Benefits and limitations of electroconvulsive therapy: efficacy, predictors for efficacy, and adverse cognitive effects of ECT

Kho, K.H.

Publication date
2005

BENEFITS AND LIMITATIONS OF ELECTROCONVULSIVE THERAPY

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adverse cognitive effects of ECT

King Han Kho

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ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor aan

de Universiteit van Amsterdam

op gezag van de rector magnificus

prof. mr. P.F. van der Heijden

ten overstaan van een door het college

voor promoties ingestelde commissie,

in het openbaar te verdedigen in

de Aula der Universiteit

op woensdag 30 maart 2005 om 12.00 uur

door

King Han Kho

geboren te Semarang, Indonesië

Benefits and Limitations of Electroconvulsive Therapy
efficacy, predictors for efficacy, and adverse cognitive effects of ECT.
Thesis, Universiteit van Amsterdam, Faculteit der Geneeskunde - with summary in Dutch.
Lay-out: Lisa van Schaick

ISBN 90-6464-856-5

The studies reported in this thesis were conducted in GGZ Delfland, St Jorisweg 2, 2612 GA Delft, The Netherlands.

Printed by Ponsen & Looijen, Wageningen, The Netherlands.

Publication of this thesis was financially supported by:
GGZ Delfland
Janssen-cilag B.V., Tilburg
Medicall Scandinavia AB, Bromma, Sweden

Promotiecommissie

Promotoren:	Prof.dr. D.H.Linszen
	Prof.dr. A.H. Zwinderman
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	Prof.dr. W.A. Nolen
Copromotor:	Dr. B.A. Blansjaar

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INTRODUCTION

Chapter 1
INTRODUCTION

History:

At the beginning of the twentieth century psychiatric institutions were barely able to absorb the increasing numbers of patients. Shorter (1997) described the history of psychiatry in this period. As no treatment options existed all that could be offered was the containment of these patients. This therapeutic nihilism was changed by the introduction of malaria fever therapy for treatment of neurosyphilis in 1917 by Wagner-Jauregg. At that time neurosyphilis was regarded as a psychiatric disorder and the psychiatric departments harboured large numbers of patients suffering from this illness. The illness rapidly progressed and soon led to death. The new treatment did not cure the illness but did offer some relief of the symptoms or at least a slowing down of the process. This heralded a period of optimism as it showed that psychiatric disorders could be treated. Other treatments soon followed. Deep sleep therapy, in which patients were kept asleep for several days with barbiturates, was introduced mainly for treatment of affective disorders. Insulin coma therapy and lobotomy were introduced for treatment of schizophrenia and depression. It was in this era that electroconvulsive therapy (ECT) was introduced in 1938 by Cerletti and Bini.

After the introduction these new therapies were widely used in several countries. Most of these treatments however became obsolete as the adverse effects became apparent and better alternatives were found. Psychotropic medication was introduced in the 1950's. Malaria fever therapy was replaced by penicillin in the 1940's. Lobotomy was pushed to the fringes of psychiatry but has survived as the much safer and refined stereotactic neurosurgery and radioneurosurgery which are still used for treating medication resistant and psychotherapy resistant obsessive compulsive disorder and depression. ECT was also pushed to the fringes of psychiatry in the 1960's and 1970's after the introduction of psychotropic medication and especially after it was targeted by the antipsychiatry movement as a symbol for the suppressive nature of psychiatry. These developments have stimulated the refinement of ECT techniques and more acceptable treatment conditions.

Current situation:

After the introduction of psychotropic medication biological treatment in psychiatry has almost become synonymous with medication, which has been shown to be efficacious and relatively safe compared to other available biological treatments. Psychotropic medication has revolutionalized psychiatry and has helped it to re-establish its connection with other medical specialties (Shorter 1997). The pharmaceutical industry invests large sums of money in research and development of psychotropic medication because the marketing of new psychotropic

medication can be very profitable. New generations of medicines with promise of higher efficacy and less adverse effects have been developed. The use of psychotropic medication has become commonplace and the influencing of brain functions with chemicals has become acceptable to the general public. This is contrary to the more negative view that the general public has on the use of ECT as treatment for psychiatric disorders (Pettinati et al. 1994; McDonald & Walter 2001; Culas et al. 2003). Despite the efforts to develop new and better psychotropic medication, 30-50% of patients treated with antidepressants and 50% of patients treated with conventional antipsychotics are still medication refractory (Hirschfeld 1999; Van Putten et al. 1990). Also the occurrence of adverse effects has not been banished with the newer medicines, which restricts the use of medicines in a large proportion of patients. Because of the existence of medication refractory disorders and adverse effects of medicines the search for alternative treatments remains necessary. ECT has developed into a much safer treatment which in some disorders is more efficacious than treatment with psychotropic medication. In fact ECT is considered a safer treatment for the elderly and medically compromised patients than the traditional heterocyclic antidepressants (APA 2001). These are good reasons why ECT has survived despite its still controversial nature.

Modern ECT techniques:

Initially patients were given electrical stimulation on the head to induce an epileptic seizure in full consciousness. This was painful and the unmodified general seizures sometimes led to fractures especially in patients who suffered from osteoporosis (Lingley and Robins, 1947; Dewald et al., 1954). Early studies suggest that patients sustained microscopic lesions in the brain because of the lack of oxygen as patients stopped breathing for several seconds to minutes after a seizure (Abrams 1997). Nowadays general anaesthesia is induced to prevent that patients suffer pain and anxiety, and a muscle relaxant is used prior to applying the electrical stimulation to prevent fractures. In fact curare is a muscle relaxant which was first used for ECT and later introduced in general surgery. The use of muscle relaxants has facilitated the development of surgical techniques. Succinylcholine is a short-acting muscle relaxant, which has replaced curare in ECT and surgery. Because a generalized seizure is followed by cessation of breathing for a period of time and muscle relaxants prevent the patients from breathing until their effect wears of, oxygenation with 100% oxygen and positive pressure is now used to prevent damage to the brain due to lack of oxygen. Concerns that ECT could lead to brain damage have been addressed by Devanand and colleagues (1994) in their review of the evidence for structural brain damage following ECT. They concluded that no credible evidence exists for brain damage caused by ECT.

Despite the improvements in ECT techniques complaints of memory problems are regularly reported as the most important adverse effect. ECT offers the opportunity to study the influence of

physiological changes in the brain on memory functions, which can explain the interest by memory researchers. Research has been conducted using neuropsychological test batteries for assessing memory functions, showing that adverse cognitive effects have been reduced after the introduction of ECT devices which generate brief pulse electrical stimulation. Older devices which generate sine wave stimulation caused more adverse cognitive effects (Weiner et al., 1986) and have become obsolete. Recent research findings have suggested that the use of devices which can deliver ultrabrief pulses even further reduces adverse cognitive effects without loss of therapeutic efficacy (Pisvejc et al., 1998; Lisanby & Sackeim 2001). Furthermore, we now know that bilateral electrode placement is more efficacious than unilateral electrode placement but carries an increased risk of memory problems (Sackeim et al., 1993). Studies have shown that the therapeutic efficacy is dependent on the generation of generalized seizures. Patients who received real ECT in which a generalized seizure was generated have been compared with patients who received sham ECT in which anaesthesia was induced and an electrical current applied on the head without generating a generalized seizure (Janicak et al., 1985). These studies showed that real ECT was superior in efficacy to sham ECT and the conclusion was drawn that generalized seizures are necessary for the efficacy of ECT. The next advance in knowledge was the discovery that the efficacy of a generalized seizure was associated with the strength of the electrical stimulus used to generate the seizure. Sackeim and colleagues (1993) showed that unilateral ECT was more efficacious if the generalized seizure was generated by an electrical stimulus which was at least two and a half times above the seizure threshold compared to an electrical stimulus just above seizure threshold. For bilateral ECT this association was not found. It was also found that higher electrical stimulations resulted in significantly more adverse cognitive effects.

ECT in the Netherlands:

In the Netherlands ECT is given according the guidelines of the Nederlandse Vereniging voor Psychiatrie (Richtlijnen Nederlandse Vereniging voor Psychiatrie 2000). For treatment of depression ECT is recommended when a rapid response is essential, for instance in life threatening situations (suicidal patients or patients who refuse to eat and drink), and also for psychotic depression, for medication refractory depression, if symptoms of catatonia are present, and if ECT has been shown efficacious in previous treatment. For treatment of bipolar disorder ECT is recommended in medication refractory mania and for treatment of a rapid cycling bipolar disorder. ECT is recommended in schizophrenia with catatonic and paranoid symptoms which are medication refractory and schizophrenia with affective symptoms or schizo-affective disorder. It can also be applied in lethal catatonia, malignant neuroleptic syndrome, delirium, and morbus Parkinson.

The latest data available on the use of ECT in the Netherlands have been collected by the LEE (Landelijke Evaluatie Commissie Elektroconvulsie Therapie 2000) on data from 1999. In that year 328 patients have received ECT in 20 ECT centres in the Netherlands. Twice as many female patients were given this treatment than male patients. The mean age was 60 years with the youngest patient being 18 years and the eldest 92 years. On average patients had to wait for one month before receiving this treatment. There is a steady yearly increase in the number of patients receiving ECT which reflects the growing acceptance of this treatment. The main reason for giving ECT is medication refractoriness (68%). Maintenance ECT was given in 7% of patients.

ECT in GGZ Delfland:

ECT was introduced to GGZ Delfland a general psychiatric hospital situated in Delft in November 1997. ECT was given following the guidelines of the Nederlandse Vereniging voor Psychiatrie (Richtlijnen Nederlandse Vereniging voor Psychiatrie 2000). All treatments were given while patients were admitted to the psychiatric hospital. Patients referred from other hospital were accepted for treatment in GGZ Delfland. From November 1997 until June 2002 100 patients received ECT. 85 were treated for unipolar (n=73) or bipolar (n=12) depression, seven for schizophrenia, three for schizoaffective disorder, five for bipolar (hypo)mania. About 30% of patients admitted to the hospital for treatment of depression received ECT. This high percentage can be explained by an "accumulation" of medication refractory depressed patients who needed ECT in the clinical wards and outpatient departments. Also outpatients were admitted to hospital for clinical ECT treatment. A departure from the Dutch guidelines (Richtlijnen Nederlandse Vereniging voor Psychiatrie 2000) was the use of ECT in patients who preferred to have this treatment without satisfying the criteria as recommended by the guidelines. These guidelines recommend the use of this treatment in depressed patients after several failed adequate trials with antidepressants in the absence of life-threatening situations, in the presence of psychosis, or catatonic symptoms, and if prior treatment with ECT has proven efficacious. Patients' preference as indication for this treatment was introduced in GGZ Delfland to shorten the period of unsuccessful trials with antidepressants.

Pharmacotherapy was continued during ECT. Patients were treated twice weekly to relieve symptoms in the acute phase. This is called index ECT. The responsible clinician assessed treatment progress by weekly Hamilton Rating Scale of Depression scores. Cognitive adverse effects were also evaluated weekly. After termination of successful index ECT pharmacotherapy was continued to prevent a relapse. Patients who relapsed were offered a second ECT course. After a successful second index ECT maintenance ECT was offered. Patients could also choose to have maintenance ECT after the first successful index ECT rather than maintenance pharmacotherapy. Maintenance ECT was started at a frequency of once weekly and tapered to the

lowest frequency to maintain remission. Once every few weeks patients were evaluated in the out-patient department for signs of relapse or adverse cognitive effects.

ECT and cognitive adverse effects:

ECT remains controversial despite the strong evidence for the superior efficacy as an antidepressant (see chapter 2). Critics warn of the dangers of ECT, especially its potential to cause loss of memories. This is called amnesia (Bregin 1998). ECT causes distinctive cognitive disturbances, summarized in the APA task force report on ECT (APA 2001, page 67). In the postictal period the patient can suffer from disorientation, and impairment in attention, praxis and memory, which disappear over time. Deficits in attention and concentration often accompany psychiatric disorders, limiting the capacity to learn new information. Remission of psychiatric symptoms during an ECT course results in the disappearance of these deficits. As attention and concentration are essential to many aspects of cognitive functioning patients improve on many aspects of cognitive functioning during ECT. Amnesia, which is the loss of memories, can be distinguished in anterograde and retrograde amnesia. Retrograde amnesia is the loss of memories acquired prior to ECT and anterograde amnesia is loss of memories acquired after ECT. ECT can cause anterograde and retrograde amnesia. Anterograde amnesia is characterized by rapid forgetting of newly learned information. This deficit resolves within a few weeks after the end of the ECT course. It is unlikely that ECT permanently affects the capacity to learn and retain new information. Research into retrograde amnesias is difficult to conduct as ideally all memories prior to and after ECT should be recorded. This of course is hardly feasible. However Lisanby and colleagues (2001) have conducted such a trial and found evidence for amnesic effects of index ECT, which were still present at two months follow up. Patients who complain of loss of memories following ECT can therefore no longer be told that these adverse effects are minor or temporary (Abrams 1997). As long as the extent of retrograde amnesia following ECT remains unclear a discussion about the dangers of ECT cannot be based on facts. The discussion is further complicated because ECT techniques have been further developed in order to reduce the risk of amnesic effects, whereas critics regularly refer to the amnesic effects of older and obsolete techniques to warn of the dangers of ECT.

It may be important for the acceptance of ECT to assess subjective complaints of memory problems reported by patients, irrespective of objective evidence for these complaints. Rose and colleagues (2003) summarized the subjective views of patients who received ECT and found different levels of memory complaints and acceptance of ECT across the studies. In the era of modern ECT techniques there has been a lack of research into patients' views on ECT. Chapter 4 explores the complaints of memory problems following ECT.

Future developments in ECT:

Because of the risk of adverse cognitive effects ECT should be given after careful consideration, explanation of the pro's and con's and discussion with the patient. For the weighing of the potential benefits and adverse effects of ECT for a particular patient the ability to predict the efficacy of ECT is essential. Chapter 5 explores the usefulness of potential predictors for the efficacy of ECT.

Improving the therapeutic efficacy of ECT is useful. Seizure parameters have been linked to the efficacy of an ECT course. Chapter 6 explores the association between seizure parameters and efficacy of index ECT.

Although initially ECT was widely used for the treatment of schizophrenia few patients with schizophrenia receive ECT nowadays. The Cochrane library (Tharyan 2001) has published a critical review on ECT as treatment for schizophrenia and has concluded that there is evidence for the short-term efficacy in schizophrenia. The evidence for the efficacy of ECT in patients who are refractory to treatment with the most efficacious antipsychotic, clozapine, is sparse. Chapter 7 discusses a case series of clozapine resistant patients suffering from schizophrenia who have been treated with ECT.

Research objectives and outline of the thesis:

This thesis explores several aspects of ECT.

Chapter 2 describes a meta-analysis which addresses the research question: what is the evidence for the efficacy of ECT in depression? Few treatments in medicine have been so extensively studied as ECT for the treatment of depression (APA 2001). This research has been summarized in a meta-analysis by Janicak and colleagues (1985), which mainly included studies using the now obsolete sine wave ECT devices. Since then studies comparing ECT using brief pulse devices, with other treatments have been published. A new meta-analysis was conducted with studies not included in previous meta-analyses.

