Electroconvulsive therapy for depression
Till min familj
Electroconvulsive therapy for depression
Abstract


Aim: The overarching aims of the thesis were to identify clinical characteristics that predict the outcomes of depressed patients treated in clinical practice by ECT, and to elucidate the effectiveness of continuation ECT at preventing relapses and recurrences.

Methods: The studies included a retrospective chart review, three studies based on a quality register for ECT, and a randomized controlled trial (RCT) examining the effectiveness of continued ECT.

Results: The overall response rate to ECT was 80%. Patients with psychotic depression (89%), older patients (84%), and inpatients (83%) had the highest response rates. Patients with personality disorders (66%) and outpatients (66%) had the lowest response rates. With regard to patients on sick leave, 59%, 71% and 88% of patients regained occupational functioning 6, 12 and 24 months after ECT, respectively.

The rate of hospitalisation after ECT was high, with rates of 25%, 34% and 44% 6, 12 and 24 months after ECT, respectively. The relapse rate was higher in patients that were taking benzodiazepines and lower in patients that were taking lithium.

The relapse rate was significantly lower in patients treated with continued ECT in combination with pharmacotherapy (32%) than in those treated with pharmacotherapy alone (61%). This difference was particularly pronounced in medication-resistant patients (31% vs. 85%)

Conclusions: The short-term response rate to ECT is relatively high in all patient subgroups, and is particularly high in older patients, inpatients and patients with severe depression. Patients often regain occupational functioning after ECT; however, this takes a considerably longer time than that required for symptom relief. Nevertheless, the relapse and recurrence rates of patients are high in the years after ECT. Continuation ECT and lithium treatment can be combined with antidepressants to reduce the risk of relapse and recurrence. Further RCTs are required to define the indications for continuation ECT and lithium treatment.

Keywords: Electroconvulsive therapy; Mood disorders; Depressive disorder, major; Bipolar disorder; Treatment outcome; Recurrence

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LIST OF PAPERS

This thesis is based on the following original papers:


The indicated Roman numerals are used throughout the text to reference these studies. Reprints were made with the permission of the publishers.
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LIST OF ABBREVIATIONS

ADAS-cog The cognitive subscale of the Alzheimer's Disease Assessment Scale

APA American Psychiatric Association

cECT Continuation ECT

CGI-I Clinical Global Impression-Improvement

DSM-IV TR Diagnostic and Statistical manual of Mental disorders IV edition Text Revision

ECT Electroconvulsive Therapy

EEG Electroencephalography

HDQ Hospital Day Quotient

ICD-10 International Classifications of Diseases 10th edition

MADRS Montgomery Åsberg Depression Rating Scale

MINI Mini-International Neuropsychiatric Interview

MMSE Mini–Mental State Examination

NICE National Institute for Clinical Excellence

SD Standard Deviation

SNRI Serotonin Nor-epinephrine Reuptake Inhibitor

SSRI Selective Serotonin Reuptake Inhibitor

UKU Utvalg for Kliniske UndersØgelser
## LIST OF ABBREVIATIONS

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<td>CGI-I</td>
<td>Clinical Global Impression-Improvement</td>
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<tr>
<td>DSM-IV TR</td>
<td>Diagnostic and Statistical manual of Mental disorders IV edition Text Revision</td>
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<tr>
<td>ECT</td>
<td>Electroconvulsive Therapy</td>
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<td>EEG</td>
<td>Electroencephalography</td>
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<tr>
<td>HDQ</td>
<td>Hospital Day Quotient</td>
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<td>ICD-10</td>
<td>International Classifications of Diseases 10th edition</td>
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<tr>
<td>MADRS</td>
<td>Montgomery Asberg Depression Rating Scale</td>
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<td>MINI</td>
<td>Mini-International Neuropsychiatric Interview</td>
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<td>MMSE</td>
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DEFINITIONS

Continuation ECT: Weekly or monthly ECT sessions used to maintain the benefits from the index ECT series. Sometimes the term maintenance ECT is used to describe continuation ECT that occurs for longer than six months. However, in this thesis, the term continuation ECT is used even when the period extends beyond six months.

Hospital Day Quotient (HDQ): The total number of days spent in hospital (HD) divided by product of the number of patients (P) and the number of days in the period investigated (Dp) and then multiplied by 365.

\[ \text{HDQ} = \frac{\text{HD}}{\text{P} \times \text{Dp}} \times 365 \]

Index ECT: An acute series of ECT that is usually administered two or three times per week. Daily treatments are occasionally used for very severe cases. The treatment is prolonged until remission or until further benefits are unlikely.

Non-response was defined as Clinical Global Impression-Improvement score of greater than 2 (much improved). This included patients that were minimally improved, were not changed, or worsened, and was assessed within one week after ECT.

Outpatients: Patients who had at least one ECT session administered in an outpatient setting. Thus, if the treatment was initiated in an inpatient setting and continued in an outpatient setting, the patient was considered to be an outpatient in the statistical analyses.

Pharmacotherapy resistant patients: Patients who did not improve during two adequate trials of different classes of antidepressants during an episode of depression (122).

Relapse: In study III, relapse was defined as a score of 20 or more on the Montgomery Åsberg Depression Rating Scale, or hospitalisation, or suspected suicide, or suicide. In study II, hospitalisation or committed suicide was used as a proxy for relapse.

Recurrence: Symptoms reoccurred after a period of at least six months of remission.
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Recurrence: Symptoms reoccurred after a period of at least six months of remission.
Remission: A score of 10 or less on the Montgomery Åsberg Depression Rating Scale.

Response: A common definition of response is a 50% reduction in a rating scale of depression. However, in the empirical studies presented in this thesis, response was defined as having a Clinical Global Impression-Improvement score of 1 or 2 (very much improved or much improved) within one week of ECT.

Severity of depression: Assessed by the physician in charge according to ICD-10 as mild/moderate, severe without psychosis, or severe with psychosis. A corresponding severity classification was used for patients with schizoaffective disorders, depressed type.

Voluntary/involuntary hospital admission: Assessed based on the legal status of the patient. (In Sweden, verbal consent to ECT is standard but the psychiatrist in charge can arrange for ECT without consent during involuntary care. Some voluntarily hospitalised patients may recognise that they are required to accept ECT or else they risk involuntary care. Some involuntarily hospitalised patients may consent to ECT.)
INTRODUCTION

I would like to share a personal anecdote that contributed to my continuing interest in electroconvulsive therapy (ECT). One of the patients I met early during my time in the psychosis department had been in compulsory inpatient care for more than one year. The patient did not speak, laid on the floor for several hours each day with a pillow over her head and occasionally started shouting and waving her arms. She had an earlier diagnosis of bipolar disorder, but her current diagnosis was “psychosis”. Several hospitalisations had been necessary after lithium treatment had been terminated due to a reduction in renal capacity. In the previous year, antidepressant medications and intramuscular antipsychotics were administered, but the patient’s status was deteriorating. The situation became urgent when the patient stopped eating and drinking. ECT was recommended for psychotic depression with catatonia. The patient fiercely resisted and had to be escorted by four persons to the ECT treatment. After the first treatment, the patient was calm, started to eat and drink, and slept for more than twelve hours. The patient cooperated fully during the following treatments. Within two weeks she had completely recovered. Afterwards, the patient and her family were very grateful for the ECT and for being able to celebrate Christmas together.

While serving in the depression ward I became aware of the effectiveness of an acute series of ECT (index ECT), but also realised that many of the patients treated with index ECT were readmitted within a few months of discharge. There were discussions in the clinic about whether continuation of ECT after discharge (continuation ECT) would be effective at preventing relapse/recurrence. However, at that time there were no randomised studies into the efficacy of continuation ECT, and it was difficult to reach a consensus among psychiatrists about the use of continuation ECT.

This thesis is concerned with the patient characteristics that are related to the reduction of symptoms, relapse/recurrence and the return to occupational functioning after index ECT for major depression, and to the efficacy of continuation ECT combined with pharmacotherapy at preventing relapse/recurrence. A prospective randomised trial, three studies of data contained in the quality register for ECT and one chart review form the basis of this thesis, and the discussion is primarily focused on the clinical implications of the results.
BACKGROUND

The background section consists of two parts: a general introduction to depression and a review of ECT.

Mood disorders

Mood disorders are classified by both the World Health Organisation International Classifications of Diseases 10th edition (ICD 10) (170) and the Diagnostic and Statistical Manual of Mental Disorders IV Text Revision (DSM IV TR) (2) into the following main categories:

- Major depressive episode (the first episode in a lifetime);
- Recurrent depression (after at least one earlier lifetime episode);
- Bipolar disorder (if the clinical history also includes at least one manic or hypomanic episode);
- Schizoaffective disorder (if the patient has also had psychotic symptoms that are not related to an affective episode).

Depressive episode

A depressive episode can occur in any of these mood disorders. According to the DSM-IV TR, a major depressive episode is diagnosed if five or more of the following symptoms, including at least one of depressed mood or loss of interest or pleasure, occurred during the same two weeks period and represented a change from previous functioning:

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, nearly every day;
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day;
4. Insomnia or hypersomnia nearly every day;
5. Psychomotor agitation or retardation nearly every day;
6. Fatigue or loss of energy nearly every day;
7. Feelings of worthlessness or excessive or inappropriate guilt nearly every day;
8. Diminished ability to think or concentrate, or indecisiveness, (either by subjective account or as observed by others), nearly every day;
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7. Feelings of worthlessness or excessive or inappropriate guilt nearly every day;
8. Diminished ability to think or concentrate, or indecisiveness, (either by subjective account or as observed by others), nearly every day;
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;

There are four additional criteria for a major depressive episode:
- The symptoms do not meet criteria for a mixed episode;
- The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning;
- The symptoms are not due to the direct physiological effects of a substance or a general medical condition;
- The symptoms are not better accounted for by bereavement.

The definition according to ICD-10 is similar. A major depressive episode can be classified as mild, moderate, severe, or severe with psychosis. In the DSM IV-TR classification, the depressive episodes can be further subtyped into melancholic, catatonic, and atypical.

**Pathophysiology of depression**

The pathophysiology of depression is not fully understood. However, genetic factors, environmental factors, and the patient's own actions can contribute to depression (132). There is a genetic vulnerability to develop depression, especially bipolar depression (79) and to a lesser extent recurrent depression (155). Many genes are involved in regulating mood, and the mechanisms by which these different genes interact are currently being explored. Depression can be caused by a stressful life. However, most people are not depressed even though stressful events are common. Environmental factors in childhood are linked to depression (71, 113), and the abuse of alcohol, other substances, and certain medications can also increase the risk of depression (38). Protective factors for depression include physical activity and social support (132).

The biological systems that are affected in depression include neurotransmitters, stress hormones, and neuronal plasticity (10, 132). The monoamine hypothesis (65) suggests that transmission of monoamines is reduced in depression. Most currently available antidepressants were developed according to this hypothesis and function by inhibiting reuptake of serotonin and/or noradrenaline (152). The stress response is also abnormal in individuals with severe depression. Cortisol production is usually increased, the diurnal variations are reduced, and the feedback-mediated control of cortisol is disturbed (158). The turnover of brain cells is also linked to depres-
sion. In animal studies, antidepressant treatments such as ECT result in increased cell replication in areas thought to be important for emotional regulation such as the amygdala, hippocampus, gyrus cinguli, and prefrontal cortex (15, 74).

