Electroconvulsive therapy for bipolar disorder depression

Effects on depressive symptoms and cognitive function

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Scientific environment

The work reported in this thesis was performed between 2008 and 2014 at the Division of Psychiatry, Haukeland University Hospital and at the Department of Clinical Medicine, University of Bergen in collaboration with the Bipolar Research and Innovation Network (BRAIN) in Norway. The Regional Research Network on Mood Disorders (MoodNet), the Western Norway Regional Health Authority, and the participating hospitals funded the study.

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Preface

Bipolar disorder (BD) is a chronic, recurrent, and often devastating psychiatric disorder exhibiting a substantially amount of treatment resistance. As a consultant in an affective ward I became familiar with electroconvulsive therapy (ECT) as a treatment option in the acute phase of the illness. The use of ECT in BD depression was supported by the results from nonrandomized studies and studies comparing the efficacy of ECT in unipolar versus BD depression, but there were no randomized controlled trials of ECT in BD depression. This lack of evidence and my interest in learning more about the cognitive effects of ECT lead to my engagement in the planning and realization of the "Norwegian Randomized Controlled Trial of ECT in Bipolar Disorder", both as the administrative head and in my own subproject.
The study was envisioned by the late Professor Dag Neckelmann, and became possible through the collaboration of enthusiastic clinicians throughout Norway, and financial support from the Regional Research Network on Mood Disorders (MoodNet), the Western Norway Regional Health Authority, and the participating hospitals.

Abstract

Background: Treating the depressive state of bipolar disorder (BD) is challenging. Pharmacological treatments often have poor outcomes. Electroconvulsive therapy (ECT) is generally considered to be the most effective acute treatment, but documentation is lacking. ECT was for decades a controversial treatment, mainly due to possible long-lasting effects on memory and other neurocognitive functions. BD itself is associated with neurocognitive impairments, and there are concerns that these might be worsened by ECT.

Aims: The overall aim of the thesis was to compare the effects of right unilateral (RUL) ECT and algorithm-based pharmacological treatment (APT) on depressive symptoms and cognitive function in treatment-resistant BD depression.

Methods: The thesis is based on a multicenter, randomized controlled trial that was carried out at seven acute psychiatric in-patient clinics throughout Norway and included a total of 73 BD patients with treatment-resistant depression. The patients were randomized to receive either ECT or APT. ECT was administered in three sessions per week for up to six weeks using RUL electrode placement and brief-pulse stimulation. The neurocognitive function was assessed with the Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery (MCCB), and retrograde memory for autobiographical events was assessed with the (Columbia) Autobiographical Memory Interview–Short Form (AMI-SF) before and shortly after the trial. Depressive symptoms were assessed with the Montgomery-Åsberg Depression Rating Scale (MADRS) as the primary outcome, and the Inventory of Depressive Symptomatology–Clinician-rated, 30-item version (IDS-C30) and the Clinical Global Impression for Bipolar Disorder (CGI-BP) as secondary outcomes.

Results: Neurocognitive impairments were evident in BD depression inpatients within all MCCB domains, more so in BD type I than in BD type II. Higher age was associated with greater neurocognitive deficits compared to age-adjusted published norms.

Linear mixed-effects modeling analysis revealed that ECT was significantly more effective than APT. The mean MADRS score was 6.6 points lower in the ECT group than in the APT group (standard error=2.05; 95% confidence interval=2.5–10.6, p=0.001). The secondary outcome measures showed similarly significant results, with the mean IDS-C30 and CGI-BP scores being 9.4 and 0.7 points lower, respectively, in the ECT group. The response rate was higher in the ECT group than in the APT group (73.9% vs 33.3%, p=0.014), but there was no significant group difference in the remission rate (34.8% vs 28.6%, p=0.75). The times to response and remission did not differ significantly between the ECT and APT groups.

Shortly after the treatment trial both groups showed improvements in all MCCB domain scores, with no significant differences between the treatment groups. Improvements in neurocognitive performance after treatment were significantly correlated with reductions in depression ratings. The AMI-SF score was significantly lower (based on consistent answers from pre- to posttreatment) in the ECT group than in the APT group (72.9% vs 80.8%, p=0.025), indicating reduced consistency in autobiographical memory after ECT.

Conclusions: A large proportion of patients with treatment-resistant BD depression exhibited global neurocognitive impairments with clinically significant severity at baseline. ECT was more effective than APT in treating treatment-resistant BD depression. The response rate was higher in the ECT than in the APT group. The remission rates were modest, with no differences between the treatment groups. General neurocognitive function was unaffected by RUL ECT and positively related to improved mood in BD depression, however autobiographical memory consistency was reduced in patients treated with ECT. These findings suggest that ECT is an effective treatment method in treatment-resistant BD depression and can be used without comprising general neurocognitive function, although the reduced autobiographical memory consistency in the ECT group is a finding that requires further investigation. Clinicians should be aware of the severe neurocognitive dysfunction that can be present in treatment-resistant BD depression independently from ECT treatment.

List of publications

This thesis is based on the following papers:

Paper I

Kessler U, Schoeyen HK, Andreassen OA, Eide GE, Hammar Å, Malt UF, Oedegaard KJ, Morken G, Sundet K, Vaaler AE: Neurocognitive profiles in treatment-resistant bipolar I and bipolar II disorder depression. BMC Psychiatry 2013, 13:105.

Paper II

Schoeyen HK[1], Kessler U[1], Andreassen OA, Auestad BH, Bergsholm P, Malt UF, Morken G, Oedegaard KJ, Vaaler AE: Treatment resistant bipolar disorder depression – A randomized controlled trial of electroconvulsive therapy versus algorithm-based pharmacological treatment. Submitted

[1]Schoeyen and Kessler contributed equally and share the first authorship of this paper

Paper III

Kessler U, Schoeyen HK, Andreassen OA, Eide GE, Malt UF, Oedegaard KJ, Morken G, Sundet K, Vaaler AE: The effect of electroconvulsive therapy on neurocognitive function in treatment-resistant bipolar disorder depression. Accepted for publication in J. Clin. Psychiatry.

Related paper not included in this thesis:

Kessler U, Vaaler AE, Schøyen H, Oedegaard KJ, Bergsholm P, Andreassen OA, Malt UF, Morken G: The study protocol of the Norwegian randomized controlled trial of electroconvulsive therapy in treatment resistant depression in bipolar disorder. BMC Psychiatry 2010, 10:16.

Abbreviations

AD	antidepressant
AMI-SF	(Columbia) Autobiographical Memory Interview–Short Form
ANOVA	analysis of variance
APT	algorithm-based pharmacological treatment
BD	bipolar disorder
BD I	bipolar disorder type I
BD II	bipolar disorder type II
BL	bilateral
BRAIN	Bipolar Research and Innovation Network
BVMT-R	Brief Visuospatial Memory Test–Revised
CANMAT	Canadian Network for Mood and Anxiety Treatments
CGI-BP	Clinical Global Impression for Bipolar Disorder
CI	confidence interval
DBS	deep brain stimulation
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision
ECT	electroconvulsive therapy
GAF-S	Global Assessment of Functioning–Split version, symptom subscale
HCL-32	Hypomania Checklist-32
HVLT-R	Hopkins Verbal Learning Test–Revised
ICC	intraclass correlation coefficient
IDS-C30	Inventory of Depressive Symptomatology–Clinician-rated, 30-item version
IPSRT	interpersonal and social rhythm therapy
LME	linear mixed effects
MADRS	Montgomery-Åsberg Depression Rating Scale

MATRICS	Measurement and Treatment Research to Improve Cognition in Schizophrenia
MCCB	MATRICS Consensus Cognitive Battery
MINI	Mini International Neuropsychiatric Interview
MST	magnetic seizure therapy
NAB	Neuropsychological Assessment Battery
NART	National Adult Reading Test
NEQ	Stanley Foundation Bipolar Collaboration Network Entry Questionnaire
OFC	olanzapine fluoxetine combination
PANSS pos	Positive and Negative Syndrome Scale for Schizophrenia, positive subscale
RCT	randomized controlled trial
rTMS	repetitive transcranial magnetic stimulation
RR	relative risk
RUL	right unilateral
SCID-I	Structured Clinical Interview for DSM-IV Axis I Disorders
SD	standard deviation
SPSS	Statistical Package for the Social Sciences
STEP-BD	Systematic Treatment Enhancement Program for Bipolar Disorder
TCA	tricyclic antidepressant
tDCS	transcranial direct current stimulation
VNS	vagal nerve stimulation
WASI	Wechsler Abbreviated Scale of Intelligence
YMRS	Young Mania Rating Scale

Contents

1 Introduction

This thesis compares the effects of electroconvulsive therapy (ECT) and pharmacological treatment in treatment-resistant bipolar disorder (BD) depression, with a focus on depressive symptoms and cognitive functioning. This section outlines the basic characteristics of BD, especially the treatment and cognitive aspects of BD depression.

1.1 BD: diagnostic and clinical aspects, with emphasis on the depressive state

BD is a chronic mood disorder, characterized by depressive, manic or hypomanic, and mixed episodes. It is one of the leading contributors to disability and the global burden of disease [1, 2]. It is commonly comorbid with other mental disorders, most frequently with one or more anxiety disorders or substance abuse [3, 4]. Comorbidity further increases the burden of BD [5]. BD has a lifetime prevalence of 1.5–2% [3, 6]. It is a highly recurrent disorder. A longitudinal study that followed 220 BD patients over 20 years found a median of 0.3–0.4 episodes per year [7]. However, approximately one-third of BD patients exhibit the phenomenon of rapid cycling, defined by four or more episodes during a 12-month period [8].

It is common for BD patients to have previously been diagnosed with conditions other than BD [9] which makes the psychiatric evaluation and proper diagnosis before treatment an important stage in managing the illness [10]. The diagnoses in this thesis are based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) [11]. The diagnosis of BD requires the presence of at least one previous manic [BD type I (BD I)] or hypomanic [BD type II (BD II)] episode. As indicated in Table 1, the diagnostic criteria for a depressive episode are similar for unipolar and bipolar mood disorders. Misdiagnosing BD depression as unipolar major depression is common, even after

the onset of the first manic or hypomanic episode [12, 13]. In fact, in most patients the diagnosis of BD is preceded by several years of undetected or misdiagnosed illness associated with nontreatment or suboptimal treatment, which increases the risk of exacerbating the illness and worsening the prognosis [12-16]. There are no pathognomonic symptoms for definitively differentiating unipolar and bipolar depression, but certain clinical characteristics—such as hypersomnia, hyperphagia, leaden paralysis, psychomotor retardation, psychotic features, pathological guilt, and lability of mood—are more common in BD depression [17]. Screening instruments [e.g., Angst's Hypomania Checklist-32 (HCL-32) [18]] should be applied to increase the likelihood of detecting BD. Since patients might not remember previous (hypo)manic behavior or feelings, or not identify these as being abnormal, family members should be involved in the diagnostic process [10].

Table 1. Diagnostic criteria for BD depression according to—and adapted from—the DSM-IV-TR

296.5x Bipolar I disorder, most recent episode depressed
A. Currently in a major depressive episode.
B. History of at least one manic episode or mixed episode.
C. The mood episodes in Criteria A and B are not better accounted for by schizoaffective disorder and are not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified.
296.89 Bipolar II Disorder
A. Presence of a major depressive episode.
B. History of at least one hypomanic episode.
C. No history of a manic episode or a mixed episode.
D. The mood symptoms in Criteria A and B are not better accounted for by schizoaffective disorder and are not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder not otherwise specified.
E. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Major depressive episode

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure (does not include symptoms that are clearly due to a general medical condition, or mood-incongruent delusions or hallucinations):

(1) Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful).

(2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)

(3) Significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day.

(4) Insomnia or hypersomnia nearly every day.

(5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).

(6) Fatigue or loss of energy nearly every day.

(7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).