The next two chapters explore adverse cognitive effects. The research question addressed in *chapter 3* is the evidence for adverse cognitive effects of maintenance ECT. Cognitive adverse effects have mainly been explored for the index ECT. Less research has been conducted on the long-term cognitive effects of ECT after a remission. In some patients a relapse can only be prevented by applying maintenance ECT. A prospective, naturalistic study examining adverse cognitive effects of maintenance ECT in comparison to maintenance pharmacotherapy after index ECT was conducted. *Chapter 4* describes a study which addresses the research question: do depressed patients who have been treated with ECT have more memory complaints that depressed patients who have only been treated with antidepressants? Several standardized and well validated tests for anterograde amnesia are available. For retrograde amnesia however few

tests are available. Retrograde amnesia can therefore only be assessed indirectly by testing the patient's knowledge of public and personal events. Because results can be compared with a population norm these are called objective tests. Due to the inherent uncertainty about reliability of memory recall subjective tests of amnesia have been developed. These assess complaints of memory problems and are called subjective because the results cannot be compared with a population norm. Studies showed that objective anterograde amnesia resolves within a few weeks after an ECT course (APA, 2001), whereas in contrast severe subjective complaints of memory problems can last much longer (APA, 2001: pg. 201; Donahue, 2000). For the acceptance of ECT these subjective complaints can be more important than favourable test results using objective tests of amnesia. Few studies have been conducted comparing objective and subjective retrograde amnesia in depressed patients who received ECT or treatment with antidepressive medication.

Chapters 5 and 6 describe a retrospective chart review using the same samples. In *chapter 5* the research question addressed is: do predictors for the efficacy of ECT exist? ECT is efficacious in around 60% of medication refractory depressions and in 80-90% as a first line treatment (Kalinowsky and Hoch, 1946; Sargent and Slater 1954). Research into predictors for the efficacy of ECT can assist in selecting patients who are most likely to benefit from a treatment. Predictors for the efficacy of this treatment can facilitate a more adequate prescription of ECT and improve the risk-benefit ratio. Little research has been done into predictors for the efficacy of ECT using brief pulse ECT devices. Several variables have been suggested which can predict the efficacy of ECT. The results of studies into these predictors for ECT efficacy are not consistent. In *chapter 6* the research question addressed is: can seizure parameters play a role in optimizing ECT treatment? It has long been thought that the seizure duration is an important parameter for the efficacy of ECT. The association between seizure duration and efficacy however is not strong (APA 2001). As many practitioners believe that a seizure should last at least fifteen seconds for an adequate treatment, the monitoring of seizure duration still remains common practice with ECT. It has been suggested that other seizure parameters are more useful for predicting the efficacy of ECT (Nobler et al., 2000; Luber et al., 2000). Little research has been done linking these parameters with clinical efficacy. The relation between these parameters and ECT efficacy however has been the subject of few studies. Using the same sample as in the study on predictors for the efficacy of an ECT course (see chapter 5) the association between several patient and ECT variables and the speed of response to ECT was explored.

In *chapter 7* the research question addressed is the efficacy in clozapine nonresponders suffering from schizophrenia. Contrary to the well proven efficacy of ECT as an antidepressant less evidence exists for the efficacy in schizophrenia. Little research has been done using modern research methods and current ECT techniques in this group of patients. Obviously it is difficult to persuade patients with schizophrenia, often suffering from paranoid delusions, to participate in a

study and undergo ECT. Clozapine has been shown to have superior antipsychotic properties compared to other antipsychotics. However, 50% of patients who are refractory to treatment with two other antipsychotics still suffer from psychosis following an adequate trial with clozapine (Kane et al., 1988). Little is known about the efficacy of ECT in these clozapine resistant patients suffering from schizophrenia. On this subject no controlled studies have been published, only case reports.

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2
A META-ANALYSIS OF ECT EFFICACY IN DEPRESSION

Kho KH
Vreeswijk van MF
Simpson S
Zwinderman AH.

Journal of ECT, 2003 Sep;19(3):139-47.

Chapter 2
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Kho KH, Vreeswijk van MF, Simpson S, Zwinderman AH.

This article is not available.

3
EFFECTS OF MAINTENANCE ELECTROCONVULSIVE THERAPY ON COGNITIVE FUNCTIONS

Vothknecht S
Kho KH
van Schaick HW
Zwinderman AH
Middelkoop H
Blansjaar BA

Journal of ECT, 2003 Sep;19(3):151-7.

Chapter 3

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Vothknecht S, Kho KH, van Schaick HW, Zwinderman AH, Middelkoop H, Blansjaar BA

This article is not available.

4

A RETROSPECTIVE CONTROLLED STUDY INTO MEMORY COMPLAINTS REPORTED BY DEPRESSED PATIENTS FOLLOWING TREATMENT WITH ELECTROCONVULSIVE THERAPY OR ANTIDEPRESSANTS

Kho KH
Vreeswijk van MF
Murre JMJ

Submitted for publication.

Chapter 4

A RETROSPECTIVE CONTROLLED STUDY INTO MEMORY COMPLAINTS REPORTED BY DEPRESSED PATIENTS FOLLOWING TREATMENT WITH ELECTROCONVULSIVE THERAPY OR ANTIDEPRESSANTS

Kho KH, Vreeswijk van MF, Murre JMJ

Acknowledgement: Liz Sluyter, Sabina van Ginkel, Adeline Sprenger and Annemieke Koppeschaar.

Abstract:

Few studies have been conducted comparing subjective complaints of memory problems in depressed patients who received ECT or treatment with antidepressive medication. Patients who suffer from depression according to DSM IV criteria and were admitted within the past five years prior to this study in GGZ Delfland were screened for inclusion. Objective retrograde amnesia was assessed using the autobiographical memory interview and the Amstedam media questionnaire. Subjective retrograde amnesia was assessed using the Squire subjective memory questionnaire and the ECT retrograde amnesia and perception scale (ERAPS), a newly developed scale. 20 of the 84 patients who received ECT and 30 of the 196 patients who received antidepressive medication participated in the study. Proxy's from the participants also participated in the study. A significant group difference was found for the patient's and proxy's ERAPS memory scores and the Amsterdam media questionnaire 1990's score. This difference could not be explained by the influence of determinants for retrograde amnesia. ECT patients equally attributed complaints about memory problems to the depression, treatment with medication and to ECT treatment. The analysis suggests that the ERAPS memory scale and the Amsterdam media questionnaire 1990's were (more) sensitive in registering retrograde amnesia than the other scales used in the study. The new rating scale ERAPS was found to have good psychometric properties i.e. validity, reliability and applicability.

Keywords:

Electroconvulsive therapy – antidepressive medication – retrograde amnesia - proxy

Introduction:

Although electroconvulsive therapy (ECT) is gaining acceptance as an important treatment for severe depressions it remains controversial. Adverse effects, of which memory problems are

the most important, are emphasized by critics of ECT. Weiner and colleagues (Weiner et al., 1986) showed the existence of selective autobiographical memory deficits at six months follow-up. Other studies however showed that memory deficits caused by ECT are temporary and cannot be observed after three to six months (Calev et al., 1993). Devanand and colleagues (1991) showed that eight patients who had received at least 100 ECT treatments were equivalent in cognitive function scores and subjective memory complaints to matched controls, who had not been treated with ECT.

Research into memory problems following treatment of depression covers several aspects of memory functions. The focus of the current study is on amnesia, which is the loss of memories. This can be differentiated in retrograde and anterograde amnesia. Retrograde amnesia is the loss of memories acquired prior to treatment of depression and anterograde amnesia is the inability to acquire new memories after treatment. Several standardized and well validated tests for anterograde amnesia are available (Hodges, 1995). This is not the case for retrograde amnesia. A reliable direct test for retrograde amnesia would require that all memories preceding treatment are recorded, which of course is not feasible. Retrograde amnesia can therefore only be assessed indirectly by testing the patient's knowledge of public and personal events. Because results can be compared with a population norm these are called objective tests. Due to the inherent uncertainty about reliability of memory recall subjective tests of amnesia have been developed. These assess complaints of memory problems and are called subjective because the results cannot be compared with a population norm. Studies showed that objective anterograde amnesia resolves within a few weeks after an ECT course (APA, 2001), whereas in contrast severe and lasting subjective complaints of memory problems exist (APA, 2001: pg. 201; Donahue, 2000). For the acceptance of ECT these subjective complaints can be more important than favourable test results using objective tests of amnesia.

The current research focuses on retrograde amnesia assessed with objective and subjective tests. Few tests for subjective memory complaints are available. Squire and colleagues have developed the Squire Subjective Memory Questionnaire (SSMQ) containing 18 questions to measure the severity of memory complaints following ECT. They showed that memory complaints can persist after ECT (Squire & Chace, 1975; Squire et al., 1979; Squire et al., 1981; Squire & Slater, 1983). Using this test Squire & Slater (1983) conducted one of the few studies which compared subjective memory complaints in depressed patients who received ECT or not. Memory complaints were found to encompass the period of six months prior until two months after the ECT course. They also found that memory complaints were worse shortly after the ECT course and persisted to a lesser degree for another three years in approximately half of the patients. Most of the studies using the SSMQ were conducted with patients treated with sine wave ECT devices, which may cause significantly more memory problems than brief pulse devices (Weiner et al.,

1986; Daniel et al., 1983). For this reason these sine wave devices are now regarded as obsolete. Even with the use of brief pulse devices, reports of subjective memory problems exist (Donahue, 2000). Memory complaints could be subject to the influence of other factors than ECT. Coleman and colleagues (1996) showed that changes in SSMQ scores following ECT is independent of changes in objective anterograde and retrograde amnesia tests but highly correlated with the degree of improvement in depressive symptoms. Prudic and colleagues (2000) reported that depressive symptoms can influence test results.

We hypothesized that depressed patients who received ECT significantly suffer more from retrograde amnesia than depressed patients who were treated with antidepressants only. This hypothesis was tested by:

1. Between group comparison using the SSMQ test and a newly developed test for subjective retrograde amnesia.
2. Between group comparison using objective tests of personal and public events.
3. Exploring the determinants of retrograde amnesia using several rating scales.
4. Exploring the properties of the newly developed test for subjective retrograde amnesia.

Methodology:

Patients who suffer from depression according to DSM IV (APA, 1994) criteria and were admitted within the past five years prior to this study in GGZ Delfland, Delft, The Netherlands, were screened for inclusion. If they were older than 18 years and able to give informed consent, they were asked to participate in this study. Patients were excluded if the medical records showed or the patients reported that they suffered from a neurological disorder that can cause memory problems or from dementia, if they abused alcohol or drugs, or if they were not fluent in Dutch.

For the ECT patients, the total duration of illness was defined as the period between the first sign of psychiatric disorder reported in the medical records and the first ECT session. The duration of index episode was defined as the period between the first sign of psychiatric disorder prior to the last admission and the first ECT session. For the non-ECT patients the same starting time points were used but the end points were defined by the date of admission as this was taken as the start of a successful treatment with antidepressive medication resulting in a discharge from hospital. The study was approved by the local medical ethical committee.

Rating scales:

The diagnosis on axis I of the DSM IV was made using the Dutch version of the Mini International Neuropsychiatric Interview (MINI; Overbeek et al., 1999), a structured interview which has been validated in relation to the Structured Clinical Interview for DSM III R, the Composite International Diagnostic Interview, and expert professional opinion (Sheehan et al., 1998).

The SSMQ was translated into Dutch by a native English speaking psychiatrist, who is fluent in Dutch. A rating scale based on the complaints from patients who have been treated with ECT was developed by one of us (KK an experienced psychiatrist). This ECT Retrograde Amnesia and Perception Scale (ERAPS) assess complaints of retrograde amnesia, the duration of amnesia and the perception and acceptation of medication and ECT. Memory complaints in four areas of memory are explored and the patients are asked how certain they are that these are a result of their illness and/or treatment (figure 1). The perception of the treatment is further explored in the perception section of the questionnaire. The SSMQ and the ERAPS assess subjective memory complaints.

The Autobiographical Memory Interview (Kopelman, 1989; Kopelman et al., 1990) tests the recall of personal events during several stages in the patients live. This scale has recently been translated into Dutch as the 'Autobiografische Geheugen Interview' (AGI; Meeter & Murre, 2002). With the Amsterdamse Media Vragenlijst (AMV; Meeter et al., 2000) the knowledge of public events from the 1970's, 1980's and 1990's was scored. The AGI and the AMV are objective rating scales for retrograde amnesia.

The Beck Depression Inventory (BDI; Beck et al., 1961) and Hamilton Rating Scale of Depression (HRSD; Hamilton, 1967) were used to score the severity of depression. Personality traits were tested using the Dutch shortened version of the Minnesota Multiphasic Personality Inventory: the Nederlandse Verkorte MMPI (Nederlandse Verkorte MMPI: NVM, Luteijn & Kok, 1985). Information on personal data and illness variables were gathered using information from the medical records.

The BDI, HRSD, NVM, personal and illness variables were used in the analyses as potential confounding variables for memory complaints. The NVM, ERAPS, SSMQ, AGI, AMV and BDI are self-rating scales.

Rating procedure:

The MINI and HRSD were administered by three trained undergraduate research students who were blind to the treatment condition received by the patient. The spouse, close relative or friend of the patient was asked to complete the ERAPS independently from the patient. To explore the presence of depressive symptoms suffered by the proxy they were also asked to score the HRSD. The tests took about two hours to complete.

Patients were invited to have the assessments in the hospital. The tests were applied counterbalanced i.e. half of the patient sample was given the tests in a particular order. This order was reversed for the other half of the sample. The ERAPS was repeated by the patients after about four weeks to allow an assessment of the test-retest reliability.

Figure 1: ECT Retrograde Amnesia and Perception Scale (ERAPS)

RETROGRADE AMNESIA

You suffer from a depression for which you have received treatment or are still receiving treatment. Complaints of memory problems, so called “forgetting”, can occur as a result of depression or can be caused by the treatment. In order to improve the treatment of depression it is necessary to gain insight into this “forgetting”. It is also important to know what patients think of their treatment. With this questionnaire it is possible to gain insight into memory complaints and into your opinion of the treatment.
It is normal for people to forget even if they are not depressed. Try to distinguish between this normal “forgetting” and “forgetting” due to your depression and treatment.

PLEASE ANSWER THE FOLLOWING QUESTIONS IF YOU HAVE LOST MEMORIES AFTER THE TREATMENT **AND** YOU SUSPECT THAT THIS COULD BE A RESULT OF YOUR DEPRESSION AND/OR THE TREATMENT.

MAIN QUESTIONS ON MEMORY

1. Have you lost memories that are precious to you, to a large part as a result of your depression or the treatment? (For example exceptional holidays, births or decease of relatives etc.)
2. Have you lost other memories for a large part as a result of your depression or the treatment?
3. Have you lost certain knowledge as a result of your depression or the treatment? (For instance important facts from politics, knowledge gained during your schooling etc.)
4. Have you lost certain skills as a result of your depression or the treatment? (For instance orientation skills, recognizing faces etc.)