In addition, a patient’s actions in response to their symptoms can result in a downward spiral that increases the severity of the disease. For example, lack of interest and drive may contribute to low levels of engagement in normal daily activities, which in turn increases sad feelings that occur due to a reduction of pleasant and interesting tasks. The basis of Cognitive Behavioural Therapy (CBT) is to alleviate symptoms through changing the patient’s thinking and actions (9).

Epidemiology of depression
Depression entails suffering, work impairment and is a burden to kindred (132). Depression is a common disease. The one month prevalence of major depression is estimated to be between 1.5 and 3 % (119), and the one-year prevalence is estimated to be 8.6 % (60). Nearly half of all women and a quarter of all men suffer a depressive episode at some time in their life (120). This high prevalence makes depression one of the most common diseases and causes of handicap world-wide (166).

Course of depression
The prognosis for depression is often unfavourable. Symptoms persist for two years or more in up to 20 % of patients (55). Repeated relapses or chronicity occur in 70–80 % of patients, and approximately 10 % of affected individuals commit suicide (4). Thirty percent of patients who are treated as inpatients require re-hospitalisation within one year of discharge (50, 153). Greater numbers of depressive episodes tend to increase the risk of subsequent relapses or recurrences in patients with major depression (159), and larger numbers of remaining symptoms are correlated with increased risks of relapse or recurrence in several studies of patients treated with pharmacotherapies (92, 159). There is also evidence that patients with co-morbid conditions have an increased risk of relapse or recurrence (22, 49), and some studies associated the severity of depressive symptoms with increased risk of relapse or recurrence (78). Psychological therapies and prolonged pharmacotherapies may reduce the risk of symptom recurrence (132, 134). However, if the patient suffers more than one episode of depression, the risk of relapse and recurrence remains high even with treatment (27). Moreover, although effective treatments are available, a large proportion of patients with depression do not receive treatment (53). Fur-
thermore, compliance is poor as only about half of the patients who receive pharmacotherapies actually take the drugs as prescribed (143).

**Mortality in depression**

There is excess mortality among depressed patients, both in different diseases and in accidents (99, 121). The risk of suicide is 15–30 times higher in individuals with depression than in the normal population (99). Suicide also occurs in young patients. Therefore, depression-related suicide has a major impact on years of life lost. Most depression-related suicides occur in patients who are not adequately treated (39). The lifetime risk of committing suicide is about 15 % among patients who receive in-hospital treatment for depression (51). The depression-related suicide rate in Sweden has decreased in recent years in correlation with increased access to antidepressant medications (52). However, suicide remains one of the most frequent causes of death for both men and women aged 15–74 years in Sweden as more than 1 000 suicides occur annually (150). More than half of those who die from suicide suffer from depression (167, 172).

**Depression and co-morbidity**

It is common for patients with depression to also have other psychiatric disorders. Data from the United States indicate that the most common co-morbidities are anxiety disorders (57 %), alcohol-related disorders (25 %), and personality disorders (44 %) (58, 59). Common genetic pathophysiology may underlie the high co-morbidity of anxiety disorders and depression (14).

**Cognitive effects of depression**

Depressive disorders can also negatively affect cognitive functioning (43), especially during the symptomatic state (5). More specifically, there can be effects on concentration and memory storage. Severe forms of depression tend to have greater impacts on cognitive functioning and memory than less severe forms of depression (76). The disturbance often persists during euthymic phases (12), and a 10-year follow-up study found that the effects are long lasting (135). Cognitive impairments contribute to poor occupational functioning (25).

**Depression and occupational functioning**

Depression is one of the most frequent causes of poor occupational functioning. Depression accounts for more than 10 % of all compensated sick leave days in many countries, including Sweden (47, 162). A large proportion of the costs due to depression are related to poor occupational func-
tioning (144). Symptomatic improvements are related to improved occupational functioning (44), but it usually takes months to regain occupational functioning after symptoms decrease (82).

**Treatment of depression**

Pharmacotherapies and psychological therapies, especially Cognitive Behavioural Therapies, are effective treatments for mild and moderate depression (133, 134). About one-third of patients who are exposed to one of these treatments achieve remission, which means they become free of symptoms. Another one-third of the patients respond to treatments (often defined as a 50% reduction in symptom severity), but have some residual symptoms. The other one-third does not respond to treatments with durations of 6–12 weeks (33, 142). There are no major differences in the efficacies of different forms of treatments in mild and moderate depression, and some studies suggest that there are no significant differences between active medications and placebo treatments (32). However, in severe depression, active medications are markedly more effective than placebo, and ECT is more effective than pharmacotherapies (61, 165).

Pharmacotherapies are a common treatment for depression. In 2010, 757,000 patients were treated with antidepressants in Sweden (149). Selective serotonin reuptake inhibitors are most commonly used because they have relatively modest side effects, although adverse sexual effects are common (118). Other classes of antidepressant medications include serotonin noradrenaline reuptake inhibitors, tricyclic antidepressants, and monoamineoxidase inhibitors.

The recommended treatments for bipolar disorder also include lithium, lamotrigine, valproate, and antipsychotic agents (40). For some patients, lithium treatment can augment the effects of antidepressants, and some studies suggest that lithium has prophylactic effects on unipolar depression (6, 7). Some second-generation antipsychotics are effective for acute treatments of major depressive disorder (64), but few studies suggest that they effectively prevent relapse of major depressive disorder (16).
Electroconvulsive therapy

History of ECT
The early history of ECT is well described by Shorter (141). Briefly, doctors have known for hundreds of years that acute manic states can be terminated by epileptic seizures. In the 16th century, Paracelsus used camphor to induce seizures when treating mental disorders. However, the modern era of convulsive therapies can be traced to the 1930s and to the Hungarian psychiatrist Meduna. Meduna studied histological preparations from diseased patients and found that patients with epilepsy have a larger number of glial cells than patients with schizophrenia. Based on this observation, Meduna decided to treat schizophrenia with induced seizures. The first patient he treated was suffering from catatonia and had been ill for four years. Meduna used a series of camphor-induced seizures as a treatment, and the patient completely recovered. However, chemically induced seizures were difficult to control and were uncomfortable for the patient in the time interval before the seizure. Therefore, attention became focused on the usage of electrically induced seizures.

Following successful attempts in animals, Cerletti and Bini administered the first electroconvulsive treatment to a human in 1938. The patient was found in a psychotic state in a railway station and was then treated in a hospital without significant improvements. The doctors were unsure of the stimulus intensity necessary to induce seizures in humans, and the first electrical stimulus attempted was too low to induce a seizure. Nonetheless, after experiencing the first electric current the patient uttered, “not again, it’s murderous”. The second stimulus elicited a generalised seizure, and the patient recovered after a series of 11 treatments.

By the 1940s, electrically induced seizures were standard and pharmacologically induced seizures had been abandoned. ECT had been introduced to many parts of the world and was recognised as a valuable treatment for schizophrenia. Interestingly, the most prominent effects were seen in patients with mood disorders. However, vertebra fractures were a feared complication of ECT. In the 1940s, trials were conducted with curare in an attempt to reduce the fracture risk, but the problem was not solved until 1951 when the Swedish psychiatrist Holmberg and anaesthesiologist Thesleff introduced succinylcholine-modified ECT (48). This modified form of ECT used anaesthesia to help the patients tolerate the muscle-relaxant. ECT was then converted from an office-based procedure to a hospital-based procedure, which reduced the availability of the treatment.
In the 1960s, Ottosson performed a series of experimental studies of ECT (102). From the 1970s onward, Ottosson, d'Elia, and others pioneered research in many areas of ECT including the mode of action, electrode placement (21), technical aspects, the importance of the seizure quality, and cognitive effects (17, 20, 28, 98, 154, 163). To this day, treatments are being technically refined with the goal of reducing the cognitive effects while retaining efficacy (1, 56, 137).

Mode of action of ECT
Knowledge about the mode of action has increased, but ECT is still not fully understood (30). In 1960, Ottosson demonstrated that generalised seizures were essential for effective ECT. Sub-convulsive seizures had no or weak antidepressant effects (102).

Several brain areas are thought to be important for the mode of action of ECT. Cortical-subcortical networks participate in the initiation and propagation of generalised seizures and the activation of the brainstem (81). Prefrontal and central areas of the brain are thought to be important in the pathophysiology of depression (35), and are hypothesised to be key areas to target for epileptic seizures. Animal experiments show that ECT can stimulate cell replication in the hippocampus (46), and magnetic resonance imaging studies in humans indicate similar effects (93). Moreover, functional magnetic resonance imaging studies show that ECT restores blood flow to networks that are disturbed in depression (105).

There are several biochemical effects of ECT. Repeated seizure inductions stimulate systems that are engaged during the tonic phases of the seizures (107) and systems that counteract and terminate the seizures (13). Therefore, ECT regulates the activity of neurotransmitters such as monoamines and the balance of gamma-aminobutyric acid (GABA) and glutamate (129, 171). Furthermore, ECT normalizes the neuroendocrine system, including the hypothalamus-pituitary-adrenal axis, which is frequently disturbed in severe depression (80). However, how these biological mechanisms interact to decrease depressive symptoms remains unknown.

ECT administration
ECT is administered during a short anaesthesia. The treatment is safe and painless, apart from the pain associated with receiving an intravenous infusion. There are no significant contraindications to ECT, but some conditions, such as severe circulatory or respiratory disease, increased intracranial pressure, metal implants in the head, and poor dental status, may be
associated with increased risks of complications. A treatment series usually consists of 6–12 treatments over a 2–4 week period. A significant improvement in mental state is often observed after a few treatments, but in some cases, as many as 20 treatments may be necessary (164).

There are currently three frequently used electrode placements in clinical practice: unilateral, bilateral, and bifrontal. Unilateral electrode placements are most common in Europe and Australia, but bilateral electrode placements predominate in most other parts of the world (66). The unilateral d’Elia placement (19) is most commonly used in Sweden since unilateral treatment is associated with a lower risk of amnesia and confusion (126). The time to symptom reduction is longer with unilateral electrode placement than with bilateral electrode placement, and markedly higher electrical charges are necessary to induce therapeutically optimal seizures (56, 126). Bilateral electrode placement may be preferable when the severity of the symptoms demands a fast response, and a fast response is prioritised over the risk of amnesia. Bifrontal electrode placement is less common, but is generally considered to be intermediate to unilateral and bilateral electrode placements (56).

The electrical pulse amplitude, width, frequency, and total stimulus time can all be adjusted with currently used ECT devices. The manufacturers provide tables with recommended initial doses based on the age and sex of the patient. The electrical charge required to induce a seizure tends to be larger in men than in women, and larger in older patients than in younger patients. Other factors that influence the seizure threshold are concurrent medication and anaesthesia. Hypocapnea is induced by hyperventilating the patient during anaesthesia to decrease the seizure threshold. In clinical work, the aim is to find the optimal stimulus intensity to balance the antidepressive effect and the risk of amnesia. In 1963, an ultra-brief pulse width was introduced but this technique was abandoned because it produced less generalised seizures (18). However, a recent clinical trial of ultra-brief pulse width (0.3–0.5 ms) ECT reported an antidepressive effect and a lower risk of amnesia than for standard brief pulse width (0.5–1.0 ms) ECT (128). However, it is possible that ultra-brief pulse width stimuli are less effective than brief pulse stimuli (72).

The immediate treatment effect of ECT is an epileptic response. This response is monitored by observation of motor activity, electroencephalogram activity, cardiovascular response, and the postictal state. The aim in the clinic is to balance the risks of suboptimal treatment effects and the risk
of amnesia by modifying the treatment technique according to the response.