(8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).

(9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms do not meet criteria for a mixed episode.

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

E. The symptoms are not better accounted for by bereavement (i.e., after the loss of a loved one), and the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

Prospective follow-up studies have demonstrated that depression is by far the predominant mood state in BD [19, 20]. Clinically, the depressive state of BD is characterized by decreased (sad, melancholic, pessimistic, or despairing) mood, behavioral changes (e.g., fatigue, lack of activity, disturbed sleep, and reduced social interaction), and cognitive changes [10, 13]. The diagnostic criteria and associated symptoms are listed in Table 1. Suicidal thoughts are common and suicide is frequent [21]. A depressive episode can be aggravated by psychotic symptoms such as delusions or hallucinations, which tend to reflect the depressive mood and revolve around guilt, sinfulness, financial ruin, and hypochondriacal and somatic concerns [10].

BD often has an unfavorable outcome with pervasive symptoms [19, 22, 23]. The depressive symptoms are especially strongly associated with a poor psychosocial and functional outcome [24-26]. Patients tend to relapse even with treatment, more than twice as often into depressive episodes than into hypomanic, manic or mixed episodes [27, 28]. Depressive symptoms are primarily responsible for the burden of BD [10, 20], and hence their management is a crucial problem in the treatment.

1.2 Cognition in BD

Cognitive dysfunction is a core feature of BD [29]. Various cognitive functions are impaired in BD patients relative to healthy controls [30-32]. These dysfunctions are present in all phases of the illness, including in euthymia, with a moderate worsening of a subset of deficits in the acute states [33-36]. Deficits in verbal learning, attention, and executive functions are the most prominent and most frequently reported [35, 37, 38]. BD patients present with heterogeneous clinical and cognitive symptoms. Subgroups of patients may have relatively preserved or markedly reduced cognitive function [10, 39-41]. Cognitive deficits are present in both BD I and BD II patients, with the impairment being more pronounced in BD I, and the most prominent difference being in memory function [41-44]. Cognitive impairment in BD has been

linked to a worse functional and occupational outcome, and it is thus an important treatment target [45-49].

There are indications of a possible neurodegenerative process in BD [50]. A worse prior course of illness—characterized by longer duration of illness and a larger number of psychotic and manic episodes and hospitalizations—has been associated with more severe cognitive dysfunction [51-53]. However, other studies have found that the duration of illness and the number of hospitalizations do not affect the neuropsychological performance [54-56]. Cognitive decline occurs in normal aging, and there are indications that this accelerates in persons suffering from BD [57, 58]. However, a meta-analysis of neuropsychological functioning in euthymic BD [30] produced the contrary finding that cognitive impairment becomes less pronounced as age increases.

Difficulties in thinking, concentration, or decision-making are diagnostic criteria for a major depressive episode [11]. Patients in the depressive phase of BD frequently report poor concentration and memory, and reduced clarity and speed of thought [10, 13]. However, there is sparse literature on the neuropsychological profiles specific to BD depression [33, 34, 59-64]. Often studies have not distinguished between BD and recurrent depressive subgroups, or they have involved heterogeneous patient groups with BD in euthymic, mixed, or unclassified mood states.

1.3 Acute treatment of BD depression

The main treatment focus during a depressive episode is to reduce depressive symptoms, including suicidality. Acute episodes require different treatment approaches than long-term treatment—the latter aims at preventing the recurrence of new episodes. Even in the acute state the maintenance treatment should be kept in mind so as to avoid therapeutic approaches that could induce switches to the opposite mood or mood instability and cycle acceleration [14, 65]. Although pharmacotherapy

is the mainstay, its efficacy is limited, and adjunctive psychosocial treatment is an essential part of BD treatment [10].

1.3.1 Psychosocial treatment of BD depression

The main targets of proven and recommended psychosocial treatment approaches, such as psychoeducation, cognitive behavioral therapy, interpersonal and social rhythm therapy (IPSRT), and family-focused therapy, are to restore psychosocial function, prevent relapse, reduce residual symptoms, and enhance the overall quality of life, rather than reduce the acute symptoms [66]. Thus, only a few trials have assessed the effect of psychosocial treatment in acute BD depression, which is in contrast to the convincing evidence for the efficacy of psychosocial treatment approaches in maintenance therapy [67, 68]. One of the trials, which formed part of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), compared intensive cognitive behavioral therapy, IPSRT, and family-focused therapy with collaborative care [69]. The times to recovery were shorter for patients receiving intensive psychotherapy than for patients receiving collaborative care. The patients receiving intensive psychotherapy were also more likely to be clinically well for at least 12 months. The results from a study comparing acute and maintenance IPSRT with clinical management suggest that IPSRT is more useful in relapse prevention than in reducing acute symptoms, since there were no differences in the time to stabilization but a significant longer period without new affective episodes in the IPSRT-treated patients [70]. Psychological treatment approaches are not recommended when severe retardation or psychotic symptoms are present during the acute phase of BD depression [71].

1.3.2 Biological treatment of BD depression

1.3.2.1 Pharmacological treatment

1.3.2.1.1 General aspects

Most BD patients spend much more time in a depressive state than in mania or other mood states [19, 20, 72]. Pharmacological treatment options for the depressive state

are limited [67, 73]. There are only three U.S. Food and Drug Administration (FDA)-approved treatments for BD depression: quetiapine, the olanzapine fluoxetine combination (OFC), and lurasidone, either in monotherapy or as adjunction to lithium or valproate. Lithium, anticonvulsant mood stabilizers, atypical antipsychotics, and antidepressants (ADs) are the most recommended and used drugs for the acute treatment of BD depression [74]. The pharmacological approaches have potentially serious side effects. The detailed review of these side effects is beyond the scope of this thesis, but they must be taken into account when the various possible treatment options are considered. The most common side effects of the presented drugs together with their dosing considerations are listed in Table 2.

Table 2. Common side effects and dosing considerations for drugs used in pharmacological first-line treatment of BD depression, adapted from [14]

Drug	Common side effects (incidence ≥1%)	Dosing considerations
Lithium	**GIT:** nausea, vomiting, epigastric discomfort, dry mouth, metallic taste, diarrhea, and weight gain. **CNS:** fatigue, headache, difficulty concentrating, vertigo, and fine tremor. **Skin:** dry skin, exacerbation of psoriasis or acne, and rash. **Metabolic:** hypermagnesemia, hypercalcemia, and hypothyroidism. **Other:** benign ECG changes and leukocytosis. **Lithium toxicity:** signs include loss of balance, increasing diarrhea, vomiting, anorexia, weakness, ataxia, blurred vision, tinnitus, polyuria, coarse tremor, muscle twitching, irritability, and agitation. Drowsiness, psychosis, disorientation, seizures, coma, and renal failure may occur.	Recommended therapeutic range 0.5–1.2 mmol/L (lower end of range recommended in maintenance). Risk of toxicity increases markedly for >1.5 mmol/L (>3.5 mmol/L is potentially lethal); toxicity can also occur within the therapeutic range (particularly in the elderly). Abrupt reduction of >0.2 mmol/L increases risk of relapse. Lithium concentration can be affected by other medications (e.g., ACE inhibitors and NSAIDs) and sodium depletion (e.g., GIT disturbance). There can be a delay of 6–8 weeks for an antidepressant effect.
Lamo-trigine	**GIT:** dry mouth, nausea, and vomiting. **CNS:** diplopia, dizziness, ataxia, blurred vision, headache, irritability, somnolence, tremor, asthenia, and insomnia. **Skin:** maculopapular rash and Stevens-Johnson syndrome (0.3–2.0% in children). **Other:** arthralgia.	No demonstrated benefits in measuring serum lamotrigine. To prevent serious skin reaction, initiate at a low dose and increase slowly. Dosage may need to be adjusted if combining with other medications, particularly valproate and carbamazepine

Valproate	**GIT:** nausea, vomiting, abdominal cramp, anorexia, diarrhea, indigestion (especially with nonenteric coated preparations), increased appetite, and weight gain. **CNS:** sedation and tremor. **Skin:** transient hair loss. **Other:** thrombocytopenia, elevated liver transaminases, and asymptomatic elevations of ammonia.	Therapeutic range not clearly established; 350–700 mmol/L is a suggested guideline dose.
Atypical anti-psychotics	**Metabolic:** weight gain, dyslipidemia, hyperglycemia, and hyperprolactinemia. **Extrapyramidal symptoms:** tremor, akathisia, rigidity, slowing, and dystonia. **Anticholinergic reactions:** constipation, dry mouth, blurred vision, and urinary retention. **Other:** sedation, increased appetite, sexual dysfunction, GIT upset, peripheral edema, nausea, cerebrovascular events (with stroke and TIA especially in the elderly)**,** orthostatic hypotension, and tachycardia.	
SSRI ADs	**GIT:** nausea and diarrhea. **CNS:** dizziness, headache, tremor, agitation, insomnia, and drowsiness. **Anticholinergic reactions:** dry mouth. **Other:** myalgia, sweating, weakness, anxiety, weight gain or loss, sexual dysfunction, and rhinitis.	Serotonin toxicity is a potentially life-threatening adverse drug reaction with cognitive, autonomic, and somatic effects. Some combinations with other drugs are contraindicated (especially MAOIs or within 14 days of stopping an MAOI and moclobemide, or within 2 days of stopping moclobemide), and so should be avoided.
MAOI ADs [75]	**GIT:** nausea. **CNS:** insomnia, sedation, dizziness, and paresthesia. **Metabolic:** weight gain. **Other:** orthostatic hypotension, edema, muscle pain, myoclonus, and sexual dysfunction. **Important:** Hypertensive crisis after intake of dietary tyramine.	Patients taking MAOI are required to follow dietary restrictions that limit tyramine intake. Serotonin toxicity when combining with drugs exerting serotonergic effects.

Abbreviations: GIT = gastrointestinal tract; CNS = central nervous system; ECG = electrocardiogram; ACE = angiotensin-converting enzyme; NSAIDs = nonsteroidal anti-inflammatory drugs; TIA = transient ischemic attack; MAOI = monoamine oxidase inhibitor; SSRI = selective serotonin-reuptake inhibitor

1.3.2.1.2 Common drugs in pharmacological treatment of BD depression

Lithium

The introduction of lithium as a therapeutic agent was a milestone in the treatment of BD [76]. Lithium is well proven and effective in treating mania [77]. It has an important place in maintenance therapy, with proven efficacy in preventing new mood episodes [78, 79] and suicide [80, 81]. Early short-term, placebo-controlled studies indicated an antidepressive effect of lithium [82]. However, the EMBOLDEN I trial of acute treatments for BD depression found no statistical significant difference between lithium and placebo in reducing depressive symptoms [83]. This might have been due to the lithium serum levels being below 0.8 mmol/L, or the 6-8 weeks delay in the acute effect of lithium [14]. Some authors have considered lithium to be the most appropriate first-line treatment for BD depression [84], since it might be efficacious in both treating depressive symptoms and in preventing further mood episodes without a tendency to induce a manic/hypomanic switch or rapid cycling. The Norwegian treatment guideline for BD depression includes lithium as a second-line drug [85].

Anticonvulsant mood stabilizers

Current evidence supports the use of valproate and lamotrigine, whereas other anticonvulsants lack evidence for efficacy. They are not supported in the current guidelines for the treatment of BD depression [86].

Lamotrigine

The efficacy of lamotrigine in BD depression has been questioned [87], with only one [88] of five studies showing its superiority to placebo. However, a meta-analysis of individual patient data concluded that lamotrigine exerts a modest effect on BD depression and supported the efficacy of lamotrigine in monotherapy as a first-line treatment [89]. Lamotrigine is listed as a second-line drug in the Norwegian treatment guideline for BD [85].

