Chapter 1

General introduction

Depression, electroconvulsive therapy (ECT) and optimizing efficacy

Depression is a highly prevalent and debilitating disorder expected to be the second-ranked disease burden in 2020 (WHO, 2004). In addition to personal suffering, depression is related to significant distress and higher levels of morbidity in family and caregivers (Shahly et al., 2013). ECT is the most effective treatment for depression (Kho et al., 2003; Pagnin et al., 2004; UK ECT Review Group, 2003), but its widespread use is hampered by the fear of cognitive side effects. The clinical effects, combined with cognitive side effects, determine the outcome of ECT for patients. Therefore since the introduction of ECT, the quest has begun to optimize ECT (i.e. maximize its efficacy and minimize its side effects).

This thesis focuses primarily on the efficacy of electroconvulsive therapy and complements Esmée Verwijk's thesis, "Neurocognitive performance in electro-convulsive therapy – to lose or not to lose?", which focuses primarily on the cognitive effects of ECT in the same group of patients.

ECT

Inspired by the therapeutic effects of the chemically induced convulsions by Meduna in 1934 in Budapest, the first electricity-induced convulsive therapy, an "elettroshock *(ital.)*" session, took place in April, 1938, in Rome, Italy, and was delivered by Cerletti and colleagues (2008). Afterward, the treatment was soon introduced and spread over the world. Probably the first treatment in the Netherlands was done in July of 1939 by Barnhoorn (1940). ECT has been used ever since but has had its ups and downs. With the development of psychiatric medications in the 1950's and the stigma associated with ECT in the 1960's, the use of ECT treatment declined. However the use of ECT increased after the 1970's because of improved treatment-delivery methods, refined safety and comfort measures, enhanced anesthesia management and, last but not least, more effectiveness in pharmacotherapy refractory cases (van den Broek et al., 2004). Started as a treatment for schizophrenia, ECT's greater effectiveness for treatment of affective psychosis, mania and depression was shown very soon after its discovery (Sogliani, 1939). ECT is widely acknowledged as effective in the treatment of psychiatric disorders (Van den Broek et al., 2010). Treatment with ECT produces rapid response and remission rates (Husain et al., 2004). Morbidity and mortality even in somatically compromised patients are low across the adult life span. ECT is now generally applied in persons diagnosed with severe depression and psychotic features, psychomotor retardation, refusal to eat and drink, suicidal ideation, catatonia or pharmacotherapy resistance (Salzman et al., 2002). The numbers of

treatments for non-affective psychosis (for example, schizophrenia) have decreased remarkably recent decades, especially in Western Europe, the USA, Australia and New Zealand. Though the absolute number of patients who receive ECT may seem large, annually estimated at 1 million worldwide (Leiknes et al., 2012; Weiner and Prudic, 2013), the number should still be regarded as low considering the estimated need. In the Netherlands, approximately 700 patients a year are treated with ECT.

The working mechanisms behind ECT

Although ECT has a history of more than 70 years, we still do not know how the therapeutic effect of ECT is achieved. The working mechanisms behind the seizure are unclear, but a generalized seizure is essential to the therapeutic effect. This was elegantly shown in the experiments of Crohnholm and Ottoson (1960), in which blocking of the seizure with lidocaine abolished the therapeutic effect. The anticonvulsive effect induced by the seizure is still one of the potential mechanisms underlying the therapeutic effect of ECT.

The apprehension that the current could be related to the cognitive side effects (Alexander, 1953), and the fear of electricity through the brain in general, encouraged a search for the most efficient application of current. Soon after the introduction of ECT, the paradigm shifted from evoking a shock inducing confusion, regression and reset to the most effective ways to produce a general convulsion (Goldman, 1949; Liberson, 1944). Changing the name from "electroshock" to "electroconvulsive" therapy reflected the physicians' perception of the therapy rather than merely a response to public's opinion (Shorter & Healy, 2007).

The quest for the mechanisms behind ECT has not ended. Although we no longer search for the "biohumoral factors of extreme defense" that ECT was supposed to induce—proposed by Cerletti at the first psychiatric world congress in Paris in 1950 (Cerletti, 1950)—the true mechanism for the fast response of ECT is still a mystery. Considering the effectiveness of ECT, it has even been suggested that more than one mechanism may be in effect at the same time. Effects have been demonstrated on brain chemistry, regional brain activity, electroencephalographic sleep stages and neurogenesis (McCall et al., 2014; Sienaert, 2014). Although we suspect ECT to have an effect on the biological clock, considering the fast effect on sleep and bipolar disorders (Sienaert et al., 2009), there is no solid evidence to support this either (Hoogerhoud et al., 2015).

