsuccessful trials with antidepressants of different types) MDD and the coexistence of fibromyalgia (FM). The diagnosis of FM was made by a rheumatologist for all the patients and was based on the diagnostic criteria for FM of the American College of Rheumatology (Wolfe et al. 1990). Patients with epilepsy, anticonvulsive medication for any reason, substance abuse or any severe medical or neurological diseases were excluded.

3.1.4 *Patients with Holter monitoring (Study IV)*

The study group consisted of 31 elderly patients referred for ECT because of treatment-refractory depression. Bipolar depression was not an exclusion criterion in this study and five patients with MDE of bipolar disorder were included. Of these 31 patients five were excluded because of technical problems with the recordings. Thus, the final analyses were performed for 26 patients (Table 1).

3.2 Methods and designs of the studies

3.2.1 *General assessment of patients*

General pre- and post-ECT evaluation was performed for all the patients included in these studies. The pre-ECT evaluation included the assessment of the patients' psychiatric and medical history and their psychiatric indication for ECT. It also included a medical examination focusing particularly on neurological, cardiovascular and pulmonary systems according to the

recommendations of APA ECT reports (1990 and 2001). In Study IV a chest X-ray was taken of all the patients. After the pre-ECT evaluation the patients were provided with oral and written information about ECT. The pre- and post ECT evaluation of all patients included the Montgomery and Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg 1979), the Beck Depression Inventory (BDI) (Beck et al. 1961), as well as the Clinical Global Impression Change Scale (CGI) (Guy 1976) and the Mini-Mental State Examination Scale (MMSE) (Folstein et al. 1975). The specific outcome measurements used in the different studies are given in Table 2.

Table 2. Outcome measures used in Studies I-IV

	Study I	Study II	Study III	Study IV
MADRS	X [#]	X [¤]	X [##]	
BDI		X [¤]		
CGI		X [#]	X [#]	
MMSE	X [#]	X [¤]		
ADL		X *		
IADL		X *		
Q-Les-Q		X *		
LSS-A		X *		
FIQ			X [##]	
Tender-point examination			X [##]	
Pain and medication diary			X [##]	
Age at onset of depression	X			
Incidence of cardiac arrhythmias				X[+]
Incidence of ST segment change				X[+]
Rehospitalization during the follow-up	X			

[#] Change between baseline and after ECT
[¤] Change during index hospitalization and follow-up
* Change during follow-up
[##] Change between baseline and after ECT and during follow-up
[+] Change after a single ECT
MADRS; Montgomery and Åsberg Depression Rating Scale (Montgomery and Åsberg 1979)
BDI; Beck Depression Inventory (Beck et al. 1961)
CGI; Clinical Global Impression (Guy 1976)
MMSE; Mini-Mental State Examination (Folstein et al. 1975)
ADL; Activities of Daily Living (Katz et al. 1963)
IADL; Instrumental Activities of Daily Living (Lawton and Brody 1969)
Q-Les-Q; Quality of Life Enjoyment and Satisfaction Questionnaire (Endicot et al. 1993)
LSS-A; Life Satisfaction Scale A (Salokangas et al. 1988)
FIQ; The Fibromyalgia Impact Questionnaire (Burckhardt et al. 1991)

3.2.2 *ECT procedure*

All the patients were treated at the ECT treatment unit in the Psychiatric Clinic of Tampere University Hospital. The ECT-team consisted of an experienced staff including a treating psychiatrist, an anesthesiologist, a treatment nurse and a recovery area nurse. The pre-ECT evaluation according to the recommendations of the APA (1990, 2001) was carried out on all patients by the treating psychiatrist (MH). The ECT was administered to all patients in these studies by the same psychiatrist (MH), except for some isolated treatments (Maire Santala, Kaija Huuhka).

ECT was administered 3 times a week with a brief-pulse, constant-current device (Thymatron DGx, Somatics, Inc., Lake Bluff, IL). The initial stimulus dosage was adjusted with the age method (Swartz and Abrams 1996) for all patients in Studies II and III. In Study I the initial stimulus dosage was adjusted with the age method for 30 patients and with the stimulus titration procedure (Sackeim et al. 1987, Sackeim et al. 1993) for 89 patients. In Study IV the age method was used for 18 patients and the stimulus titration for 8 patients.

Anesthesia was induced with methohexital (except in 13 patients in Study IV with propofol, because of the unavailability of methohexital at that time) and muscle relaxation with succinylcholine. The initial dose was 1 mg/kg of methohexital (or 1.5 mg/kg of propofol) and 0.5 mg/kg of succinylcholine. If the seizure threshold was determined, patients were pretreated with 0.5 mg of atropine. At subsequent treatments the doses of anesthetic medications were adjusted individually on clinical grounds.

The patients were ventilated with 100% oxygen until resumption of spontaneous respiration. Physiological monitoring included pulse oximetry, blood pressure, ECG, 1-channel

electroencephalogram (EEG), and electromyography (EMG). The criteria for an adequate generalized seizure duration was at least 20 seconds of motor response and 25 seconds EEG seizure activity. During the treatment course of ECT, the dosage was adjusted upwards if needed to maintain adequate seizure duration. In the Study III all the patients were treated with RUL ECT and in Studies I, II and IV all the patients were treated with standard BL ECT.