**Indications for ECT**
The American Psychiatric Association (APA) guidelines (164) give the following indications for the use of ECT among patients with depression:

- the need for a rapid and definitive response (e.g., because of the severity of psychiatric or medical condition or deterioration of the patient’s status)
- a lack of response to, or intolerance of, antidepressant medications in the current episode
- a history of poor medication response or good ECT response in one or more previous episodes
- when the risks of other treatments outweigh the risks of ECT
- patient’s preference

The APA guidelines say that ECT may be safer than alternative treatments for the infirm elderly and during pregnancy. The decision to use ECT depends on several factors, including the severity and chronicity of depression, the likelihood that alternative treatments would be effective, the patient’s preference and capacity to consent, and weighing the risks relative to the benefits. The APA guidelines (164) state that severe major depressions with psychotic features, manic delirium, or catatonia are conditions where there is a clear consensus that favours early ECT. Mania is an indication for ECT, but the treatment is generally reserved for patients with very severe symptoms or patients who do not remit with pharmacotherapies. Neuroleptic malignant syndrome and Parkinson’s disease can also be indications for ECT.

The UK National Institute for Health and Clinical Excellence (NICE) guidelines (90, 91) have similar recommendations for ECT as the APA guidelines for patients with severe or treatment resistant depression, catatonia, or prolonged or severe mania. The NICE guidelines do not recommend ECT for schizophrenia, which is different than the APA guidelines. The APA guidelines say that ECT is rarely used as a first-line treatment for schizophrenia, but can be considered after unsuccessful treatments with antipsychotic medications, and may also be considered when treating patients with schizoaffective or schizophreniform disorders. The latest Cochrane review offer some support for the combined use of antipsychotics and
ECT in schizophrenia (161), but there are few randomised controlled trials that use this combination of treatments.

Swedish recommendations and Swedish clinical practice conform relatively well to these international guidelines (3, 94, 103, 148).

ECT worldwide
It is estimated that one million patients worldwide receive ECT each year (111). However, the rates of use vary considerably across countries. In the US and Western Europe, about five patients per 10 000 people are treated with ECT annually. However, the treatment is less common in countries in Southern and Eastern Europe. The annual rate is estimated to be only 0.11 patients per 10 000 people in Poland (66). Over the past two decades, there has probably been a slight increase in the number of ECT treatments administered in Sweden, and the most recent estimate is that approximately 3000–4000 Swedish patients receive ECT each year, with a total of 30 000–40 000 treatments administered annually (3). In Western countries, ECT is primarily used for treatment of depression. However, in Asia, ECT is more commonly administered for treatment of schizophrenia than depression. In some developing countries, ECT still occurs without anaesthesia (66).

Effectiveness of ECT
Randomised studies show that ECT is significantly more effective than sham-ECT in reducing depression symptoms (115). In clinical trials, the efficacy of ECT in severe depression is high, with remission rates of 60–70% or more (106, 165). By contrast, remission rates are approximately 30% in trials of pharmacotherapies or psychotherapies (133). In severe depression, active medications are markedly more effective than placebo and ECT is even more effective than pharmacotherapies (165). In fact, no randomised trial has ever reported that pharmacotherapies are more effective than ECT for severe depression (158). ECT has not been extensively compared to medication in randomised trials of moderate depression (133).

Despite these convincing results, there may be a gap between the results achieved by ECT in clinical trials and the effectiveness of ECT in clinical practice. In a study by Prudic et al. that was conducted outside of the framework of a clinical trial, the remission rate was only 30–47%, depending on the criteria for remission (110). Suboptimal treatments or too few treatments could contribute to the discrepancy. Another possibility is that lower remission rates in clinical practice may be due to patient selec-
tion since patients with co-morbidities are often excluded from clinical trials but are included in clinical practice. If these patients are less likely to benefit from ECT, then this may contribute to the discrepancy. Regardless, the fact that a significant proportion of patients do not respond to ECT in clinical practice is a severe clinical problem. By the time ECT is considered, drug therapies have likely been tried alone or in parallel with ECT, and the prognosis for these non-responders is already poor. The ability to identify individuals that are likely to respond to ECT would therefore be of great benefit to clinical practices.

Predictors of the short-term effectiveness of ECT
The presence of psychotic symptoms (29, 106), lower degrees of prior treatment resistance (23, 26, 109), and shorter symptom durations (26, 62) are relatively well established predictors of response to ECT (73). In addition, the Collaboration for research in ECT (CORE) group reported higher ages to be associated with favourable outcomes (96). Patients with co-morbid personality disorders have lower responder rates to ECT (130) and other treatments for depression (89) than patients without personality disorders. In a study from Finland, younger patients suffering from moderate depression and with co-morbidity had a lower response rate than severely depressed older patients without co-morbidity (45). However, there are variations in the results and the importance of several factors is debated. In particular, the importance of psychotic depression (23, 146) and greater initial severity (63) have been questioned. Thus, more data is needed to determine the importance of various predictors for the response to ECT.

Cognitive effects of ECT
The cognitive effects of ECT, and in particular the effects on memory, are regarded as one of the most important limitations of the treatment (91, 94, 164).

During a series of ECT sessions, the ability to concentrate usually normalises rapidly but memory encoding may be temporally impaired. The ability to store memories tends to normalise within a few weeks (137). However, the effect of a series of ECT sessions on long-term memory is still debated (11). Memory involves a number of complex cognitive functions and is influenced by many factors including emotional state, disease, and therapy. Memory dysfunctions can be divided into objective dysfunctions in specific domains and subjective dysfunctions. Objective and subjective dysfunctions are not well correlated (117).
At least three separate processes are involved in memory: encoding, consolidation and storage, and retrieval. Encoding requires attention and concentration, functions that are commonly affected by mental disorders. Consolidation and storage are thought to involve temporal regions of the brain and the hippocampus, and retrieval involves prefrontal cortical areas (24, 95).

Memory dysfunctions related to ECT can be divided into anterograde amnesia, which involves impairments in episodic short-term memories during and after treatment, and retrograde amnesia, which involves impairments in episodic memories from before the treatment.

**Anterograde amnesia**
Anterograde amnesia is common in patients treated with ECT due to temporary dysfunctions in encoding (17). The frequency and severity of anterograde amnesia is influenced by electrode placement (bilateral treatment causes more dysfunction than unilateral), treatment spacing (one treatment per week causes less dysfunction than three treatments per week), and stimulus dosing (164). In addition to a reduced ability to encode and store new memories, ECT can result in a temporarily reduced ability to retrieve old memories. The degree of impairment can vary over the treatment period. Some patients have longstanding memory gaps throughout the treatment period, and both the disease and the treatment could contribute to this phenomenon.

Some cognitive functions, including attention and concentration, tend to improve during treatment in parallel with reduction of disease symptoms. A recent meta-analysis showed that objective memory functions were restored within two weeks of treatment (137). Although some studies indicate that subjective memory impairments can remain for longer periods of time (34), most patients do not show any residual impairments by two to six months after the completion of treatment (138). However, even if there are no evident objective dysfunctions, temporary anterograde amnesia during the treatment period could influence confidence in memory, and decreased confidence in memory functions may affect the subjective perception of memory (151).

**Retrograde amnesia**
Neuropsychologists evaluate retrograde amnesia by testing functions important for retrieval of long-term memory (67). A recent meta-analysis
concluded that there were no long-lasting impairments in these functions after ECT at the group level (137). However, some patients reported retrograde amnesia after ECT. Memories from time points around the treatment periods are most vulnerable. However, a causal link is difficult to demonstrate from these case reports.

In one observational study, there was a dose-response relation between the number of treatments with bilateral electrode placement and memory performance as assessed with an autobiographical memory inventory short form at six months after treatment (127). However, this questionnaire has been criticised and is not validated (139). The answers given in the depressed state before ECT are recorded. All later deviations from the pretreatment answers are considered incorrect. Therefore, the patients cannot improve their performance after ECT. If something is remembered incorrectly in a depressed and confused state, but is remembered differently and clearly in a non-depressed state, then the score is zero points. This type of construction risks that the association between the performance on the questionnaire and the different treatment intensities is biased by the severity of the disease. Therefore, although this study is interesting and widely cited, there is no firm evidence that retrograde amnesia occurs after ECT. In fact, the results from a controlled trial indicated that long-term memory functions are similar in patients treated with ECT and patients treated pharmacologically. The authors of this trial concluded that potential memory problems are not a reason to refrain from ECT (145). Nonetheless, in clinical practice patients are often afraid of long-term memory impairments caused by ECT, and further research is needed to clarify the cognitive effects of both depression and ECT.

There are additional factors that are important to consider when impairments in memory functions are suspected in patients who have been treated with ECT. For example, residual depression or anxiety symptoms, other mental disorders including early stages of neurodegenerative disorders, and benzodiazepine treatments can all affect attention and concentration, and can thus potentially impact memory functions (112).

Common side effects and complications of ECT
Adverse reactions to ECT are usually mild and treatment is well tolerated. Headaches and muscle pains are frequent in ECT treated patients, but are usually mild and subside with paracetamol. Tooth fractures are infrequent but can occur despite standard dental protection. There are descriptions of patients who have received thousands of ECT sessions without harm (69).
However, the safety of ECT for patients who are being treated with lithium has been questioned (131).

**Serious complications related to ECT**
The most serious complications of ECT are caused by anaesthesia and the fast increase in pulse and blood pressure that are induced by the seizure. The risks are increased if the patient had a recent myocardial infarction or stroke, or has vascular malformations and processes that increase intracranial pressure. Severe osteoporosis and poor dental status are other conditions that increase the risks associated with ECT. The mortality from ECT is mostly connected to the anaesthesia and is estimated at one to two deaths per 100,000 treatments (169).

**Stigma associated with ECT**
Stigma is a common experience for people with psychiatric diseases. This stigma contributes to the reluctance of societies to allocate resources to treatment, to hesitation of patients to seek care, and to poor compliance with treatment. Several factors make ECT especially prone to stigma. ECT was introduced at the same time as insulin therapy and lobotomy, two therapies that are now considered obsolete. ECT is also associated with severe psychiatric conditions and restraints. The view of ECT in the general population has been heavily influenced by the exaggerated depictions of ECT in movies as a brutal and suppressing treatment (77). In addition, fears of seizures, electricity, and memory effects are widespread.

**Ethics of ECT**
In biomedicine there are four ethical principles that should be balanced: beneficence (doing good), non-maleficence (not doing harm), autonomy, and justice (8). In ECT the principles of beneficence and showing respect for the patient’s autonomy can collide. About 15% of patients who receive ECT are involuntarily hospitalised patients (3). In my clinical experience, many of these patients would prefer not to have ECT when ECT is initiated. However, when the symptoms abate, these patients often acknowledge the necessity of the treatment. It has been argued that involuntary ECT should be reserved for patients with psychotic or suicidal symptoms (101). It could be argued that a reasonable balance between beneficence and respect for autonomy can be achieved with involuntary ECT treatment in cases where medication is not likely to be helpful, the prognosis with ECT is good, and the suffering of the patient would be long and severe without ECT. In cases of involuntary hospitalisation, it could be considered unjust to withhold the treatment that provides the highest probability
of helping the patient. My view is that respect for the patient’s autonomy should incorporate the likely opinion of the patient once the treatment is concluded. However, if the patient will receive only a few benefits and there will be side effects, then ECT may not be worthwhile. Therefore, the risk of a poor outcome must be accounted for in all involuntary patients.