Search for the most effective treatment technique: (ultra)brief pulse?

The original current from the Italian socket delivered a sine wave stimulus with a pulse width of 12.5 ms. Shortening of the pulse wave closer to the chronaxia of the neurons is an effective way to increase the epileptogenicity of the stimulus, resulting in a lowering of the initial seizure threshold (Liberson, 1944, 1945). These modifications in pulse width ended about a decade ago with the introduction of commercially available devices that could produce ultrabrief stimuli, with a pulse width < 0.5 ms. However, the terms "ultrabrief" and "brief" have been used for different pulse widths through the years. Shortly after the introduction of ECT in the 1940's, the term "brief pulse" (BP) was used for pulse widths as small as 0.01 ms (Liberson, 1944). In the 1980's BP was used for pulse width of at least 1.0 ms (Weaver et al., 1982), while presently pulses ≥ 0.5 ms are referred to as BP and <0.5 ms as ultrabrief pulse (UBP) (Abrams, 2002).

In 1998, modern ECT machines became available. A few years later many clinicians started to use UBP stimulation as their preferred stimulus setting (Galletly et al., 2014; Loo et al., 2007; McCormick et al., 2009; McCormick et al., 2011; Niemantsverdriet et al., 2011; van Waarde et al., 2009). At the same time, doubts have been cast upon the increasing use of UBP stimulation because of limited evidence for its efficacy (Cronholm & Ottosson, 1963; Galletly et al., 2014; McCormick et al., 2011; Wiwanitkit, 2011). Depending on the ECT machine, 0.25 ms (Thymatron IV from Somatics LLC, Lake Bluff, IL) or 0.3-0.4 ms (spectrum 5000 Q from MECTA Corp, Tualatin, OR) is considered UBP in research studies. Besides some important operational differences and specifications between these machines, the differences between UBP 0.25 ms and 0.3 ms are negligible.

Accepted definitions of BP and UBP stimulation complicate transparent scientific debate because distinctions are taken too literally. The actual neurophysiological differences between 0.3 ms and 0.5 ms are debatable. Rodents treated with an electroconvulsive stimulus (ECS) with a 0.5 ms pulse width showed more antidepressant-related molecular, cellular and behavioral changes compared to animals treated with ECS using 0.3 ms (O'Donovan et al., 2012). However, in humans, a study by Rosa et al. (2013) demonstrated equal seizure thresholds for 0.3 ms and 0.5 ms, but thresholds for 1.0 ms are 2 to 3 times higher (Loo et al., 2008; Mayur et al., 2013; Spaans et al., 2013). Thus a BP pulse width of 0.5 ms should be avoided to detect differences in UBP versus BP comparison studies, and 1.0 ms or more should be used instead. This insight leads to our first research question.

- **Research question 1**: What is the scientific evidence for the increased use of UBP (0.25 ms or 0.3 ms) stimulation in ECT?

Besides pulse width, several other changes in ECT techniques have been introduced since the original alternating sine wave current, aiming to maximize the therapeutic effect and to minimize the adverse effect. These changes include the use of a unidirectional current, pulse frequency, stimulus duration, amplitude, and electrode positioning from bitemporal to bifrontal and from bilateral (BL) to unilateral (UL) (Peterchev et al., 2010; Prudic, 2008).
Not every seizure, however, is therapeutic. A UL stimulus just above seizure threshold produces a long seizure but is far less therapeutic than a higher stimulus dose (Sackeim et al., 1987; Sackeim et al., 1993). The efficacy of UL (BP) stimulation is related to the stimulus-dose-relative-to-the-seizure-threshold (SDRST), not to the absolute charge. This has to be taken into account in comparative studies (Kellner et al., 2010; McCall et al., 2002; Sackeim et al., 1993; Sackeim et al., 2000; Sackeim et al., 2008). Electrical stimulation with a smaller pulse width lowers the seizure threshold. As a result, UBP could, theoretically, match the efficacy of BP stimulation and is expected to have a lower risk of adverse cognitive effects (Loo et al., 2008; Sackeim et al., 2008; Sienaert et al., 2010). Pulse width, though, is only one of the factors determining therapeutic and cognitive effect.
BL treatments seem to be less dependent on the SDRST than UL treatments, but BL UBP stimulation was shown to be less efficacious than BL BP stimulation (Sackeim et al., 2008). ECT with BL electrode placement and BP stimuli is reported to be equally efficacious or superior to UL ECT (Kellner et al., 2010; UK ECT Review Group, 2003) also in respect to speed of response and remission, but carries an increased risk for memory problems (Sackeim et al., 2008; Semkovska et al., 2011).

