Chapter 8

Summary and general discussion

Aims and research questions revisited

The main theme of this thesis was to study the efficacy of RUL ECT in major depression. This thesis is complementary to Esmée Verwijk's thesis, "Neurocognitive performance in electroconvulsive therapy – to lose or not to lose?", which focuses primarily on the cognitive effects of ECT in the same group of patients.

In Chapter 2 we reviewed the literature to summarize the level of evidence for the efficacy of UBP compared to the "old standard" BP stimulation in electroconvulsive therapy. In Chapters 3 and 4 of the central study of this thesis, we investigated the efficacy and cognitive side effects of RUL ECT with high dose (8 times seizure threshold) UBP versus high dose BP stimulation, in the short term and in follow up. In Chapter 5 we examined more closely the efficacy of ECT in an attempt to identify the subgroup of fast complete remitters, those who remitted within only four ECT sessions. In Chapters 6 and 7 we focused on participants above 60 years of age with unipolar depression. We considered participants from a RCT comparing nortriptyline with venlafaxine in contrast to a subset from the study in Chapter 3. In Chapter 6 we analyzed the speed of remission with ECT versus antidepressant medication and in Chapter 7 we studied the influence of vascular risk factors on the efficacy of both ECT and medication.

Summary of main results

Efficacy of BP versus UBP ECT review (Chapter 2)

Despite the fact that UBP ECT is increasingly used in daily practice, the evidence to support this current practice is limited. We reviewed the literature published before April of 2012 and found that for unilateral ECT only one high-quality prospective randomized head-to-head comparative trial (Sackeim et al., 2008) was available, along with just one other prospective non-randomized study (Loo et al., 2008) that reported on response and remission of UBP v. BP ECT. Many studies (Bayless et al., 2010; Galletly et al., 2012; McCormick et al., 2009; Merkl et al., 2011; Quante et al., 2011; Roepke et al., 2011; Sienaert et al., 2009) on UBP RUL ECT have proven that this ECT stimulus technique is effective for treatment of depression, but do not answer the question, is this technique as effective as BP RUL ECT in treating depression? We concluded that the increasing use of RUL UBP ECT as first line method for depression was not supported by the current evidence.

RUL BP versus RUL UBP ECT: RCT and naturalistic follow up (Chapters 3 & 4): too brief or not too brief?

In Chapters 3 and 4 we described an RCT comparing the short-term and naturalistic long-term efficacy and cognitive side effects of high dose BP versus UBP RUL ECT. In contrast to our hypothesis, the principal finding of this study was that although BP RUL ECT and UBP RUL ECT were both highly effective treatments for depression, BP RUL ECT was significantly more efficacious (Chapter 3). This effect was demonstrated in the intention-to-treat (ITT) group, where 50.0% (29/58) achieved remission in the BP group versus 41.4% (24/58) in the UBP group (*P*=.039), as well as in the completers group, where 68.4% (26/38) of those in the BP group achieved remission versus 49.0% (24/49) of those in the UBP group (*P*=.019). Higher remission rates were associated with higher age of patients and with shorter duration of the current depressive episode. The BP group needed fewer treatment sessions to achieve remission: mean (SD) of 7.1 (2.6) versus 9.2 (2.3) sessions (*P*=.008). The difference in efficacy was clinically relevant, as remission in the completer group was achieved with two sessions (one week) less using BP RUL ECT, compared to UBP. The number of treatment sessions was significantly associated only with the current depressive episode duration in both the ITT (B=0.01, *P*=.008) and completers (B=0.09, *P*=.015) groups.

Also in contrast to our hypothesis, our results demonstrated no difference in the impairment of retrograde memory, either in autobiographical memory or in public events (for more detailed information, see Spaans et al. (2013); and see Esmée Verwijk's thesis).