The number of treatments in Studies I and II was based on the clinical judgement done of the treating psychiatrist in the ECT unit together with the treating hospital ward. ECT was continued until patients were free from symptoms or had received at least 8 treatments without any further improvement being observed during the past 2 treatments. In Study I the number of treatments ranged between 7 and 15, 9.4±1.8 (mean±SD) and in the Study II 5 and 12, 8.0±1.5. In Study III the number of treatments was fixed at eight (with the exception of one patient with seven treatments and another with three treatments because of excellent response). In Study IV Holter monitoring was performed during the first ECT session.

3.2.3 *Special features in different studies*

3.2.3.1 *Clinical assessment and APOE genotyping (Study I)*

The clinical outcome measures are given in Table 2. The MADRS was used to assess the severity of depression and the clinical change. Patients scoring less than 8 in MADRS after ECT were considered to be responders and patients scoring more than 15 were considered to be non-responders. Cognition was assessed in 78 patients using the MMSE. The patient's age at first onset of MDD was defined by using information of medical records and patient's interview. The age of 45 years was used as a cut-off between early and late onset depression.

Genomic DNA was extracted from peripheral blood leukocytes using a commercially available kit (Qiagen Inc, Hilden, Germany) and DNA samples were then genotyped by employing the 5'exonuclease assay (Livak 1999). For the APOE 112 genotyping, fluorogenic allele-specific TaqMan probes and primers were used as described by Koch and coworkers (2002). APOE 158 genotypes were, in turn, determined using primers and allele-specific fluorogenic probes with conjugated minor groove binder group that were synthesized in conjugation with Applied Biosystems (Foster City, CA, USA). Polymerase chain reaction (PCR) mixture consisted of genomic DNA, 1 × Universal PCR Master Mix, 900 nM of each primer and 200 nM of each probe in a total reaction volume of 25 μl. Amplification was performed in 96-well plates using the TaqMan Universal Thermal Cycling Protocol. After PCR, end-point fluorescence intensity was measured by the ABI Prism 7000 Sequence Detection System (Applied Biosystems, Foster City, CA, USA) and allelic discrimination performed. All genotyping was performed blind to patient outcome. Negative and known control samples previously typed by RFLP-PCR analysis were run in parallel with unknown DNA samples.

3.2.3.2 *Clinical assessment of elderly patients in follow-up study (Study II)*

The patients were assessed on admission, at discharge and after 12 months' follow-up. The change of MADRS in acute phase and rehospitalization in the follow-up were the primary outcome measures. These and other measures used in this study are given in Table 2. The functional capacity assessment and the quality of life evalutions were performed at disharge and at month 12.

3.2.3.3 *Clinical assessment in patients with concomitant MDD and fibromyalgia (Study III)*

The baseline demographic and clinical data were assessed one week before the first ECT session (Table 1). The patients were then followed up for three months after ECT. The follow-up

assessments were carried out one week, one month and three months after the last ECT session. The MADRS and CGI were used to assess the severity of depression and the clinical change of the patients (Table 2).

The physical symptoms of FM were evaluated by the Fibromyalgia Impact Questionnaire (FIQ) (Table 2), a brief 10 item self-administered instrument (Burckhardt et al. 1991). The first item of the FIQ focuses primarily on the patient's ability to perform large muscle tasks and contains 10 subitems. The next item asks the number of days in the past week that the patient felt good. The next 2 items elicits the patient's ability to work and the number of days they missed work. The last 6 items measured by visual analog scales elicit pain, fatigue, morning tiredness, stiffness, anxiety and depression.

Additionally, the tender-point examination using digital palpation with the force of 4 kg (Wolfe et al. 1990) was performed. During the whole study the patients daily recorded their FM pain and medication in the diary. The intensity of the pain was evaluated using a 6-point scale 0–5 (0 = no pain, 5 = very severe pain). The mean values of the pain scores of the previous week were calculated and used in the statistical analyses to represent the pain at the baseline and at the follow-up visits.

3.2.3.4 *Holter monitoring of patients treated with ECT (Study IV)*

The outcome measure was the incidence of cardiac arrhythmias between pre and post treatment (Table 2). Automated Holter monitoring (Del Mar model 461, Del Mar Avionics, Irvine, CA, U.S.A.) was performed for 48 hours: for 24 hours before ECT, interrupted during the electrical stimulation, and resumed immediately for 24 hours after the ECT. The incidence and number of ECG changes were studied throughout this 48-hour period. The 24-hour post-ECT recording was

compared with that of the 24 hours pre-ECT, with each patient serving as his or her own control. A separate comparison was performed between the records taken in the first hour after and the last hour before ECT. Ventricular extrasystoles (VESs) were graded according to the classification proposed by Lown and Wolf (1971). VESs occurring less often than 1/min were regarded as isolated (even isolated VESs were counted), and others were regarded as frequent. Ventricular tachycardia was defined as three or more consecutive ventricular ectopic beats at a rate greater than 120/min, and supraventricular tachycardia (SVT) was defined as three or more consecutive beats at a rate greater than 130/min. ST segment changes were analysed 60 msec after the J-point. The Holter recordings were analysed blind to the pre-ECT and post-ECT clinical status of the patients.

3.2.4 *Statistical methods*

The distributions of categorical variables between the different study groups were compared by the Fisher exact test (I) or $\chi 2$-test (I, II). The difference in continuous clinical variables within the patient groups before and after ECT was tested by paired t-test (I, II, III). Differences in means for independent samples were tested using Student's t test (II). One-way ANOVA was used in determining differences in clinical variables between APOE genotype groups (I). Mean ± SD were given (I, II, III). Pearson's correlation coefficient was used to find associations between the MMSE score change and the number of ECT treatments and the age of the patients (I). Comparisons of arrhythmias between pre-ECT and post-ECT periods were analysed using the Wilcoxon matched-pairs signed ranks test (IV). This nonparametric test was used because the variables were not normally distributed and the number of patients in the subgroups was small. Medians (ranges) were given (IV).