Valproate

Valproate has shown antidepressive effects on BD depression in two small studies [90, 91]. A meta-analysis that also included two unpublished studies [92] concluded that valproate is effective in reducing depressive symptoms in BD depression, without inducing a switch to mania. The Norwegian treatment guideline for BD recommends valproate as a second-line drug in combination with an AD in BD I [85].

Atypical antipsychotics

The efficacy of quetiapine, olanzapine, and lurasidone in monotherapy has been demonstrated in BD depression, whereas studies of other atypical antipsychotics have produced negative or contradictory results [93-95].

Quetiapine

Several large RCTs (BOLDER I and II, EMBOLDEN I and II) [83, 96-98] have demonstrated the efficacy of quetiapine monotherapy in BD depression. Data from a meta-analysis on pharmacological treatment in BD depression highlighted quetiapine (together with OFC) as the most potent drug in reducing depressive symptoms [87]. In line with this, quetiapine is recommended as a first line monotherapy in recent guidelines [99], including the Norwegian treatment guideline for BD [85] (see also Table 4).

Olanzapine

The efficacy of olanzapine both in monotherapy and in combination with fluoxetine (i.e., OFC) has been demonstrated in a large RCT [100]. Both olanzapine and OFC are therefore recommended as first-line treatments in some guidelines [99], whereas it appears as a second-line treatment in the Norwegian guideline.

Lurasidone

Lurasidone is a novel atypical antipsychotic. It has shown antidepressive properties in BD I depression both in monotherapy and in combination with lithium or valproate

[95, 101]. It has only recently been approved by the U.S. Food and Drug Administration. It is not mentioned in the Norwegian guideline.

Antidepressants

ADs are listed here since they are the most commonly prescribed drugs for BD depression in the US [102]. This is despite them not being recommended as a first-line monotherapy drug, at least in BD I. Initial placebo-controlled studies indicated that AD monotherapy produced favorable outcomes in BD depression [103, 104]. However, the use of ADs is associated with a switch to manic or mixed states, might lead to cycle acceleration, and worsen the course of illness [12, 105, 106]. The use of ADs in monotherapy is therefore not recommended [107]. Although the use of an AD in combination with a mood stabilizer seems safer than AD monotherapy [106, 107], the use of ADs in BD depression remains controversial [108]. At present the data seems insufficient to draw definitive conclusions about the risk-to-benefit ratio. There are studies, systematically reviewed in a paper by Gijsman and colleagues [109], documenting the effectiveness of ADs in combination with mood stabilizer as a short-term treatment of BD. One of those studies was a placebo-controlled study comparing olanzapine with OFC, which found OFC to be superior, with remission rates of 32.8% vs 48.8% [100]. However, a large double-blind placebo-controlled study concluded that there is no positive effect of adding an AD to a mood stabilizer as an adjunctive treatment [110]. This study also found no indication that ADs induced mood switches. A more recent review found ADs to be safe but ineffective in BD depression [111].

The current evidence does not allow a conclusive statement to be made about the use of ADs in BD depression [85, 112], and their use in clinical practice requires individualized treatment decisions [113]. Monoamine oxidase inhibitors might be more useful than other ADs, especially TCAs, but the data do not allow one drug to be favored over another [109, 114].

Benzodiazepines

Benzodiazepines exert anxiolytic and sedative effects and may therefore be useful as concomitant medication [115].

1.3.2.1.3 Definition of treatment resistance in BD depression

Despite numerous drugs from different pharmacological classes showing at least some efficacy, the treatment of BD remains inadequate and suboptimal [116]. This is reflected in sluggish and inadequate responses in clinical trials [116], and unfavorable long-term outcome in naturalistic studies [19] characterized by chronic and partly subsyndromal mood symptoms, frequently fluctuating polarity, and high recurrence rates. Although treatment resistance is common in BD depression, there is a lack of agreement as to what constitutes treatment-resistant BD [117]. The unclear and changing definitions hamper research activity [118]. The difficulties in defining treatment resistance reflect both the heterogeneity of the response to pharmacological treatment and the fluctuating course of the illness. Despite some clinical and therapeutic differences [17, 119, 120], the depression associated with BD has much in common with unipolar depression (see Table 1). For defining treatment resistance in BD depression, some authors therefore suggest applying criteria for treatment resistance in unipolar depression (e.g., failure to respond to two or more adequately tried antidepressive psychopharmacological treatment options), and to also add the failure to respond to mood stabilizers [116, 121]. On the other hand, it has been argued that defining a nonresponse to an AD as treatment resistance in BD depression would be meaningless due to the questionable efficacy of ADs [118]. Several proposals have been put forward for defining treatment resistance in BD depression, and numerous definitions are used in the literature, as listed in Table 3.

Table 3. Examples of proposed or applied definitions of treatment resistance in BD depression

Reference	Definition
Sachs, 1996 [120]	Depression without remission despite two adequate trials of standard classes of ADs, lasting at least 6 weeks each, at adequate doses, with or without augmentation strategies
Yatham, Calabrese, and Kusumakar, 2003 [84]	Depression that failed to respond to a trial with lithium at serum levels of 0.8 mmol/L and above for 6 weeks
Goldberg, Burdick, and Endick, 2004 [122]	Nonresponse to at least two adequate trials of standard ADs with concomitant mood stabilizers during the current episode
Nierenberg et al., 2006 [123]	Nonresponse to treatment during the first 12 weeks of standard or randomized care pathways for BD depression in the STEP-BD or Well-documented failure to respond to at least two trials of ADs or an AD and a mood stabilizer
Gitlin, 2006 [116]	Same criteria used for treatment-resistant unipolar depression, i.e., nonresponse to two ADs from different classes (6 weeks each), with the addition of failure to respond to mood stabilizers as well as ADs
Frye et al., 2007 [124]	Inadequate response to a mood stabilizer with or without concomitant AD therapy
Pacchiarotti et al., 2009 [119]	BD I: Nonremission to adequately dosed lithium (0.8 mmol/L) or to other adequate ongoing mood-stabilizing treatment, plus lamotrigine (50–200 mg/day) or with full dosage (≥600 mg/day) of quetiapine as a monotherapy BD II: Nonremission to adequately dosed lithium (0.8 mmol/L) or to other adequate ongoing mood-stabilizing treatment, plus lamotrigine (50–200 mg/day) or quetiapine (300–600 mg/day) as a monotherapy
Kelly and Lieberman, 2009 [125]	Failure to attain stabilization with medications taken previously
Medda et al., 2009 [126]	Nonresponse to two trials lasting at least 8 weeks [one trial with mood stabilizer(s) plus a TCA and one trial with mood stabilizer(s) plus an SSRI]. Additional criterion in psychotic depression: the concomitant administration of an antipsychotic medication at a dosage equivalent to at least 300 mg/day chlorpromazine

Mendlewicz et al., 2010 [127]	Failure to reach a HAM-D-17 score of <17 after at least two adequate consecutive AD trials lasting at least 4 weeks at the optimal dose and adequate and well-established mood-stabilizer treatment (lithium, valproate, carbamazepine, or lamotrigine)
Kessler et al., 2010 [128]	Nonresponse to two trials (during lifetime) with an AD and/or a mood stabilizer with proven efficacy in BD depression (lithium, lamotrigine, quetiapine, or olanzapine) at adequate doses for at least 6 weeks or until cessation of treatment due to side effects
Ahn et al., 2011 [129]	Syndromal or subsyndromal mood symptoms despite ongoing treatment with quetiapine or lamotrigine
Lipsman et al., 2010 [130]	Nonresponse to adequate trials of monotherapy with lithium or lamotrigine, as well as lithium or lamotrigine in combination with at least one anticonvulsant or antipsychotic
Diazgranados et al., 2010 [131] Zarate et al., 2012 [132]	Nonresponse to at least one adequate AD trial and to a prospective open trial of a mood stabilizer [either lithium or valproate for at least 4 weeks at therapeutic levels (serum lithium, 0.6-1.2 mmol/L; or valproic acid, 50–125 μg/mL)]
Malhi et al., 2012 [117]	Nonremission despite two or three adequate trials of a first-line medication, such as a mood stabilizer

Abbreviations: HAM-D-17 = Hamilton Depression Rating Scale–17-item version, SSRI = selective serotonin reuptake inhibitor

Treatment-resistant BD depression was defined in this thesis as depression that failed to respond to two trials (during lifetime) with an AD and/or a mood stabilizer with proven efficacy in BD depression (lithium, lamotrigine, quetiapine, or olanzapine) at adequate doses for at least six weeks or until cessation of treatment due to side effects [128]. This was based on a proposed definition for treatment resistant major depression [121] extended with pharmacological treatment options for BD and put into a lifetime perspective.

1.3.2.1.4 Pharmacological treatment in treatment-resistant BD depression

There is very little evidence available for determining what treatment to apply in patients who are resistant to the initial treatment [67, 133]. The combination of several medications from different classes of psychoactive drugs is the most

commonly used clinical strategy for treatment-resistant BD patients, often despite no or only few studies supporting the practice [116]. There is some evidence supporting the use of certain combination therapies, such as the addition of lamotrigine to lithium [134], the combination of valproate and lithium [135], the addition of lurasidone to lithium or valproate [101], the combination of lamotrigine and quetiapine [129], and the OFC [100]. However, studies of other combinations of ADs with mood stabilizers have produced contradictory results, both regarding the response and switch rates (see Section 1.3.2.1.2).

Several drugs, with differing pharmacological approaches have some evidence from smaller, often uncontrolled studies (reviewed in [118] and [136]). Among those drugs, the dopamine agonist pramipexole, when added to a mood stabilizer, demonstrated significant antidepressive effects in patients with BD I and BD II depression [122, 137]. Rapid but short-lasting antidepressive and antisuicidal effects were shown for the N-methyl-D-aspartate antagonist ketamine when added as a single intravenous infusion to ongoing lithium or valproate treatment [131, 132]. Adding the stimulant modafinil to ongoing medication resulted in a greater reduction of depressive symptoms compared to placebo [124].

1.3.2.1.5 Treatment guidelines

The complexity of treatment of BD depression is reflected by the development of treatment guidelines and consensus statements [112]. Several guidelines have been published during the last five years, including by Australian experts based on the evidence criteria provided by the National Health and Medical Research Council [71], the British Association for Psychopharmacology [138], the World Federation of Societies of Biological Psychiatry [139], the Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders [140], and the Norwegian Directorate of Health [85]. These guidelines contain differing recommendations for the preferable treatment strategies [74, 99], as simplified in Table 4. These differences are mainly due to differences in interpreting the evidence and the paucity of research [141]. The most controversial issue seems to be the use of ADs [112]. There are also discrepancies regarding the place of lithium

or lamotrigine in monotherapy and special recommendations for BD II [141]. However, all guidelines recommend quetiapine as a first-line treatment.

Treatment algorithms have been developed for guiding treatment decisions in individual patients, such as the psychopharmacology algorithm project at the Harvard South Shore Program [142] and the Texas Implementation of Medication Algorithms [143]. The place of ECT differs between these algorithms. For example, the psychopharmacology algorithm project at the Harvard South Shore Program states that the psychiatrist should first assess whether there is an urgent indication for ECT based on the findings of the initial evaluation and diagnosis, whereas the Texas Implementation of Medication Algorithms introduces ECT in stage 4. When the present study was planned, the treatment algorithm suggested by Goodwin and Jamison [10] (see Section 3.4.3) was one of the most up-to-date, and had the advantage of taking into account differences in the treatment of BD I and II and previous treatment trials.

BD is a recurrent and life-long illness. When choosing treatment for BD depression, data on efficacy in the acute phase have to be balanced against tolerability and the likelihood of preventing switching, recurrence, and relapse [14]. Other considerations include family history, past and present symptoms, the course of illness including past treatment responses, side effects, and patient preferences [10].