- **Research question 2:** Are there differences in efficacy or cognitive side effects between BP (1.0 ms) and UBP 0.3 ms right unilateral (RUL) ECT, with a SDRST of 8 in both the BP and UBP group, in the short-term and in the long-term?

Full clinical improvement early after the start of ECT

Electroconvulsive therapy (ECT) is an effective treatment for depression with a relatively fast onset of action. In most studies, remission is achieved after 6 to 8 treatment sessions, (i.e. 2 to 4 weeks depending on the treatment schedule). Many

clinicians share the experience of some patients responding almost immediately after starting an ECT course, although published reports of remission after a single or a few treatments are rather scarce.
Obviously a quick relief of depression and suicidality can save lives, alleviate personal and caregiver burdens, shorten admissions and reduce costs. The absence of residual symptoms, after improvement with medication, has been shown to result in a lower risk of relapse and recurrence. Similarly, fewer residual symptoms after ECT probably also portend lower relapse rates. Therefore gaining insight into the factors influencing a fast and full remission is of great importance, as well as understanding the patient characteristics associated with this particular response pattern.

> **Research question 3:** Can we identify and characterize patients who achieve full remission within two weeks of starting ECT?

Depression in the elderly—ECT versus medication:
Speed of remission
In this age group, depression is associated with a lower quality of life and functioning. In view of decreased mobility, compromised food and fluid intake and a higher incidence of lethal suicide attempts than in younger people, depression in the elderly should be considered a life-threatening disease. Especially in the elderly, prognosis is poor without treatment (Baldwin, 2000).
Therefore, the initial speed of response to antidepressant treatment is of major importance in these patients. ECT is considered a safe and effective treatment for elderly people and is recommended as a preferential treatment in psychotic depression in the case of medication resistance or intolerance; it is also regarded as life-saving in somatically compromised patients (NICE, 2010; Van den Broek et al., 2010; Weiner, 2001). Although older age is a positive predictor for ECT outcomes—with remission rates from 73 to 90% in patients over 65 years of age (O'Connor et al., 2001; Tew et al., 1999)—psychiatrists seem reluctant to prescribe ECT for elderly patients (van der Wurff et al., 2004).

> **Research question 4**: Do older patients achieve clinically relevant faster remission with ECT than with antidepressant medication?

Depression in the Elderly—ECT versus medication:
Influence of vascular risk factors

It is suggested that a causal link exists between late-life depression and comorbid vascular risk factors such as cerebrovascular accident, transient ischemic attack, diabetes mellitus, hypertension, and myocardial infarction and that this influence may also be reciprocal (Glassman & Shapiro, 1998; Sheline et al., 2010; Steffens et al., 2001; Teodorczuk et al., 2010). Vascular lesions are much more common at a higher age and may play a more prominent etiologic role in late-life depression, particularly in late-onset depression in comparison to early onset depression (Naismith et al., 2012; Valkanova & Ebmeier, 2013). Depression with vascular MRI-lesions has been linked to inferior response to antidepressant medication (Baldwin et al., 2004; Brunoni et al., 2011; Sheline et al., 2010; Simpson et al., 1998), although other studies have reported no influence of vascular burdens on treatment response to pharmacotherapy (Janssen et al., 2007; Krishnan et al., 1998; Salloway et al., 2002). Response to ECT, however, has been reported not to differ significantly in patients with MRI-defined vascular changes (Simpson et al., 1997). In other studies, the efficacy of ECT in patients with MRI lesions less associated with vascular changes like medial temporal lobe atrophy (Oudega et al., 2011) and grey matter hyperintensities (Steffens et al., 2001) was inferior to the efficacy of ECT in patients with deep white matter hyperintensities (Oudega et al., 2011), which are more associated with microvascular lesions (Thomas et al., 2002). These findings could indicate an increased effectiveness of ECT compared to antidepressive medication in the treatment of depression with vascular burden (Baldwin & O'Brien, 2002; Lavretsky & Meeks, 2009; Ramos-Rios et al., 2007; Simpson et al., 1998; Simpson et al., 1997).

> **Research question 5**: Compared to medication, is ECT of extra benefit for older patients with vascular risk factors?