Categories:

1. certainly not
2. probably not
3. maybe not
4. I don’t know
5. maybe yes
6. probably yes
7. certainly yes

ECT PERCEPTION QUESTIONS

1. Do you think that this “forgetting” of memories, knowledge or skills is caused by your depression?
2. Do you think that this “forgetting” of memories, knowledge or skills is caused by the treatment with medicines?
3. Would you have accepted treatment with medicines if you would have known in advance that medicines caused this “forgetting” of memories, knowledge or skills?
4. Do you think that this “forgetting” of memories, knowledge or skills is caused by treatment with ECT?
5. Would have accepted treatment with ECT if you could have known in advance that ECT caused this “forgetting” of memories, knowledge or skills?

Categories:

1. certainly not
2. probably no
3. maybe no
4. I don’t know
5. maybe yes
6. probably yes
7. certainly yes
8. not applicable

How annoying do you find this “forgetting” of memories, knowledge or skills?

1. no problem
2. somewhat annoying
3. annoying
4. very annoying
5. I don’t know

ECT procedure:

Prior to the ECT course, patients were informed on the adverse cognitive effects of ECT. Patients were told that after ECT they could loose memories mainly from the most recent past. Psychotropic medication prescribed prior to ECT was continued throughout the ECT course. Anaesthesia was induced with intravenous thiopentone sodium (4-5 mg/kg) and succinylcholine (0.5-1 mg/kg). The blood oxygen level was kept above 95%. Seizures were induced with a customized brief-pulse, constant-current device (Thymatron DGx) with a maximum stimulus level of 1008mC twice weekly. Treatment was started with unilateral electrode placement, which was changed to bilateral placement if there was an insufficient response after six sessions. In life-threatening conditions patients were given bilateral treatment from the onset. The stimulus settings were initially based on the age (Abrams, 1997) and adjusted for the concurrent medication used; the stimulus setting was adjusted 5-10% upwards with the use of benzodiazepines and anti-epileptics. The length of the seizures measured by the EEG was kept above 20 seconds. If seizure duration fell below 20 seconds the stimulus setting was raised at the next session. During once weekly consultations the clinician and patient evaluated the treatment. The decision to stop ECT was made after discussion with the patient if remission was achieved defined as a HRSD score less than eight, if there was a lack of further improvement, or in case of intolerable side effects.

Patients who relapsed after a successful ECT course were offered another treatment course. If this proved successful, maintenance ECT was offered in a frequency of once weekly initially. The frequency was tapered after every three sessions if the mood remained stable to once monthly or less.

Statistical analysis:

Differences between patients who had been treated with ECT or with antidepressive medication only were analyzed using Student's t-tests, Chi-square test, and Mann Whitney *U* test, where appropriate. Differences in correlation coefficients between both groups were analyzed by performing a Fisher *r*-to-*Z* transformation on the correlation coefficients to produce z values. The Z-test was then performed on the z values (Hays, 1988: pg. 591). Analysis of covariance (ANCOVA) was used to explore the confounding influence of covariates on differences in memory scores. The convergent validity of the ERAPS memory scale was assessed by calculating correlations with the AGI, AMV and the SSMQ using Spearman's rho correlation. Cronbach alpha coefficient was used to quantify homogeneity and reliability of the ERAPS memory scale. The test-retest reliability was assessed by calculating correlations between the first and second ERAPS memory scores using Spearman's rho correlation. Agreement between patient and proxy was assessed by calculating the Intraclass Correlation Coefficients. A P-value of 0.05 or less was considered significant.

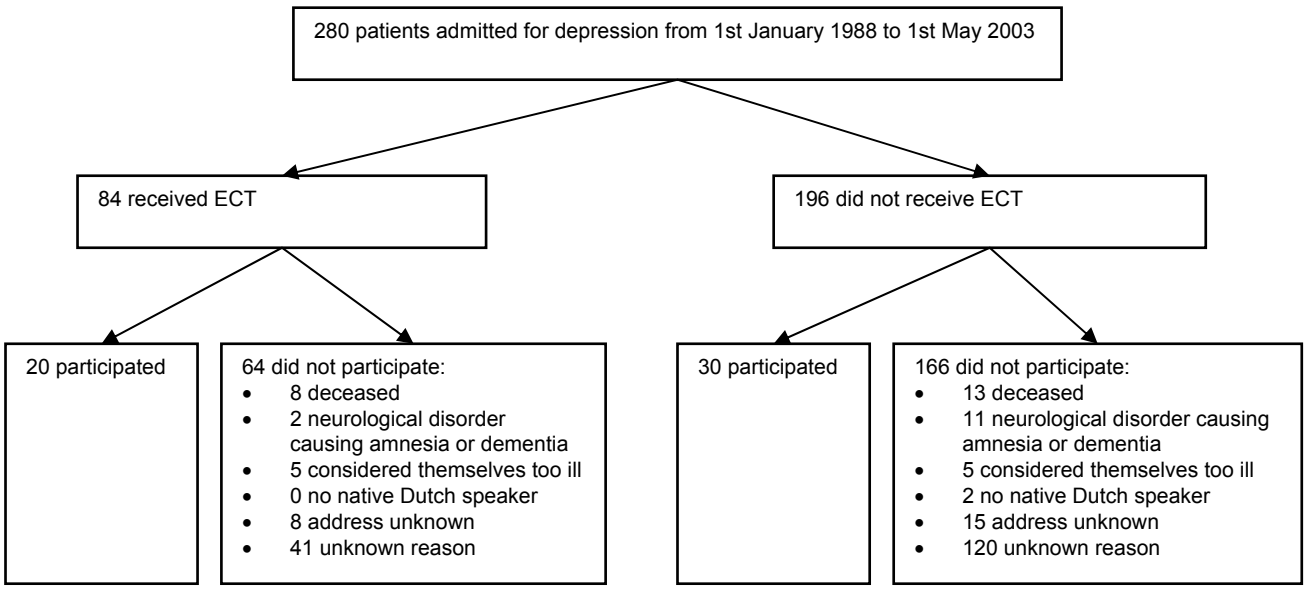
Results:

General results:

From 1st January 1998 to 1st May 2003, 280 patients were admitted to our psychiatric hospital for treatment of their depressive disorder. Figure 2 shows the flow chart of patient selection for the study.

Of the 84 patients who received ECT 64 did not participate and of the 196 non-ECT patients 136 did not participate in the study. The reasons for non-participation were: deceased (8 ECT / 13 non-ECT), neurological disorder which can cause amnesia or dementia (2 ECT / 11 non-ECT), patients considered themselves too ill to participate (5 ECT / 5 non-ECT), no native Dutch speaker (0 ECT / 2 non-ECT), and address unknown (8 ECT / 15 non-ECT). 41(49%) of the ECT patients and 120 (61%) of the non-ECT patients did not participate for unknown reasons. The study population consisted of 20 ECT (24%) and 30 non-ECT (15%) patients.

Figure 2. Flow chart of patient selection:



The average age of the 50 participants was significantly lower than of the 161 non-participants with mean ages of 53 years (S.D. = 13) and 62 years (S.D. = 17) respectively ($T = -3.55$; $P < 0.001$). The gender distribution was 18 male to 32 female patients for the participants and 50 male to 111 female patients for the non-participants. This difference was not statistically significant (Chi-square = 0.43; Fisher's exact test $P = 0.60$).

Group comparisons:

For clarity the abbreviations are summarized in table 1.

Table 1. Abbreviations used in this article.

AGI	"Autobiografische Geheugen Interview"= Autobiographical Memory Interview
AMV	"Amsterdamse Media Vragenlijst" = Amsterdam Media Questionnaire
BDI	Beck Depression Inventory
ECT	Electroconvulsive therapy
ERAPS	ECT Retrograde Amnesia and Perception Scale
HRSD	Hamilton Rating Scale of Depression
MINI	Mini International Neuropsychiatric Interview
NVM	"Nederlandse Verkorte Minnesota Multiphasic Personality Inventory" = Dutch Shortened MMPI
SSMQ	Squire subjective memory questionnaire
SSRI	Selective serotonin re-uptake inhibitor
TCA	Tricyclic antidepressant

Table 2 shows the differences in patients' and illness' variables, medication use, and rating scales between both groups.

No significant differences were found between the ECT and non-ECT groups in age (55 vs. 52 yrs; T = -0.79; P = 0.43) and gender (Chi-square = 1.75; P = 0.24).

No significant difference was found in SSMQ score (59 vs. 64; Mann-Whitney *U, z* = -1.04; P = 0.30). A significant difference was found in patient ERAPS memory score with a higher score in the ECT group compared to the non-ECT group (15 vs. 8; *z* = -2.29; P = 0.02), in proxy ERAPS memory score (15 vs. 10; *z* = -2.94; P = 0.003) and in AMV 90's score (7 vs. 10; *z* = -3.04; P = 0.002). The difference in AMV 80's did not reach statistical significance (6 vs. 7; *z* = -1.70; P = 0.09) whereas no difference was found for the AMV 70's (9 vs. 9; *z* = -0.54; P = 0.59). No significant difference was found in AGI total score (71 vs. 76; *z* = -1.24; P = 0.22). The differences in AGI incidents (18 vs. 21; *z* = -1.93; P = 0.053) and AGI recent memory scores (18 vs. 19; *z* = -1.88; P = 0.06) did not reach statistical significance. Also the difference in total AMV (22 vs. 27; *z* = -1.88; P = 0.06) did not reach statistical significance.

The ECT group had a significantly longer index episode compared to the non-ECT group (4.9 vs. 0.6 yrs; *z* = -3.75; P < 0.001). Excluding the two outliers with the longest index episode (26.3 and 27.6 years, both from the ECT group) still showed a significantly longer index episode for the ECT group (2.3 vs. 0.6 yrs; *z* = -3.39; P = 0.001). No significant difference was found in patient HRSD (11 vs. 9; *z* = -0.17; P = 0.87), BDI (20 vs. 15; *z* = -0.79; P = 0.43), and proxy HRSD (2 vs. 4; *z* = -1.25; P = 0.21).

In order to correct for the confounding effects of duration of index episode, we performed ANCOVA using AMV 90's and ERAPS memory score as dependent variables with treatment group

Table 2: Group differences between ECT and non-ECT patients.

	Total Mean (s.d.)	ECT Mean (s.d.)	Non-ECT Mean (s.d.)	P*
N	50	20	30	
Age at test date	53 yrs (13)	55 yrs (11)	52 yrs (14)	0.43
Gender (m:f)	18:32	5:15	13:17	0.24
Education level (3-7)	5 (1)	5 (1)	5 (1)	0.52
Duration of illness	16.1 yrs (12.4)	18.0 yrs (9.7)	14.8 yrs (13.9)	0.10
range	0.08-51.9 yrs	2.1-30.4 yrs	0.08-51.9 yrs	
Duration of index episode	2.3 yrs (5.5)	4.9 yrs (8.1)	0.6 yrs (0.7)	**<0.001**
range	0.0-27.6 yrs	0.08-27.6 yrs	0.0-2.6 yrs	
TCA**	14 (28%)	4 (20%)	10 (33%)	0.35
SSRI**	17 (34%)	5 (25%)	12 (40%)	0.37
Benzodiazepine**	21 (42%)	8 (40%)	13 (43%)	1.00
Antipsychotic**	10 (20%)	3 (15%)	7 (23%)	0.72
Lithium**	15 (30%)	7 (35%)	8 (27%)	0.55
Time to test	2.9 yrs (1.9)	3.3 yrs (2.2)	2.7 yrs (1.6)	0.45
range	0.08-9.72 yrs	0.13-9.72 yrs	0.08-5.92 yrs	
HRSD patient	10 (10)	11 (12)	9 (9)	0.87
range	0-35	0-35	0-30	
BDI	17 (16)	20 (19)	15 (15)	0.43
range	0-53	0-53	0-48	
HRSD proxy	3 (3)	2 (2)	4 (4)	0.21
range	0-14	0-5	0-14	
NVM negativism	21 (9)	22 (9)	20 (9)	0.52
NVM somatization	16 (11)	15 (12)	17 (11)	0.42
NVM shyness	15 (9)	15 (8)	15 (9)	0.77
NVM severe psychopath.	4 (5)	4 (4)	4 (6)	0.93
NVM extraversion	10 (6)	10 (6)	10 (6)	0.52
AGI total	73 (11)	71 (13)	76 (9)	0.22
AGI incidents	20 (5)	18 (5)	21 (5)	0.053
AGI early childhood	18 (4)	17 (5)	18 (4)	0.62
AGI adulthood	17 (2)	17 (3)	18 (2)	0.72
AGI recent memory	19 (2)	18 (3)	19 (2)	0.06
AMV total	25 (9)	22 (10)	27 (9)	0.06
AMV 70's	9 (4)	9 (4)	9 (4)	0.59
AMV 80's	7 (4)	6 (4)	7 (3)	0.09
AMV 90's	9 (3)	7 (3)	10 (2)	**0.002**
SSMQ	62 (27)	59 (34)	64 (21)	0.30
ERAPS memory score patient	11 (9)	15 (9)	8 (8)	**0.02**
ERAPS memory score proxy	9 (10)	15 (10)	10 (7)	**0.003**
Mean no. unilateral ECT		23 (25)		
Range		0-87		
Mean no. bilateral ECT		5 (9)		
Range		0-36		
Mean number total ECT		27 (23)		
Range		4-87		

*T-test two-tailed, Chi-square test or Mann-Whitney *U* test where appropriate.

**Patients were rated whether they received medication during the tests or not.

as a between-subjects factor and the duration of index episode as covariate. The main effect of treatment group for the AMV 90's [$F(2, 46) = 6.99$, $P < 0.01$] and the ERAPS memory score [$F(2, 42) = 5.23$, $P < 0.05$] remained significant. Duration of index episode was not significantly associated with either AMV 90's [$F(1, 46) = 0.09$, $P = 0.76$] or ERAPS memory score [$F(1, 42) = 1.80$, $P = 0.19$].

Spearman's rho analysis did not show significant correlations between the ERAPS memory score with the number of unilateral ECT sessions (r = 0.31; P = 0.21), with the number of bilateral ECT sessions (r = 0.08; P = 0.75), with the total number of ECT sessions (r = 0.32; P = 0.19), and with the time between the last ECT session and test date (r = -.03; P = 0.92). The AMV 90's did not show significant correlations with the number of unilateral ECT sessions (r = -0.19; P = 0.42), with the number of bilateral ECT sessions (r = -0.19; P = 0.44), with the total number of ECT sessions (r = -0.34; P = 0.14), and with the time between the last ECT session and test date (r = 0.18; P = 0.62).

The patients' opinion on the causes of memory complaints was explored by calculating Spearman's rho correlation between the ERAPS memory score and the ECT perception questions of the ERAPS (see table 3). The ECT perception scores were dichotomized to "No" (score 1-3) and "Yes" (score 5-7). The "I don't know" score (score 4) was omitted.

For the total study population the ERAPS memory score was significantly and positively correlated with the perception that memory complaints were caused by the depressive disorder and by the treatment with medication. ECT patients also significantly attributed memory complaints to the depressive disorder and treatment with medication and the non-ECT group significantly attributed memory complaints to the depressive disorder. No significant group differences in correlations were found as shown by the non significant Z-test. The level of annoyance about memory problems was significantly higher in the ECT group than in the non-ECT group ($z = -2.16$; $P = 0.04$).