Table 4: Recommended first- and second-line treatments for BD depression in several guidelines published since 2009

	Australian guidelines based on the evidence criteria provided by the National Health and Medical Research Council [71]	British Association for Psychopharmacology [138]	World Federation of Societies of Biological Psychiatry [139]	Norwegian Directorate of Health [85]	CANMAT and International Society for Bipolar Disorders [140]
First-line treatment	quetiapine, lamotrigine, olanzapine, lithium, valproate	**mild:** quetiapine, lamotrigine **moderate:** quetiapine, lamotrigine, SSRI or other AD, not TCA (BD I: add anti-manic mood stabilizer) **severe:** consider ECT	quetiapine, lamotrigine, olanzapine, valproate, OFC	**BD I and BD II:** quetiapine	**BD I:** lithium, lamotrigine, quetiapine, SSRI*+ lithium or valproate, olanzapine + SSRI*, lithium + valproate, bupropion + lithium or valproate
					BD II: quetiapine
Second-line treatment	adjunctive risperidone, adjunctive AD, OFC, lithium + valproate, lithium + lamotrigine	augmentation strategies derived from experience in unipolar depression	optimize dosage or switch to another first-line medication adjunctive quetiapine AD + antimanic mood stabilizer, lithium + lamotrigine, adjunctive modafinil	**BD I:** lamotrigine, AD + antimanic mood stabilizer (lithium, valproate, carbamazepine, antipsychotics), lithium, quetiapine + lithium	**BD I:** valproate, lurasidone, quetiapine + SSRI*, adjunctive modafinil, lamotrigine + lithium or valproate, lurasidone + lithium or valproate
				BD II: OFC, lamotrigine, lithium	**BD II:** lithium, lamotrigine, valproate, AD + lithium or valproate, lithium + valproate, AD + atypical antipsychotic

Other recommen-dations	augment with atypical antipsychotics if concurrent psychotic symptoms are present	lithium or valproate may be considered in less severe depression	adjunctive N-acetyl-cysteine, adjunctive Chinese herbs		not recommended: gabapentin, aripiprazole, ziprasidone, adjunctive ziprasidone or levetiracetam
ECT	if risk to self or others is high, psychotic features are present, or there has been a previous response to ECT	consider in severe depression (high suicide risk, psychosis, severe depression during pregnancy, or life-threatening inanition)	for very severe depression, suicidal patients, catatonic or psychotic features, during pregnancy (fourth grade of recommendation based on uncontrolled studies, case reports). Readiness to use ECT differs between countries, and reflects public opinion rather than usefulness	for patients resistant to other treatments, recommend cautious use of ECT	recommended as third line treatment, could be used as first- or second-line treatment in certain situations (psychotic features, high suicidal risk, significant medical complications due inanition)

* except paroxetine

1.3.2.2 Electroconvulsive therapy

ECT was introduced into clinical practice in 1938 [144]. It is regarded as an effective treatment in all phases of BD [145, 146]. ECT is a treatment option also for patients with catatonia, psychotic symptoms, high risk of suicide, or during pregnancy [147, 148]. However, the clinical use of ECT is accompanied by safety concerns, mainly due to possible long-lasting effects on memory and other neurocognitive functions [149, 150]. These effects are described in Section 1.4.2.

The antidepressive effect of ECT depends on several treatment parameters including electrode position [mainly right unilateral (RUL) or bilateral (BL)] and treatment dose. Although some studies have found BL treatment to be more effective than RUL treatment [151], other studies support the use of high-dosage RUL ECT. This has been shown to be as effective as BL treatment and to result in cognitive side effects that are less severe and persistent [152].

In 1993, Zornberg and Pope [82] reviewed the literature on studies comparing ECT with antidepressive pharmacological treatment in BD depression. They concluded that five out of seven studies comparing ECT with ADs found ECT to be clearly more effective, including in patients who previously did not respond to pharmacological treatment. In the largest of the reviewed studies [153], 56% of the patients who did not improve from pharmacological treatment recovered after subsequent treatment with ECT. However, the reviewed studies have methodological weaknesses, such as use of ADs rather than mood stabilizers in the pharmacological group, outcomes measured in broad clinical terms (e.g., the numbers who recovered, improved, and were unchanged, and the length of hospitalization) rather than formal rating instruments, imprecise diagnostic classification, and nonrandomized design [146]. So far there are no published RCTs comparing ECT to pharmacological treatment in BD depression. ECT has proven efficacy in the short-term treatment for depressive disorders [154, 155]. In the absence of RCTs comparing drug treatment or placebo to ECT specifically in BD depression, several studies have compared the effects of ECT between BD depression and unipolar depression. Those studies have produced somewhat conflicting results, as listed in Table 5. Whereas several studies

documented that BD-depression patients respond as well as unipolar depressed patients to ECT [156], Medda and colleagues found that the effect of ECT was superior in unipolar patients [126]. However, a meta-analysis including 6 studies concluded that ECT is equally effective in BD and unipolar depression [157]. Studies investigating the efficacy of ECT in BD depression and studies that compare the effect of ECT in BD and unipolar depression are listed in Table 5. Comparisons of different electrode placements or treatment parameters are not presented. To summarize, few studies have employed reliable methodologies to investigate the effects of ECT in BD [145], and there is limited evidence for assessing the role of ECT in treatment guidelines for BD depression (see also Table 4). ECT is often reserved for the most treatment-resistant or severely affected patients [147], but this contrasts with clinical experiences and the relatively high response and remission rates reported [145, 157].

Besides the lacking evidence, there are other factors limiting the role of ECT in treatment guidelines for BD depression, mainly relating to concerns about cognitive side effects and the stigma associated with ECT in the public opinion [139]. Cognitive effects are the most feared adverse effects of ECT, further described in Section 1.4.2. Other side effects include headache, myalgia, nausea, and transient cardiovascular changes (increased heart rate, blood pressure, and cardiac oxygen consumption) with a low risk of ischemia, hypertensive intracerebral bleeding, or embolic stroke [158]. A treatment-induced switch to (hypo)mania is a concern not only in pharmacological treatment of BD depression but also in ECT [159, 160]. There are few and inconclusive data on ECT-induced mood switches. Some authors consider such mood switches to be of less clinical importance [161, 162], whereas others consider them to be a common problem that might be associated with adverse outcomes [163]. In the few studies addressing the ECT-induced mood switches, the prevalence rates have ranged from less than 7% [162] to more than one-third [164]. The differences in the prevalence rates might be due to methodological problems, such as the absence of a commonly accepted definition of treatment-induced mood switches. It has been defined as developing a manic episode in some studies [162] or

hypomania in others [159]. There are no data on the impact of ECT-induced mood switches on the future course of the illness.

To clarify the role of ECT in treatment-resistant BD depression, RCTs on both efficacy and cognitive side effects are urgently needed [118, 145].

Table 5. Studies of ECT in BD depression, partly based on previous research [82, 145]

Reference	Research question	Patients	Study design	Results
Greenblatt, Grosser, and Wechsler, 1962 and 1964 [165, 166]	ECT vs AD	Early stage of the study: 5 ECT, 20 AD Entire study: 76 BD	Controlled trial	ECT more effective than AD (markedly improved: 78% vs 37%)
Bratfos and Haug, 1965 [153]	ECT vs AD	112 ECT, 133 AD	Open study	ECT more effective than AD (recovery rate: 61% vs 25%)
Perris and D'Elia, 1966 [167]	ECT vs AD and BD vs UP depression	40 ECT, 23 AD 40 BD, 84 UP	Chart review	ECT and AD equally effective (based on relapse rate) Equal relapse rate for BD and UP. UP required a larger number of ECT sessions than did BD
Strömgren, 1973 [168]	BD vs UP depression	26 BD, 26 UP	Controlled trial	Equal reduction of depression score in BD and matched UP
Abrams and Taylor, 1974 [169]	BD vs UP depression	15 BD, 28 UP	Chart review	Equal response to ECT in BD and UP (% reduction in depression score: 63% vs 58%, n.s.)
Avery and Winokur, 1977 [170]	ECT vs AD and BD vs UP depression	14 ECT, 3 AD, 17 ECT + AD 14 BD, 125 UP	Chart review	ECT and AD equally effective (improvement rate: 43% vs 33% vs 39%, n.s.) Equally effective in BD and UP (improvement rate: 43% vs 52%, n.s.)
Avery and Lubrano, 1979 [171]	ECT vs AD	8 ECT, 15 AD	Reevaluation of a prospec-tive study	Improvement rates: 100% and 47%

Homan et al., 1982 [172]	ECT vs AD and BD vs UP depression	30 ECT, 16 AD, 7 ECT + AD 30 BD, 76 UP	Chart review	ECT and AD equally effective (improvement rate: 23% vs 12.5% vs 14%, n.s.) Equally effective in BD and UP (improvement rate: 23% vs 43%, n.s.)
Black, Winokur, and Nasrallah, 1986, 1987 [173, 174]	ECT vs AD and BD vs UP depression	55 ECT, 30 AD 55 BD, 368 UP	Chart review	ECT and AD equally effective (improvement rate: 69% vs 47%, n.s.) Equally effective in BD and UP (improvement rate: 69% vs 70%, n.s.)
Zorumski et al., 1986 [175]	BD vs UP depression		Chart review	Equally effective in BD and UP (improvement rate: 100% vs 91%, n.s.)
Devanand et al., 2000 [176]	BD depression	38 BD	Chart review	Response rate: 76%
Ciapparelli et al., 2001 [177]	BD depression vs mixed episode	23 BD, 41 mixed	Controlled trial	ECT less effective in BD depression than in mixed episode (response rate: 26% vs 56%)
Daly et al., 2001 [178]	BD vs UP depression	66 BD, 162 UP	Controlled trial	More rapid improvement in BD than UP depression. Equal rates of response (54% vs 46%, n.s.) and remission (48% vs 42%, n.s.)
Grunhaus et al., 2002 [179]	BD vs UP depression	20 BD, 111 UP	Controlled trial	Equal rates of response (50% vs 58%, n.s.) and remission (30% vs 36%, n.s.) in BD and UP depression
Kho, Zwinderman, and Blansjaar, 2005 [180]	Predictors for remission in BD and UP depression	11 BD, 62 UP	Chart review	Remission rates 73% and 65%. Duration of index episode as predictor for remission
Sackeim and Prudic, 2005 [156]	BD vs UP depression	54 BD, 279 UP	Controlled trial	Equal response (69% vs 64%, n.s.) and remission rates (56% vs 46%, n.s.). UP required more treatments
Sienaert et al., 2009 [181]	BD vs UP depression	13 BD, 51 UP	Controlled trial	More rapid response of BD than UP. Equal response (85% vs 76%, n.s.) and remission rates (69% vs 64%, n.s.)

Medda et al., 2009 [126]	BD I vs BD II vs UP depression	46 BD I, 67 BD II, 17 UP	Controlled trial	Response rates: 67% vs 79% vs 94%, n.s. Remission rate: 34% vs 43% vs 71%, BD I<UP
Bailine et al., 2010 [182]	BD vs UP depression	170 UP, 50 BD	Controlled trial	Equal response (80% vs 79%, n.s.) and remission rates (64% vs 61%, n.s.)
Agarkar et al., 2012 [183]	BD vs UP depression	8 BD, 17 UP	Chart review	More treatments prescribed to UP than BD. Equal change in GAF scores

Abbreviations: UP = unipolar; n.s. = not significant; GAF = Global Assessment of Functioning

1.3.2.3 Other biological treatment methods

The nonpharmacological biological treatment methods for BD depression include invasive techniques such as deep brain stimulation (DBS) and vagal nerve stimulation (VNS), and noninvasive neuromodulation techniques such as repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and magnetic seizure therapy (MST). DBS has shown antidepressive effects in treatment resistant major depression, and it might be reasonable to use DBS in BD depression [130]. An open study involving seven treatment-resistant BD-depression patients found that subcallosal cingulate DBS produced positive results for both efficacy and safety [184]. A paper by Nierenberg and colleagues reported secondary post hoc analyses of the outcomes of VNS for BD compared to unipolar depression. No outcome differences between the groups were found, with roughly one third of the patients responding to treatment [185]. As for DBS and VNS, the evidence for the efficacy of rTMS in BD depression is very scarce, with most studies investigating major depression without reporting results for BD patients separately [146]. A small open study of the effects of augmentative low-frequency rTMS in 11 BD-depression patients found a response in six patients and remission in four of them [186], whereas two smaller RCTs produced inconclusive results [187, 188]. The results from an open study suggested that tDCS can be beneficial in BD depression [189]. The use of MST, a treatment which offers greater control of the intracerebral current intensity

and is associated with reduced cognitive impairment compared to ECT [190], has been reported for one BD-depression patient only [191]. In summary, there is only highly preliminary evidence for the potential usefulness of neuromodulating techniques in BD depression [146].