A linear regression analysis was used to explain the correlation between the FIQ items, tender point counts, self-assessed pain and MADRS (III) and the change of MADRS score by the variables, which had statistically significant differences between the groups at baseline (II). The Cox regression analysis was used to create a model to explain rehospitalization by age, length of current period of depression, MADRS scores at discharge, somatic illnesses (5 variables) and the explaining variables used in the linear regression analysis (II). These analyses were stratified by "group" (II). The Kaplan-Meier method was used to test differences in rehospitalizations between the groups (II) and the association between age at onset and APOE polymorphism (I).

The statistical analysis was carried out using SPSS/Win (Versions 10.0 (II), 11 (I) and 11.0.1 (III, IV), SPSS Inc, Chicago, IL). The limit for statistical significance was set equal to 0.05.

The study protocol was approved by the Ethics Committee of Tampere University Hospital according to the principles of the Helsinki Declaration. All participants gave written informed consent.

4 Results

4.1 Apolipoprotein E polymorphism and response to ECT (I)

In the whole group, the pre-ECT values of the MADRS score decreased from 32.5±8.2 (mean±SD) to 11.3±8.8 after ECT treatment (mean±SD, $p<0.0001$). Using the cut-off points < 8 for responders and > 15 for non-responders in the MADRS, 45 out of a total of 119 patients were considered responders and 32 non-responders.

No association was found between APOE genotype and treatment response to ECT. APOE alleles ε2, ε3, and ε4 were equally distributed between responders and non-responders ($p=0.23$, $p=0.64$, and $p=0.69$ respectively). However, in non-psychotic patients ε2 allele tended to be more frequent in responders (5/26) than in non-responders (0/18) ($p=0.07$).

APOE alleles ε2, ε3, and ε4 were equally distributed between patients and controls ($p=0.15$, $p=0.60$, and $p=0.60$) respectively. However, in men ε3 allele was more frequent in patients than in controls ($p=0.03$). In women, ε4 allele tended to be more frequent in patients vs. controls ($p=0.09$).

An earlier onset of depression was observed in the patients with ε4 allele, but only in the late onset depression group ($p=0.0495$). In the whole group there was no association between the APOE genotypes and the change of the MMSE scores during ECT ($p=0.16$). In women, however, there was a trend for APOE ε4 alleles to increase dose-dependently (groups having 0, 1 or 2 ε4 alleles respectively) the risk of lowered MMSE score ($p=0.06$). In addition, in women APOE ε2 allele was associated with better or equal MMSE scores after the treatment course than at baseline ($p=0.04$).

4.2 Outcome of elderly patients with MDD (II)

4.2.1 *Acute efficacy*

When elderly patients with MDD were treated even with ECT or with antidepressants the MADRS total scores diminished during index hospitalization treatment within both groups: from 31.6±8.5 (mean±SD) to 8.1±6.0 in the ECT group ($p<0.001$), and from 28.5±5.4 to 13.4±10.6 in the ADT group ($p<0.001$). There was no significant difference in MADRS scores between the groups at admission. At discharge, however, this difference was significant ($p=0.02$). Accordingly BDI scores decreased from 29.4±10.3 to 10.6±9.9 in the ECT group ($p<0.001$) and from 28.9±6.6 to 17.1±14.1 in the ADT group ($p=0.003$).

At admission, according to CGI, the patients in the ECT group were more severely ill than patients in the ADT group ($p=0.002$). After treatment 26 out of 30 patients in the ECT group and 11 out of 21 patients in the ADT group were much or very much improved according to the CGI change scale ($p=0.007$).

MMSE scores diminished in the ECT group from 27.2±2.0 to 26.3±3.6 and increased in the ADT group from 27.7±1.8 to 28.7±1.5; the difference between the groups at discharge was significant ($p=0.01$).

4.2.2 *Outcome in 12-month follow-up*

Twenty-one out of a total 51 patients were rehospitalized. Four patients died (2 in each group) during the 12-month follow-up. Five patients (3 in the ECT group and 2 in the ADT group) declined to undergo the follow-up assessment. Thus, in total 21 patients were followed up for 12 months: 12 in the ECT group and 9 in the ADT group.

Thirteen out of 30 patients (43%) in the ECT group and 8 of 21 patients (38%) in the ADT group were rehospitalized during the follow-up (p=0.71). Six out of 13 patients in the ECT group and 1 out of 8 patients in the ADT group were rehospitalized during the first month after discharge. The mean time before rehospitalization was 8.33 (95% CI: 6.68-9.98) months for the ECT group and 9.14 (95% CI: 7.40-10.89) months for the ADT group (p=0.67). Hospitalization during the 12 months before the index episode significantly predicted rehospitalization (Odds ratio 4.00, 95% CI: 1.09-14.73, p=0.04).

There was a significant increase in the MMSE scores in the ECT group from discharge to 12-month assessment (p<0.001). In the ADT group there was no significant change in the MMSE scores. No differences were found within the ECT or within the ADT group in functional capacity and the quality of life assessments between discharge and 12-month follow-up (Study II, Table 3). At discharge the IADL scores were better in the ECT group compared to the ADT group (p=0.05). After 12-month follow-up there were no differences in any assessments of functional capacity or the quality of life between the groups (Study II, Table 3).