Table 3: Spearman's rho correlation between ERAPS memory score and dichotomized ERAPS perception score of the ERAPS.

	Total population (N)	ECT group (N)	Non-ECT group (N)	Z-test	P#
Attribute to depression	0.68** (40)	0.55* (15)	0.66** (25)	-0.49	0.63
Attribute to medication	0.50* (35)	0.57* (13)	0.41 (22)	0.54	0.59
Accept medication	0.11 (34)	0.22 (12)	-0.02 (22)	0.60	0.55
Attribute to ECT		0.40 (16)			
Accept ECT		0.22 (15)			

* = P < 0.05
** = P < 0.001
# = two-tailed significance

Properties of the ERAPS:

The Spearman's rho correlation between the first and second scores was 0.83 (N = 31; P < 0.001). The Cronbach Alpha was 0.87. The Spearman's rho correlations between the patient's and proxy's ERAPS memory scales with SSMQ, total AMV, and total AGI scores are shown in table 4.

Table 4: Convergent validity of the ERAPS memory scale using Spearman's rho correlations.

	SSMQ	Total AMV	Total AGI	Multiple R#
ERAPS memory scale patient	-0.37* N = 38	-0.45** N = 44	-0.60** N = 45	0.684
ERAPS memory scale proxy	-0.45* N = 31	-0.45* N = 35	-0.57** N = 36	0.741

*P < 0.05
**P < 0.005
#Multiple R represents the correlation between the ERAPS with the SSMQ, AMV, and AGI.

The agreement in ERAPS memory scores between the patient and their proxy was compared by calculating the Intraclass Correlation Coefficients (ICC). The ICC were 0.74 (N = 32; 95% C.I. = 0.47 to 0.87; P = 0.0002) for the question "Have you lost memories that are precious to you, to a large part as a result of your depression or the treatment? (For example exceptional holidays, births or decease of relatives etc.)", 0.78 (N = 32; 95% C.I. = 0.55 to 0.89; P<0.0001) for the question "Have you lost other memories for a large part as a result of your depression or the treatment?", 0.60 (N = 32; 95% C.I. = 0.17 to 0.80; P = 0.007) for the question "Have you lost certain knowledge as a result of your depression or the treatment? (For instance important facts from politics, knowledge gained during your schooling etc.)", and 0.49 (N = 31; 95% C.I. = -0.07 to 0.75) for the question "Have you lost certain skills as a result of your depression or the treatment? (For instance orientation skills, recognizing faces etc.)"

Discussion:

A significant between group difference was found in the patient's ERAPS memory, the proxy's ERAPS memory, and the AMV 90's scores (P = 0.02, 0.003, and 0.002 respectively). These results suggest, that patients who have been treated with ECT (and their proxy) were more convinced that they suffered from retrograde amnesia due to their illness or treatment. This conviction found an objective support by the finding that the ECT patients had a significantly lower score on the AMV 90's. As the difference in AMV 80's and AMV 70's did not reach statistical significance this suggests that patients who received ECT suffered from retrograde amnesia for the most recent past. This is also supported by the AGI, where the AGI recent memory just failed to reach significance while the more remote periods did not show such a trend. In contrast no difference was found in subjective memory complaints using the SSMQ. This is consistent with the finding by Coleman and colleagues (1996) who found no difference in SSMQ scores two months after brief pulse ECT compared to a normal control group. It is possible that the SSMQ is less

sensitive in detecting long term retrograde amnesic effects of ECT than the ERAPS memory scale and the AMV 90's. As already mentioned, research on the SSMQ has mainly used patients treated with sine wave devices which are now regarded as obsolete. It may be that the use of brief pulse ECT devices has lowered the extent of memory complaints to the point where they can no longer be detected with the SSMQ.

The finding that ECT is associated with retrograde amnesia for the recent past is consistent with the results from studies by Squire and colleagues (Squire et al., 1979; Squire et al., 1981; Squire & Slater, 1983). These studies concluded that ECT causes retrograde amnesia. An alternative explanation for our finding that ECT patients suffer significantly more from retrograde amnesia is that the more severe retrograde amnesia reflects the more severe depression suffered by ECT patients compared to non-ECT patients. In the Netherlands ECT is mainly prescribed to patients who suffer from severe depression after several trials with antidepressive medication have failed. As the level of depression is known to affect memory functions (Prudic et al., 2000), a more severe depression could result in more severe impairment in the formation of new memories. In our analysis a longer index episode prior to treatment was taken as a measure for the severity of depression. We found that the ECT group indeed showed a significantly longer index episode and a lower AMV 90's score compared with the non-ECT group. This was true even if two outliers with the longest duration of index episode, who both received ECT, were excluded from analysis. As the ECT group had a longer index episode, suffered more from memory problems for the recent past, and the duration of index episode is positively correlated with memory problems further analysis was necessary to explore the association between ECT, duration of index episode, and retrograde amnesia. The other potential determinants for retrograde amnesia age, gender, education level, total duration of illness, duration of index episode, NVM scores, HRSD and BDI scores did not differ significantly in the between group comparisons and were therefore not used for further analysis. The duration of index episode was used as covariate for the ANCOVA of ERAPS memory scale and AMV 90's. The results showed that even if the influence of duration of index episode was taken into account the ERAPS memory and AMV 90's scores remained significantly associated with having received ECT or not. The severity of depression, as expressed by the duration of index episode, did not influence the finding that ECT patients complained more of subjective and objective retrograde amnesia.

Retrograde amnesia in the ECT group was further explored. The analysis showed that the number of unilateral, bilateral, total ECT sessions, and the time between the last ECT session and test date were not significantly correlated with the ERAPS memory and AMV 90's score. Retrograde amnesia was not associated with the number of ECT treatments given or when the last ECT treatment was given.

With the ERAPS perception questions, the attribution of memory complaints to depression or treatment was further explored by correlating these questions with the ERAPS memory scores. The analysis using patients from both groups showed that patients attributed the complaints mainly to the depressive disorder and to a lesser degree to treatment with medication. Both correlations were significant. ECT and non-ECT patients attributed memory complaints roughly equally to depression and treatment with medication. The differences between the two groups were not significant. Surprisingly the ECT patients tended not to attribute memory complaints to treatment with ECT but rather to depression or treatment with medication. These findings suggest that although ECT patients were more convinced that they suffered from retrograde amnesia due to their illness or treatment, they put equal “blame” on the depression and treatment with medication or ECT. ECT was not perceived as the most important cause of amnesia.

ECT patients found their memory problems significantly more annoying than the non-ECT patients. In both groups the severity of memory complaints did not affect the acceptance of treatment with medication or ECT as shown by the small and non-significant correlations between acceptance of treatment and ERAPS memory score. The number of patients in this study was small limiting the generalizability of the findings. Further research is necessary with a larger population to resolve the association between memory complaints and attribution.

The properties of the ERAPS memory scale were explored as well. The test-retest reliability was good as shown by the Spearman’s rho between the first and second score, and so was the internal consistency as shown by the Cronbach alpha. The convergent validity was analyzed by calculating the correlations between the ERAPS memory score with the SSMQ, total AMV and total AGI. This showed a good convergent validity of the ERAPS memory scale. In order to assess the reliability of the patient’s complaints of amnesia the patient ERAPS memory score was compared with the proxy memory score. The Intraclass Correlation Coefficients for the four main questions reflect the agreement between the patient and proxy ratings. The coefficients ranged from 0.49 to 0.78, which showed that the patient and the proxy had a reasonably good agreement for the ERAPS memory scale. It is possible that the proxy’s ratings are influenced by the presence of depressive symptoms in the proxy. This however was not the case as the group comparisons did not show a statistical difference in depressive symptoms using the HRSD scores of the proxy. The analysis showed that using the ERAPS memory scale the proxy was able to reliably assess the patient’s memory complaints.

A large proportion of patients did not participate in the study for unknown reasons in the ECT and non-ECT groups (49% and 61% respectively). The low participation rate in this study limits the generalizability of results. The non-participants were significantly older than the patients who agreed to participate. This particularly lowers the generalizability of results to the older age group. Although the low participation rate to this study could give rise to selection bias, it is not very

probable that this bias could explain the differences found in the between groups comparisons. In spite of these limitations the analyses show some interesting results.

The literature review by Rose and colleagues (2003) showed that 29 to 79% of patients complained of memory loss. Using a new rating scale, we found that in our study ECT patients were more convinced that they suffered from memory problems as a result from depression or treatment than non-ECT patients. This is supported by a lower score in knowledge of recent public events in the ECT group. ECT patients did not see ECT as the main cause of their memory problems; memory problems were equally attributed to the depression and treatment with medication or ECT.

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PREDICTORS FOR THE EFFICACY OF ELECTROCONVULSIVE THERAPY: CHART REVIEW OF A NATURALISTIC STUDY

Kho King Han
Zwinderman Aeilko H
Blansjaar Ben A

In press, Journal of Clinical Psychiatry, 2005.

Chapter 5

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6
A STUDY INTO PREDICTORS FOR THE SPEED OF RESPONSE TO ELECTROCONVULSIVE THERAPY

K.H. Kho
B.A. Blansjaar
S. Vothknecht
N.M.P. Cornelissen
E. Koomen
A.H. Zwinderman
D.H.Linszen.

Journal of ECT, 2004 Sep;20(3):154-159.

Chapter 6

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K.H. Kho, B.A. Blansjaar, S. Vothknecht, N.M.P. Cornelissen, E. Koomen, A.H. Zwinderman, D.H.Linszen.

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7

ELECTROCONVULSIVE THERAPY FOR THE TREATMENT OF CLOZAPINE NONRESPONDERS SUFFERING FROM SCHIZOPHRENIA: AN OPEN LABEL STUDY.

Kho K.H.
Blansjaar B.A.
de Vries S.
Babuskova D.
Zwinderman A.H.
Linszen D.H.

European Archives of Psychiatry and Clinical Neuroscience, 2004 Nov;12.
The original publication is available at www.springerlink.com
DOI: 10.1007/s00406-004-0517-y

Chapter 7

ELECTROCONVULSIVE THERAPY FOR THE TREATMENT OF CLOZAPINE NONRESPONDERS SUFFERING FROM SCHIZOPHRENIA: AN OPEN LABEL STUDY

Kho K.H., Blansjaar B.A., de Vries S., Babuskova D., Zwinderman A.H., Linszen D.H.

Abstract:

Objective: This open label study describes the efficacy of electroconvulsive therapy (ECT) as adjunctive treatment in clozapine nonresponders suffering from schizophrenia.

Method: The results of clozapine and ECT treatment in 11 clozapine nonresponders suffering from schizophrenia are reported in terms of remission and relapse.

Results: Eight patients had a remission with this combination treatment. After remission of symptoms five patients had a relapse. Three of the five patients who relapsed had a second successful ECT course and remained well with maintenance ECT and clozapine. No evidence for adverse effects was found.

Conclusion: Adjunctive ECT can be efficacious in clozapine nonresponders suffering from schizophrenia.

Keywords:

Electroconvulsive therapy - clozapine nonresponders – schizophrenia - open label study

Introduction:

Treatment with conventional antipsychotic medication is usually efficacious in 50% of patients suffering from schizophrenia (Van Putten et al. 1990). Kane et al. (1988) showed that clozapine could be efficacious in 50% of patients who still suffer from schizophrenia after unsuccessful treatment with two different antipsychotics at adequate doses including a depot medication. Although the superior efficacy of clozapine compared to conventional antipsychotics has been shown in a meta-analysis by Wahlbeck et al. (1999), in theory 25% of all patients suffering from schizophrenia cannot be treated adequately with either conventional antipsychotics or with clozapine. Adjunctive treatment with electroconvulsive therapy (ECT) is one of the treatment options used for clozapine nonresponders. To the authors knowledge no controlled trials on the efficacy of adjunctive ECT treatment in patients suffering from clozapine resistant schizophrenia have been published. The evidence for its efficacy is mainly based on case reports and case series.

A Medline search using the keywords ECT and clozapine identified 21 case reports and case series published between 1991 and 2000 describing 60 patients who have been treated with clozapine and ECT (see table 1).

Patients suffering from schizophrenia nonresponsive to clozapine were described in nine case reports and case series (Safferman & Munne 1992, Frankenburg et al. 1993, Cardwell & Nakai 1995, Benatov et al. 1996, Petrides et al. 1998, Bhatia et al. 1998, James & Gray 1999, Kales et al. 1999, Husni et al. 1999) comprising 23 patients. 21 of these patients were reported to have responded well to the clozapine and ECT combination treatment, whereas two did not improve. Patients who responded well to this combination treatment remained well for three weeks to two years. Except for two reports (Bhatia et al. 1998, Kales et al. 1999) no information was given on relapse rates. The patient described by Bhatia et al. (1998) had a relapse within two weeks after a successful ECT course. This patient however was clozapine noncompliant following ECT. The case series by Kales et al. (1999) reported relapses occurring after one to four months in four out of five patients who responded well to adjunctive ECT treatment. The only patient who did not have a relapse remained well during two years of follow up.

Despite concerns raised by several authors there were only a few reports of adverse effects. Masiar and Johns (1991) reported the occurrence of grand mal seizures several days after one ECT session in a patient who was tapered of diazepam and clozapine prior to ECT. Although these seizures could be precipitated by the single ECT session the tapering of diazepam and clozapine could also be the cause. A prolonged seizure, which seemed to be benign, was reported in two case studies (Bloch et al. 1996, Poyurovsky & Weizman 1996). Cardwell and Nakai (1995) specifically reported the absence of prolonged seizures with this combination treatment. Several reports described tachycardia as adverse effect (Landy 1991, Klapheke 1991, Beale et al. 1994). This side effect seemed to be benign although Beale et al. (1994) reported that a patient treated with clozapine, ECT, and caffeine for a psychotic depression, died three weeks after her last ECT session. The authors considered it unlikely that ECT precipitated her death. Chanpattana described post seizure delirium, which occurs in 10% of ECT treatments (Poyurovsky & Weizman, 1996).

These reports support the use of ECT as adjunctive treatment for clozapine resistant schizophrenia. To add to the literature on this combination treatment we describe results of an open label study of clozapine plus ECT treatment for 11 clozapine nonresponders suffering from schizophrenia.

<Insert Table 1>: Published articles on ECT and clozapine.

Materials and methods:

From January 2001 to May 2003 13 clozapine nonresponders suffering from schizophrenia were given adjunctive ECT treatment in GGZ Delfland, a general psychiatric hospital in the Netherlands. Clozapine nonresponse was defined as persistence of psychotic symptoms (hallucination or delusion) despite treatment with clozapine. All patients had to be admitted due to the severity of their psychotic symptoms except for case 2. This patient was treated at the outpatient department but requested to have ECT because of persistence of psychotic symptoms. His PANSS score was the lowest (see table 2). All patients who gave informed consent were included in the analysis even if the treatment course was terminated prematurely.