Chronotherapeutical approaches control the exposure to environmental stimuli that act on biological rhythms [192]. In particular, sleep deprivation has shown to result in a rapid but short-lived reduction of symptoms in BD depression [193, 194]. It is necessary to combine chronotherapy with pharmacological mood stabilizers in order to enhance and sustain the acute antidepressive effects [192]. Physical exercise might be another promising—although little researched—adjunctive treatment that has few side effects [195].

1.4 Cognitive effects of biological treatment methods

1.4.1 Cognitive effects of pharmacological treatment

Pharmacological treatment may either improve cognition by targeting psychotic and mood symptoms or worsen it due to adverse effects mediated by anticholinergic, sedative, extrapyramidal, and blunting mechanisms [196].

Lithium is the mood stabilizer that has the longest history of use and is the most extensively studied [197]. Lithium exerts mild negative effects on verbal learning, verbal memory, and creativity, and more pronounced negative effects on psychomotor speed [197]. However, it has also shown neuroprotective and neurotrophic effects [198], such as increases in the gray-matter and hippocampal volumes in lithium-treated BD patients [199, 200].

Data on the cognitive side effects of anticonvulsants are mostly obtained in epilepsy patients. These side effects seem to be modest, and newer drugs (e.g., lamotrigine) have a more favorable cognitive profile than classical drugs (e.g., valproate or carbamazepine), and monotherapy at therapeutic dosages produces less pronounced side effects than polypharmacy and high-dose treatment [201-203]. There

are only preliminary results from anticonvulsant-treated BD patients, which are supporting the safer neurocognitive profile of lamotrigine compared to other anticonvulsants [204].

BD patients treated with atypical antipsychotics have shown reduced cognitive performances [205, 206]. Some authors suggest that a higher degree of cognitive impairment is associated with a history of treatment with antipsychotics rather than a history of previous psychotic episodes [207]. However, other authors have found that the cognitive deficits observed in BD patients are associated with illness factors, such as concurrent or previous psychotic symptoms, rather than the use of antipsychotics themselves [33].

The impact of ADs on cognition in BD patients has not been studied previously [208], but there are data from unipolar-depression patients. The impact is less severe for selective serotonin-reuptake inhibitors and non-TCAs than for TCAs and other drugs with anticholinergic effects [208]. Sedative or anticholinergic ADs have been shown to reduce attention, learning, and psychomotor function [209].

Benzodiazepines are associated with reduced cognitive function in BD [210]. Long-term treatment regardless of the diagnosis has been found to reduce performance in various cognitive domains, especially attention, psychomotor speed, and verbal learning [211, 212].

To summarize, the present evidence on the cognitive side effects of psychoactive drugs on BD is limited and somewhat inconsistent [196, 197]. Most patients receive a combination of mood stabilizers, antipsychotics, ADs, and/or benzodiazepines [213], which makes it difficult to accurately determine how specific drugs contribute to cognitive impairment in BD [210].

1.4.2 Cognitive effects of ECT

The first reports of cognitive side effects associated with ECT appeared shortly after its introduction in clinical practice [214]. Since then, the techniques used to administer ECT have been subject to considerable research efforts aimed at reducing the unfavorable effects on cognition and memory. However, cognitive impairment remains the most important side effect of ECT [215]. There are especially concerns about potentially long-lasting memory dysfunction [149, 216]. The literature on the pattern, severity, and persistence of ECT-induced cognitive impairment is inconsistent, which has largely been attributed to methodological problems [217]. These are related to difficulties in distinguishing between ECT-related cognitive deficits and those associated with the underlying illness itself, differences in ECT techniques and treatment parameters, and methodological issues of neurocognitive assessment, such as differences in the nomenclature for various types of cognitive function, choice of cognitive test battery, and timing of testing [150, 215, 218-220].

ECT induces a seizure which is followed by transient postictal disorientation [221]. Patients are often amnestic for this period and most patients do not experience significant disturbance [158]. However, prolonged postictal disorientation has been associated with more pronounced retrograde amnesia after treatment [222].

Cognitive impairment beyond the postictal disorientation covers various cognitive domains, of which retro- and anterograde memory dysfunctions are the most important [223]. A meta-analysis of the objective performances for numerous cognitive variables concluded that ECT-induced deficits are mainly limited to the first three days posttreatment, and then subsequently resolve, with some of the measures improving beyond their baseline values [217]. A limitation of the meta-analysis was the lack of data on retrograde amnesia and autobiographical memory, which has been found to be the most persistent adverse effect [224, 225]. Autobiographical memory (i.e., memory of personal events and facts) is essential for self-definition [226], social interaction [227], and as a guide for present and future activities and problem-solving [227]. Retrograde amnesia and loss of

autobiographical memory are also the most important complaints from patients who have received ECT [149]. Whereas assessments using objective measures of memory found the impairment to be short term (i.e., lasting less than six months), subjective reports indicate more persistent difficulties [228]. The discrepancy between objectively measured and subjectively experienced memory deficits is not unique to ECT patients [229, 230]. However, it might at least partly reflect the methodological challenges associated with assessing retrograde and especially autobiographical memory, including the possible insensitivity of current tests to some of the memory deficits experienced by the patients [231, 232].

Treatment techniques and parameters that have an impact on cognitive impairment include placement of treatment electrodes, treatment frequency, and stimulus parameters such as the waveform and dosage. Brief- or ultrabrief-pulse ECT, unilateral electrode positioning, and lower treatment doses have a more favorable cognitive outcome than sine-wave ECT, BL electrode positioning, and higher treatment doses [218, 225, 228]. Patient characteristics that have an impact on cognitive outcome include the patient's age and pretreatment cognitive status. Older patients and those with pretreatment global cognitive impairments are more vulnerable to posttreatment memory deficits [222, 233].

No RCTs have compared the cognitive effects on BD depression between ECT and pharmacological treatment. MacQueen and colleagues compared memory function between euthymic BD patients who previously had received ECT and patients with an assumed equal past burden of illness without prior ECT [216]. The ECT group showed greater memory impairment. However, some of the characteristics defining the burden of illness were not controlled for, such as the number of psychotic episodes or the symptom severity. Only randomized allocation of patients to different treatment conditions can ensure the absence of bias and an equal burden of illness among groups.

2 Aims of the study

The overall aim of the present study was to compare the effects of ECT and algorithm-based pharmacological treatment (APT) on depressive symptoms and cognitive function in acutely admitted, treatment-resistant BD-depression patients in a randomized controlled setting.

More specifically, we aimed:

1. To assess the neurocognitive profiles in treatment-resistant, acutely admitted BD-depression patients, to compare the neurocognitive function in patients with BD I and II, and to identify the demographic and clinical illness characteristics associated with cognitive function (Paper I).
2. To compare the efficacy of ECT and APT in treatment-resistant BD depression, based on repeated Montgomery-Åsberg Depression Rating Scale (MADRS) measures (primary outcome), scores on the Inventory of Depressive Symptomatology–Clinician-rated, 30-item version (IDS-C30, and the Clinical Global Impression for Bipolar Disorder (CGI-BP), response and remission rates and the times to response and remission after a 6-week intervention period (secondary outcomes) (Paper II).
3. To compare the effects of ECT and APT on general neurocognitive function and autobiographical memory shortly after treatment (Paper III).

3 Material and methods

3.1 Setting

3.1.1 The Bipolar Research and Innovation Network

This thesis is based on the Norwegian Randomized Controlled Trial of ECT in BD, a study conducted within the Bipolar Research and Innovation Network (BRAIN) in Norway. The BRAIN is a clinical network of outpatient clinics and hospital departments in different parts of Norway. Clinicians with a special interest in affective disorders have joined forces to assess several aspects of BD, such as age at onset [16], suicidality [234], and treatment of insomnia [235]. The BRAIN study is thus a multicenter study describing BD patients in Norway. All patients in the current study were also included in the BRAIN study.

3.1.2 Recruiting centers

The 73 patients included in this study came from the following seven BRAIN centers:

1. Bergen University Hospital, Bergen (32 patients).
2. St. Olav's University Hospital, Trondheim (16 patients).
3. Stavanger University Hospital, Stavanger (15 patients).
4. Østfold Hospital, Fredrikstad (3 patients).
5. Ullevål University Hospital, Vardåsen (3 patients).
6. Aker Hospital, Oslo (3 patients).
7. Ullevål University Hospital, Oslo (1 patient).

3.2 Study population

Treatment-resistant BD-depression patients with clinical indications for ECT were included in this study.

3.2.1 Diagnostic process

Patients who were acutely admitted to one of the study centers with severe depressive symptoms and a possible indication for ECT were asked if they were willing to be screened for the study. During the screening the recruiting clinician determined whether the patient fulfilled all of the inclusion criteria and none of the exclusion criteria. The HCL-32 [18] was applied when it was necessary to increase the awareness of hypomanic symptoms. The diagnosis was made primarily on the basis of a clinical interview supported by information from significant others and hospital records, and subsequently verified by the Mini International Neuropsychiatric Interview (MINI; specifically the MINI-Plus) [236] or the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) [237]. The assessing psychiatrists had participated in structured SCID-I or MINI-Plus training programs.

3.2.2 Inclusion and exclusion criteria

3.2.2.1 Inclusion criteria

The following inclusion criteria were applied during the selection of patients:

1. Acutely admitted inpatients.
2. Age ≥18 years.
3. DSM-IV-TR diagnosis of BD I or BD II, verified using the SCID-I or MINI-Plus.
4. Clinical indications for ECT.
5. Severity: meeting the DSM-IV-TR criteria for a depressive episode, with a MADRS score ≥25 [238].
6. Treatment resistance: Nonresponse (less than 50% reduction in MADRS score or still meets the DSM-IV-TR criteria for a depressive episode) to two trials

(during lifetime) with mood stabilizers with documented efficacy in BD depression (lithium, lamotrigine, quetiapine, or olanzapine) and/or ADs. A trial was defined as a minimum of six weeks on an adequate or tolerated dose as reported by the patient, or for a shorter period when treatment was terminated prior to six weeks due to side effects.

7. Sufficiently fluent in Norwegian to ensure valid responses in psychometric testing.
8. For neuropsychological assessment, having Norwegian as the primary language or having received compulsory schooling in Norwegian.

Initially the severity criterion was set to an MADRS score of ≥30. After one month (with one included patient) we found this cutoff score to be too high. Several patients with a clinical indication for ECT and otherwise eligible for inclusion but with MADRS scores between 25 and 30 could not be included. The steering committee therefore decided to reduce the severity criterion to an MADRS score of ≥25. This protocol change was approved by the regional ethical committee.

3.2.2.2 Exclusion criteria

The following exclusion criteria were applied during the selection of patients:

1. Previous nonresponse to ECT.
2. ECT within the previous six months.
3. Rapid-cycling BD (e.g., at least four episodes within the previous 12 months).
4. Current use of medication, alcohol, or substances incompatible with the treatments in this study. Such medications had to be terminated at least five half-lives before starting ECT treatment.
5. Current use of all other psychotropic medications during the study period with the exception of the concomitant medication listed in Section 3.4.4.
6. Inability to comply with the study protocol.
7. Unstable and/or serious medical conditions, including clinically relevant laboratory abnormalities.
8. Conditions that affect neuropsychological assessments, such as Parkinson's disease, multiple sclerosis, or stroke.