4.3 Outcome in patients with concomitant MDD and fibromyalgia (III)

4.3.1 *Acute efficacy*

There was a significant improvement in MADRS and in those FIQ items, which may reflect mood i.e., "feel good", "fatigue", "anxiety" and "depression" (Table 3). The MADRS total score diminished from 27.17±5.01 (mean±SD) to 13.17±10.54 (p<0.001**).** According the CGI, six out of 13 patients were "much or very much improved", four patients "minimally improved", while there were three "no change" patients. There was no significant change in the number of tender-point count and in the daily self-reported pain score (Table 3).

Table 3. Acute efficacy and the outcome of three-month follow-up to ECT of patients with concomitant MDD and fibromyalgia (Study III)

	Baseline mean ± SD	One week after ECT mean ± SD	Three months after ECT mean ± SD
MADRS (0-60)	26.17±5.01	13.17±10.54 (p<0.001)	15.85±(p=0.19)*
Self-reported pain (0-5)	3.13±0.49	3.00±1.24 (p=0.73)	3.40±1.24
Tender points	15.83±2.33	15.08±2.79 (p=0.19)	14.7±3.57
FIQ:			
Physical function (0-3)	1.43±0.80	1.43±0.54 (p=0.98)	1.41±0.64
Feel good (0-7)	1.09±0.95	2.27±1.79 (p=0.007)	2.29±2.20 (p=0.85)*
Pain (0-10)	8.96±1.06	8.25±2.01 (p=0.81)	8.14±2.98
Fatigue (0-10)	8.17±2.02	6.17±2.36 (p=0.04)	5.62±2.89 (p=0.67)*
Morning tiredness (0-10)	7.71±2.17	6.46±2.56 (p=0.15)	6.96±2.67
Stiffness (0-10)	7.38±1.61	6.46±2.56 (p=0.26)	6.54±2.95
Anxiety (0-10)	8.08±2.08	5.42±3.12 (p=0.02)	5.73±3.07 (p=0.90)*
Depression (0-10)	7.67±1.96	5.42±3.04 (p=0.03)	5.27±3.37 (p=0.79)*

MADRS; Montgomery and Åsberg Depression Rating Scale
FIQ; Fibromyalgia Impact Questionnaire.
* = p value between one week and tree months after ECT

4.3.2 *Outcome in 3-month follow-up*

There was no change during the three-month follow-up in those parameters which had improved after ECT: MADRS and FIQ items "feel good", "fatigue", "anxiety" and "depression" (Table 3).

4.4 Cardiac arrhythmias induced by ECT (IV)

The numbers of ventricular arrhythmias are presented in Table 4. There was a significant increase in the incidence of bigeminy/trigeminy (p=0.02), but not in the other VES variables in the 24-hour post-ECT recording when compared with the pre-ECT recording (p=0.22). There were no differences in ventricular arrhythmias between 1 hour post-ECT and pre-ECT recordings (p=0.18). Supraventricular tachycardias (SVTs) were more common in the post-ECT than in the pre-ECT 24-hour Holter analysis (p=0.004) (Table 4). There was no significant difference in the incidence of SVTs between the 1hour period after and before the ECT (p=0.16). In

supraventricular extrasystoles (SVES) no differences were found between the post-ECT and pre-ECT recordings at either 24-hour or 1-hour intervals (Table 4).

Nine patients had an ST change of more than 1 mm, and five of them had an ST change of more than 2 mm in the 1 hour post-ECT recording. Only two of them, however, reached their maximal ST change during the first hour after treatment.

Table 4. Number of cardiac arrhythmias before and after ECT (patients, n=26)

	24 hours before ECT				24 hours after ECT				One hour before ECT				One hour after ECT			
	Median	Range	n	%	Median	Range	n	%	Median	Range	n	%	Median	Range	n	%
BiTri	0.0	1-142	3	12	0.0	1-267*	8	31	0.0	25	1	4	0.0	1-12	4	15
VES	10.0	1-7055	22	85	22	1-9102	22	85	1.5	0-470	15	58	1.5	1-386	16	62
VT	0.0	1	2	8	0.0	1-4	4	15	0.0	1	1	4	0			
SVES	35.5	3-816	26	100	40.5	3-1274	25	96	1.5	1-68	17	65	2.5	1-93	18	69
SVT	1.0	1-4	15	58	2.0	1-25**	17	65	0.0	1	1	4	0.0	1-6	4	15

n = number of patients

(%) = percent of patients

BiTri; Bigeminy/Trigeminy

VES; Ventricular extrasystoles

VT; Ventricular tachycardia

SVES; Supraventricular extrasystoles

SVT; Supraventricular tachycardias

* p=0.02

** p=0.004

5 Discussion

5.1 Main findings

According to the present results APOE polymorphism was not associated with the treatment response to ECT in major depression. Elderly patients with MDD had a good acute response to ECT, however, relapses were frequent. ECT was also effective in the treatment of depressive symptoms of the patients with concomitant MDD and FM, but had no effect on their pain symptoms. In addition ECT increased the frequency of bigeminy/trigeminy and supraventricular tachycardia and caused ST changes.