The diagnosis of schizophrenia according to DSM IV criteria was made using the Mini International Neuropsychiatric Interview (MINI, Overbeek et al. 1999). When the MINI pointed to the presence of an affective disorder the 17-item Hamilton Rating Scale of Depression (HRSD, Hamilton 1967) or the Mania Scale (Young et al. 1978) were applied. As affective symptoms frequently occur in the course of schizophrenia (Johns & Thompson 1995) and ECT is an effective treatment of affective disorders, the monitoring of affective symptoms is necessary to allow discrimination between the effects of ECT on affective and psychotic or negative symptoms of schizophrenia. Information on patient and illness characteristics and clozapine treatment was obtained from the medical files. Once weekly the symptoms of schizophrenia were monitored using the Positive and Negative Scale of Schizophrenia (PANSS, Kay et al. 1987) by KK, SdV and DB. Two raters assessed several patients, in order to achieve good inter-rater reliability. Good inter-rater reliability was defined as a difference in total PANSS score less than ten points achieved on several simultaneous assessments. Thereafter each patient was followed by one rater throughout the course or replaced by the second rater if necessary. At follow up the PANSS was applied once weekly to once every four weeks.

Prior to the ECT course the PANSS was applied at least three times to ensure that a reduction in PANSS scores was not due to spontaneous remission of schizophrenic symptoms. The ECT course was only started when the baseline PANSS scores remained stable or increased. Remission was defined as a drop of at least 30% from the mean baseline total and positive PANSS scores. Relapse after a successful ECT course was defined as an increase of the total and positive PANSS scores to at least the mean baseline scores. Clozapine blood levels were assessed before and after the ECT course, which allowed the comparison of changes in blood levels and PANSS scores.

Analyses were conducted using the Statistical Package for Social Science software version 10 (SPSS, Chicago, IL). With paired t-tests the mean baseline total PANSS score and clozapine blood level were compared to the mean score and blood level post-ECT; tests were two-tailed.

ECT was given twice weekly. Prior to and during the ECT course clozapine and other psychotropic medication were continued (see table 2). Anaesthesia was induced with intravenous thiopentone sodium (4-5 mg/kg) and succinylcholine (0.5-1 mg/kg). The blood oxygen level was kept above 95%. Seizures were induced with the Thymatron DGx twice weekly. Treatment was started with unilateral electrode placement, which was changed to bilateral placement if there was an insufficient response after six sessions. The stimulus settings were initially based on the age (Abrams 1997) but raised in following sessions when the length of the seizures measured by the EEG fell below the required minimum of 20 seconds. The adequacy of the treatment was discussed weekly with the patients by KK. Patients were weekly asked to report any adverse events which may be related to ECT. A decision to stop the treatment was made by the patient and KK taking into account the change in total and positive PANSS scores, adverse effects of ECT and the preference of the patient. If the total and positive PANSS scores remained above 70% of the mean baseline scores after six bilateral treatments the ECT course was stopped. After such a failed course treatment with clozapine was continued. If the total and positive PANSS scores fell below 70% of the mean baseline scores the course was continued until no further improvement was seen. After such a successful course the patient was followed up for signs of relapse, in which case a second ECT course was recommended. Patients could decide to end the ECT course prematurely because of adverse effects or without giving any reason.

Results:

Using the MINI the diagnosis of schizophrenia was confirmed in all patients. Out of the 13 patients one did not give informed consent and was therefore excluded from analysis. Another patient was excluded because she was monitored using the Brief Psychiatric Rating Scale (BPRS) instead of the PANSS. The analysis was performed on 11 patients, which included two patients (cases 3 and 4), who stopped the ECT course prematurely. Case 3 stopped the course prematurely because of lack of efficacy after six unilateral sessions and case 4 because he experienced a reduction of auditory hallucinations, which he enjoyed hearing. The patient characteristics are given in table 2.

Six male and five female patients were treated with ECT. At the start of ECT the mean age was 43 years (s.d. = 14, range= 23-67), with a mean duration of total illness of 194 months (s.d. = 157, range= 30-528) and mean duration of current psychotic episode of 24 months (s.d. = 35, range= 2-120). Except for case 11, who previously responded well to a combination of risperidon 6 mg daily, lithium 600 mg daily and ECT but relapsed when ECT was stopped, none of the patients had previously received ECT.

Figure 1 shows the changes in mean total, positive, negative and global PANSS scores at baseline, during and after ECT. Three baseline scores are shown: the first, the lowest and the last

score. At the baseline a 10 points difference between the mean highest and lowest scores was seen. During the ECT course two scores are shown: the first and the last score. During the course a drop in mean PANSS scores was seen. The last score shown is the endscore after termination of the ECT course. The criteria for remission (a drop of at least 30% from baseline total and positive PANSS scores) applied to eight patients who had a successful course after a mean number of 10 sessions (s.d. = 5, range= 3-17).

There were significant differences between the mean baseline and post-ECT PANSS scores for the total (n=11, t=4.14, P=0.002), positive (n=11, t=4.03, P=0.002), negative (n=11, t=3.16, P=0.01) and global scores (n=11, t=4.50, P=0.001). Case 6 remained psychotic despite clozapine treatment prior to the ECT course. Clozapine was stopped prior to the course so she did not have adjunctive ECT treatment. During the course clozapine was restarted. Analysis excluding this patient did not affect the significant differences between mean baseline and post-ECT total (n=10, t=3.64, P=0.005), positive (n=10, t=3.55, P=0.006), negative (n=10, t=2.73, P=0.02) and global scores (n=10, t=3.99, P=0.003). Excluding patients who had clozapine treatment for less than eight weeks or clozapine blood levels below 0.30 ng/ml (n=8) did not affect the significant drops during the ECT course with P-values remaining <.05 for all comparisons. Of the eight patients who responded well to ECT six had received clozapine treatment for at least eight weeks with blood levels of at least 0.30 ng/ml prior to ECT. On average blood levels even dropped (n=6, t=2.52, P=0.053) during the ECT course. The MINI showed that only case 5 suffered from an affective disorder, depression, as well as schizophrenia. In this patient the HRSD score fell from 13 pre-ECT to 8 post-ECT.

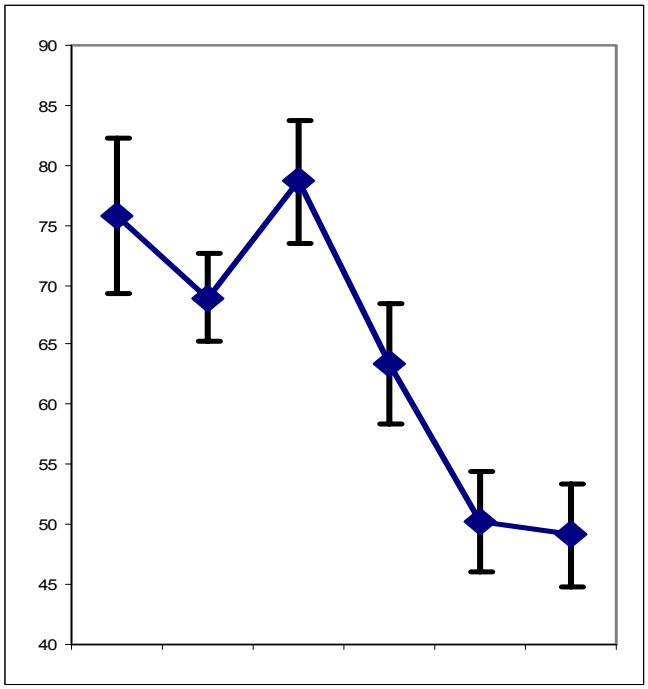
The eight patients who responded well to ECT were followed up for signs of relapse for a mean period of 16 weeks (s.d. = 12, range= 4-42). Relapses occurred in four patients after 3-19 weeks (cases 7, 9, 10, and 11). Case 8 did not have a relapse according to the definition but did so clinically. Cases 7, 8 and 10 received a second successful ECT course followed by adjunctive maintenance ECT in a frequency of once weekly for a period of 6, 12, and 8 weeks respectively. These patients did not have a relapse since.

No evidence was found for prolonged seizures or for cardiac arrhythmia. Two patients (cases 2 and 8) reported memory problems during the course. Case 8 also complained of confusion for several hours after each session. This patient was treated with a combination of lithium carbonate, clozapine, and ECT.

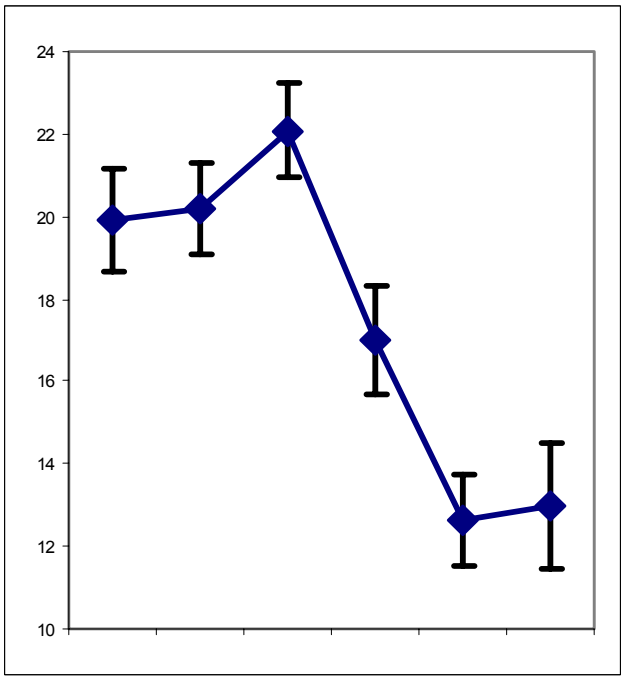
<Insert Table 2>: 11 patients suffering from schizophrenia treated with ECT and clozapine.

Figure 1. Total, positive, negative, and global PANSS scores prior to, during, and after ECT.

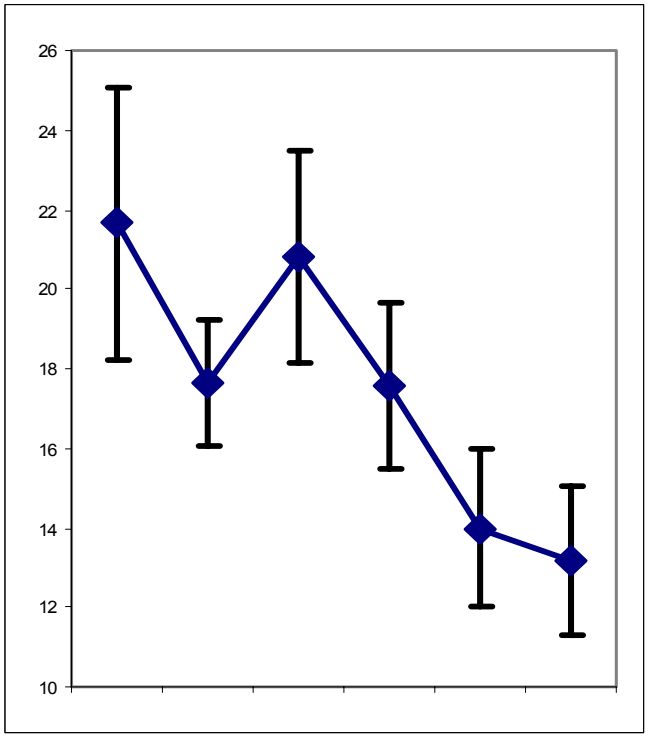
Mean Total



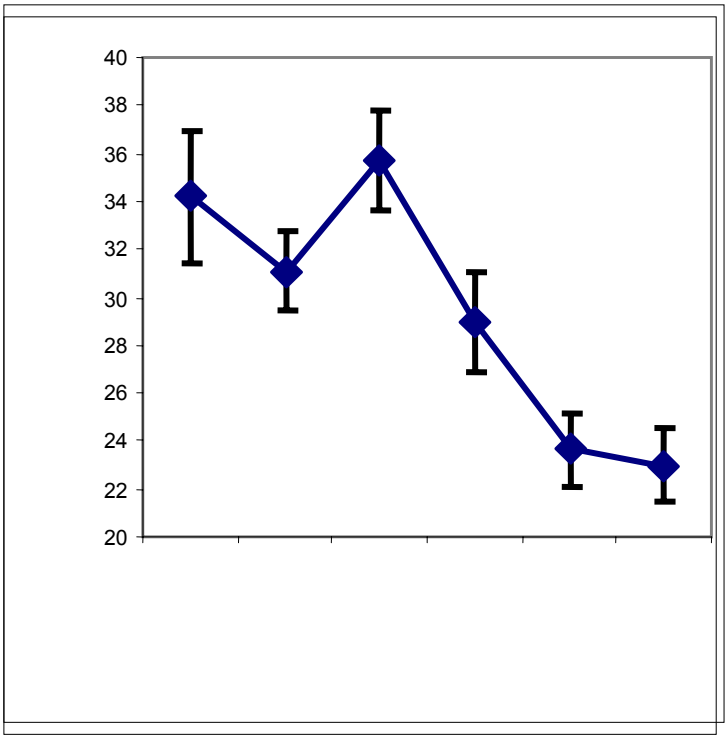
Mean Positive



Mean negative



Mean Global



Discussion:

Our open label study describes the results of adjunctive ECT treatment in 11 clozapine nonresponders suffering from schizophrenia. All patients except one had never received ECT before. These patients have suffered from psychosis for two months to ten years prior to ECT despite treatment with clozapine monitored by blood levels. The graphs in figure 1 show that the changes in mean total, positive, negative and global PANSS scores follow a similar pattern. Previous reviews (Christison et al. 1991, Fink & Sackeim 1996) concluded that ECT is more efficacious for the treatment of positive than negative symptoms of schizophrenia. In this case series however comparable efficacy for positive and negative symptoms of schizophrenia was found as shown by significant results from paired *t*-test comparing mean baseline and post-ECT scores. A possible explanation is the causal relationship between positive, negative and global symptoms. Patients who suffer from positive symptoms tend to withdraw increasing the negative PANSS score. Equally, patients with positive symptoms are likely to show more global symptoms of schizophrenia (anxiety etc.). Still the possibility that ECT is effective for alleviating negative symptoms separate from its antipsychotic properties cannot be excluded as some antipsychotic medication may be specifically efficacious for negative symptoms (Möller 1999, Möller 2001).

The monitoring of schizophrenic symptoms with the PANSS and of affective symptoms with the HRSD was not done blind to the treatment condition. Another source of bias, which may exaggerate treatment results, is the inclusion of patients who despite the persistence of psychotic symptoms agreed to have ECT. Despite these possible sources of bias the efficacy of ECT in this group of patients is remarkable as eight out of 11 patients achieved remission defined by a 30% decrease in total and positive PANSS scores compared to the mean baseline PANSS scores. Two of the three patients who did not have a remission ended the ECT course prematurely.

The criteria for clozapine resistance in schizophrenia are still under debate. Two variables, clozapine blood levels and duration of clozapine treatment, can be used to define these criteria. Studies by Miller et al. (1994), Kronig et al. (1995), VanderZwaag et al. (1996), and Spina et al. (2000) showed that remission rates increase significantly with clozapine blood levels exceeding 350 ng/ml. Meltzer et al. (1989) described the possibility of late response to clozapine even after nine months of treatment and Lieberman et al. (1994) estimated that it can take 12 to 24 weeks before optimal efficacy of clozapine is reached. Conley et al. (1997) however showed in a well-designed study that patients who responded to clozapine showed a significant remission within eight weeks after reaching an effective dose. Group analyses excluding patients with less adequate clozapine treatment (less than 8 weeks clozapine or clozapine blood levels below 0.30 ng/ml) showed significant drops in PANSS scores after adjunctive ECT treatment. Most patients had a remission of their symptoms after 3 to 17 ECT sessions. Remissions cannot be explained by a more adequate clozapine treatment, as blood levels dropped (non-significantly) during the ECT

course. Nor can it be explained by successful treatment of affective symptoms, as only one patient had symptoms of depression prior to ECT.