9. Pregnancy.
10. Fertile women without adequate contraception (adequate contraception includes: abstinence, oral contraceptives, intrauterine devices, or barrier method).
11. Elevated mood as defined by a score of >20 on the Young Mania Rating Scale (YMRS) [239].
12. High suicide risk according to the clinician's judgment.

3.2.3 Withdrawal criteria

A patient was withdrawn from the study if the treating clinician found that the patient was in need of or would be better served with other treatments, or if exclusion criteria were met. A patient was also withdrawn from the study if the clinical condition significantly worsened or if the patient withdrew his or her consent.

3.3 Study design

3.3.1 Baseline assessment

Paper I addresses the neurocognitive function in BD depression. It is based on the pretreatment neurocognitive and clinical assessment, and retrospectively obtained data on the course of illness. It is thus a cross-sectional study.

3.3.2 Longitudinal study: RCT

The prospective, six-week acute-treatment trial comparing the effects of ECT and APT on depressive symptoms and neurocognitive function in treatment-resistant BD depression was set up as a multicenter RCT. It was conducted from May 2008 to April 2011. The eligibility of patients was established before they were randomized to one of the treatment options. Patients were randomized strictly sequentially to the two treatment groups as soon as they were evaluated to be eligible for randomization. The randomization was stratified separately at each study center, using the default random-number generator of the Statistical Package for the Social Sciences (SPSS; version 15, Chicago, IL, USA) with a random seed. The randomization lists were kept concealed from the investigators. The patient and treating psychiatrist were not blinded about the treatment modality. To compensate for the lack of blinding, the assessments of depressive symptoms at baseline and week six (or when the patient left the study, if this occurred earlier) were audiotaped. The audiotapes were rated by independent trained study personnel who were blinded about the treatment modality and not involved in the treatment of the study patients. The neuropsychological assessment was performed by test assistants or neuropsychologists who were blinded about the treatment modality. The flow chart for the study is shown in Figure 1. The reasons for leaving the study are presented in detail in Papers II and III.

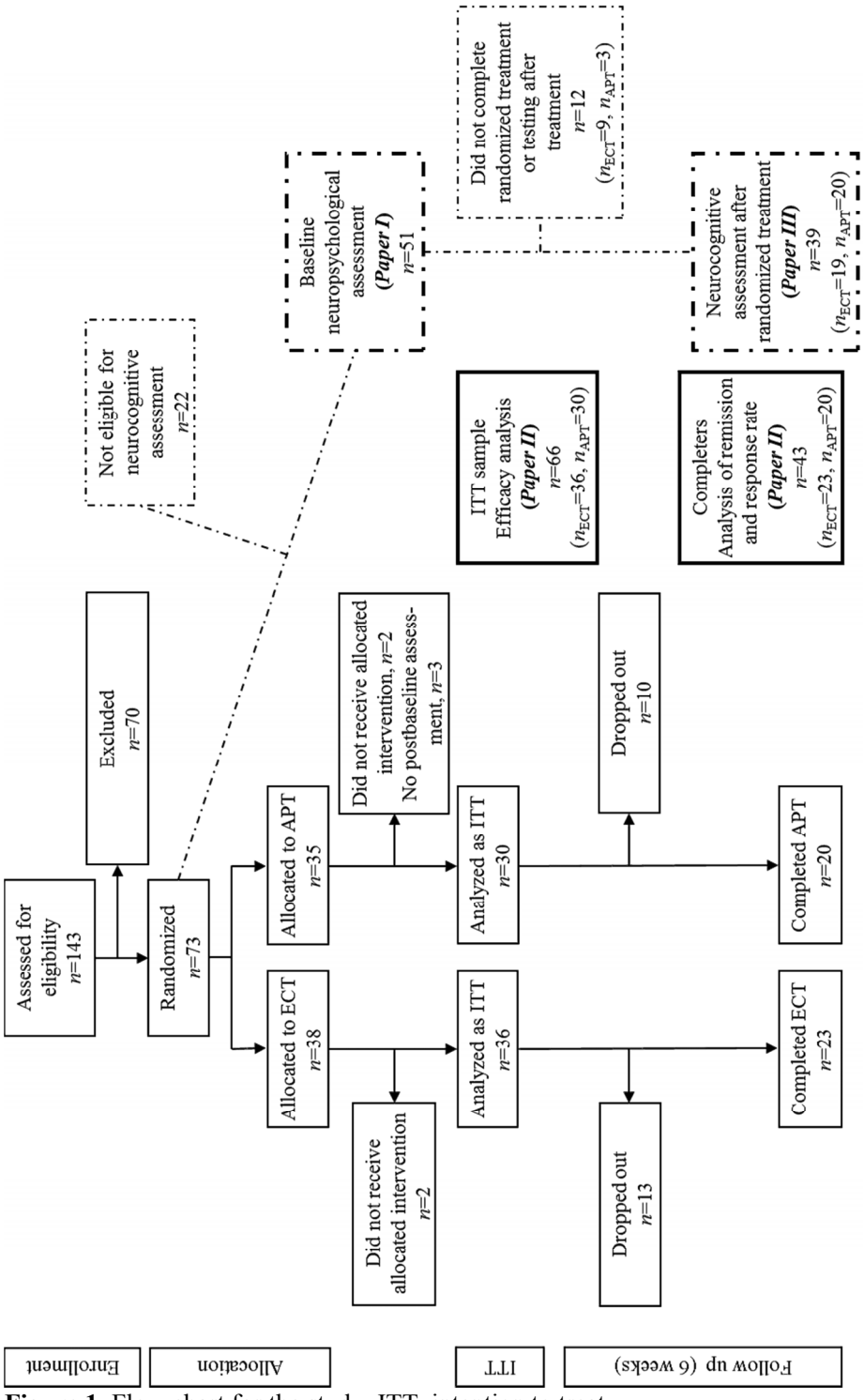

Figure 1. Flow chart for the study. ITT, intention to treat

3.4 Treatment

3.4.1 General aspects

The treatment trial lasted six weeks. The medication that would have been used if a patient was randomized to APT was determined at enrollment, before randomization. Before starting the treatment the patients entered a washout phase if they were receiving medication that contradicted the study protocol (five half-lives for patients randomized to receive ECT and a varying time for patients randomized to APT). If a patient received ECT and reached remission earlier than six weeks, the ECT treatment was terminated and the patient was changed to pharmacological maintenance therapy. If a patient or the treating clinician decided that the patient could receive better treatment outside of the study, the patient could leave the study at any time, as specified in the informed consent. After the six-week trial the patient continued with maintenance drug treatment according to the clinician's decision.

3.4.2 Electroconvulsive therapy

The ECT procedures were standardized across all the study centers. ECT was administered with either a Thymatron System IV or a MECTA 5000 (one patient). Both of these devices provide brief-pulse, square-wave, constant currents. The pulse amplitude and width were 900 mA and 0.5 ms, respectively. Stimulation electrodes were placed as described by d'Elia (RUL) [240]. Treatment was administered three times a week for up to six weeks, with a maximum of 18 sessions.

The short-acting anesthetic thiopental (mean of 3.9 mg/kg) was used for anesthesia. An excessive anesthetic dosage may increase the seizure threshold and shorten the seizure duration, and hence the appropriateness of the thiopental dosage was determined at each treatment and adjusted at subsequent treatments. Succinylcholine at a dose of 0.5–1.0 mg/kg (mean of 0.8 mg/kg) was administered intravenously as a muscle relaxant. All patients were hyperoxygenated during treatment. The anesthesia procedures followed the study protocol [128], which is

compatible with currently accepted standards of care [241]. The initial stimulus dose was determined by an age-based, gender-adjusted method, in which the applied energy was calculated as follows [242]:

patient's age in years × 5 ≅ stimulus charge in mC.

The stimulus device (Thymatron, Somatics) delivers a charge of 25.2 to 504 mC in 20 equal steps, with the magnitude set by the "% Energy" dial on the device. According to the above formula this yields the following:

patient's age in years ≅ % Energy.

In order to consider gender specific differences in seizure threshold, the "% Energy" value was adapted as follows: % Energy + 5 to 10% (for male patients) and % Energy – 5 to 10% (for female patients). After each treatment the seizure adequacy was determined based on seizure duration, quality of δ-waves, seizure ending, postictal suppression, postictal reorientation time, and clinical effect. When seizures were inadequate the stimulus dose was adjusted at subsequent treatments.

3.4.3 Algorithm based pharmacological treatment

The treatment in the pharmacological control group was based on a treatment algorithm published in 2007 by Goodwin and Jamison [10]. The algorithm listed in Table 6 was adapted to match Norwegian clinical practice. It is separated into treatments for BD I and BD II depression, and the treatment advice varies depending on whether or not the patients are receiving a mood stabilizer. The treatment suggestions are divided into different steps that are to be followed step-by-step. If a patient had used a medication listed in step 1 during the lifetime without positive effect on depressive symptoms or with intolerable side effects, he/she proceeded to the medication listed at step 2. The chosen medical intervention had to be continued throughout the six-week study. Patients who experienced intolerable side effects to a medication applied during the study were changed to the next treatment step according to the algorithm.

Table 6. Treatment algorithm for the control group, based on—and adapted from—Goodwin and Jamison [10], with reprint permission from Oxford University Press

Treatment of BD I depression

Step	If not on a mood stabilizer	If on lithium or valproate
1	Start lamotrigine combined with lithium or valproate For severe depression consider an AD* plus an antimanic mood stabilizer*** For psychotic depression add an atypical antipsychotic	If on lithium, increase dose** Add lamotrigine
2	Add quetiapine	Add quetiapine
3	Consider OFC as an alternative to quetiapine	Consider OFC as an alternative to quetiapine
4	Discontinue OFC and add an AD, while maximizing the dosage of the antimanic mood stabilizer	Discontinue OFC and add an AD, while maximizing the dosage of the antimanic mood stabilizer

Treatment of BD II depression

Step	If not on a mood stabilizer	If on a mood stabilizer
1	Start lamotrigine For severe depression consider an AD* plus an antimanic mood stabilizer*** For psychotic depression add an atypical antipsychotic to lamotrigine For persistent irritability consider adjunctive valproate	If on lithium, increase dose** Add lamotrigine
2	Consider a second-generation AD plus an antimanic mood stabilizer or quetiapine	Consider a second-generation AD plus an antimanic mood stabilizer or quetiapine
3	Consider combinations of two mood stabilizers or of one mood stabilizer and an AD	Consider combinations of two mood stabilizers or of one mood stabilizer and an AD

*ADs: first- and second-generation ADs, Parnate (tranylcypromine sulfate) and Nardil (phenelzine)

** Increase lithium to produce a serum concentration of 0.8–1.2 mmol/L.

*** Antimanic mood stabilizers: lithium, valproate, carbamazepine, oxcarbazepine, and atypical antipsychotics.

3.4.4 Concomitant medication

The use of alimemazine (maximum dosage of 30 mg daily), chlorpromazine (maximum dosage of 25 mg twice daily), chlorprothixene (maximum dosage of 20 mg twice daily), and mianserin (maximum dosage of 10 mg daily) was allowed in both treatment groups. In the APT group the use of oxazepam (15 mg up to three times daily), zolpidem (maximum dosage of 10 mg daily), or zopiclone (maximum dosage of 7.5 mg daily) was also allowed.