5.2 Study populations

The patients in the present studies included a representative sample of patients with a depression severe enough to warrant ECT. More than 40% of the whole population had psychotic features and as many even comorbid physical diseases. All the patients, except for 10 outpatients in Study III, were hospitalized for severe acute MDD (and five for MDE of bipolar disorder in Study IV). All of the patients who fulfilled the actual inclusion criteria and agreed to participate gave their written consent. Only few patients declined. The excellent compliance of the patients may partly be based on careful patient selection. In Study IV five patients were excluded because of technical problems with the Holter recording.

All the patients in these studies were clinically carefully assessed. Most of them (except those in Study III) were severely depressed and the reason for ECT in all cases was treatment resistance to antidepressants.

5.3 Study methods

General evaluation of outcome for all the study population was performed according to the recommendations of APA (1990, 2001).

5.3.1 *ECT treatment*

BL ECT was chosen because this method is considered to be the most effective strategy even though it may induce cognitive disturbances more than would RUL ECT. However, it has been shown that these cognitive dysfunctions are reversible (Calev et al. 1991b, Sackeim et al. 1993, McCall et al. 2002) and that patients with poor response are more likely to report subjective memory deficit after ECT than patients with a good response (Prudic et al. 2000). It has even been suggested that there is no justification for favoring RUL ECT over BL ECT when treating depressive patients (Fink et al. 2001). In addition, earlier rehospitalizations in patients treated with RUL ECT compared to those with BL ECT have been reported (Little et al. 2004). In Study III the RUL ECT was used because most of these patients were younger outpatients and less depressed than the patients in the other studies. Prejudice against the cognitive side-effects of ECT may have influenced the recruitment of patients in this study.

The initial stimulus dosage was adjusted with the age method (Swartz and Abrams 1996) for all patients in Studies II and III. In Study I the initial stimulus dosage was adjusted with the age method for 30 patients and with the stimulus titration procedure (Sackeim et al. 1987, Sackeim et al. 1993) for 89 patients. In Study IV the age method was used in 18 patients and the stimulus titration in 8 patients.

The dose titration method has been recommended because it is the most precise method for the individual selection of ECT stimulus dose relative to the ST (Sackeim et al. 1987, Heikman

et al. 1999, APA 2001). The antidepressive effect of RUL ECT increases when the stimulus dosage is increased in relation to the seizure threshold. However, the optimal dosage level may still be unknown (Fink et al. 2001, Abrams 2002). However, the value of the dose-titration method has also been criticized (Abrams 2002) and some practitioners still prefer the pre-selected stimulus dose method (Petrides and Fink 1996, Swartz and Abrams 1996). The Thymatron DGx ECT device user's manual recommends a preselected dosing strategy based on the age of the patient in which the dose (percentage of energy which is equal to the percentage of maximum output charge) is adjusted according to the patient's age in decades (Swartz and Abrams 1996). However, it is a relatively rough method and some patients may thereby receive a too low or a markedly suprathreshold stimulus dose. On the other hand, the dose-titration method requires multiple stimulations, which may increase the risk of cardiovascular adverse events, such as bradyarrhythmias and even asystole (Petrides and Fink 1996, Burd and Kettl 1998). In the present series of studies most of the patients were elderly with various somatic diseases, including cardiovascular disease, and therefore the age method was chosen for some studies (II, III) and patients (I, IV).

5.3.2 *Rating scales used in the present studies*

The MADRS was chosen because it has been approved as a reliable and valid instrument to evaluate the severity and the change of depressive symptoms (Davidson et al. 1986). The sensitivity and specifity of the MADRS has been found to be good and it has been considered as a suitable instrument even in the trials of management of older depressive patients (Mottram et al. 2000). The BDI is a widely used self-administered scale in simple language and easy to score **(**Yonkers and Samson 2000).

CGI is widely used in psychopharmacological clinical trials. It allows the clinician to rate the severity of illness, the change over time and the efficacy of treatment. It is a rough but simple and fast measure (Leon et al. 1993).

MMSE is a brief easily administered cognitive status examination. It is widely used in clinical practice and in studies. MMSE has been shown to be sensitive in assessing the severity of cognitive impairment and changes occurring over time. The sensitivity of this scale may still not be high enough for detecting the minor changes in cognition (Tombaugh and McIntyre 1992).

Functional capacity (Study II) was assessed with the ADL and the IADL. The ADL is intended to assess selfcare functions in chronically ill and aging populations. Because it attains only the lower end of selfcare function, it may not be sensitive when functioning is normal or nearly normal (Rubin et al. 1993). The IADL measures performance on everyday tasks instrumental living in the community (Lehman et al. 2000).

The Q-Les-Q is a quality of life instrument that has been shown to be sensitive to change following the treatment for depression. It has been approved as reliable and valid in its psychometric properties (Ferrans and Powers 1992). The LSS-A is a 26-item scale developed to assess life satisfaction in elderly Finnish people. It is easy to use and a reliable and valid scale for measuring life satisfaction (Salokangas et al. 1988).

The Fibromyalgia Impact Questionnaire (FIQ) was designed to evaluate physical functioning ability and was used to evaluate the severity and change of the FM symptoms (Study

III). It has been proven to be a reliable and valid instrument in both research and clinical situations (Burckhardt et al. 1991).

5.3.3 *APOE genotyping*

The 5' nuclease assay has been successfully used to discriminate alleles that differ by a single base substitution (Livak 1999). TaqMan assays allow for fast and sensitive genotyping and are especially suitable for studies including large numbers of participants (Koch et al. 2002). A standard method of analysis has been developed that enables automated genotype determination. Applications of this assay have included typing a number of polymorphisms e.g. in human drug metabolism genes (Livak 1999).