Relapse after ECT
Nearly half of all patients who receive ECT relapse within six months after the conclusion of treatment despite receiving pharmacotherapies (57, 84, 108, 124, 160). As a result of relapse, psychiatric re-hospitalisation is often necessary (50). The relapse/recurrence of severe symptoms is also associated with high risk of suicide. A suicide rate of about 10 % within ten years after pharmacotherapies or ECT was reported in one Danish study (86).

In clinical practice, various combinations of pharmacological agents are used to reduce the risk of relapse/recurrence, but there are few studies that compare the outcomes achieved with the different treatment strategies. One of the most common strategies is the use of antidepressant medications. However, ECT is often given to patients who have already received antidepressant drugs without benefits. These patients tend to have reduced benefits from antidepressants after ECT relative to patients who did not try antidepressants prior to ECT (116). One randomised trial found that a lithium/antidepressant combination is more effective than antidepressants alone for the prevention of post-ECT relapses and recurrences (124). However, a recent larger study testing this strategy resulted in a disappointing 50 % relapse rate (108). Thus, more effective treatments are needed to prevent relapse/recurrence.

Continuation ECT to prevent relapse after index ECT
Weekly to monthly ECT can be used to prevent relapse after index ECT (57, 97). This is referred to as continuation ECT. Before the pharmacological era, continuation ECT was the only effective measure to reduce the relapse rate. However, this practice became uncommon after the introduction of antidepressants. Since there is a high relapse risk after ECT, and most patients receiving ECT have already tried antidepressants with limited benefits, recently there has been a renaissance of continuation ECT. This practice is supported by a randomised trial in which continuation ECT alone resulted in relapse rates similar to an antidepressant-lithium combination (57).
Continuation ECT is used in most hospitals in Sweden, but there are considerable variations in the proportion of patients who receive the treatment (3). Most (114), but not all (75), retrospective studies have found that medication combined with continuation ECT is effective in preventing relapse. These studies suggest a reduced need for hospital care if continuation ECT is provided (36, 123, 136, 157, 168). Navarro and associates performed a randomised trial of continuation ECT and nortriptyline in 33 elderly patients with psychotic depression. Five of the 13 patients who completed the study in the nortriptyline group had relapse/recurrence, relative to only one out of 11 patients who completed the study in the continuation ECT plus nortriptyline group (87). However, more data from randomised trials are needed to establish the relative effectiveness of pharmacotherapies, continuation ECT, and the combination of both of these modes of treatment.

**Summary and scope for the empirical studies**

In summary, ECT is the most effective treatment for severe depression. However, not all depressed patients respond to ECT. Accurate information about the outcomes with ECT is necessary to correctly inform and guide patients in the decision between treatment alternatives. However, recent studies into the outcomes of ECT in routine clinical practice have been scarce. Therefore, it is unclear how the outcomes in routine clinical practice compare to the good results reported from clinical trials.

Moreover, it remains a challenge to sustain any improvements that are achieved with ECT. Despite continuation pharmacotherapies to prevent relapse/recurrence, approximately half of all patients relapse within one year. Retrospective studies have indicated that continuation ECT combined with pharmacotherapies may be effective to reduce the high relapse rates, but there has been only one small randomised trial that has explored this combination.
The overarching aims of the thesis were to identify clinical characteristics that predict the outcomes of depressed patients treated in clinical practice by ECT, and to elucidate the effectiveness of continuation ECT at preventing relapses and recurrences. The specific aims of the separate studies were:

I. to investigate the responder rate of ECT, in clinical routine work and to define clinical characteristics predictive of response to ECT

II. to define predictors of time to relapse after ECT for major depressive disorder, single or recurrent

III. to test the hypothesis that relapse prevention with continuation ECT plus pharmacotherapy is more effective than pharmacotherapy alone after a course of ECT for depression and to compare the safety of the treatments

IV. to describe the need for inpatient care before, during and after continuation ECT combined with pharmacotherapy

V. to investigate the rate of regained occupational functioning after ECT and to define predictors related to time to regained occupational functioning in patients treated with ECT for major depressive disorders
### METHODS

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Number of patients</th>
<th>Diagnoses</th>
<th>Additional inclusion criteria</th>
<th>Primary outcome</th>
<th>Outcome measure</th>
<th>Main statistical method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study V</td>
<td>Cohort study based on data from the quality register for ECT and other registers</td>
<td>394</td>
<td>Unipolar depression</td>
<td>Personal identification number; Social insurance coverage during ECT</td>
<td>Treatment response</td>
<td>Restored occupational functioning</td>
<td>Cox-regression, Kaplan-Meier</td>
</tr>
<tr>
<td>Study IV</td>
<td>Retrospective chart review</td>
<td>27</td>
<td>Unipolar depression, bipolar depression and schizoaffective disorder, depressed type</td>
<td>Treatment with continuation ECT initiated</td>
<td>Hospitalisation or suicide</td>
<td>Hospitalisation or suicide</td>
<td>Kaplan-Meier, Log rank, Cox regression</td>
</tr>
<tr>
<td>Study III</td>
<td>Multicentre randomised trial</td>
<td>56</td>
<td>Unipolar and bipolar depression</td>
<td>MADRS ≤15 and Clinical Global Impression Improvement at least much improved</td>
<td>Relapse</td>
<td></td>
<td>Kaplan-Meier</td>
</tr>
<tr>
<td>Study II</td>
<td>Cohort study based on data from the quality register for ECT</td>
<td>496</td>
<td>Unipolar depression, bipolar depression and schizoaffective disorder, depressed type</td>
<td>Personal identification number</td>
<td>Treatment response</td>
<td></td>
<td>Kaplan-Meier, Log rank, Cox regression</td>
</tr>
<tr>
<td>Study I</td>
<td>Cohort study based on data from the quality register for ECT</td>
<td>936</td>
<td>Unipolar depression, bipolar depression and schizoaffective disorder, depressed type</td>
<td>Clinical Global Impression Improvement score available</td>
<td>Clinical Global Impression scale</td>
<td></td>
<td>Logistic regression</td>
</tr>
</tbody>
</table>
## Table 2. Patient characteristics in each study

<table>
<thead>
<tr>
<th></th>
<th>Study I (n=936)</th>
<th>Study II (n=486)</th>
<th>Study III (n=56)</th>
<th>Study IV (n=27)</th>
<th>Study V (n=394)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td>Women</td>
<td>Women</td>
<td>Women</td>
<td>Women</td>
<td>Women</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>57 ± 18</td>
<td>55 ± 18</td>
<td>57 ± 15</td>
<td>48 ± 19</td>
<td>45 ± 11</td>
</tr>
<tr>
<td><strong>Diagnoses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major depression, single episode</td>
<td>16 %</td>
<td>22 %</td>
<td>18 %</td>
<td>3 %</td>
<td>21 %</td>
</tr>
<tr>
<td>Major depression, recurrent</td>
<td>60 %</td>
<td>78 %</td>
<td>64 %</td>
<td>66 %</td>
<td>79 %</td>
</tr>
<tr>
<td>Bipolar disorder, depressive episode</td>
<td>19 %</td>
<td>0 %</td>
<td>18 %</td>
<td>19 %</td>
<td>0 %</td>
</tr>
<tr>
<td>Schizoaffective disorder, depressive episode</td>
<td>5 %</td>
<td>0 %</td>
<td>0 %</td>
<td>11 %</td>
<td>0 %</td>
</tr>
<tr>
<td><strong>Severity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild/moderate</td>
<td>32 %</td>
<td>36 %</td>
<td>23 %</td>
<td>0 %</td>
<td>33 %</td>
</tr>
<tr>
<td>Severe, non-psychotic</td>
<td>44 %</td>
<td>44 %</td>
<td>39 %</td>
<td>N/A</td>
<td>48 %</td>
</tr>
<tr>
<td>Severe, psychotic</td>
<td>25 %</td>
<td>20 %</td>
<td>38 %</td>
<td>N/A</td>
<td>19 %</td>
</tr>
<tr>
<td><strong>Type of care</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Involuntary care</td>
<td>15 %</td>
<td>13 %</td>
<td>13 %</td>
<td>N/A</td>
<td>15 %</td>
</tr>
<tr>
<td>Voluntary care</td>
<td>85 %</td>
<td>87 %</td>
<td>87 %</td>
<td>N/A</td>
<td>85 %</td>
</tr>
<tr>
<td>Outpatient care</td>
<td>19 %</td>
<td>25 %</td>
<td>23 %</td>
<td>4 %</td>
<td>13 %</td>
</tr>
<tr>
<td>Inpatient care</td>
<td>81 %</td>
<td>75 %</td>
<td>77 %</td>
<td>96 %</td>
<td>87 %</td>
</tr>
<tr>
<td><strong>Co-morbid axis I diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With diagnosed co-morbid anxiety</td>
<td>27 %</td>
<td>30 %</td>
<td>38 %</td>
<td>7 %</td>
<td>31 %</td>
</tr>
<tr>
<td>With co-morbid substance dependence</td>
<td>11 %</td>
<td>10 %</td>
<td>0 %</td>
<td>7 %</td>
<td>13 %</td>
</tr>
<tr>
<td><strong>Co-morbid axis II diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With diagnosed co-morbid personality disorder</td>
<td>8 %</td>
<td>8 %</td>
<td>9 %</td>
<td>33 %</td>
<td>10 %</td>
</tr>
</tbody>
</table>
Table 3. ECT-techniques (mean, standard deviation in parenthesis)

<table>
<thead>
<tr>
<th></th>
<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
<th>Study IV</th>
<th>Study V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrode placement</td>
<td>Unilateral (82 %)</td>
<td>Unilateral (88 %)</td>
<td>Unilateral (100 %)</td>
<td>Bifrontal (100 %)</td>
<td>Unilateral (83 %)</td>
</tr>
<tr>
<td>Index-ECT sessions</td>
<td>8.0 (3.2)</td>
<td>7.9 (3.0)</td>
<td>8.8 (2.1)</td>
<td>N/A</td>
<td>8.1 (3.2)</td>
</tr>
<tr>
<td>Pulse-width, ms</td>
<td>0.49 (0.14)</td>
<td>0.46 (0.10)</td>
<td>0.36</td>
<td>0.5</td>
<td>0.47 (0.12)</td>
</tr>
<tr>
<td>Frequency, Hz</td>
<td>73 (23)</td>
<td>75 (25)</td>
<td>74 (20)</td>
<td>70</td>
<td>70 (21)</td>
</tr>
<tr>
<td>Current, mA</td>
<td>840 (53)</td>
<td>833 (50)</td>
<td>813 (35)</td>
<td>900</td>
<td>840 (48)</td>
</tr>
<tr>
<td>EEG seizure duration, s</td>
<td>33 (14)</td>
<td>34 (15)</td>
<td>39 (14)</td>
<td>N/A</td>
<td>35 (26)</td>
</tr>
</tbody>
</table>

Table 4. Pharmacotherapies assessed at the conclusion of index ECT

<table>
<thead>
<tr>
<th></th>
<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
<th>Study IV</th>
<th>Study V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td>87 %</td>
<td>91 %</td>
<td>98 %</td>
<td>79 %</td>
<td>92 %</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>39 %</td>
<td>29 %</td>
<td>30 %</td>
<td>61 %</td>
<td>37 %</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>24 %</td>
<td>21 %</td>
<td>0 %</td>
<td>0 %</td>
<td>30 %</td>
</tr>
<tr>
<td>Lithium</td>
<td>16 %</td>
<td>10 %</td>
<td>56 %</td>
<td>32 %</td>
<td>10 %</td>
</tr>
</tbody>
</table>
Figure 1: Overlap of the participating patients in the different studies in this thesis

Figure 1 shows that all patients in study II, III and IV participated in study I. Many of the patients in study III and V also participated in study II. Study IV was based on a separate cohort of patients.
Methods used in the separate studies
An overview of the methods used in the separate studies is presented in table 1.