The follow up study showed no statistically significant differences in relapse rates between RUL BP and RUL UBP ECT (*Chapter 4*). Of the 50 patients who remitted after index ECT, 44 (24 BP; 20 UBP) were monitored for follow up. Relapse had occurred in 25% of the BP group and in 25% of the UBP group (χ^2=0.00, *p*=1.0) at the three-month follow up, whereas 43.5% of the BP group and 35% of the UBP group had relapsed (χ^2=0.322, *p*=0.57) at the six-month follow up.

Also no cognitive differences were shown during the six-month follow up events (for more detailed information, see Verwijk et al. (2015) and Esmée Verwijk's thesis).

Fast complete remission of depression with ECT (chapter 5)

Clinicians practicing ECT will all have the experience that some patients respond extraordinarily well within only a few sessions. Using this observation as a starting point our study confirmed the clinical impression that ECT resulted in a fast complete clinical remission in 14% (12/87) of the patients based on a) a score of 1 out of 7

(=normal, not at all ill) on the Clinical Global Impressions (CGI) scale within 2 weeks of treatment (≤ 4 ECT sessions) and b) remission during the treatment course. A specific depression profile was found for these early complete remitters, with a higher age, psychotic features, a shorter episode duration and a dysexecutive profile with cognitive slowing at baseline and less relapse during the six months of follow up, compared with the late complete remitters or non-remitters. Early complete remission was not associated with gender, level of education, baseline depression severity (MADRS), bipolarity, treatment-refractoriness (ATHF) or age of onset.

Speed of remission: ECT versus medication (Chapter 6)

In this study we have shown that the subgroup of elderly inpatients with severe unipolar depression achieved earlier remission by nearly 1 week if treated with ECT in comparison with antidepressants. Mean time to remission for ECT was 3.1 weeks (s.d.=1.1); for medication, 4.0 weeks (s.d.=1.0). Survival analysis favored ECT over medication based on both MADRS and HRSD scores; the adjusted Hazard Ratios for remission within 5 weeks (ECT vs. medication) were 3.4 (95%CI 1.9-6.2) based on the MADRS and 2.7 (95%CI 1.5-4.9, p=.001) based on the HRSD. The final remission rates of 63.8% (30/47) after 6 weeks in the ECT group and 33.3% (27/81) after 12 weeks in the medication group further underlined the superiority of ECT over antidepressants. In this age group depression is reported to decrease the overall quality of life and because of decreased mobility, compromised food and fluid intake, and a higher incidence of lethal suicide attempts than in younger persons, depression should be considered a life-threatening disease. Therefore, earlier remission could be of crucial clinical importance for an elderly patient who is severely depressed.

Vascular risk factors (VRF) and remission rates: ECT versus medication (Chapter 7)

The overall suggestion from the literature is increased effectiveness of ECT compared to antidepressant medication in the treatment of depression with vascular burden. However, contrary to common belief and our hypothesis of a preferential advantage of ECT over antidepressants, we could not confirm this. Our data even suggested that the efficacy of ECT was decreased in the presence of vascular risk factors, while the outcome of medication treatment remained virtually unchanged. Remission rates were 58% (19/33) in the ECT group with ≥1 VRF and 32% (23/73) in the medication group with ≥1 VRF (χ2=6.456, p=0.011). Comparing patients with no VRF to those with ≥1 VRF, remission rates decreased from 80% to 58% (p=0.276) in ECT patients and from 38% to 32% (p=0.707) in medication patients.

Therefore we concluded that the clinical impression that ECT would be more effective in depression with vascular risk factors, is merely the consequence of the efficacy of ECT per se and not of additional beneficial effect in depression with vascular burden.

Overall conclusions

- High dose BP RUL ECT is more efficacious than high dose UBP RUL ECT within 12 sessions and results in a clinically significant faster remission. We did not find an advantage of UBP in respect to cognitive performance.
- Older patients with a psychotic depression and a profile of cognitive slowing have a high chance of achieving complete remission within four ECT sessions, with a favorable six-month prognosis. These early complete remitters may represent a clinically distinct subtype of depression.
- Considering the substantially higher speed of remission compared to medication, ECT deserves a more prominent position in the treatment of older patients with severe depression.
- The superior efficacy of ECT compared to pharmacotherapy in older patients with depression was independent of the presence of VRF.