3.5 Assessments

3.5.1 Clinical assessment and demographic information

3.5.1.1 Initial subject and illness characteristics

The patients were interviewed according to the Norwegian adaptation of the Stanley Foundation Bipolar Collaboration Network Entry Questionnaire (NEQ) used by the Bipolar Collaboration Network [243, 244] and the BRAIN network [16, 245]. The NEQ has 48 items and covers a wide range of demographic and clinical factors describing the course of illness, family history, and past treatment. Substance abuse was defined as fulfilling the DSM-IV-TR criteria for lifetime abuse of alcohol, psychotropic medication, or illicit substances. Psychosis was defined as lifetime admission to hospital with a psychotic illness, as verified by the MINI-Plus or SCID-I. Length of education was quantified as the duration of completed education in years. Previous serious suicide attempts were defined as attempts that required medical attention, an emergency-room visit, or hospitalization [246].

3.5.1.2 Assessment of symptoms

Symptom intensity was assessed weekly by trained clinicians (psychiatrists, psychologists, and psychiatric nurses) using the MADRS [238], IDS-C30 [247], YMRS [239], and CGI-BP [248]. At baseline, patients were assessed with the Positive and Negative Syndrome Scale for Schizophrenia, positive subscale (PANSS

pos) [249] and the Global Assessment of Functioning–Split version, symptom subscale (GAF-S) [250].

The end-of-treatment MADRS score had to be obtained within eight days of the termination of the six-week acute treatment phase. Response was defined as a decrease in MADRS score of ≥50% relative to the baseline. Remission was defined as an MADRS score of ≤12.

Prior to the study, all participating raters were trained in the use of the MADRS and IDS-C30. All clinicians rated at least 10 interviews that achieved an intraclass correlation coefficient (ICC) ≥0.7 for both the MADRS and IDS-C30. During the study, 35 of 73 taped interviews were randomly selected for reliability testing by two separate raters blinded to the treatment status of the patients. The inter-rater correlation between the blinded and the regular raters was high (ICC >0.90).

3.5.2 Neurocognitive measures

Neurocognitive assessment was carried out pre- and posttreatment (the latter at a mean of 3.3 weeks) by neuropsychologists or test assistants who had received training in standardized neuropsychological testing. Current IQ was assessed using the Wechsler Abbreviated Scale of Intelligence (WASI) [251]. The National Adult Reading Test (NART) [252] is designed to estimate the premorbid intelligence in adults. Reading skills are significantly correlated with WASI-based IQ scores and are relatively unaffected by most nonaphasic brain disorders [253]. The premorbid IQ was estimated in the present study using a Norwegian research version of the NART [254].

The neuropsychological profile [consisting of the six neurocognitive domains (I–VI) listed below] was assessed using the following nine tests from the Norwegian version [255] of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) [256]:

I. Speed of processing:

1. Brief Assessment of Cognition in Schizophrenia: Symbol Coding (total number correct).
2. Category Fluency: Animal Naming (total number of animals named in 60 seconds).
3. Trail-Making Test: part A (time to completion).

II. Attention/vigilance:

4. Continuous Performance Test–Identical Pairs (mean d′ value across two-, three-, and four-digit conditions, where d′ is an index of signal–noise discrimination).

III. Working memory:

5. Wechsler Memory Scale–third edition: Spatial Span (sum of raw scores for the forward and backward conditions).
6. Letter-Number Span (total number correct).

IV. Verbal learning:

7. Hopkins Verbal Learning Test–Revised (HVLT-R) (total number of words recalled correctly over three learning trials).

V. Visual learning:

8. Brief Visuospatial Memory Test–Revised (BVMT-R) (total recall score over three learning trials).

VI. Reasoning and problem solving:

9. Neuropsychological Assessment Battery (NAB): mazes (total raw score).

Raw scores from each of the nine administered MCCB tests were converted into standardized *T* scores with a mean of 50 and a standard deviation (SD) of 10, based on age- and gender-corrected norms from the MCCB manual [257]. The *T* scores for the six assessed domains were used to compute a mean neurocognitive composite score.

Autobiographical memory was assessed using a Norwegian version of the (Columbia) Autobiographical Memory Interview–Short Form (AMI-SF) [258]. The AMI-SF score is based on answers to 30 questions about six autobiographical events. The patients were asked to generate details about presented topics at both pre- and posttreatment assessment, and the consistency of the answers was measured.

3.6 Statistical analysis

The power analysis in the current study was performed for the primary outcome variable (i.e., the change in MADRS scores). The initial rather conservative power calculation was based on a power of 0.90 and an SD of 7, which estimated that 132 patients would need to be included in the study. However, a power of 0.90 is very conservative, and so we repeated the power analyses and found that based on an MADRS difference of 4 and with a power of 0.80 and a SD of 6, a sample of 72 patients would be sufficient. Based on the new power estimates, the study was terminated after the inclusion of 73 patients. A formal power analysis was not performed for changes in cognitive measures since there were no published results about cognitive changes and variances after ECT for treatment-resistant BD depression.

The characteristics of the patients in the two groups were compared using *t*-tests for normally distributed continuous variables, Mann-Whitney tests for nonnormally distributed continuous variables, and exact chi-square tests for categorical variables (Papers I–III). Correlation and multiple linear regression analyses were performed between neuropsychological measures and demographic variables (gender, age, length of education, and premorbid IQ), course of illness (BD

subtype, number of hospitalizations due to depressive episodes, number of psychotic episodes, comorbid substance abuse, and comorbid anxiety), and current symptoms (MADRS, PANSS pos, and GAF-S scores). Due to the small number of patients relative to the large number of independent variables, analyses were conducted unadjusted, and adjusted for age and length of education only (Paper I).

The efficacy analyses were performed on an intention-to-treat sample comprising all randomized patients who had at least one postbaseline assessment. In analyses of the continuous efficacy outcome, the longitudinal trajectories of the MADRS scores over the treatment course were compared for the ECT and APT groups using linear mixed-effects (LME) modeling [259] (Paper II). The data were registered as missing in the continuous outcome variables (i.e., MADRS, IDS-C30, and CGI-BP scores) if the patients did not return for the final assessment within eight days of finishing the six-week acute treatment phase. This occurred in 14 patients, who are included in the 23 indicated as dropouts in the flow chart for the study shown in Figure 1. However, analyses involving the full longitudinal profile of MADRS, IDS-C30, and CGI-BP scores did not require imputation of missing values since LME modeling accommodates missing data (Paper II). Response and remission rates were compared using *t*-tests. Times to response and remission with the MADRS score as the outcome measure were quantified in Cox regression analyses. A frailty model was used to handle the multicenter structure, without producing changes in the results. Missing values were in the survival analyses handled through censoring.

The effects of the two treatment alternatives on neurocognitive function were compared by performing mixed between–within repeated-measures analyses of variance (ANOVAs) for each of the domain scores as well as for the composite score, with treatment group (APT vs ECT) as the between-group variable and assessment time (pre- vs posttreatment) as the within-group variable. Effect sizes (partial η^2 values) for the effects of time and group and the interaction effect between time and group were computed (Paper III). The AMI-SF pre- and posttreatment scores were analyzed by mixed between–within ANOVAs, whereas the AMI-SF consistency scores in the two groups were compared using *t*-tests. Correlational analyses were

performed between neurocognitive measures and depressive symptoms (using the MADRS) (Paper III).

The cutoff for statistical significance was set at $p \leq 0.05$. All statistical analyses were performed using SPSS (version 18 or 20.0) and R [260].

3.7 Ethical considerations

The study was approved by the Regional Committee for Medical Research Ethics, Central Norway, the Norwegian Data Inspectorate, and the Norwegian Medicines Agency. All subjects were evaluated by the treating clinician as being capable of giving informed consent, and they provided informed written consent to participate after both the treatment options and the possible side effects had been fully explained to them. The study is registered at ClinicalTrials.gov (no. NCT00664976).

4 Results and summary of the papers

In the study described in Paper I we assessed the neurocognitive functioning in treatment-resistant, acutely admitted BD-depression inpatients. We found that neurocognitive impairments were evident in the BD I and BD II depression inpatients within all assessed cognitive domains. The MCCB profiles indicate neurocognitive functioning at a level between 1 and 1.5 SDs below normal means across domains. The scores for all MCCB measures were numerically lower in the BD I group than the BD II group, with a significant difference for one of the measures: category fluency. BD I patients had higher rates of global deficits: 68.4% of the BD I patients had clinically significant impairment (>1.5 SDs below the normal mean) in two or more domains, compared to 37.5% of the BD II patients (p=0.045). Higher age was associated with greater neurocognitive deficits compared to age-adjusted published norms. The estimated premorbid IQ did not differ between the groups, both of which performed in the "above normal" range. The performance on the WASI was significantly worse for the BD I patients than for the BD II patients. This indicates a decline in IQ in the BD I patients from the premorbid to the current level.

In Paper II we report data on the efficacy of ECT compared to APT in treatment-resistant BD depression. LME analysis revealed that treatment with ECT was significantly more effective than APT: the mean MADRS score at 6 weeks was 6.6 points lower in the ECT group [standard error=2.05; 95% confidence interval (CI)=2.5–10.6, p=0.001]. The IDS-C30 and CGI-BP secondary outcome measures showed similarly significant results, with the mean IDS-C30 and CGI-BP scores being 9.4 and 0.7 points lower, respectively, in the ECT group. The response rate was higher in the ECT group than in the APT group (73.9% vs 33.3%, p=0.014), but there was no significant group difference in the remission rate (34.8% vs 28.6%, p=0.75). The times to response and remission did not differ significantly between the ECT and APT group, however there was a nonsignificant tendency for both times to be shorter in the ECT group.

In the study described in Paper III we compared the effects of ECT and APT on neurocognitive function in treatment-resistant BD depression. In both treatment groups we found a significant improvement of cognitive function from pre- to posttreatment toward a normalization of MCCB scores, with no significant group differences. Improvements in neurocognitive performance were significantly correlated with reductions in the posttreatment depression ratings. We found a reduced autobiographical memory consistency in both groups from pre- to posttreatment, and an additional reduction in autobiographical memory consistency in the ECT group compared to the APT group.

5 Discussion

5.1 Discussion of the main results

5.1.1 Antidepressive effect

The treatment options for BD depression are poor, and for treatment-resistant depression the treating clinician needs to decide whether to start ECT or to continue with pharmacological treatment. The current study represents the first RCT to compare the effects of ECT and APT on treatment-resistant BD depression. The main finding is that ECT is more effective than APT in the acute treatment phase (Paper II), and hence the current study supports the superiority of ECT in the acute treatment of treatment-resistant BD depression.

The primary outcome was the longitudinal profile of weekly MADRS scores, which was significant at 6.6 points between the two treatment groups. Consistent findings were obtained with the secondary outcome measures IDS-C30 and CGI-BP, with differences of 9.4 and 0.7 points, respectively. Since this is the first RCT of ECT in BD depression, our results are not directly comparable to other studies. A meta-analysis of trials investigating mixed samples of unipolar and bipolar major depression [154] found ECT to be significantly more effective than pharmacotherapy. This finding, together with other studies documenting that ECT is equally effective in bipolar and unipolar depression [157], supports our main finding of ECT being more effective than pharmacotherapy in the acute treatment of BD depression.

The analyses of the response and remission rates are based on a dichotomization of the MADRS score and thus less powerful than the linear mixed-effects analyses. In the current study the response rate was significantly higher in the ECT group than in the APT group (73.9% vs 33.3%), whereas there was no group difference in the remission rates (34.8% vs 28.6%). These remission rates are low, and hence the results imply that although patients in a severe treatment-resistant depressive episode respond to an intensified treatment trial, with the depressive symptoms being reduced to a greater extent in the ECT group, the improvement is not

sufficient to achieve remission. Our results of a low remission rate are in accordance with two open studies of treatment-resistant BD depression [126, 179].

Given that the treatment goal for ECT is remission, the low remission rates were disappointing. However, it could be argued that any response in a currently very ill and treatment-resistant study population constitutes a relatively successful outcome. Studies that have involved patients who were not defined as treatment resistant have found substantially higher remission rates [181, 182]. This emphasizes the importance of describing the degree of treatment resistance. Further, it suggests that ECT should be applied earlier in a treatment course, before a high degree of treatment resistance has been documented [261].