Patients included in the separate studies
An overview of the patients included in the separate studies is presented in table 2 and figure 1.

Quality register for ECT
In Sweden, ECT is provided by the psychiatric hospital responsible for the treatment of all patients within a defined geographical area. At the beginning of 2008, a quality register for ECT was initiated as part of a regional collaboration involving Örebro County Council, Uppsala University hospital and the Psychiatric Department in Säter. Löwenströmska hospital joined the register in 2009, and Danderyd hospital joined in 2010. Patients are informed about the register and can choose not to participate, but written informed consent is not necessary for participation. Very few patients abstain from participation. The aim of the quality register for ECT is to collate data regarding patients treated with ECT to be used for research and quality assurance. All data are recorded on paper forms by physicians and nurses that are involved in the delivery of ECT, and the forms are then sent to Örebro and registered in a database. The diagnoses recorded in the quality register for ECT conform to the International Classification of Diseases 10th version (ICD-10) and are transferred to the register from the hospital charts. A registered nurse pays monitoring visits to participating hospitals to ensure the completeness and high quality of the data.

Studies I, II, and V of this thesis are based on data from the quality register for ECT. Data collected during the first four years of the register were used. Eight hospitals participated in the register during this time period. The data included in the quality register for ECT were personal registration numbers, diagnoses, numbers of ECT sessions, ECT treatment parameters, involuntary/voluntary statuses, outpatient/inpatient statuses, Clinical Global Impression-Improvement CGI-I (41) scores, Montgomery Åsberg Depression Rating Scale (MADRS) (85) scores, Montgomery Åsberg Depression Rating Scale-Self-assessment (MADRS-S) (156) scores, and the treatments used to prevent relapses (pharmacotherapies/continuation ECT). The psychiatrist in charge of each patient determined the diagnosis, and experienced nurses assessed the CGI-I.
Rating scales
The Clinical Global Impression–Improvement (CGI-I) scale (41) score is a global scale for clinical assessment. It includes scores of: 1 (very much improved); 2 (much improved); 3 (minimally improved); 4 (not improved); 5 (minimally worse); 6 (much worse); and 7 (very much worse). CGI-I was used in studies I, II, III, and V.

The Clinical Global Impression–Severity (CGI-S) scale (41) score is a global scale for clinical assessment. It includes scores of: 1 (normal, not ill at all); 2 (borderline mentally ill); 3 (mildly ill); 4 (moderately ill); 5 (markedly ill); 6 (severely ill); and 7 (among the most extremely ill). CGI-S was used in study I.

The Montgomery Åsberg Depression Rating Scale (MADRS) is a 10-item interview-based scale designed to assess changes during treatment of major depression. The scores range from 0 (without symptoms of depression) to 60 (maximal symptoms) (85). The MADRS-S is a nine-item variant of the MADRS scale that is designed for self-assessment of depression (156). The scores range from 0 (without symptoms of depression) to 54 (maximal symptoms). MADRS and MADRS-S were used in studies I and III.

Cognitive status was evaluated using the mini-mental state examination (MMSE) and the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) (83). The MMSE scores range from 0 (maximal deficit) to 30 (no deficit) (31). The ADAS was developed to assess cognitive status among patients with Alzheimer’s disease. The cognitive subscale scores range from 0 (no mistake) to 85 (no correct task). MMSE and ADAS-cog were used in study III.

Side effects were evaluated using the Utvalg for Kliniske Undersogelser (UKU) scale that was designed by the Subcommittee of the Scandinavian Society of Psychopharmacology to detect side effects in clinical trials of psychopharmacology (68). More specifically, the memory item in UKU was used in study III to assess subjective memory disturbances. It was administered at 2, 6, and 12 months after inclusion in the study and at relapse. The scores range from 0 (no problem) to 3 (severe memory loss).

The mini-international neuropsychiatric interview MINI-PLUS 5.0 (140) was administered in study III by investigators at each hospital prior to randomisation as a diagnostic aid. In addition, the investigators had access to the patients’ charts and clinical history.
Statistical analysis

The statistical methods used in the different studies are described in table 1. Frequency distributions across groups of patients were tested using chi-square tests (studies I, II, III, and V). Differences between means across groups of patients were tested by Student's t-test (studies I, II, III, and V). The factors evaluated for the analyses in studies I, II, and V were age, sex, diagnosis, co-morbidity, outpatient/inpatient status, and involuntary/voluntary status. In addition, clinical improvements from ECT and pharmacotherapies at the end of ECT were evaluated in studies II and V. In study V, the duration of antidepressant treatment before ECT and the duration of sick leave prior to ECT were also evaluated. Multivariate logistic regressions were used to calculate odds-ratios of responses relative to factors with statistical trends (p<0.10) of association to responses as determined by chi-square tests (study I). Kaplan-Meier survival curves were used to calculate the cumulative probability of patients without relapses (study III), patients without psychiatric hospitalisations (studies II and IV), and patients who regain occupational functioning (study V). All randomised patients were included in the intention to treat analysis (study III). The relapse rates in the treatment groups were compared among patients with and without resistance to pharmacotherapies, with and without lithium treatment, and with and without remaining depressive symptoms (MADRS score of 10–15) after index ECT. Cox proportional hazards models were used to generate 95% confidence intervals of hazard ratios and to test if there were statistically significant differences in hospitalisations (study II), relapses (study III), and occupational functioning (study V). Repeated measures analyses of variance were used to compare measures of cognitive functions (MMSE, ADAS-cog) across time points (baseline, 2 months, 6 months, and 12 months) and treatment groups (pharmacotherapy alone, continuation ECT plus pharmacotherapy) (study III).

All statistical tests performed were two-sided and alpha was set to 0.05. All analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, Ill). Data are reported as mean (standard deviation) unless otherwise stated.

ECT

Mainly unilateral electrode placements were used in studies I, II, III and V. In study IV, bifrontal electrode placements were used. Details about the dosages that were used are presented in table 3.
Pharmacotherapies
The pharmacotherapies that were used are presented in table 4. Nearly all patients were exposed to at least one psychotropic drug. Antidepressants were the most common, but nearly one third of all patients also received antipsychotics and benzodiazepines. Lithium was used in only about 10% of the patients. However, in study III, lithium was used by half of the patients and benzodiazepines were not used.

Study I

Design
Study I was designed as a naturalistic cohort study based on data from the quality register for ECT (table 1).

Patients
Nine hundred and ninety patients who were treated with ECT for a major depressive episode of unipolar depression, bipolar depression, or schizoaffective disorder, depressed type were identified. Information about the clinical outcome was available for 936 patients, and these patients formed the study sample (table 2).

Outcome measure
Response to treatment was the primary outcome, and it was evaluated using the CGI-I score. Patients who were rated as “very much improved” or “much improved” were classed as responders to ECT.

Study II

Design
The design was a naturalistic cohort study based on data from the quality register for ECT with additional follow-up data collected from the national Causes of Death Register (table 1).

Patients
All 486 patients with a diagnosis of major depressive disorder (either single episode or recurrent) were included (table 2).

Follow-up
Follow-up data were reported to the register during summer/autumn, 2010. The mean follow-up time was 582 (183) days after the end of index-ECT.
Outcome measure
Time to psychiatric hospitalisation and death due to suicide were used as indicators of relapse/recurrence. The starting point for these measures was the last day of the first index ECT series recorded in the register.

Study III

Design
The study was a multicentre, non-blinded randomised trial with two parallel groups: pharmacotherapy alone and pharmacotherapy with continuation ECT. The allocation ratio was 1:1 (table 1).

Patients
Fifty-six patients were randomised in the study (table 2). Inclusion criteria were a major depressive episode (either a single episode, recurrent episodes, or an episode of bipolar depression) verified by MINI-PLUS, a score of no more than 15 points on the MADRS scale at the end of index ECT, a rating of at least “much improved” on the CGI-I scale at the end of index ECT, and informed consent. Patients were excluded if they had substance dependence or a history of substance abuse within the last year. Patients were enrolled within three weeks of the final index ECT session. Two hundred patients who completed an index ECT series at one of the four participating hospitals were considered for enrolment (figure 2).

Randomisation
A separate randomisation sequence was generated for each hospital. Small blocks of different sizes were used. A statistician provided envelopes containing information about the randomised treatments.
Interventions
All patients received individualised medication. Venlafaxine was the first choice and lithium augmentation was offered to all patients. The serum concentration of lithium was 0.56 (0.21) mmol/L in the pharmacotherapy group and 0.60 (0.15) mmol/L in the ECT plus pharmacotherapy group. In addition, antipsychotic medications were allowed. Anticonvulsant drugs were not used in either group due to the hypothetical risk of interaction with ECT. The pharmacotherapies at randomisation consisted of antidepressants (98 %), lithium (56 %), and antipsychotics (30 %) (table 4). If the patient experienced a relapse, then the psychiatrist in charge was free to recommend any treatment judged to be beneficial for the patient. This included ECT for patients who were randomised to pharmacotherapy only. The patients randomised to continuation ECT plus pharmacotherapy were offered weekly ECT for six weeks and then biweekly ECT for 46 weeks, for a total of 29 sessions of ECT over one year. Unilateral ultra-brief pulse ECT was used (table 3).
Follow-up
Patients were telephoned weekly for the first six weeks and then biweekly to complete a MADRS-SA. If the rating was above 20 points, then the patient was seen by the investigator within one week to determine if there was a relapse. The patients were also seen and evaluated by an investigator using rating scales (MADRS, MMSE, ADAS-cog, and UKU) at the time of randomisation and at two, six, and twelve months post-randomisation. Four patients in the pharmacotherapy arm and two patients in the ECT plus pharmacotherapy arm declined to be interviewed by telephone for completion of the MADRS-SA forms.

Sample size
A power analysis before the study anticipated a relapse rate of 55% in the pharmacotherapy group and 25% in the combined ECT and pharmacotherapy group. Forty-five patients were considered to be necessary for each group based on a two-sided log-rank test with alpha set at 0.05 and 80% power. However, the study was terminated when there were 28 patients in each group due to slow recruitment.

Outcome measure
The primary outcome was relapse defined as a score higher than 20 on the MADRS, or hospitalisation, or suicide, or suspected suicide. The secondary outcome was safety and included cognitive functions as measured with MMSE, ADAS-cog, and the memory item of the UKU.

Study IV

Design
The study design was a retrospective chart review (table 1).

Patients
The 27 patients included are described in table 2. The study sample comprised of all patients who had commenced continuation ECT at the Örebro University Hospital for treatment of a depressive episode in the years before the randomised trial was initiated.

Continuation ECT
Continuation ECT was defined as ECT administered once per week or less and provided in a voluntary outpatient setting. Continuation ECT was usually given once per week during the first four weeks after index-ECT, and then once every two weeks for an additional four weeks, and then
once per month for four months. However, there were individual adaptations in the schedule with some patients having shortened continuation ECT schedules and some patients having continuation ECT initiated at a frequency of once every two weeks.

**Pharmacotherapies**
The pharmacotherapies are described in table 4. Only one patient chose not to have pharmacotherapy during continuation ECT.

**Outcome measure**
The uses of inpatient care during the three years before index ECT, during the continuation ECT, and during the two years after continuation ECT were quantified by a hospital day quotient (HDQ). The formula is described in the definitions section.

The hospitalisation rates were also calculated.