Methodological considerations

This thesis contains studies among one of the largest double-blind, randomized controlled ECT designs. With only a few exclusion criteria and continuation of most psychotropic medication, the results can be generalized to daily clinical practice. Another important benefit is a follow up period of six months.

Choice for an ECT machine with a maximum output of 200 Joules

One technical issue regards the initial seizure threshold of the BP group and the energy output limits of the ECT machines. The Food and Drug Administration (FDA) in the United States has set energy limits to ≈100 Joules (576 mC for the spectrum 5000Q from MECTA Corp. and 504 mC for the Thymatron IV from Somatics Corp.). Due to this limitation, it was probably not feasible to treat all patients at six times seizure threshold for the BP group in the American study (Sackeim et al., 2008), which could have diminished differences between the samples in this study.

In Europe, the same ECT machines are available in a 200 Joule version, which is considered medically safe. In our study with a stimulus dose at 8 times seizure threshold (ST), 6 remitters (5 BP, 1 UBP) were treated above 576 mC (resp. 768 mC and 614 mC). With the maximum setting of a 100 J machine this would have resulted in

treatment at respectively 6 and 7.5 times ST. My educated guess would be that these 6 cases from our study would have been remitters with this 100 Joule maximum setting.

Choice of titration schedule

The MECTA spectrum 5000 Q 200 Joule machine we used allowed us exact predetermined variable settings, not only for pulse width but also for pulse frequency, stimulus duration and amplitude. Longer stimulus duration has been reported to be related to lower seizure threshold, and frequency to treatment efficacy (Andrade et al., 2002). We wanted to control for these confounders in our BP v. UBP pulse comparison study without compromising the SDRST. Therefore we increased the stimulus duration in our titration scheme (see Table 1) by one second in every step, with an obligatory dependent increase in stimulus charge. All other variables (pulse width, frequency, amplitude), however, remained fixed. Comparable steps existed in the BP and UBP titration schedule, with the same frequency, duration and amplitude. Frequency, duration and amplitude parameters in the treatment schedule were also kept the same, except for the upper limits of the used settings.

Table 1 Titration procedure

	Threshold						Treatment level (8 x ST)					
	Step	**PW**	**PF**	**SD**	**Current**	**Charge**	**Step**	**PW**	**PF**	**SD**	**Current**	**Charge**
ultrabrief	1	0.3	20	1	800	*9.6*	1	0.3	80	2	800	*76.8*
	2	0.3	20	2	800	*19.2*	2	0.3	80	4	800	*153.6*
	3	0.3	20	3	800	*28.8*	3	0.3	80	6	800	*230.4*
	4	0.3	20	4	800	*38.4*	4	0.3	110	6	800	*316.8*
	5	0.3	20	8	800	*76.8*	5	0.4	120	8	800	*614.4*
brief	1	1.0	20	1	800	*32*	1	1.0	80	2	800	*256*
	2	1.0	20	2	800	*64*	2	1.0	80	4	800	*512*
	3	1.0	20	3	800	*96*	3	1.0	80	6	800	*768*
	4	1.0	20	4	800	*128*	4	1.0	110	6	800	*1056*

PW=pulse width (ms); PF=pulse frequency (Hz); SD=stimulus duration (s); Current=electrical current (mA); Charge (mC); ST=Seizure Threshold

Specifics of our ECT procedure

In the studies presented in this thesis, the seizure is induced with unilateral stimulation. On average, two stimulations in the case of BP and three stimulations in the case of UBP were needed to induce a (threshold) convulsion. The subthreshold

stimulation added to the effects of succinylcholine causes direct vagal stimulation that can trigger a bradycardia and sometimes even a short pause (asystole) for ten seconds. The anesthesiologists consider tachycardia a greater risk than bradycardia, especially for the elderly population where bradycardia and reflex bradycardia affect mostly the younger patients. For that reason atropine and glycopyrrolate are abandoned as standard premedication in our hospital.
Bilateral treatment requires about the same amount of titration steps to induce a seizure as unilateral treatment. The number of treatments in bilateral treatment can be lower because the therapeutic effect of a bilateral threshold seizure is comparable with the therapeutic seizure at 1.5 or 2.5 times the threshold dose (Sackeim et al., 1993). We tried to minimize the number of non-therapeutically dosed titration sessions by adding a therapeutic session with the SDRST in the first session whenever possible. In a way, studies that used a separate titration session gave bilateral treatment a head start.