5.3.4 *Holter monitoring*

Most of the arrhythmias induced by ECT have been reported to occur during the ictal and briefly post-ictal period **(**Zielinski et al. 1993, Zvara et al. 1997). However, even delayed arrhythmias are possible. Holter monitoring enables a continuous long lasting recording of heart rhythm during normal activity. It is a reliable method for determining cardiac arrhythmias and ST-segment changes.

5.4 Apolipoprotein E polymorphism is not associated with response to ECT (I)

APOE has been found to be a major risk factor of Alzheimer's disease (Strittmatter et al. 1993), and may be associated with cerebrovascular diseases (Lavretsky et al. 2000). The polymorphism of APOE has been previously connected to response of antidepressants (Murphy et al. 2003) and ECT (Fisman et al. 2001).

In the present study no association was found between APOE genotype and the treatment response to ECT according to MADRS. APOE alleles ε2, ε3, and ε4 were equally distributed between responders and non-responders. Thus, the findings of Fisman et al. (2001) that the patients with ε4 allele were more likely to respond to ECT in late-onset depression than patients with other genotypes could not be replicated here. In the present study the definition of response to ECT was stricter (responders < 8 and nonresponders > 15) than in the study by Fisman et al. (2001) who used only one cut-off point (10) in the MADRS defining response or non-response. Even when further analysing the data using the same cut-off point as Fisman, no significant association was found in the present study group (data not shown).

Moreover, no difference was found in APOE allele distribution between the present patients and controls. In men, however, ε3 allele was more frequent in patients than in controls. In women, ε4 allele tended to be more frequent in patients vs. controls. The clinical significance of these findings is obscure. In some studies the increased APOE ε4 allele frequency has been associated with late-life depression (Krishnan et al. 1996, Zubenko et al. 1996, Rigaud et al. 2001).

In the present study earlier onset of depression was found in the patients with ε4 allele than patients without this allele, but only in patients with late-onset depression. An earlier onset of depression in ε4 carriers has also been reported by Lavretsky et al. (2000) and Butters et al. (2003). The latter also found that age at onset of late-life depression was significantly reduced in APOE ε4 carriers, which is in line with the present findings. In contrast, Fisman and others (2001) found a trend towards later onset of depression in patients with ε4 allele. This finding may be difficult to interpret, but the overall study group was small and the ε4 infrequent.

In the whole group there was no association between the APOE genotypes and the change of the MMSE scores during ECT. However, in the present group of women, APOE ε2 could be protective against cognitive impairment, whereas APOE ε4 may increase the risk of cognitive impairment. These findings, however, are preliminary and should be replicated before further conclusions are drawn.

5.5 ECT is effective in acute treatment of elderly patients with MDD, but relapses are common (II)

5.5.1 *Acute efficacy*

Acute efficacy of ECT and antidepressive therapy in elderly patients with MDD was good. In the present study the acute efficacy in the ECT group was clearly better than in the ADT group, despite the fact that the patients in the ECT group may have been more severely ill than those in the ADT group. The acute efficacy of ECT in late-life depression has been shown in several previous studies (Mulsant et al. 1991, Black et al. 1993, Flint and Rifat 1998, O'Connor et al. 2001, Petrides et al. 2001) which are thus in line with the present findings.

In the ECT group there seemed to be a higher proportion (10/30) of patients with psychotic depression than in the ADT group (3/21). The present results might be in line with the previous ones, where psychotic depressions have responded to ECT even better than nonpsychotic depression (Petrides et al. 2001, Birkenhager et al. 2003, Kho et al. 2003). Many practitioners consider ECT to be a first-line treatment in psychotic major depression in the elderly (Alexopoulos et al. 2004).

The MMSE scores decreased in the ECT group and rose in the ADT group. Thus, at disharge the MMSE scores were higher in the ADT group than in the ECT group. This is in line

with the previous reports where the cognitive adverse effects induced by ECT have been common (Sackeim et al. 1993, McCall et al. 2002).

5.5.2 *Long-term outcome*

In the present study the 1-year rehospitalization rate of the patients was relatively high in both groups (around 40%), but there were no significant differences between the groups. According to earlier follow-up studies the risk of relapse is associated with residual symptoms i.e. partial remission (Pintor et al. 2003, Steffens et al. 2003a, Pintor et al. 2004). Pintor et al. (2003) reported that 68% of patients with partial remission after ADT relapsed during 24-month follow-up, whereas only 15% of patients with complete remission. In the present study groups, however, the relapse rates were similar despite the fact that the patients in the ADT group had more depressive symptoms than those in the ECT group at disharge (MADRS 13.4 vs. 8.1). In the ADT group the patients continued to have the same medication which was originally effective in acute treatment in contrast to patients in the ECT group where the continuation ECT was not used.

A high relapse rate after successful ECT has been demonstrated in several clinical trials and patients given ECT in a community setting (Sackeim et al. 2000, Sackeim et al. 2001, Prudic et al. 2004). In a study by Sackeim et al. (2000) 53% patients with MDE responding to ECT relapsed within one year, 94% of the relapses occurred during the first 6 months. Birkenhager et al. (2004) reported a 6-month relapse rate of 28% and 12-month relapse rate of 41%. Prudic et al. (2004) reported that 64.3% of the patients given ECT in a community setting had relapsed within 24-week after ECT. Stoudemire and others (1991) found that 28% of ECT treated patients and 25% of ADT treated patients were rehospitalized within 1 year. Psychopharmacological treatment (and in some cases even continuation ECT) is essential to prevent early relapses after

ECT. Sackeim et al. (2001) found that 84% of patients had relapsed within six months when treated with placebo after ECT. Grunhaus et al. (2001) reported that 28.5% of patients relapsed within 3 months after a successful course of ECT despite subsequent pharmacotherapy with fluoxetine. The findings in the present study replicate the previous reports showing a high relapse rate in patients with MDD treated with ECT and/or antidepressant therapy. However, the relapse rate may be still underestimated in this study because of the strict definition of relapse judged by readmission.