**Study V**

**Design**
The design was a nested cohort study based on data from the quality register for ECT and the Swedish Social Insurance Agency Registry (MIDAS). Additional information was obtained from the Prescribed Drug Register and the Causes of Death Register. The National Board of Health and Welfare in Sweden holds both of these registers (table 1).

**Patients**
Three hundred and ninety-four patients were included (table 2). Of these patients, 266 had a non-permanent sick leave certificate and 128 were granted disability pension. All patients with a diagnosis of major depressive disorder (either single episode or recurrent) who were treated with ECT in one of the seven hospitals that participated in the quality register for ECT were considered for this study. Patients were included in this study if they had insurance coverage (full day) from the Swedish Social Insurance Agency during ECT (sick leave or disability pension) and a Swedish personal identification number. Patients were excluded if they had bipolar disorder or if they were more than 62 years old at the time of ECT.

**Outcome measure**
The mean follow-up time was 772 (339) days after the last day of the first index ECT series. Data about all compensations due to sick leave and dis-
ability pension that were longer than 14 days from 1995 to September, 2011, were obtained from the Swedish Social Insurance Agency based on the personal identity numbers of the patients. The primary outcome measure was time to regain occupational functioning. This measure was identified by the termination of full day sick leave compensation.

The National Board for Health and Welfare administers the Causes of Death Register and the Prescribed Drug Register, which are both based on the personal identity number. Information about all causes of deaths up to December, 2010, and medications provided for outpatient care from 2005 to August, 2011, were obtained. Medications collected within three months of ECT were analysed and the durations of antidepressant medications before ECT were estimated.

**Ethical considerations**

Participation in a controlled study involves a certain degree of intrusion into the autonomy of patients since the treatments are selected by chance rather than by choice. All patients in study III provided informed consent to participate and the families were informed. For the studies based on the quality register of ECT (studies I, II, and V), the patients were informed about the register and could choose not to participate. However, very few patients declined registration.

When considering the ethical justification for these studies, we accounted for the severity of the disease, the seriousness of the prognosis, and the large variation in the proportion of patients treated with continuation ECT between different hospitals. When studies III and IV were initiated, no randomised studies about the effects of continuation ECT had been published. Knowledge about the outcomes of different treatments increases through research. Due to the high risk for symptom relapse/recurrence in depression, many of the participating patients may benefit from the results of these studies during future episodes of depression. When all of the risks and benefits were accounted for, our view was that the clinical and scientific benefits of these studies outweighed the risks for the participating patients. All studies were conducted in compliance with the Helsinki declaration and were approved by the Regional Ethical Vetting Board.
**Table 5.** Ninety-five percent confidence intervals of the odds ratios of response, hospitalisation, and regain of occupational functioning after ECT relative to clinical variables (studies I, II and V), significant correlations in bold.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study I</th>
<th>Study II</th>
<th>Study V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females vs. males</td>
<td>0.76; 1.45</td>
<td>0.86; 1.53</td>
<td>0.79; 1.34</td>
</tr>
<tr>
<td>Younger than 50 years vs. 50 years and older</td>
<td><strong>0.39; 0.74</strong></td>
<td>0.88; 1.60</td>
<td><strong>0.56; 0.98</strong></td>
</tr>
<tr>
<td>First episode of depression vs. recurrent depression</td>
<td>0.82; 2.23</td>
<td>0.88; 1.79</td>
<td>0.64; 1.19</td>
</tr>
<tr>
<td>Mild or moderate depression vs. severe depression with psychosis</td>
<td>0.20; 0.54</td>
<td>0.67; 1.52</td>
<td>0.57; 1.18</td>
</tr>
<tr>
<td>Severe depression without psychosis vs. severe depression with psychosis</td>
<td><strong>0.34; 0.89</strong></td>
<td>0.76; 1.66</td>
<td>0.69; 1.37</td>
</tr>
<tr>
<td>With diagnosed co-morbid anxiety disorder vs. without</td>
<td>0.51; 1.37</td>
<td>0.83; 1.52</td>
<td>0.57; 1.03</td>
</tr>
<tr>
<td>With diagnosed co-morbid substance dependence vs. without</td>
<td><strong>0.27; 0.74</strong></td>
<td><strong>1.28; 2.82</strong></td>
<td><strong>0.42; 1.00</strong></td>
</tr>
<tr>
<td>Outpatient vs. inpatient ECT treatment</td>
<td><strong>0.27; 0.56</strong></td>
<td><strong>0.29; 0.64</strong></td>
<td>0.69; 1.26</td>
</tr>
<tr>
<td>Involuntary vs. voluntary hospital admission during ECT</td>
<td><strong>1.12; 3.18</strong></td>
<td>0.66; 1.55</td>
<td>0.82; 1.72</td>
</tr>
<tr>
<td>With benzodiazepine treatment vs. without</td>
<td>0.54; 1.12</td>
<td><strong>1.03; 1.99</strong></td>
<td><strong>0.36; 0.66</strong></td>
</tr>
<tr>
<td>With antipsychotics vs. without</td>
<td>0.74; 1.43</td>
<td><strong>1.10; 2.04</strong></td>
<td>0.77; 1.33</td>
</tr>
<tr>
<td>With lithium vs. without</td>
<td>0.73; 1.80</td>
<td><strong>0.29; 0.92</strong></td>
<td>0.74; 1.72</td>
</tr>
</tbody>
</table>
Response to ECT (study I)

Table 5 shows the unadjusted 95% confidence intervals of the odds-ratios of response to ECT relative to clinical factors. A higher proportion of older patients (>50 years of age) than younger patients responded to ECT (84.3% vs. 74.2%, p<0.001). The response rate was similar in men and women. Patients with severe, psychotic depression had a higher response rate (88.9%) than patients with severe, non-psychotic depression (81.5%) and patients with mild/moderate depression (72.8%, p<0.001). However, the response rates were similar among patients suffering from either a depressive episode of bipolar I or bipolar II disorder or a first or recurrent episode of major depressive disorder. There was a trend toward a lower response rate in patients with a depressive episode of schizoaffective disorder (68.8%, p=0.060, four degrees of freedom). The lower response rate in patients with schizoaffective disorder, depressed type was statistically significant in a post hoc comparison to all other patients (p=0.04, one degree of freedom). Patients with co-morbid anxiety or dependence disorders had similar response rates to patients without such diagnoses. Patients with personality disorders had a lower response rate than patients without personality disorders (66.2% vs. 81.4%, p=0.001). Table 6 shows the relative influences of clinical factors in a multivariate model.
Table 5 shows the unadjusted 95% confidence intervals of the odds-ratios of response to ECT relative to clinical factors. A higher proportion of older patients (>50 years of age) than younger patients responded to ECT (84.3% vs. 74.2%, p<0.001). The response rate was similar in men and women. Patients with severe, psychotic depression had a higher response rate (88.9%) than patients with severe, non-psychotic depression (81.5%) and patients with mild/moderate depression (72.8%, p<0.001). However, the response rates were similar among patients suffering from either a depressive episode of bipolar I or bipolar II disorder or a first or recurrent episode of major depressive disorder. There was a trend toward a lower response rate in patients with a depressive episode of schizoaffective disorder (68.8%, p=0.060, four degrees of freedom). The lower response rate in patients with schizoaffective disorder, depressed type was statistically significant in a post hoc comparison to all other patients (p=0.04, one degree of freedom). Patients with comorbid anxiety or dependence disorders had similar response rates to patients without such diagnoses. Patients with personality disorders had a lower response rate than patients without personality disorders (66.2% vs. 81.4%, p=0.001). Table 6 shows the relative influences of clinical factors in a multivariate model.

**Hospitalisation after ECT (study II)**

Out of a total of 486 patients, 185 (38.1%) were hospitalised for psychiatric reasons during the follow-up period. The cumulative proportions of the total sample of patients who were hospitalised were: 25% within six months, 34% within one year, and 44% within two years after the last index ECT.

Fifteen patients died during the follow-up period. Nine patients died from suicide and six from somatic diseases. The cumulative proportion of patients who died from suicide within one year after ECT was 2%.

Table 5 shows 95% confidence intervals of the unadjusted hazard ratios of hospitalisation or suicide relative to clinical factors. The influences of clinical factors on the hazard ratios of hospitalisation and suicide in a multivariate model are presented in table 7.
Table 7. Multivariate Cox-regression analyses of the influences of clinical factors on the risk of psychiatric hospitalisation or suicide during the follow-up period ($n=479$).

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>95% confidence interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient</td>
<td>0.42</td>
<td>0.28–0.64</td>
<td>0.00</td>
</tr>
<tr>
<td>Substance dependence</td>
<td>1.88</td>
<td>1.26–2.80</td>
<td>0.00</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>1.50</td>
<td>1.08–2.10</td>
<td>0.02</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>1.39</td>
<td>1.02–1.88</td>
<td>0.04</td>
</tr>
<tr>
<td>Lithium</td>
<td>0.58</td>
<td>0.32–1.02</td>
<td>0.06</td>
</tr>
</tbody>
</table>
Efficacy of continuation ECT (study III)

Figure 3. Kaplan-Meier function of the cumulative probability of remaining without relapse for patients treated with continuation ECT plus pharmacotherapy versus pharmacotherapy alone.
Relapse in the intention-to-treat sample
In the intention-to-treat cohort, the one-year relapse rates were 61 % in the pharmacotherapy alone group and 32 % in the ECT plus pharmacotherapy group (figure 3; p=0.036). The Cox proportional hazard ratio was 2.32 (95 % confidence interval: 1.03–5.22). The two-month relapse rates were 29 % in the pharmacotherapy alone group and 18 % in the ECT plus pharmacotherapy group. The six-month relapse rates were 54 % in the pharmacotherapy alone group and 29 % in the ECT plus pharmacotherapy group. In the pharmacotherapy alone group, 36 % of patients required inpatient care during the follow-up period, while only 20 % required inpatient care in the pharmacotherapy plus ECT group. All hospitalised patients had relapses of depression. There was one suspected suicide by intoxication during the follow-up. The patient died from intoxication with mitragynin and O-desmethyltramadol. Although suicidal intent could not be proven, the event was classified as a suspected suicide. The patient belonged to the pharmacotherapy alone group.

Relapse in post hoc subgroups
Among patients receiving lithium therapy, the one-year relapse rate was 56 % in the pharmacotherapy alone group (n=16) and 13 % in the ECT plus pharmacotherapy group (n=15). Among patients not receiving lithium, the relapse rate was 73 % in the pharmacotherapy alone group (n=12) and 64 % in the ECT plus pharmacotherapy group (n=13).

Among patients with a baseline MADRS scores ≤10 (indicating remission), the relapse rate was 56 % in the pharmacotherapy alone group (n=24) and 24 % in the ECT plus pharmacotherapy group (n=25). Six out of seven patients (86 %) relapsed among the patients with baseline MADRS scores ranging from 11 to 15 (indicating remaining symptoms).

Among patients resistant to medication, the relapse rate was 85 % in the pharmacotherapy alone group (n=13) and 31 % in the pharmacotherapy plus ECT group (n=16). The relapse rate was 35 % in the pharmacotherapy alone group (n=15) and 33 % in the ECT plus pharmacotherapy group (n=12) among the patients not resistant to medication.

Cognitive functions
The patients in the ECT plus pharmacotherapy group had better MMSE and ADAS-cog scores at baseline than the patients in the pharmacotherapy alone group (MMSE 28.4 (1.1) vs. 27.0 (2.7) and ADAS-cog 11.7 (13.7) vs. 13.0 (15.2)). The scores of the ECT plus pharmacotherapies group were
better throughout the study. For patients who did not relapse, there were no statistically significant differences in the development of the measures of cognitive function (MMSE and ADAS-cog) or subjective memory (UKU-memory item score) between the ECT plus pharmacotherapy group and the pharmacotherapy alone group.