In the search for new and improved antipsychotics the interactions between different neurotransmitters are studied (Carlsson et al. 1999). ECT as well as antipsychotics influence different neurotransmitters. The interaction between ECT and clozapine on neurotransmitters may yield interesting avenues for further research and aid in gaining insight into the efficacy of antipsychotic medication.

Patients who had a remission were followed for variable periods of time. Although after a successful ECT course five out of eight patients relapsed despite continuation of clozapine, some patients remained well for a long period of time. This suggests that ECT followed by maintenance clozapine treatment can have a prolonged effect in some patients. Three patients received a second successful ECT course followed by maintenance adjunctive ECT treatment and have not relapsed since. The follow up period with maintenance ECT is too short and the number of patients too small to allow conclusions on the beneficial effect of adjunctive maintenance ECT.

In this case series no evidence for serious adverse effects was found. Prolonged seizures were not observed contrary to findings from previous reports (Miller et al. 1994, Bloch et al. 1996). One patient was confused for several hours after each session, which could be due to the combination of lithium, clozapine, and ECT. The combination of ECT and lithium has been reported to cause prolonged periods of confusion (Abrams 1997). This study serves as a pilot to the design of a randomised, controlled study into the efficacy of this combination treatment. The results of this study justify and demand such a randomised controlled trial in patients suffering from clozapine resistant schizophrenia.

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8
DISCUSSION

Chapter 8
DISCUSSION

The meta-analysis in chapter 2 identified fifteen studies which fulfilled the inclusion criteria. From these controlled trials twenty effect sizes of ECT were calculated. The speed of action during the course and the efficacy after a full course of ECT were explored. The efficacy of sine wave and brief pulse machines were compared. The comparison between ECT and four other comparative treatments was made. Predictive variables were explored using homogeneity tests. The analysis showed that ECT was superior in comparison to other treatment conditions, which is consistent with results from other meta-analyses (Janicak et al., 1985; The UK review group, 2003). Severely depressed patients especially those who also suffer from psychosis have a high risk for committing suicide (Roose et al., 1983). Antidepressive treatment with high speed of response is needed for these patients. It has been suggested that ECT is superior in speed of response. Our meta-analysis however could not find evidence for a superior speed of response to ECT compared to other treatments. This finding is contrary to the study by Husain and colleagues (2004) who found evidence a rapid speed of response to ECT in their study using bilateral ECT thrice weekly with stimulus titration. The study however did not compare the speed of response with other antidepressive treatments. The suggestion that sine wave ECT is superior to brief pulse ECT could not be confirmed by our analysis. The wide spread use of brief pulse devices is justified as these are equally efficacious and are known to have less adverse cognitive effects than sine wave devices (Daniel et al., 1983; Weiner et al., 1986). Separate comparisons between ECT and the four other treatment conditions showed that ECT is superior to simulated ECT and antidepressive medication. Comparisons with rTMS and other treatments did not show superior efficacy mainly because too few studies have been published for an adequate analysis. The suggestion that patients suffering from depression with psychosis have a superior response to ECT found some evidence in our analysis. The conclusion that ECT is the most effective treatment for depression still stands.

In chapter 3 clinical outcome data and neuropsychological measurements were compared in 11 maintenance ECT patients and 13 control-patients treated with maintenance pharmacotherapy after index ECT. No difference was found in patient characteristics between the maintenance pharmacotherapy and maintenance ECT groups. After a successful index ECT patients from the maintenance ECT group were followed up for an average of 1.5 years during which one out of 11 patients relapsed. The maintenance pharmacotherapy group was followed up for one year during which four out of 13 patients relapsed. During this follow up cognitive functions were tested on four neuropsychological domains: attention, memory, cognitive flexibility and speed of information processing. Global cognitive functioning was measured by intelligence and memory

quotients. On average maintenance ECT was given once every 2.2 weeks. A comparison of test results immediately after index ECT and after six months maintenance treatment shows on average no changes in test results in the maintenance pharmacotherapy group. In the maintenance ECT group however some evidence was found for improvement of test results. These results showed that maintenance ECT does not have significant adverse cognitive effects compared to maintenance pharmacotherapy on the neuropsychological domains tested. No evidence was found for mood improvement in both groups, which can influence test results. A comparably short mean interval of 2.2 weeks between sessions seems to be sufficient to allow a recovery of cognitive functions to occur. The lack of evidence for sustained deficits in attention, concentration and for anterograde amnesia in patients receiving maintenance ECT is consistent with results from studies on index ECT (APA 2001, page 67). The results of this and other studies may be used as evidence for reassuring patients who fear the permanent loss of memory function following ECT. The evidence for retrograde amnesia was addressed in the next chapter.

Chapter 4 discussed the presence of memory complaints following ECT. Patients who suffer from depression according to DSM IV criteria and were admitted between 1st January 1998 and 1st May 2003 to GGZ Delfland were screened for inclusion. Objective retrograde amnesia was assessed using the autobiographical memory interview and the Amsterdam media questionnaire. Subjective retrograde amnesia was assessed using the Squire subjective memory questionnaire and the ECT retrograde amnesia and perception scale (ERAPS), a newly developed scale. In the study period 280 patients were admitted for treatment of their depressive disorder. 20 of the 84 patients who received ECT and 30 of the 196 patients who received antidepressive medication participated in the study. Participants' proxy's also participated in the study. Patients who received ECT and their proxy's complained more of memory problems as evidenced by a significantly higher ERAPS memory scores and a significantly lower score on the Amsterdam media questionnaire 1990's. ECT patients equally attributed complaints about memory problems to the depression, treatment with medication and to ECT treatment. The analysis suggests that the ERAPS memory scale and the Amsterdam media questionnaire 1990's were (more) sensitive in registering retrograde amnesia than the other scales used in the study.

Chapter 5 describes a study into predictors for the efficacy of ECT. 73 patients suffering from depression were given ECT in the study period lasting from November 1997 until June 2002. 56 patients (77%) were classified as suffering from medication refractory depression. Remission was defined as a reduction of depressive symptoms of at least 60% from baseline and a HRSD end score of less than eight. The influence of the concurrent use of psychotropic medication during ECT was explored. 48 (65.7%) of the 73 patients who participated in the study showed a remission. Only duration of index episode was found to be a significant predictor for ECT efficacy. Contrary to other studies (Prudic et al., 1996; Shapira et al., 1996) medication treatment failure

was not found to be a significant predictor. The recognition of medication treatment failure or duration of index episode as predictor(s) for remission could be theoretically and clinically relevant. If medication treatment failure is an important predictor for ECT efficacy, it could be used to define a group of patients who does not respond to pharmacotherapy or ECT. It would be important to recognize as soon as possible such patients so that other specific treatments, which should be developed for this group of patients, could be given. A search for markers for medication and ECT treatment failure would be warranted. If on the other hand duration of index episode predicts the results of ECT and not medication treatment failure the search for that particular group of patients is not relevant. A search for markers would not be productive. All patients should receive pharmacotherapy and ECT instead. It would however be important not to wait too long before applying ECT to prevent a reduction in efficacy. This is supported by our findings. The analysis showed that concurrent use of psychotropic medication during ECT did not influence the efficacy.

Chapter 6 explores the association between speed of response and seizure parameters in 57 patients suffering from major depression, who received ECT. Speed of response was defined as a drop in HRSD score of at least 35% from baseline after three or four ECT sessions. No significant relation between speed of response and seizure duration was found. In contrast high baseline HRSD score and high seizure energy index (SEI) were significantly and independently associated with a rapid response. Rapid responders to ECT achieved complete remission, defined as a drop in HRSD score of 60% or more from baseline and an end score of less than eight, significantly more often than slow responders did. SEI can be modified by the clinician. Krystal and colleagues (1995) have developed a model for estimating the seizure threshold based on 25 patients who received right unilateral ECT with stimulus intensity at seizure threshold or 2.5 times seizure threshold. The model, which included age and ictal EEG indices, predicted the seizure threshold with 90% accuracy. Further developments incorporated treatment number in the model (Krystal et al., 2000). This model was found to predict the efficacy of ECT adequately in their retrospective study. Such a model including age, seizure quality variables, and possibly other variables will be valuable for clinicians using ECT if it could be shown to adequately predict the speed of response to ECT and the efficacy of an ECT course in a prospective study. The current study shows a promising use of seizure quality variables for optimizing ECT treatment.

Chapter 7 discussed the publications on the combined use of ECT and clozapine. The combined treatment was described in patients suffering from schizophrenia nonresponsive to clozapine in nine case reports and case series comprising 23 patients. 21 of these patients were reported to have responded well, whereas two did not improve. Patients who responded well to the combined treatment remained well for three weeks to two years. Despite concerns raised by several authors there were only few reports of adverse effects. An open label study on the efficacy of ECT as adjunctive treatment in clozapine nonresponders suffering from schizophrenia was

conducted. The results of the combined treatment in eleven patients were reported in terms of remission and relapse. Eight patients achieved remission. In the follow-up phase five of the patients who remitted subsequently relapsed. Three of the five patients who relapsed had a second successful ECT course and remained well with maintenance ECT and clozapine. No evidence for adverse effects was found. This study suggests that adjunctive ECT can be efficacious in clozapine nonresponders suffering from schizophrenia.

Mechanism of action:

How ECT exerts its therapeutic effect is not yet understood. A possible mechanism of action involves the anticonvulsive properties of ECT. Sackeim (1999) has elaborated on the anticonvulsant hypothesis. Seizures can continue for days on end in patients who suffer from epilepsy, possibly because seizure termination does not depend on lack of metabolic substrates or neuronal exhaustion but on an active inhibitory process (Engel, 1989). That this inhibitory process also occurs during an ECT course is evidenced by the increase of seizure threshold during a course with the highest increase occurring in patients with the best response to ECT. Also a reduction of the cerebral blood flow and the cerebral metabolic rate has been reported after a successful ECT course.

Although neuro-imaging studies have shown that different areas of the brain are affected in different psychiatric disorders and epilepsy ECT is an effective treatment for depression, mania, schizophrenia, and epilepsy. How ECT exerts its therapeutic efficacy in disorders localized in different brain regions is unclear. A common pathological pathway for these diverse disorders could explain the wide therapeutic effect of ECT. Edelman (1987) has proposed the theory of neuronal group selection explaining the development of brain functions. Brain neurons are initially randomly connected. Specific brain functions are acquired by pruning of unused neuronal connections and enhancing often used connections. This process explains how the brain develops the regulation of complex tasks without a detailed blue print for its circuitry. Normal development requires the establishment of functional connections between several areas of the brain through regular use of these pathways. Initially these connections will be weak and based on neurochemical substrates. In this stadium it is flexible and easily influenced by other chemical substrates. Often used circuits are stronger as neurochemical connections will gradually be replaced by micro anatomic connections because of dendritic sprouting. These strong connections are less prone to changes. Epilepsy is a brain disorder, which in status epilepticus is characterized by a self perpetuating stimulation of vast areas of the brain. Once this process is initiated it continues independent of external stimulation. This is a characteristic shared by psychiatric symptoms. Patients suffering from auditory hallucinations continuously hear voices without an external stimulus. Patients who are depressed continuously feel depressed without obvious

reason. Self perpetuating stimulation leading to psychiatric symptoms can occur when reverberating loops develop. These loops are circular connections of groups of neurons. Like in epilepsy a pathological process can occur in which these groups of neurons continuously activate each other. Stimulation in one part of the loop leads to stimulation of adjacent parts of the loop until it activates the initial starting point. Auditory hallucinations can develop as a reverberating loop within the auditory cortex. The self perpetuating stimulation within this loop results in the chronic perception of voices without an external stimulus. Affective disorders can develop through a self perpetuating reverberating loop in the emotional centres resulting in continuous feelings of depression or elation independent of external stimuli. The longer these loops are allowed to continue the more difficult it is to stop the self perpetuating stimulation within the loop as flexible neurochemical connections are replaced by more rigid micro anatomic connections. This can explain why treatment in patients with longer illness episodes is less successful. The explanation of altered connections between brain areas in patients suffering from psychiatric symptoms is supported by Huble and colleagues (2004), who have recently found alterations in white matter fibre tracts in patients with frequent auditory hallucinations using magnetic resonance imaging.

An epileptic seizure is thought to occur when the seizure threshold is low, allowing the activation and reactivation of sets of neurons. The inhibitory process caused by ECT is efficacious for treatment of epilepsy as it increases the seizure threshold. This process likewise can stop the localized reverberating loops causing psychiatric symptoms. Because this process occurs in many areas of the brain ECT is efficacious for treatment of psychiatric disorders affecting different areas of the brain. The mechanism of action of psychotropic medication could be more selective because different medicines more selectively attach to different parts of the brain.

Clinical implications and recommendations:

Although the Dutch ECT guidelines recommend the use of ECT as first line treatment in depression with psychosis or in life threatening situations, most patients are offered this treatment only after several failed trials of antidepressive medication. This lowers the chance of a successful treatment with ECT as longer index episodes predict a less favourable outcome. The results from our study support the view that ECT should be offered earlier in the treatment of depression. The patients' preference for ECT may be added to the Dutch guidelines for ECT to prevent unnecessary long suffering because "the best treatment (i.e. ECT) is saved for last". In fact this indication has been included in the APA ECT guidelines (APA 2001, page 23). A major obstacle for the more widespread use of this most effective antidepressant is adverse cognitive effects. Patients can be informed that ECT does probably not affect the functioning of memory but it may cause loss of memories. This loss most often applies to the short-term memory, may be irreversible, and in few cases may affect the distant past. Patients who are informed about the

possible adverse cognitive effects, which should be monitored regularly during the course, are generally able to give informed consent to this treatment. Some evidence was found for ECT efficacy in clozapine nonresponding schizophrenia. This indication may be added to the Dutch guidelines. Another obstacle for the more widespread use of ECT is the relative unavailability of this treatment. ECT is given in few centres in the Netherlands. Unfamiliarity with this treatment during psychiatric training can contribute to the hesitation by psychiatrists in recommending ECT to depressed patients. Awareness of the efficacy of ECT for treatment of depression and other psychiatric disorders and the extent of adverse effects can be much improved by training.