Outline of the thesis

Research question 1

What is the scientific evidence for the increased use of UBP (0.25 or 0.3ms) stimulation in ECT? To answer this question, we aimed in Chapter 2 to review in the literature the evidence of equal efficacy of UBP compared to BP ECT and describe all studies published before 25 April 2012 that reported validated rating scales as outcome measures on the comparison between UBP (< 0.5ms) versus BP (≥0.5ms) ECT in depressed patients. The Jadad scale was used to evaluate the quality of the studies.

Research question 2

Are there differences in efficacy or cognitive side effects between BP (1.0 ms) and UBP (0.3 ms) RUL ECT, with a SDRST of 8 in both the BP and UBP group, in the short-term and in the long-term? To answer this question, we aimed to design and conduct a large double blind, randomized controlled study (RCT) to examine the short-term efficacy and cognitive side effects of high dose BP (1.0 ms) and UBP (0.3 ms) RUL ECT, with a naturalistic follow up of six months. Chapter 3 focuses on the RCT where we compared the short-term (≤ 6 week) efficacy and cognitive side effects of high dose unilateral BP ECT with high dose unilateral UBP ECT in the treatment of major depression**.** Chapter 4 describes the naturalistic follow up, where we compared the differences in relapse rate and cognitive performance three and six months after index ECT.

Research question 3

Can we identify and characterize patients who achieve full remission within two weeks of starting ECT? We aimed to characterize the patients who achieve fast and full remission. In Chapter 5 we describe how we screened all remitted patients of the ECT trial for early complete remission within only four sessions of the ECT and compared them with the late remitters and non-remitters.

Research question 4

Do older patients achieve clinically relevant faster remission with ECT; faster than with antidepressant medication? We aimed to compare the speed of remission of ECT with antidepressant medication treatment in older patients. In Chapter 6 we describe how we compared a subgroup of elderly unipolar depressed inpatients participating in the randomized controlled ECT trial (BP v. UBP) with a randomized control trial

(RCT) of a group using medication (nortriptyline v. venlafaxine) (Kok et al., 2007) considering the speed of remission.

Research question 5

Is ECT of extra benefit, compared to medication, for older patients with vascular risk factors? We aimed to study the influence of vascular risk factors (VRF) on the efficacy of ECT and medication. Therefore we identified VRF in the same subgroup of older ECT patients and in the patients of the medication trial (Kok et al., 2007) and compared remission rates of patients with and without VRF in Chapter 7.

Finally, in Chapter 8, the main findings of these studies are summarized, and methodological considerations and the clinical implications for depressed patients treated with ECT are discussed.

Study in this thesis

A randomized controlled multicenter ECT trial (Spaans & Verwijk, 2013)

From April 2007 until March 2011, a prospective, double blind, randomized multicenter trial was conducted comparing the efficacy and cognitive side effects of BP and UBP RUL ECT (Netherlands National Trial Register number NTR1304). The randomized phase of the trial ended when the patients achieved remission or after the maximum of 6 weeks. At three and six months after the randomized phase, naturalistic follow up assessments were performed. One hundred sixteen patients were recruited from three ECT centers: Parnassia (The Hague) and GGZ Delfland (Delft) in The Netherlands and the University Psychiatric Center Catholic University Leuven, Campus Kortenberg (Kortenberg) in Belgium. The Institutional Review Boards (IRBs) of these hospitals approved the study. All eligible patients were asked to participate, and baseline assessments were done after the patients provided informed consent.
All in- and outpatients of 18 years and older suffering from major depressive disorder or bipolar depression (with or without psychosis) according to DSM-IV TR criteria (APA, 2000) confirmed by the MINI (Sheehan et al., 1998) who were referred for ECT were screened for inclusion in the study. Patients with a diagnosis of schizophrenia, dementia or substance use disorder or who were treated with ECT within the past six months were excluded from participation.

For blind assessment of efficacy, trained nurses rated the severity of depression using the Montgomery Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979) and the Hamilton Rating Scale for Depression (HRSD, 17 item version) (Hamilton, 1967). Severity was rated at baseline and weekly until the end of the study period, after 48 hours but within 7 days of the ECT sessions, and after a follow up of three and six months.

On a weekly basis during the treatment phase and at the three and six month follow ups, the patients visited their treating psychiatrist. He was not necessarily blind to the treatment condition. During this visit the physician rated the patients' condition based on the semi-structured MADRS interview and the Clinical Global Impressions (CGI) scale (Guy, 1976). The concomitant medication was kept stable during the randomized phase of the study.

Cognitive assessments were done a week before the first ECT (pre-ECT), after three weeks, one week after finishing the treatment course and after a follow up of three and six months.

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