**Hospitalisation relative to continuation ECT (study IV)**
The hospital day quotients (HDQ) were 28 in the three years preceding ECT, 15 during continuation ECT, and 20 in the two years after continuation ECT. The hospitalisation rate was 50 % in the first year after index ECT. Seven hospitalisations occurred (25 %) while the patients were receiving continuation ECT.

**Time to regain occupational functioning after ECT (study V)**
Out of the total sample of 394 patients, 245 (62 %) returned to work during the follow-up period. The cumulative proportions of the total sample of patients returning to work were 31 % in the three months after ECT, 41 % in the six months after ECT, 49 % within one year after ECT and 64 % within two years after ECT.

Out of the 266 patients with non-permanent sick leave, the cumulative proportions returning to work were 43 % in the three months after ECT, 59 % in the six months after ECT, 71 % within one year after ECT, and 88 % within two years after ECT.

Out of the 128 patients with disability pension, the cumulative proportions returning to work were 3 % in the three months after ECT, 3 % in the six months after ECT, 5 % within one year after ECT, and 19 % within two years after ECT.

The influences of clinical factors on time to regain occupational functioning in a multivariate model are presented in table 8.
Table 8. Factors associated with regain of occupational functioning. Hazard ratios and 95 % confidence interval values derived from multivariate Cox proportional hazards-regression analyses among patients with non-permanent sick leave that were treated for unipolar depression with ECT (n=252).

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>95 % confidence interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age below 50 years vs. 50 years and older</td>
<td>0.82</td>
<td>0.60–1.10</td>
<td>0.18</td>
</tr>
<tr>
<td>With anxiety disorder vs. without</td>
<td>0.99</td>
<td>0.70–1.39</td>
<td>0.94</td>
</tr>
<tr>
<td>With substance dependence vs. without</td>
<td>0.59</td>
<td>0.36–0.96</td>
<td>0.03</td>
</tr>
<tr>
<td>Pre-ECT sick leave 0–29 days vs. more than 365 days</td>
<td>2.89</td>
<td>1.68–4.97</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pre-ECT sick leave 30–89 days vs. more than 365 days</td>
<td>1.90</td>
<td>1.05–3.45</td>
<td>0.04</td>
</tr>
<tr>
<td>Pre-ECT sick leave 90–365 days vs. more than 365 days</td>
<td>1.18</td>
<td>0.64–2.19</td>
<td>0.60</td>
</tr>
<tr>
<td>Mild/moderate depression vs. severe without psychosis</td>
<td>0.57</td>
<td>0.40–0.81</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Severe depression with psychosis vs. severe without psychosis</td>
<td>0.83</td>
<td>0.56–1.22</td>
<td>0.34</td>
</tr>
<tr>
<td>Benzodiazepine treatment vs. no benzodiazepine treatment</td>
<td>0.36</td>
<td>0.25–0.52</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CGI much improved vs. very much improved</td>
<td>0.97</td>
<td>0.71–1.39</td>
<td>0.97</td>
</tr>
<tr>
<td>CGI minimally improved vs. very much improved</td>
<td>0.42</td>
<td>0.25–0.69</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CGI not improved vs. very much improved</td>
<td>0.52</td>
<td>0.24–1.13</td>
<td>0.10</td>
</tr>
</tbody>
</table>

DISCUSSION

Overall, four out of five patients responded to ECT in clinical practice. Patients with psychotic depression had the highest response rate. Approximately 90 % of these patients responded to ECT. The other patient groups with high ECT response rates were: patients with severe depression, older patients, and inpatients. These results were similar to published studies (96, 106). The patients groups with the lowest response rates were outpatients and patients with personality disorders. However, two out of three patients in these groups responded within three weeks of treatment. This response rate is better as compared to a recent large randomised study of pharmacotherapy resistant depressed outpatients. In that study, 22 % of the patients responded to pharmacotherapy alone and 44 % to pharmacotherapy plus cognitive behavioural therapy after 6 months (100). Interestingly, study V showed that a higher severity of depression was associated with reduced time to regain occupational functioning. Psychotic depression tends not to respond as well to medication (37, 54, 104). Therefore, the high response rate to ECT emphasises the importance of ECT for treatment of psychotic depression. Currently, only a minority of inpatients who are treated for psychotic depression in Sweden receive ECT (3). The results of the studies in this thesis suggest that there should be wider use of ECT in this patient group.

Relapses/recurrences were very common. One-third of the patients treated with ECT for unipolar depression required hospitalisation for a depressive relapse and nearly 2 % committed suicide within one year of index ECT. Patients with co-morbid substance abuse had an increased risk of hospitalisation, which suggests that these patients need to be identified and treated differently.

A key finding of the studies in this thesis is that after patients were treated with index ECT for depression, those who received continuation ECT and lithium treatments had a lower rate of relapse/recurrence than the patients who did not receive these treatments (study II, study III). Continuation ECT also tended to reduce the need for inpatient treatment (study IV). Nevertheless, the relapse rates were substantial for both treatment groups in the randomised study. The estimated reduction in relapse rate with continuation ECT was 29 % (a relapse rate of 61 % for pharmacotherapy alone vs. 32 % for pharmacotherapy and ECT). Thus, the number-to-treat for one patient to benefit would be three to four. This level of risk reduc-
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tion may be clinically relevant, especially if the disease is severe, the suicide risk is high, or other treatments were unsuccessful. These results are consistent with other randomised studies that investigated the effects of antidepressant-lithium pharmacotherapies (108, 124), continuation ECT (57), and continuation ECT combined with antidepressant medication (87). Furthermore, the results support other studies that reported the efficacies of lithium (124, 160) and continuation ECT (114) for depressed patients who benefitted from index ECT. Importantly, study III in this thesis is the first randomised study to investigate the effects of combined therapies including an antidepressant, lithium, and continuation ECT. The observation that pharmacotherapy resistant patients received the largest benefit from continuation ECT is very relevant for the clinic. Other studies found that if patients did not respond to pharmacotherapies prior to ECT, then they had a higher risk of relapse with pharmacotherapies after ECT (125). If continuation ECT can considerably reduce this relapse rate (study III suggests that it can be reduced from 85 % to 31 %), then continuation ECT should be recommended for this patient group. However, only a small minority of patients receive lithium or continuation ECT treatment in current Swedish clinical practice (3). Our research, in combination with earlier studies, suggests that the wider use of these treatments would be beneficial. However, additional studies are necessary to confirm the effects of combined continuation ECT and lithium treatments and to further define the indications for these treatments. These studies are currently being performed (70).

Despite a high response rate to ECT, it often took months for patients to regain occupational functioning. This finding is consistent with earlier studies of pharmacotherapies and psychotherapies that found it takes long time to regain occupational functioning after symptoms have decreased (82). This has important implications for insurance practices. The current decision issued by the National Board of Health and Welfare for physicians and insurance personnel reads: “In severe first episode depression, occupational functioning can be impaired up to six months. Depressive symptoms can remain for an additional six months or longer. The individual variation is large.” Our research suggests that in two-fifths of patients with severe depression who received ECT, occupational functioning was impaired for longer than six months and that residual impairments for two years or longer were not unusual. Furthermore, the time to regain occupational functioning was not significantly different between patients with first or recurrent depressive episodes. Our data confirm that there are large inter-
individual variations in the time taken to regain occupational functioning after index ECT.

Patients who presented with depression with co-morbid personality disorder had a lower acute response rate to ECT (study I), a higher risk for rehospitalisation (study II), and a trend toward longer time to regain occupational functioning (study V) than patients without personality disorders. This information is important for determining the prognosis of a patient. Depressed patients with personality disorders also tend to respond poorly to medication (89). Therefore, it is possible that ECT has the highest probability of providing responses when severe depressions are complicated by personality disorders. The risks of non-response and side effects should always be considered. However, the complication of co-morbid personality disorders should not prevent physicians from using ECT to treat patients suffering from severe depressions.

In study II, treatment strategies during the follow-up period were analysed relative to the need for subsequent hospitalisations. It is difficult to draw firm conclusions from naturalistic studies since the patients are not randomised and different factors that are related to selection might influence the results. However, it is remarkable that the use of benzodiazepines and antipsychotics during the follow-up period were associated with an increased risk of hospitalisation. Treatment with benzodiazepines, but not antipsychotics, was also associated with an increased time to regain occupational functioning (study V). There are some indications that second-generation antipsychotics are effective for the acute treatment of mood disorders (64, 88), but there are no published studies that support the long-term use of antipsychotics after ECT in patients with major depressive disorder. The results of the studies in this thesis confirm the current guidelines that discourage long-term treatments with benzodiazepines. However, in some Swedish hospitals, long-term benzodiazepine treatments are used for patients who are treated with ECT (3). Therefore, smaller variations between hospitals and closer compliance to guidelines are preferable.

**Methodological considerations**

Study I was an observational study based on prospectively collected data. Ultimately, the patients hope to become free of symptoms and to regain social functioning (to attain remission). In research settings, symptomatic remission is usually evaluated with rating scales such as the Hamilton depression rating scale (HDRS) (42) or MADRS. In the quality register, the MADRS scores were available for a minority of the patients. We consid-
erred the possibility that selection-bias might be introduced if the response rates were influenced by the use of MADRS. For instance, if the use of MADRS was associated with higher quality assessments and individualised treatments, then patients rated with MADRS might have better outcomes than other patients. Therefore, we did not use MADRS to assess the effects of the treatments, and we did not evaluate remission. Instead, the main outcome measure was response, which was based on the clinical global impression-improvement (CGI-I) scores. This measure was chosen because it was available for nearly all of the patients in the register. One disadvantage of CGI-I is that improvements among patients with mild symptoms might be less apparent than improvements among very ill patients. Therefore, patients with milder symptoms may more often be rated as non-responders than severely depressed patients. Similarly, for patients with personality disorders, symptoms of personality disorders may be misinterpreted as remaining symptoms of depression. Further studies are necessary to compare the CGI-I and MADRS ratings among different subgroups of patients. Furthermore, it is important for future studies to evaluate the proportions and characteristics of patients who achieve remission of symptoms with ECT treatments in routine clinical practices. The quality register could contribute valuable information for these future studies.

Double-blind placebo controlled randomised clinical trials are the gold standard for comparing the effects of different treatments. These types of trials demand considerable resources. However, suboptimal treatments are very unfavourable for patients and are also costly for the health care system. Therefore, it is important that treatments be evaluated by controlled clinical trials.

Study III was a controlled clinical trial conducted without industry sponsors within the framework of routine clinical work. One limitation is that the study enrolment was terminated early due to slow recruitment. Therefore, the estimations of the relative effectiveness of the treatments are wide. The study is also limited by the absence of blinded assessors. Therefore, the results could be biased if the doctors involved in the assessments had preconceived comprehensions about the treatment effects. This risk is only partially balanced by the fact that patients participated in the assessments of treatment effects, because the patients may also have been influenced by similar perceptions. It was not feasible to employ qualified personnel to assess outcome measures who were blinded to the treatments because of the limited resources. In non-pharmaceutical interventions, such as surgery and psychotherapies, it is generally challenging to blind the patients. It is
unknown whether patients would feel a difference between sham treatments and the actual ECT. Also, well-informed patients might not accept sham treatments that still include the risks of anaesthesia. Therefore, even though double-blinded studies provide a better level of evidence, there are ethical limitations that can prevent these types of studies.