Future research:

Several studies described in this thesis were retrospective in design limiting the conclusions that can be drawn and suggesting the need for further research using a prospective design. An important research question which has received too little attention is the speed of response to antidepressive treatment. Depression has a high mortality rate, which may be reduced by applying the fastest acting antidepressive treatment as soon as possible. ECT may be the fastest acting antidepressant, but as yet no prospective study has been conducted comparing antidepressive medication with ECT in the speed of response. Such a trial is urgently needed. ECT patients were found to have more complaints of memory problems than patients treated with pharmacotherapy. This may be explained by cognitive adverse effects of ECT, but there is an alternative explanation. Patients who received ECT may be more severely ill than patients who received pharmacotherapy resulting in more impairment in memory functions. As a consequence ECT patients may be less able to retain new memories prior to treatment. To address this possible explanation a prospective study is needed. Retrograde amnesia should be assessed prior to treatment with ECT or pharmacotherapy and followed up after treatment. Future developments in ECT techniques aim to reduce retrograde amnesia. Research into retrograde amnesia is hampered by the lack of clinically useful tests for assessing this adverse cognitive effect. Although the Amsterdam media vragenlijst was shown to significantly distinguish between ECT and non-ECT patients it may not be relevant for patients' complaints of memory disturbance as it does not assess memories for personal events. Another avenue which can be followed is the research into the perception of ECT and its adverse effects. Clinically useful tests are urgently needed. Throughout the decades several studies have explored the presence of predictors for ECT efficacy. These studies cannot be compared easily as the characteristics of patient populations vary widely. In the Netherlands ECT is offered relatively late in the treatment of depression compared to the United States and the United Kingdom, countries which have produced research on the predictors for ECT efficacy. ECT techniques have steadily changed adding to the difficulty in comparing studies across the decades. Research on predictors of ECT efficacy has been conducted on relatively small samples

contributing to the heterogeneity of results. A concerted effort of several ECT centres in the Netherlands with standardized ECT techniques using a prospective study design may offer a better insight into the predictors of ECT efficacy. Few clinical studies have been conducted on the use of ictal EEG characteristics to improve the quality of an ECT course. Research in this field may further increase the efficacy of ECT and reduce its adverse cognitive effects. Following the results of the open label study into the efficacy of ECT in schizophrenia a prospective, randomized, single-blind study comparing the efficacy of adjunctive ECT in clozapine nonresponding patients suffering from schizophrenia with continuation of clozapine has been started in GGZ Delfland. Such a prospective study is necessary to address the question of ECT efficacy in this patient group.

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SAMENVATTING

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Ondanks de bezwaren tegen ECT heeft deze behandeling zich kunnen handhaven in het arsenaal van de psychiater. Het grootste bezwaar tegen ECT vormen de geheugenproblemen die deze behandeling kan veroorzaken. Om aan dit bezwaar tegemoet te komen zijn de ECT technieken in de loop der jaren verder ontwikkeld. Tegenwoordig kan op basis van onderzoek gesteld worden dat ECT een veilige behandeling is, geïndiceerd voor de behandeling van verschillende psychiatrische stoornissen. Het is mogelijk gebleken om de geheugenproblemen te beperken.

ECT kan een stoornis geven in het concentratievermogen en het vermogen om nieuwe herinneringen op te slaan. Deze problemen zijn van tijdelijke aard en verdwijnen waarschijnlijk volledig na het stoppen van de behandeling. ECT kan echter een blijvende stoornis geven in de bestaande herinneringen. Herinneringen kunnen als het ware gewist worden. Dit betreft vooral herinneringen uit de periode vlak voor de ECT behandeling. De omvang en intensiteit van dit probleem zijn nog niet goed bekend. Voor de acceptatie van de behandeling met ECT is het van belang om onderzoek te verrichten naar deze subjectieve geheugenklachten. Nader onderzoek biedt bovendien de mogelijkheid om beter te kunnen voorspellen welke patiënten goed zullen reageren op ECT en welke niet, waardoor het therapeutische effect verbetert. Onderzoek naar voorspellers van een succesvolle ECT kuur kan hierbij van belang zijn. Het verbeteren van het therapeutische effect is wellicht mogelijk als gebruik wordt gemaakt van insult parameters, omdat deze mogelijk een maat kunnen zijn voor de effectiviteit van een behandeling. In Nederland wordt ECT voornamelijk gebruikt voor de behandeling van depressie hoewel ECT aanvankelijk gebruikt werd voor de behandeling van schizofrenie. Het is nuttig om de effectiviteit van de behandeling bij schizofrenie te onderzoeken. In de verschillende hoofdstukken worden enkele van deze vraagstukken nader uitgewerkt.

In hoofdstuk 2 werd door middel van een meta-analyse onderzocht wat de effectiviteit van ECT bij de behandeling van depressie is. Een vergelijking werd gemaakt in effectiviteit tussen ECT met placebo ECT enerzijds en antidepressiva anderzijds. ECT blijkt significant effectiever te zijn dan behandelingen van depressie met antidepressiva. Voor de klinische praktijk is het daarnaast soms van belang om een snelle behandeling van de depressie te bewerkstelligen. Hoewel van ECT gezegd wordt dat het een snel antidepressief (therapeutisch) effect heeft kon dit in de meta-analyse niet bevestigd worden. Vroeger werd ECT gegeven met apparaten die gebruik maakten van een sinus golf. Tegenwoordig wordt gebruik gemaakt van apparaten die een korte golf stroom genereren omdat bekend is dat dit minder geheugenproblemen tot gevolg heeft. De suggestie dat ECT met korte golf apparaten minder effectief is dan met sinus golf apparaten kon niet bevestigd worden in de meta-analyse.

In hoofdstuk 3 werden de cognitieve bijwerkingen vergeleken tussen patiënten die na een succesvolle ECT kuur onderhoudsbehandeling met ECT of met psychofarmaca kregen. Voor het meten van geheugenproblemen werd gebruik gemaakt van een neuropsychologische testbatterij die het functioneren van het geheugen mat. De testen werden afgenomen direct na de ECT kuur en vervolgens na zes maanden onderhoudsbehandeling. Er werd geen bewijs gevonden voor een verschil in het functioneren van het geheugen bij onderhouds-ECT of onderhoudsbehandeling met psychofarmaca.

In hoofdstuk 4 werd de ernst van geheugenklachten bij depressieve patiënten die behandeld zijn met ECT en met antidepressiva vergeleken. Amnesie, het verlies van herinneringen, kan onderscheiden worden in retrograde en anterograde amnesie. Weinig studies zijn uitgevoerd die de objectieve en subjectieve klachten van retrograde amnesie vergelijken bij depressieve patiënten die behandeld zijn met ECT en patiënten met antidepressiva alleen. Er werd een significant hogere score in retrograde amnesie gevonden bij ECT patiënten op zowel de objectieve als subjectieve schalen.

Hoofdstuk 5 beschrijft een onderzoek naar de aanwezigheid van voorspellers van de effectiviteit van ECT. Dit onderzoek kan helpen bij het bepalen welke patiënten het best zullen reageren op deze behandeling. Voorspellers kunnen bovendien behulpzaam zijn bij de afweging van de voor- en nadelen van ECT bij een individuele patiënt. Alleen de duur van de huidige ziekte episode bleek een voorspeller te zijn voor de effectiviteit van de ECT kuur. In tegenstelling tot andere studies bleek het niveau van medicatie resistentie niet voorspellend te zijn voor de effectiviteit.

Hoofdstuk 6 beschrijft een onderzoekt naar het gebruik van insult parameters voor het optimaliseren van ECT. Het verband tussen insult parameters en de snelheid van response van ECT werd onderzocht. Insultduur bleek geen voorspeller te zijn voor een snelle response op ECT. Daarentegen bleken een hoge baseline HRSD score en een hoge seizure energy index wel een snelle response op ECT te kunnen voorspellen. Snelle responders bereikten vaker een remissie dan langzame responders. Seizure energy index kan beïnvloed worden door de clinicus.

In hoofdstuk 7 wordt de effectiviteit van ECT bij clozapine-resistente schizofrenie onderzocht. In tegenstelling tot ECT bij depressie is er weinig bewijs van de effectiviteit van ECT bij schizofrenie. Hoewel clozapine het meest effectieve antipsychoticum is, zijn sommige patiënten die lijden aan schizofrenie resistent tegen dit medicijn. Tussen 1991 en 2000 zijn er 23 patiënten beschreven die lijden aan schizofrenie en zijn behandeld met clozapine en ECT. De combinatie behandeling bleek effectief te zijn bij 21 patiënten. Patiënten die een effectieve behandeling ondergingen vielen terug na drie weken tot twee jaar. Er werden nauwelijks bijwerkingen gemeld. De behandeling met ECT bij 11 clozapine resistente patiënten van GGZ Delfland die lijden aan schizofrenie werd bovendien beschreven. Acht patiënten ondergingen een succesvolle ECT kuur

naast een behandeling met clozapine waarvan vijf patiënten een terugval kregen. Drie van de vijf gedecompenseerde patiënten ondergingen een tweede ECT kuur en zijn niet teruggevallen met onderhoudsbehandeling met ECT en clozapine. ECT additie naast clozapine kan effectief zijn bij patiënten die lijden aan clozapine resistente schizofrenie.

Klinische aanbevelingen:

Hoewel de Nederlandse richtlijnen voor ECT het gebruik van ECT adviseren als eerste lijnsbehandeling bij psychotische depressie of in levensgevaarlijke situaties, krijgen de meeste patiënten deze behandeling pas na enkele (mislukte) behandelingen met antidepressiva. Dit verkleint de kans op een succesvolle behandeling met ECT omdat een langere ziekte episode een slechtere uitkomst van ECT voorspelt. Het verdient aanbeveling om ECT eerder toe te passen bij de behandeling van depressie, waarbij de voorkeur van de patiënt voor deze behandeling een indicatie kan zijn. Een belangrijk obstakel voor het vaker voorschrijven van deze meest effectieve behandeling van depressie vormen de geheugenproblemen als bijwerking. ECT veroorzaakt waarschijnlijk geen blijvende schade aan het functioneren van het geheugen. Het kan echter wel gaten teweegbrengen in het geheugen zodat patiënten herinneringen van het recente verleden kwijt kunnen raken en in een enkel geval ook van het verre verleden. Onderzoek naar geheugenproblemen blijft nodig om patiënten zo goed mogelijk te kunnen inlichten over de behandeling met ECT. Patiënten die goed ingelicht zijn over de mogelijke geheugenproblemen en die regelmatig beoordeeld moeten worden tijdens de ECT kuur, kunnen meestal een goede afweging maken om in te stemmen met deze behandeling. Het verdient aanbeveling om clozapine resistente schizofrenie toe te voegen als indicatie voor ECT. De onbekendheid met deze behandeling tijdens de psychiatrische opleiding draagt bij aan het laat voorschrijven van deze behandeling. Psychiaters zouden beter geïnformeerd moeten worden over de indicaties, de effectiviteit en bijwerkingen van ECT tijdens hun opleiding.

Conclusies:

ECT is nog steeds de meest effectieve behandeling van depressie. Geheugenproblemen als gevolg van ECT, vooral retrograde amnesie, beperken de toepassing van deze behandeling. Ontwikkelingen van ECT technieken hebben deze geheugenproblemen echter verminderd. Toekomstige ontwikkelingen zullen deze problemen verder reduceren. Onderzoek naar voorspellers van het effect van ECT maken het mogelijk om beter in te schatten welke patiënten deze behandeling niet moeten ondergaan. Ander onderzoek laat echter zien dat de indicatie voor ECT verruimd kan worden.

DANKWOORD

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Dit onderzoek kon slechts uitgevoerd worden dankzij de medewerking van de patiënten van GGZ Delfland. Hiervoor wil ik u allen hartelijk bedanken. Het zal zeker niet altijd meegevallen zijn om, terwijl je ziek bent, verschillende keren vragenlijsten in te moeten vullen.

Van Ben Blansjaar mijn co-promotor kreeg ik menig nuttig advies. Daarnaast ontdekte ik snel je waarde als kritische lezer van manuscripten waarbij ik de gesuggereerde correcties haast blindelings kon overnemen. Naast adviezen over het werk kreeg ik ook de nodige steun op andere gebieden. Ik hoop nog lang met je te kunnen samenwerken en nog lang te kunnen genieten van je vriendschap.

Michiel van Vreeswijk wil ik bedanken voor de aanzet die je mij gegeven hebt voor het starten van het promotieonderzoek. Ik heb genoten van mijn eerste onderzoek, een meta-analyse, die we samen uitgevoerd hebben. Ik heb ook daarna altijd op je kunnen rekenen.

Koos Zwinderman mijn promotor wil ik bedanken voor de inzichten die hij mij gegeven heeft in de statistiek. Ik had zonder jou waarschijnlijk nooit ontdekt dat statistiek ook leuk kan zijn. Je heldere en zeer deskundige uitleg over dit vak zal me altijd bijblijven. Ik wil je ook bedanken voor het aanbod om mijn onderzoek tot een promotieonderzoek uit te bouwen. Dit aanbod nam ik natuurlijk met beide handen aan.

Don Linszen mijn promotor wil ik bedanken voor de warme en waardevolle aanmoedigingen die ik altijd van je kon krijgen. Je optimisme en enthousiasme werken aanstekelijk.

Rigo van Meer wil ik bedanken voor zijn steun in het mogelijk maken van mijn onderzoek. Je hebt je ingezet om voor mij tijd en geld vrij te maken voor mijn onderzoek. Ook Bert Mostert wil ik hiervoor bedanken.

Henri van Schaick wil ik bedanken voor de samenwerking om de ECT afdeling in GGZ Delfland op te zetten. Je gezelligheid en goede humor zijn waardevol voor een prettige samenwerking. Bedankt voor je vriendschap. Lisa van Schaick wil ik bedanken voor het prachtige ontwerp van dit proefschrift.

Joost Sven, Piet Burggraaf, Ruud Stienstra, Jack van Kleef en Bart-Jan Lombaert wil ik bedanken voor het mogelijk maken van de ECT behandelingen in GGZ Delfland. Zonder deze betrouwbare anesthesisten was het niet mogelijk geweest om deze behandeling uit te voeren.

Barbara Bergwerf, Tjitske Dijkman, Vincent Passchier, Karin Sikkema, Anty Rusiantiningsih en alle andere ECT verpleegkundigen die meegewerkt hebben aan deze behandeling wil ik bedanken. Jullie inzet is een belangrijke voorwaarde gebleken voor de efficiënte toepassing van deze behandeling. De vriendelijke benadering wordt door veel patiënten gewaardeerd.

Wolter Birza en Olaf Nielsen wil ik bedanken voor hun hulp bij de pre-ECT voorbereidingen.

Jolanda de Vreede, Willie Menninga en Carla van der Meij wil ik bedanken voor het organiseren van het ECT rooster.
De leden van de promotie commissie wil ik bedanken voor hun tijd die zij hebben gestoken in het lezen van mijn manuscript.
Een tijdrovende bezigheid als een promotieonderzoek kan slechts uitgevoerd worden met een stevige steun op het thuisfront. Mijn echtgenoot Anco Sesselaar is de afgelopen paar jaren een rots in de branding gebleken. Bedankt voor je zorgen en de ruimte die je mij gegeven hebt.