There was a significant increase in the MMSE scores in the ECT group from disharge up to 12-month assessment in the present study. In 12 months the MMSE scores exceeded the baseline scores. This finding is in accordance with earlier studies (Calev et al.1991b, Sackeim et al. 1993, McCall et al. 2002). There were no significant changes between disharge and 12-month follow-up in the depression rating scales, functional capacity assessment or quality of life assessment within either the ECT or the ADT group. Moreover, there were no significant differences in these clinical variables between the groups at the 12-month assessment.

5.6 Depression but not pain symptoms improved by ECT in patients with concomitant MDD and fibromyalgia (III)

In patients who had concomitant MDD and FM there was a significant improvement after ECT in depressive symptoms. However, no change was found in pain related FIQ items, self-reported pain severity and tender-point count. The improvement in those parameters with a statistically significant change after ECT (MADRS and FIQ items, "feel good", "fatigue", "anxiety" and "depression") was maintained for the whole follow-up period of three months. These findings are in line with previous suggestions that depression is independent of the pain symptoms of FM. Okifuji et al. (2000) found that there were no differences in severity of pain, number of positive

tender points, and pain intensity of tender points in 39 depressive and 30 nondepressive FM patients. Thus, the authors suggest that improvement of depression does not lead directly to improvement of pain.

The prognosis of FM has been reported to be poor (Henriksson 1994, Wolfe et al. 1997). In a 7-year follow-up by Wolfe et al. (1997) it was found that the symptoms of FM did not change over time. The illness in the present patients also tented to be chronic. The mean duration of FM had been 6.1 years. All the patients had several previous or present antidepressant medications during their illness.

It has been shown that antidepressants are moderately effective in FM symptoms (O'Malley et al. 2000, Goldenberg et al. 2004, Samborski et al. 2004). The best symptomatic benefits are reported in fatigue, sleep and overall well-being as well as in pain severity (O'Malley et al. 2000). In the present patients fatigue and well-being also improved, but no change in pain was noted. The present finding of no change in trigger-point tenderness but improvement in depression is in line with some reports where antidepressants relieved depression but had no effect on trigger points (Nicassio et al. 2000, Arnold et al. 2002).

The PET studies have shown decreased CBF in thalamus in patients with chronic neuropathic pain (Di Piero et al. 1991, Iadarola et al. 1995). Di Piero et al. (1991) concluded that chronic pain results in a decrease of synaptic activity in the thalamus. Fukui et al. (2002) investigated the mechanism of the analgesic effect of ECT in patients with CRPS. They found in a Single-Photon Emission Tomography that patients with CRPS had reduced ipsilateral regional CBF in the thalamus and pain relief after ECT was associated with increase of regional CBF.

The authors suggested that the analgesic efficacy of ECT in chronic pain is related to the normalization of the balance of regional cerebral blood flow in the thalamus.

In the abovementioned study by Fukui et al. (2002) BL ECT was used. It has been speculated that BL ECT may be more effective than RUL ECT in chronic pain (King and Nuss 1993, McDaniel 2003). Electrode placement may thus partly explain the lack of efficacy of ECT on pain symptoms in the present study. The patients were treated with RUL ECT to avoid cognitive adverse effects. The number of treatments was 8 in 11 patients, 7 in one patient and 3 in one patient. Because the primary reason for ECT was depression and not the symptoms of FM, ECT was continued until depression had been relieved or the patient had received at least 8 treatments without any further improvement being observed during the past 2 treatments. It is unknown if an increase in the number of treatments would have improved the efficacy in pain relief.

5.7 ECT increases cardiac arrhythmias in patients with pre-existing arrhythmias (IV)

In this study, the influence of ECT on the incidence of arrhythmias and ST changes was observed in elderly depressed inpatients using a 24-hour pre- and post-ECT Holter recording. The major finding was an increased incidence of bigeminy/trigeminy and SVTs in the 24-hour post-ECT recording when compared with the pre-ECT recording. Interestingly, this increase was not found between 1-hour post-and pre-ECT recordings.

There are only a few previous studies using long-time Holter monitoring to investigate cardiac arrhythmias induced by ECT (Troup et al. 1978, Zvara et al. 1997, Rumi et al. 2002). Troup et al. (1978) performed a 24-hour Holter monitoring in young and middle-aged physically

healthy patients before, during and after ECT. They found no significant difference in the frequency of premature ventricular or supraventricular contractions between the pre- and post-ECT recordings. Rumi et al. (2002) performed a 24-hour Holter recording in 47 young patients without cardiac disease. They found some isolated VES and SVES, but not other arrhythmias. Zvara et al. (1997) performed Holter monitoring in 19 elderly patients for at least 2 hours after two ECT sessions. They found a high incidence of ST-segment depression and premature ventricular contractions during ECT and postictal period. In a recent study by Rasmussen et al. (2004) no significant differences were found in ventricular or supraventricular arrhythmias in medically healthy patients between post- and pre-ECT Holter recordings. However, their 3-hour pre- ECT recordings were performed a day before ECT and 3-hour post-ECT recordings from several hours up to 3 days after ECT. Obvious differences in the results compared to the present ones may be due to different patient population and schedule.