The patients in both treatment groups were contacted more often than most other patients in routine clinical practice. Therefore, the intensified access to care might also explain the lower rate of hospitalisation for patients in study III than for the patients in study II. Earlier detection of symptom relapse/recurrence and adaptation is more likely when the patients are regularly assessed. Also, continuation ECT may have had a placebo effect that contributed to the reduced relapse rate of the patients randomised to that treatment group relative to the patients who received pharmacotherapy alone.

Out of all patients eligible for inclusion in the randomised study, one-third was included and two-thirds declined participation. The results that continuation ECT can prevent relapse are strong because the patients were randomised. The patients included in the randomised trial were similar to the patients in the population-based cohorts with regard to sex, age, diagnoses, severity of depression, and treatment setting (table 2). However, some patients who received strong benefits from ECT were not included because they preferred to obtain continuation ECT outside of the study. There is a possibility that this biased the results toward a reduced efficacy of continuation ECT. Other patients preferred pharmacotherapy alone and were not included in the study because they would not accept additional treatments with ECT. If those patients would have had received reduced benefits from continuation ECT, then the results may be biased toward an increased effect of continuation ECT. Therefore, although this study provides evidence that some patients benefit from continuation ECT, additional studies are necessary to estimate the relative effectiveness in subgroups of patients and to further define the indications.

It is appropriate to follow a cohort longitudinally when studying disease prognosis. One advantage of cohort studies is that large data sets can be collected with limited resources. The influence of recall bias is limited when patients are followed and information is gathered prospectively. By contrast, recall bias can be a serious problem in case-control studies. Broader categories of patients are more often included in cohort studies than in randomised studies. Therefore, it is usually easier to generalise the results.
of cohort studies to clinical settings. Moreover, it is possible to relate pos-
sible prognostic factors and exposures (such as treatments) to outcomes,
but it can be challenging to draw conclusions about causal relationships.
Selection bias can influence the association between treatment and out-
come if certain patient groups with inherent differences in prognosis tend
to receive different treatments. Therefore, selection biases may explain why
continuation ECT was not associated with statistically significantly re-
duced risks of hospitalisation (study II) or time to regain occupational
functioning (study V). Although selection biases limit the conclusions that
can be drawn from observational studies, the associations found in observ-
vational studies can be used to form hypotheses, which can then be tested
in experimental studies.

The proportion of time spent hospitalised was compared before, during,
and after continuation ECT in study IV. The study was designed in this
manner because the patients who received continuation ECT could poten-
tially be different than patients who received pharmacotherapies. For ex-
ample, there may have been differences in response or adherence to phar-
macotherapies. The patients act as their own controls in this design. The
results clearly showed that relapses/recurrences occurred with continuation
ECT and that there was a possible treatment effect on the need for hospi-
talisation. However, the index ECT series could also affect the disease.
Therefore, a control group that receives acute ECT and not continuation
ECT would also provide a relevant comparison. This type of group was
available for comparison in study II. Although the rate of hospitalisation
tended to be lower in the group that received continuation ECT than in the
group that only received medication, the difference was not statistically
significant. It is likely that the doctors anticipated higher relapse risks for
some patients because of differences in adherence or benefits from pharma-
cotherapies. If the doctors prescribed continuation ECT to patients with
higher relapse risks, then a differential relapse risk in the treatment groups
was introduced. This may have created a bias that increased the relative
relapse rate of patients who received continuation ECT relative to patients
who did not.

**Scientific implications**

This thesis presents the first randomised controlled trial of the combined
use of antidepressant-lithium pharmacotherapy and continuation ECT.
There was a statistically significant reduction in the relapse/recurrence risk
when patients were treated with combined antidepressant-lithium pharma-
cotherapy and continuation ECT. This result was expected and consistent
with clinical experience and earlier observational research. Larger studies are required to confirm this result, and the results of study III provide an assumption for the effect sizes in these future studies.

There have been only a few studies on the prognosis for occupational functioning in depression. The data in Study V in this thesis showed that data on sick leave could be obtained and analysed among different groups of patients who received different treatments. Therefore, it is likely that future studies will use similar approaches. Furthermore, sick leave data can also be used as a relatively hard end-point for future randomised studies in addition to symptom rating scales.

Most of the clinical characteristics that influenced response rates were previously demonstrated (96, 106, 130). However, these results add to this field of work and provide additional information about the strengths of the associations because of the large sample size.

**Clinical implications**

Guidelines recommend that ECT be used to treat severe cases of depression. The results in this thesis are consistent with those recommendations and strengthen the indication for ECT in the most severe cases of depression. The maintenance of remission is a great challenge when treating major depression. Many clinicians believe that continuation ECT is effective in reducing relapse rates, but there is little evidence to support this hypothesis. The results in this thesis strengthen the indication for continuation ECT, especially for patients who did not receive benefits from pharmacotherapies alone.

In routine clinical practice, there is a high risk of relapse after treatment, and a variety of different pharmacological agents are used to control the symptoms of depression. Previous studies provided evidence for the efficacy of antidepressants and lithium in reducing the risk of relapse, but lithium treatments are given as a post-ECT prophylaxis in only a small fraction of the patients (3, 124). The results of the studies in this thesis support the wider use of lithium. The use of benzodiazepines is sometimes unavoidable because they reduce intolerable anxiety in severe psychiatric disorders. The results of the studies in this thesis indicate that long-term benzodiazepine treatment is associated with an increased risk of relapse/recurrence of depression and an increased time to regain occupational functioning. Therefore, the benefits of benzodiazepines should be carefully balanced against these risks.
Prescriptions of antipsychotics for unipolar depression have probably increased in the last decade. The scientific foundation underlying the adjunctive effects of antipsychotics combined with antidepressants in the long-term treatment of unipolar depression is weak. There are no published studies that support prophylactic treatments with antipsychotics to reduce relapse rates in patients treated for unipolar depression without psychotic symptoms. Furthermore, there are no guidelines that recommend treating such patients with antipsychotics. It is difficult to draw a firm conclusion based on observational data because of the risk of selection bias. However, the patients in our cohort who were treated with antipsychotics had a higher relapse rate than patients who did not receive antipsychotics. All antipsychotics have side effects and most are associated with weight gain. Unless controlled trials are published that support the use of antipsychotics in the long-term treatment of depression, the use of antipsychotics after ECT in non-psychotic major depression should be restricted.

In recent years, there has been an ongoing debate about the contribution of ECT to declining cognitive functions in patients with affective disorders. The results of this thesis do not suggest that continuation ECT results in long-term deficits in subjective memory or declines in cognitive functions. This finding is consistent with published research (145), but more studies are required.

In conclusion, the short-term response rates to ECT are relatively high for all subgroups, and especially for older inpatients and patients with severe depressions. Occupational functioning is often regained after ECT, but it takes a considerably longer amount of time than symptom relief. However, relapse/recurrence rates are high in the first few years after ECT. Continuation ECT and lithium treatment can be used to supplement antidepressants in order to reduce this risk. More randomised controlled trials are necessary to define the indications for continuation ECT and lithium.

Further developments of other strategies that reduce the risks of relapse/recurrence of depression are required. To date, there have been no clinical trials assessing combinations of ECT given in conjunction with psychotherapy. Therefore, the effects of different combinations of ECT, pharmacotherapy, and psychotherapy need to be assessed.

Also, no randomised trials that compare ECT to pharmacotherapies exclusively in patients suffering from moderate severity depression are published. Therefore, it is unknown if pharmacotherapies in combination with
ECT are more effective than pharmacotherapies in patients with moderate depression. Randomised trials would be valuable to estimate the efficacy of ECT plus pharmacotherapies relative to pharmacotherapies and pharmacotherapies combined with psychotherapies in moderately depressed patients who do not remit within weeks of pharmacotherapy treatment. Moreover, randomised studies are required to clarify whether there are any persistent cognitive effects of ECT.

In other fields of medicine, there are biomarkers that can guide clinicians to treatment alternatives. However, there are no biomarkers that are currently used in the routine clinical practice of treating mood disorders. Hopefully there will be advances made that will allow combinations of genes or other biomarkers to be useful for tailoring combinations of treatments to individual depressed patients.
SAMMANFATTNING PÅ SVENSKA (SUMMARY IN SWEDISH)


I kliniska försök har ECT visat sig ge goda resultat vid behandling av svår depression. Men det är osäkert om resultaten är lika goda i klinisk praktik. Dessutom är återinsjuknande vanligt, omkring hälften av patienterna återfår symptom inom ett år efter ECT, trots förebyggande läkemedelsbehandling. Det finns indikationer på att fortsättnings-ECT kombinerat med läkemedel kan skydda mot återfall men det behövs studier där patienterna slumpmässigt fördelas till olika behandlingsgrupper för att undersöka om sådan behandling är effektiv.

Syfte: Det övergripande syftet med avhandlingen var att identifiera kliniska faktorer relaterade till utfallet av ECT för depression och att belysa effekтивeteten av fortsättnings-ECT för att förebygga återinsjuknande.

Metod: Kvalitetsregistret användes i tre studier för att beskriva utfall efter ECT: vilka patientgrupper som tenderade att förbättras, vilka patientgrupper som snabbast kunde avsluta sjukskrivning och vilka patientgrupper som tenderade att bli återinlagda på sjukhus. Andelen som återinsjuknade i två behandlingsgrupper som patienterna slumpmässigt fördelades till, fortsättnings-ECT i kombination med läkemedel eller endast läkemedel, jämfördes i ett kliniskt försök. I en journalstudie undersöktes konsumtionen av inneliggande vård bland patienter som behandlats med fortsättnings-ECT.

Resultat: Åttio procent av patienterna förbättrades omedelbart efter ECT. Högst andel förbättrade sågs bland patienter med psykotisk depression (89 %), bland äldre patienter och bland inneliggande patienter. Den lägsta andelen förbättrade sågs bland patienter med personlighetsstörning (66 %) och bland polikliniska patienter (66 %).
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Patienter som var sjukskrivna under ECT avslutade sjukskrivningen i 59 %, 71 % och 88 % av fallen efter 6, 12 och 24 månader.

Andelen patienter som blev återinlagda på sjukhus var 25 %, 34 % och 44 % efter 6, 12 och 24 månader. Andelen som återinsjuknade var högre bland dem som hade bensodiazepin-behandling och lägre bland litium-behandlade.

Risken för återinsjuknande var signifikant lägre bland patienter som fick fortsättnings-ECT i kombination med läkemedel (32 %) jämfört med dem som endast fick läkemedel (61 %). Särskilt stor var effekten bland patienter som före ECT hade prövat minst två antidepressiva läkemedel med otillräcklig effekt; bland dessa patienter återinsjuknade 85 % vid behandling med endast läkemedel jämfört med 31 % vid behandling med fortsättnings-ECT i kombination med läkemedel. Behandlingen var också associerad med minskat behov av slutenvård.

Slutsats: Andelen patienter som förbättras inom ett par dagar efter ECT är relativt hög i alla studerade patientgrupper och särskilt bland inneliggande patienter och patienter med svåra former av depression. De flesta patienter återfår arbetsförmåga efter ECT, men det tar längre tid än symptomlindringen. Risken för återinsjuknande är hög de första åren efter ECT. Fortsättnings-ECT och litium behandling kan adderas till antidepressiva för att minska risken för återinsjuknande. Fler studier behövs för att ytterliggare definiera vilka patientgrupper som bör få sådan tilläggsbehandling.
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