Still, our studies faced various methodological concerns regarding patient selection and study design (RCT, naturalistic follow up, comparison of two RCTs and subsets of the RCTs). All these factors may have compromised the validity of the data and the generalizability of our results.

Selection of patients
With only a few exclusion criteria and continuation of most psychotropic medication, the efficacy results from the BP vs. UBP RUL ECT RCT (Chapter 3) can be generalized to daily clinical practice. Patients were treated as inpatients during index ECT and could be discharged from the hospital during follow up. ECT is increasingly practiced on an outpatient base even from the start of the treatment. The hospital staff and environment offers rhythm, support and safety and is used to deal with temporary confusion after ECT. It is possible that our results cannot be generalized to an outpatient group.

Concomitant medication
Practically all of the patients (98%) used concomitant psychotropic medication. Lithium was continued at serum levels below <0.8 mM and benzodiazepines at a maximum of 10 mg diazepam equivalents. Tapering off antidepressant medication before ECT takes time but, more importantly, may worsen a depression that showed only partial response. In some cases this may even lead to patients refusing ECT.

However, we did not control for the different type of psychotropic used. Since the augmenting effects of psychotropics have been suggested (Prudic et al., 2013), this must be noted as a confounder.

Multicenter study

Recruiting the patients from three psychiatric centers may have introduced biases, notwithstanding the adjustments made in the statistical analysis. Between the hospitals, there were major differences in the number of patients included and the mean age of the groups of included patients differed. It can be hypothesized that the staff of the hospital with the oldest patients may have been the most experienced in handling patients with temporary cognitive problems due to ECT.

Naturalistic follow up

A naturalistic follow up study (Chapter 4) entails limitations, since risk of relapse can be influenced by medication and other unknown factors, like social support, medical comorbidity, and psychotherapy (Altman et al., 2006; Lampe et al., 2013). The control over these factors was even less than during index ECT, because the remitted patients were likely discharged from the hospital and treatment was no longer controlled for. Dropout due to missed appointments was 14% (7/50). Medication to prevent relapses was given to the majority of our patients but was not recorded. Nevertheless, our relapse rates were comparable to previous studies.

Samples size

In a power analysis undertaken to design the study, we calculated for an assumed effect size of 0.25, a sample size of 65 patients in each group to achieve a power of 0.80 with an alpha of 0.05 to detect differences in efficacy and cognitive effects during index treatment with BP and UBP RUL ECT. Unfortunately, although one of the largest ECT studies (n=116), this resulted in small numbers of interesting subgroups, which may have hampered statistical analysis of possible associations between bipolarity, depressive episode duration and relapse in the follow up study (Chapter 4), between cognitive measures and fast complete remission (Chapter 5) and between absence of vascular risk factors and differences in ECT or medication remission rates (Chapter 7).

Comparison of two RCTs

The use of two published RCTs (Chapter 6 and 7) to compare differences between medication and ECT treatment had some disadvantages. The maximum treatment

duration differed between the original RCTs: six weeks for the ECT study and 12 weeks for the medication study. While important covariates were controlled for, our study could not control for some other potential confounders through randomization to treatment, such as the distribution of vascular risk factors. Due to divergent means of assessment, potentially relevant covariates, including cognition, psychiatric and somatic morbidity, could not be included in the analysis.