CURRICULUM VITAE

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King Kho werd op 30 juli 1962 in Indonesië geboren. Samen met zijn ouders, twee broers en een zus emigreerde hij in 1970 naar Nederland. Na de lagere school en het Atheneum begon hij in 1980 met de studie medicijnen op de Erasmus Universiteit. In 1987 behaalde hij zijn artsdiploma waarna hij in Engeland ging werken als arts-assistent orthopedie. Na een aantal maanden als arts-assistent op de EHBO gewerkt te hebben begon hij in 1988 met de opleiding psychiatrie aan de Charing Cross rotation in Londen. Tijdens de Britse opleiding deed hij ervaring op in de volwassenen psychiatrie, ouderen psychiatrie, forensische psychiatrie en onderzoek. Tijdens de opleiding behaalde hij twee examens waarna hij toegelaten werd als "member of the Royal College of Psychiatrists". In 1992 keerde hij terug naar Nederland waar hij in Amsterdam een beoordelingsstage liep als psychiater-in-opleiding op de adolescenten kliniek van de afdeling psychiatrie van het Amsterdams Medisch Centrum. Na een stage sociale psychiatrie op de crisisdienst in Amsterdam werd hij op 1 oktober 1994 als psychiater ingeschreven in het specialisten register. Sinds 1994 werkte hij als psychiater in GGZ Delfland te Delft. Hij werkt momenteel op als psychiater op een gesloten opname en een open opname afdeling van de kliniek van GGZ Delfland. Hij is lid van de opleidingscommissie van GGZ Delfland en lid van de Werkgroep ECT Nederland. In oktober 2001 trad hij in het huwelijk met Anco Sesselaar.

Table 1. Published articles on ECT and clozapine.

Study	No. of pat. & gender	Age (yrs)	Diagnosis	Cloz. blood level	Results	Adverse effects	Follow up results	Comments
Masiar & Johns 1991	1m	26	Chronic paranoid schizophrenia	n.a.	No improvement after 1 and only ECT session	2 grand mal seizures 4 and 6 days after ECT		14 days prior to ECT clozapine 800 mg daily was tapered and stopped 4 days prior to ECT. 14 days prior to ECT diazepam 20 mg daily was tapered to 5 mg daily 3 days prior to ECT.
Landy 1991	1f	34	Major depression with psychosis	n.a.	Improvement of depression GAF25 to 55	Tachycardia	Remained well for at least 6 weeks with clozapine.	Psychosis improved with clozapine, but depression remained. ECT was given for depression.
	1f	26	Major depression with psychosis	n.a.	Improvement of depression and psychosis GAF28 to 50	Tachycardia	Remained well with maintenance ECT and clozapine for at least 2 months.	Tachycardia probably due to clozapine.
Klapheke 1991	1f	26	Schizoaffective disorder bipolar type, mania	n.a.	Improvement	Tachycardia during several ECT sessions	Remained free of psychosis for at least 3 weeks with clozapine.	
*Safferman & Munne 1992	1f	33	Chronic paranoid schizophrenia	>662 ng/ml for 12 months	Improvement of auditory hallucinations and delusions	None	Remained well for at least 3 weeks with clozapine	.
*Frankenburg et al. 1993	2m	32, 39	Schizophrenia	n.a.	1 minimal improvement 1 moderate improvement	None		Retrospective review of medical records.
	4m:2f	28-50	Schizoaffective depressed	n.a.	Improvement: 4 none 3 minimal 3 marked	None		Retrospective review of medical records.
	1m	32	Schizoaffective bipolar					
	1m	48	Bipolar manic					
	2f	30,47	Major depression with psychosis					
Klapheke 1993	1?		Schizoaffective dis.	n.a.	Improvement	None?		
Dassa et al. 1993	1f	40	Major depression with psychosis	n.a.	Improvement: 88% reduction of BPRS	None	Remained well for more than a year	ECT was inefficacious, afterwards good response to clozapine.
Green et al. 1994	1f	38	Schizoaffective disorder, disruptive behaviour	n.a.	Improvement	None	Remained well for more than 3 years	In both patients ECT was completed before clozapine was started.
	1f	53	Schizoaffective disorder, mute and catatonic	n.a.	Improvement	None	Remained well for more than 2 years	
Beale et al. 1994	1f	66	Recurrent depression with psychosis	n.a.	Improvement	Supraventricular tachycardia	Died 3 weeks after her last ECT session	Caffeine used to counteract a decrease in seizure duration could have caused tachycardia.
*Cardwell & Nakai 1995	3m:4f	Mean: 41.25 (36-45)	3 par.schizophrenia 1 des.schizophrenia 2 schizoaff.bip. 1 schizoaff.depr.	n.a.	Improvement on BPRS: • 26.9% total • 25.3% positive	Absence of: • Prolonged seizure. • Tachycardia.		All patients received ECT and clozapine. In 4 ECT preceded clozapine. In 3 clozapine preceded ECT

					• 21.3% negative	• Tardive seizure within 1 year following ECT.		
Factor et al. 1995	1f	69	Parkinson psychosis	n.a.	Improvement of psychosis, mobility and depression	None	Remained well for 8 months with clozapine	ECT was started after clozapine treatment was stopped.
	1m	70	Parkinson psychosis	n.a.	Improvement of psychosis	None	Remained well for 22 months with clozapine	
Lurie 1996	1m	47	Bipolar disorder	n.a.	Improvement	None		ECT was efficacious but caused memory problems. Titration of clozapine started during ECT treatment.
Bloch 1996	1?	18	Refractory psychosis	n.a.	Improvement of psychosis	Prolonged seizure		ECT was inefficacious. Improvement after addition of clozapine.
*Benatov et al. 1996	2f:1m	35, 45, 47	Disorganised schizophrenia	n.a.	2 improved: >40% BPRS reduction 1 no improvement	None	Improvement was maintained for 6 and 24 months	Clozapine was inefficacious. Improvement after adjunctive ECT.
	1m	24	Disorganised schizophrenia	n.a.	Improvement: >50% BPRS reduction	None	Remained well for 24 months	ECT was inefficacious. Improvement after adjunctive clozapine (not medication refractory).
Poyurovsky & Weizman 1996	1m:1f	24, 41	Acute Mania	n.a.	Improvement	Prolonged seizure		Clozapine was started to augment ECT.
*Petrides et al. 1998	7	23-45	6 schizophrenia 1 schizoaffective dis.	n.a.	All improved	None		
*Bhatia et al. 1998	1m	35	Paranoid schizophrenia	>266 ng/ml	Improvement: 46% reduction in BPRS score	None	Remained well for 20 months	Clozapine was inefficacious. Improvement after adjunctive ECT.
*James and Gray 1999	2f:4m	Mean: 30 (22-42)	Schizophrenia	n.a.	All patients were less disturbed. Mean BPRS score dropped by 32% (23-37%) at 6 weeks.	None	Only 1 patient became disturbed again after 6 months.	ECT was used to achieve a rapid response. Clozapine was started after 2 ECT sessions.
*Kales et al. 1999	2f:3m	Mean: 49 (36-66)	Schizophrenia: 4 clozapine refractory 1 intolerant to therapeutic clozapine dose	n.a.	3 markedly effective 2 modestly effective	None	Remained well for several weeks to 2 years	Clozapine refractory patients were given adjunctive ECT. Following ECT maintenance therapy with clozapine was given.
*Husni et al. 1999	1m	25	Schizophrenia	n.a.	Improved	None		
Chanpattana 2000	1m	26	Mania	n.a.	Improved	Post seizure delirium	Remained well for 18 months	The patient remained well with maintenance ECT and low dose clozapine

*Case reports/series describing adjunctive ECT for clozapine nonresponders suffering from schizophrenia.
n.a. = not available

Table 2. 11 patients suffering from schizophrenia treated with ECT and clozapine.

Case no.	Gender	Age (yrs)	Dur. of illness (mnths)	No. of previous adm.	$No. of adequate trials prior to cloz.	Dur. of current psychotic episode (mnths)	Cloz. dose prior to ECT (mg)	Dur. of cloz. treatment prior to ECT (wks)	Concurrent medication (except clozapine)	Cloz. blood level prior to ECT (ng/ml)	Mean baseline PANSS score	Uni/bil ECT	Mean charge during course (mC)	Cloz. blood level post ECT (ng/ml)	Post ECT total PANSS score	Adverse effects	#Follow up dur. (wks)	Relapse
1	M	23	30	1	4	5	600	14	Sodium valproate 1000 mg	0.47	63	9/0	176	0.48	40		18	No
2	M	25	48	1	2	48	400	> 8	None	>0.30	47	6/2	158	n.a.	38	Memory problems		
3	M*	33	96	7	5	39	600	14	Paroxetine 40 mg	0.49	67	6/0	160	0.36	70			
4	M*	36	192	4	6	120	700	10	Pipamperon 160 mg	0.26	63	2/0	202	0.26	74			
5	F	38	72	1	3	2	200	8	Oxazepam 50 mg	0.48	86	7/0	202	0.35	56		20	No
6	F‡	39	96	3	2	3	300.	10	Oxazepam 50 mg Zucl. 200mg/2wk	0.06	76	6/0	227	n.a.	40		42	No
7	M	43	144	3	2	16	800	16	Clonazepam 6 mg	0.33	101	12/0	208	0.29	44		4	Yes
8	F	52	300	4	5	5	450	12	Lithium 1000 mg Oxazepam 50 mg	0.87	77	3/0	218	0.42	31	Memory problems and confusion	7	No according to criteria, yes clinically
9	F	56	240	10	5	3	300	10	None	0.66	67	11/0	252	0.5	39		4	yes
10	M	58	384	3	5	18	400	20	None	0.71	92	7/10	273	0.47	62		19	yes
11	F	66	528	8	4	10	250	2	Lithium 600 mg	0.26	81	0/15	302	0.18	47		3	Yes

*Patient stopped ECT course prematurely.

‡This patient stopped clozapine treatment 2 months prior to ECT. ECT was started with zuclopenthixol decanoate. During the ECT course zuclopenthixol decanoate was replaced by clozapine.

$An adequate trial was defined as treatment with an antipsychotic from one group for at least four weeks with a dose within the recommended range

#Patients were followed up until the end of the study or until relapse occurred.

n.a. = not available

BENEFITS AND LIMITATIONS OF ELECTROCONVULSIVE THERAPY

King Han Kho

SUMMARY

Memory problems are the most important adverse effect of ECT and contribute to the controversial nature of this treatment. Psychiatrists still maintain ECT as an important treatment tool. Adverse effects including memory problems have been reduced by developments in ECT techniques, allowing the conclusion that this is a safe treatment tool for several psychiatric disorders.

ECT can interfere with ability to concentrate and store new memories. These problems are temporary and probably completely disappear after termination of the treatment. ECT however can cause permanent problems in existing memories. Some of the memories, mainly from the period immediately before the ECT course, can be erased. There is a lack of research into the extent of this problem. For the acceptance of ECT it is important to investigate subjective memory complaints. Further research into predictors for ECT efficacy is necessary in order to increase the efficacy of this treatment. Because seizure quality measures may be associated with efficacy, this can be used to improve the efficacy. In the Netherlands ECT is mainly used for treatment of depression although it was initially used for treatment of schizophrenia. It is useful to explore the efficacy in treatment of schizophrenia. This thesis explores these statements.

Chapter 2 described a meta-analysis exploring ECT efficacy in depression. ECT was compared with antidepressive medication and with placebo and was found to have superior efficacy compared to the other treatment conditions. In clinical practice it is sometimes important to an antidepressive treatment with a rapid response. It has been suggested that ECT has a rapid speed of response. This however could not be confirmed in the meta-analysis. Initially ECT devices used sine wave current for electrical stimulation. Modern devices use brief pulse current for electrical stimulation because this causes less adverse cognitive effects. The suggestion that brief pulse devices are less efficacious than sine wave devices was not confirmed by the meta-analysis.

In chapter 3 the adverse cognitive effects were explored in patients receiving maintenance treatment with ECT or pharmacotherapy after a successful ECT course. Memory problems were assessed using neuropsychological tests on several memory

functions. Tests were applied immediately after termination of the ECT course and after six months maintenance treatment. No evidence was found for a difference in memory functioning in patients using maintenance treatment with ECT or pharmacotherapy.

In chapter 4 the severity of memory complaints in depressed patients who have been treated with ECT and antidepressive medication was compared. Amnesia, which is the loss of memories, can be distinguished in retrograde and anterograde amnesia. Few studies have explored objective and subjective complaints of retrograde amnesia in depressed patients who have been treated with ECT and patients who have treated with antidepressive medication only. A significantly higher score of retrograde amnesia was found in ECT patients using objective and subjective scales.

Chapter 5 described a study into predictors for the efficacy of ECT. Research into predictors for ECT efficacy can assist in selecting patients who are most likely to benefit from a treatment. Predictors can facilitate a more adequate prescription of ECT and improve the risk-benefit ratio. Only duration of the current illness episode was shown to be a predictor for ECT efficacy. Contrary to findings from other studies the level of medication resistance was not found to be a predictor for efficacy.

Chapter 6 described a study into the use of seizure quality measures for optimizing ECT. The association between seizure quality measures and the speed of response to ECT was explored. Seizure duration was not a predictor for the speed of response. A high baseline depression score and a high seizure energy index predicted a high speed of response. Fast responders to ECT achieved remission significantly more often than slow responders did. Seizure energy index can be influenced by the clinician.

In chapter 7 the efficacy of ECT for treatment of clozapine refractory patients suffering from schizophrenia was explored. Contrary to ECT in depression little evidence exists for the efficacy in schizophrenia. Clozapine is the most efficacious antipsychotic medication. Still some patients suffering from schizophrenia are clozapine refractory. Between 1991 and 2000 23 case reports and case series describing treatment of schizophrenia with clozapine and ECT have been published. The combination was efficacious in 21 patients. Patients who responded well relapsed within three weeks to two years. Few adverse effects were reported. ECT treatment in 11 clozapine refractory patients admitted to GGZ Delfland suffering from schizophrenia was also described. Eight patients remitted after ECT was combined with clozapine. Five of these patients relapsed after termination of ECT. Three of the five patients who relapsed received a second ECT course and have not relapsed with maintenance treatment using clozapine and ECT. Adding ECT to clozapine can be efficacious in clozapine refractory schizophrenia.

Clinical recommendations:

Although the Dutch ECT guidelines recommend the use of ECT as first treatment for psychotic depression or in life-threatening situations, most patients received this treatment after several (failed) trials with antidepressive medication. This lowers the chance of a successful treatment because ECT is less efficacious in patients with a long duration of current illness. A recommendation can be made to offer ECT earlier for treatment of depression, taking into consideration the patient's preference for this treatment. An important limitation for the more frequent use of this most efficacious antidepressive treatment is adverse cognitive effects. Most probably ECT does not cause permanent damage to the functioning of memory. It can however cause loss of memories most often for the recent past and occasionally from the remote past. Further research into memory problems is necessary in order to adequately inform patients about the benefits and limitations of ECT. Patients who have received adequate information on ECT and are regularly assessed during the course are usually able to give informed consent. It is recommended to add clozapine refractory schizophrenia as indication for ECT. The limited opportunity to learn about this treatment during psychiatric training contributes to the delay in offering this treatment. Psychiatrists should be better informed about the indications, efficacy and adverse effects of ECT during training.

Conclusions:

ECT remains the most efficacious treatment of depression. Adverse cognitive effects of ECT, especially retrograde amnesia, limit the use of this treatment. Developments of ECT techniques have reduced these adverse cognitive effects. Future developments will further limit the adverse cognitive effects. Research into predictors for ECT efficacy allows clinicians to decide which patients should not receive this treatment. Other research suggests that the use of ECT can be expanded.