Arrhythmias associated with ECT are relatively common findings, most of them being premature atrial and ventricular contractions (Troup et al. 1978, Gerring and Shields 1982, Mokriski et al. 1992, Zvara et al. 1997, McCully et al. 2003). In the present study it was also found that pre-existing arrhythmias predict the development of post-ECT arrhythmias, which is in line with several previous studies (Gerring and Shields 1982, Dec et al. 1985, Zielinski et al. 1993).

In contrast to the studies by Troup et al. (1978) and Rumi et al. (2002), an increase of some ventricular and supraventricular arrhythmias was found after ECT in the present study. The patients in the present study were old and physically ill, whereas the patients in the above mentioned studies were young or middle-aged and physically healthy.

Consistent with earlier findings (Zielinski et al. 1993, Zvara et al. 1997, Rumi et al. 2002), a high incidence (in nine out of 26 patients) of ST changes after ECT was found in the present study. Only two of these patients with ST changes had a pre-existing cardiovascular disease (one hypertension and one had a ischemic heart disease). The cardiac effects of ECT may be a direct consequence of hypoxia during seizure, or a disturbance in central regulation (Mokriski et al. 1992, Robinson and Lighthall 2004). The clinical significance of ECT related cardiac side-effects depends on their quality as well as on the age and possible concomitant diseases of the patient.

5.8 Limitations of the study

Several limitations of the present studies should be noted. The main limitation in all the present studies was relatively small sample size. In Study I the original number of patients was moderate. However, in subanalyses the groups were small, which may increase the risk of false negative findings (type II error). In Study II the initial number of patients in each treatment group was reasonable enough, but during the follow-up there were some drop-outs. In Study III it was more difficult than expected to recruit patients and the final number remained relatively small. However, there were no drop-outs during the whole study period. In Study IV the Holter recording failed for five patients who could therefore not be included in the analyses.

Another limitation of these studies was also that no formal structural clinical interview for DSM-IV (SCID) was used and that the diagnostic interviews were conducted by only one clinician. Moreover, the outcome evaluations were not blinded.

In addition, in Study II the patients were not randomly assigned to ECT and ADT groups, which may have caused a selection bias. In the ECT group the patients were slightly more

severely depressed than in the ADT group. Thus the comparison between the groups may be questionable. Another confounding factor is that the responders in the ECT group in follow-up were switched to the antidepressant drug treatment, which had not previously helped them, whereas in responders to pharmacotherapy the effective treatment was continued. Moreover, a limitation in Study II was that the functional capacity assessments and the quality of life evaluations were not performed at baseline and thus the effect of treatments in the index episode could not been evaluated.

In Study III patients were given max. 8 RUL ECT. On the basis of the present study procedure it is not possible to estimate whether BL ECT or a large number of treatments would have been more efficacious for pain symptoms.

One limitation is also the variability in stimulus dosing strategy, age method versus dose titration method, in Studies I and IV. Other limitations in Study IV were that the affects of cardiovascular or other physical diseases, as well as medications could not be evaluated because of small subgroups. Moreover, the limitation in this study was that anesthesia was induced either with methohexital or with propofol, because of the unavailability of methohexital at that time. Because the patients were not randomised concerning to the anesthetics, no comparison was made.

6 Summary

The main findings of the study were:

Study I

APO-E polymorphism was not associated with the treatment response to ECT in major depression.

Study II

Elderly patients with MDD had a good acute response to both ECT and ADT. Relapses, however, were frequent in both groups and many of them occurred soon after discharge.

Study III

ECT is an effective treatment in depression of patients with MDD and concomitant FM.
However, it has no effect on the pain symptoms of these patients.

Study IV

ECT caused a significant increase in bigeminy/trigeminy and supraventricular tachycardia in elderly patients. Pre-ECT arrhythmias predicted post-ECT arrhythmias. Moreover, ECT caused ST changes in some patients. Although arrhythmias were common all the patients completed the ECT course.

7 Conclusions and future implications

In accordance with earlier reports the present results indicate that ECT is an effective treatment method in elderly patients with MDD. In spite of continuation pharmacotherapy relapses were common and in many patients occurred soon after treatment. The high relapse rate emphasizes the need for careful follow-up of elderly patients who have recovered from a depressive episode. In some cases the continuation ECT should also be considered to prevent early relapses.

ECT is a safe treatment even in elderly patients with somatic illness, although it may increase the risk of some cardiac arrhythmias. Arrhythmias caused by ECT are usually clinically inconsequential and do not obstruct the course of ECT. However, especially in elderly patients, the cardiovascular status should be carefully assessed before ECT.

There is only little data of the effectiveness of ECT in certain special groups such as pain patients. Especially patients suffering from FM often also have depressive symptoms in addition to pain and other somatic symptoms. According to the present study ECT is an effective treatment of depression in these patients, but it has no effect on their pain symptoms. However, on the basis of some reports, studies on the effectiveness of the ECT in pain patients should be continued.

According to the present study the APOE polymorphism is not associated with the response to ECT in MDD. In spite of this, studies on connections between genetics and treatment response to ECT should be continued in order to find the possible genetic polymorphisms, which may predict the response. Our group continues to study other gene polymorphisms which may be associated with the outcome of ECT.

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