Maximum number of treatment sessions in the study

Although twelve was the maximum number of treatment sessions in our protocol, it could be theorized that the treatment duration was too short for the UBP treatment to deploy to the maximum effect and approach the efficacy of BP treatment. If normally distributed, an average treatment duration of 7.1 (sd 2.6) sessions for the BP group would suggest that probably 95% would be in remission before the end of the study protocol (12 sessions). Since the UBP group remitted in 9.2 (sd 2.3) sessions, extending the study by one week could have resulted in equal remission rates for BP and UBP.
It is conceivable that for unilateral ECT, efficacy is a function of SDRST, pulse width and maximum number of sessions allowed in the study. In our study the SDRST was the same for UBP and BP. This makes clear that distinction between BP and UBP pulse width is more important for speed of remission than for efficacy. ECT studies interested in speed of response and efficacy of UBP should take into account that study length and early switching can be major confounders.

(In)adequacy of seizures?

Study designs of ECT often include the adjustment of the charge for alleged inadequacy of seizure, which is most often based on shortening of the seizure duration during the treatment course (Loo et al., 2008; Sackeim et al., 2008). From the literature (Chung, 2002; van Waarde et al., 2010; Wild et al., 2004) and in my own clinical experience, increasing the charge by raising the stimulus frequency or stimulus duration does not produce a long lasting increase in seizure duration. No dose adjustments were made before the seventh session. Then we retitrated our patients, and the treatment dose was adjusted accordingly. Remitters before the 7th session, who were predominantly 72% (13/18) treated with BP, were not retitrated. Seizure thresholds do tend to rise primarily in UBP treatment (Table 2). Therefore treatment with RUL BP has the advantage that adjustments based on the seizure threshold are rarely necessary. Despite the fact that we did not adjust the treatment charge continuously during the treatment, remission rates were also good in the UBP sample.

Table 2 Change at retitration

Pulse width	Equal	Higher	Lower
BP (n=11)	9 (82%)	1 (9%)	1 (9%)
UBP (n=30)	16 (53%)	14 (47%)	0

BP=brief pulse
UBP= ultrabrief pulse

Clinical implications

Our results have several clinical implications for the daily practice of ECT.

- To achieve fast remission, high-dose RUL BP ECT is the preferred treatment over high-dose RUL UBP ECT. We found no differences in executive and retrograde amnesia.
- ECT deserves a more prominent position in the treatment of older patients with severe depression, considering the substantially higher speed of remission compared to medication.
- Especially in older patients with a psychotic depression and a profile of cognitive slowing, the chances of a favorable outcome and a good six-month prognosis are high, despite the grave clinical picture.

Suggestions for further research

- **BL ECT versus high dose UL ECT**
  If patients do not improve with UL ECT, we switch to BL ECT. We do not regularly start with BL ECT, out of fear for cognitive side effects. If the longer recuperation time between treatments (Chapter 3) twice weekly may be important to reduce cognitive side effects, a twice weekly BL BP ECT versus high dose RUL BP ECT trial is the next step forward, with emphasis on the cognitive side effects.
- **Actigraphic changes during ECT**
  ECT is suggested to have an effect on the biological clock and often psychomotor and changes in sleep patterns happen early in the course of treatment. Actigraphic changes after the first ECT should be studied focusing on daily activity and sleep patterns.
- **Brain stimulation with ECT: Efficacy and cognition connected?**
  An interesting phenomenon of antidepressant drugs is the early, immediate unconscientious change that occurs in cognitive attribution bias. This change long precedes the clinical improvement of depression after treatment with SSRI's (Harmer et al., 2009). Another inspiring study by Kroes and colleagues

showed that memories activated just before ECT were vulnerable to loss (Kroes et al., 2013). This latter mechanism could be important for the fast improvement of ruminating psychotically depressed patients.
If ECT influences the networks implicated in depression through yet unknown pathways (Kaiser et al., 2015) and this results in this fast change in attribution bias, while in the meantime negative ruminations get blurred, the cognitive effects of ECT would be more central to the fast action of ECT in severe depression than we thought and hoped for.

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