Treatment-emergent affective switching is a recognized problem both in pharmacological treatment and ECT. In the current study two patients were excluded before starting treatment due to mood switches. A further two patients in the ECT group and two patients in the APT group scored >15 on the YMRS during the six-week treatment period. With only two patients in each treatment group, the switch rate in the current study was low compared to other studies [164, 262]. This might be due to the exclusion of patients with rapid cycling BD. Our results regarding treatment-emergent mood switches might therefore not be representative of unselected clinical populations. On the other hand, in the current study patients were not using antimanic agents when they were randomized to receive ECT. The use of antimanic agents is usually regarded as a strategy to avoid mood switches to (hypo)mania. The current study was not designed to assess the occurrence of mood switches, and the total number of patients experiencing mood switches was low. This makes it difficult to draw conclusions beyond that mood switches occur both in the natural course of BD depression and as a result of treatment.

There was one death during the six-week treatment phase of the study. The patient had received ECT. This death was attributed to an accidental overdose of illicit substances after discharge from hospital. The risk of death due to the ECT procedure itself is small [263]. Fatalities associated with ECT for severe mood disorders are often due to unnatural causes or suicide [264]. Immediately after

discharge from hospital the patients are in a vulnerable state. This has been shown for psychiatric treatment in general [265]. Large-scale cohort or register studies are more appropriate to investigate the mortality secondary to ECT or pharmacological treatment. However, such studies are associated with the possibility of selection bias due to nonrandomized allocation to treatment. The number of suicides within 14 days after ECT was reported to be 6 out of 8148 patients who received ECT during a five-year period in Texas [263]. A Danish register study from a population of patients admitted to a psychiatric hospital between 1976 and 2000 found that the suicide rate was slightly higher [relative risk (RR)=1.20, 95% CI=0.99–1.47] in patients who had received ECT compared to those who had not received ECT, especially within the first seven days after the last ECT session (RR=4.82, 95% CI=2.12–0.95). Due to the selection of severely ill, treatment-resistant patients to receive ECT, the results of the study do not allow a conclusion to be drawn about the impact of ECT on suicidality [264]. An increased risk of drug-related deaths after discharge from hospital has been shown in people receiving treatment for drug dependence [266]. The results from the referred studies underline the need for close monitoring and prevention strategies to avoid unnatural deaths after discharge from hospital.

5.1.2 Cognitive function

The main findings of the present study related to cognitive side effects were that patients in the ECT group had no reduction in general neurocognitive performance shortly after ECT, but exhibited reduced autobiographical memory consistency compared to patients randomized to APT (Paper III). Since this is the first RCT comparing the effects of ECT with pharmacological treatment, the reported results are not directly comparable to previous findings. The finding that ECT was not associated with a reduction in general neurocognitive function shortly after treatment is consistent with previous findings of a normalization of neurocognitive function in patients with mainly major depression shortly after ECT [217]. Findings of impaired cognition after ECT [151, 225, 267, 268] might be due to the shorter interval between the last ECT session and the posttreatment assessment in those studies. The current finding of reduced consistency in autobiographical memory in the ECT group is

consistent with previous findings of impairment of autobiographical memory after applying RUL brief-pulse ECT to patients with major depression [152, 269].

The present findings were obtained in a patient group characterized by pretreatment cognitive deficits. Patients with treatment-resistant BD depression exhibited reduced performance in all of the cognitive domains assessed by the MATRICS battery (Paper I). BD I patients had higher rates of global deficits and greater IQ decline than BD II patients. Moreover, age and length of education but not illness characteristics were associated with the severity of cognitive impairment. Almost half of the patients were impaired in two or more domains, which is a higher proportion than reported for stable outpatients [41]. This may be attributable to the specific group of treatment-resistant, acutely admitted depressed inpatients included in the present study. The current results therefore add to the body of data showing that cognitive deficits are relatively common and nonspecific in BD depression. The findings further suggest that clinicians should be aware of the possibility of severe neurocognitive dysfunction in treatment-resistant BD depression, particularly in BD I, independent of the treatment approach.

5.1.3 Clinical implications

Many of the current treatment guidelines for BD depression do not favor ECT. However, this guidance is not based on the results of RCTs. This first RCT of ECT in BD depression showed that ECT is more effective than APT in the acute phase of treatment-resistant BD depression without reducing general cognitive function. This makes ECT justifiable as a treatment option which should not be viewed as a last-resort treatment modality. The neurocognitive impairment associated with ECT was limited to a reduction in autobiographical memory. The risk of this side effect has to be evaluated against the benefits of the possible symptomatic and functional recovery, but also against the alternative risk of the cognitive decline due to poorly treated depression and the consequences of treatment delay [270]. The clinical relevance of our finding of reduced autobiographical memory consistency also depends on how long this impairment persists.

Even if BD patients presented a reduced cognitive performance during a depressed episode and no cognitive decline after ECT at a group level, this does not necessarily apply to every individual receiving ECT. Patients experiencing cognitive impairment after ECT must be carefully monitored and should undergo a full neuropsychological assessment if the impairment persists.

Patients with treatment-resistant BD depression show global neurocognitive impairments that—independent from the chosen treatment approach—must be addressed in clinical practice. Patients with cognitive impairments as described in the present study will probably experience difficulties in situations that demand rapid processing of information, such as following complex instructions, sustaining attention, and remembering new information. This may result in problems with treatment adherence as well as dealing with practical tasks in daily life, including maintaining social relationships. Neurocognitive functioning should therefore be assessed routinely in BD depression in order to identify particular strengths and difficulties for the individual patient and to provide individualized therapeutic strategies.

5.2 Methodological considerations

5.2.1 The patient sample

The current study assessed the effects of ECT and pharmacological treatment on treatment-resistant BD depression. Treatment-resistant BD-depression patients constitute a significant proportion of inpatients. Only about half of the patients assessed for eligibility could be included in the current study, which questions the extent to which the results of this study can be generalized to all patients with treatment-resistant BD depression. This can be addressed by considering several factors.

The psychiatric health-care system in Norway is available to everyone, publicly funded, and based on catchment areas. All patients requiring hospitalized

treatment within a defined catchment area are referred to the local study center. This approach indicates that the patient sample at a local study center is representative of the total population and hence that selection bias due to how health care is organized is unlikely.

Patients had to be well enough to give informed consent and to cooperate with the clinical and neuropsychological assessments. This means that the most severely ill patients were not included in the study. Since there are some indications that ECT is particularly beneficial for the most severely depressed patients [271], we assume that excluding the most severely ill could have reduced the observed effects of ECT.

The patients in the current study were included on the basis of a diagnosis of BD depression and being classified as treatment resistant. The diagnoses were established following the DSM-IV-TR criteria for BD, and possible misdiagnosis is discussed in Section 5.2.3. Treatment resistance in BD depression is difficult to define due to both the lack of effective treatment options and the natural course of the illness, with mood shifts toward the opposite pole. The lack of consensus regarding definitions of treatment resistance and the large number of possible definitions that had been proposed when we initiated the study reflects these difficulties. The definition in the current thesis referred to pharmacological treatment during the lifetime rather than during the current episode. The included patients were characterized by a high recurrence of episodes, and a large proportion of the patients had been treated with several types of drugs during their lifetimes. We found it relevant to take treatments in former admissions into account [272]. We reasoned that there would be a low probability that a patient who had not responded to a specific pharmacotherapy trial with adequate dosage and duration in an earlier episode would respond to the same pharmacotherapy trial in a new episode. We thus chose to define treatment resistance as two nonresponses to treatments during the lifetime. In the absence of an accepted definition of treatment resistance, the patients in the current sample might not be directly comparable with other samples of treatment-resistant BD-depression patients.

Moreover, all of the included patients had to accept a possible randomization to receive ECT. This might have inhibited patients with preferences for one of the treatment options from participating in the study, and the current sample might therefore not be representative of all patients with treatment-resistant BD depression. However, it is difficult to evaluate the direction in which this might have biased the results.

The indication for and attitudes to ECT in Norway may differ from those in other countries. This might also have implications for the generalizability of the results of the study. Further, some participating clinicians might have regarded ECT as superior to pharmacological treatment or vice versa, and such attitudes might have differed between the study centers. The risk of bias due to differences between the study centers was reduced by the use of stratified randomization. The severity of depression at inclusion did not differ significantly between centers. However, the number of patients recruited from each center was too low to correct for response differences across centers. Thus, a selection bias across study centers cannot be ruled out.

As discussed in Section 5.1.1, excluding patients with rapid cycling might have biased the results, especially the rate of mood switches. Still, we consider the current sample of treatment-resistant BD-depression patients as typical for acutely admitted BD-depression patients, but with the exception that the most severely ill patients were not included.

The dropout rate was higher in this study than in many previous studies. This was particular the case in the neuropsychological part of the study, with only 53% of the randomized patients fulfilling the final neurocognitive assessment. We attribute this to the naturalistic design involving acutely admitted, treatment-resistant patients. The listed demographic variables, course of illness, baseline symptoms, and baseline neuropsychological measures did not differ significantly between the 12 patients who dropped out after baseline assessment and the 39 patients included in the

posttreatment assessment. However, we cannot exclude that this could have biased the outcomes in both directions.

5.2.2 Research design

The effects of ECT and APT on BD depression were compared in a prospective longitudinal RCT. However, the correlation of the neurocognitive profile with demographic and clinical illness characteristics (Paper I) was investigated in a cross-sectional design. The data on the course of illness were collected retrospectively, mainly based on the information given by the patients. The nonsignificant associations must be interpreted with caution not only because of the small sample size (see Section 5.2.5), but also because of the possibility of a recollection bias. Patients assessed in the depressive phase may more easily recapitulate negative life events than positive ones [273], or their cognition might be impaired to a degree that makes it difficult for them to recollect anamnestic information. To reduce these effects, we have supplied the information from the patients with information both from significant others and hospital records. We found age and length of education to be the only factors associated with cognitive measures, and neither of these should be subject to a recollection bias. The other demographic and illness factors analyzed with respect to a possible association to cognitive function are more likely to become subject to recollection bias. This could have resulted in possible type II errors. The current finding of the cognitive deficits increasing with age might indicate a possible neurodegeneration or neuroprogression in the course of BD. However, the cross-sectional design does not allow definite conclusions on the longitudinal course in single patients.

The use of a randomized design in the longitudinal part of the study reduced the possibilities of spurious causality and bias. However, there might have been a bias due to an increased placebo effect in the ECT group. The patients in both groups were assessed weekly as part of the study and evaluated almost daily as part of ordinary hospital routines. However, the more intensive treatment procedure in the ECT group may indicate that these patients received more time and attention from the staff than

patients in the APT group. This is an intrinsic part of the ECT procedure. Thus we cannot exclude that the increased attention given to ECT patients might have biased the results and increased the response to ECT. This reflects some of the problems arising in a study designed without blinding. The lack of blinded raters represents a potential bias, as does the lack of blinding for patients. An "ideal" design could have been to administer anesthesia to both groups, and ECT plus placebo to the ECT group and active medication to the APT group. Finally a blinded rater should have evaluated the patients. The inclusion of a sham ECT group could have made it possible to control for a possible placebo response. We could thereby have controlled for the expectations of the patients and the differences in the follow-up through the study. But even with this "ideal" design ECT more often than anesthesia only leads to acute cognitive impairments that are obvious to the patient and the rater, and so a pseudo blinding could have been the result. Most importantly, we found a design with patients receiving repeated anesthesia without a medical indication to be unethical. An approval from the regional ethical committee was regarded as highly unlikely. To reduce the bias due to the unblinded design, we audiotaped the assessment of depressive symptoms at the time of inclusion and at the final assessment. There should have been 132 taped interviews since data from 66 patients were analyzed. Some patients left the study without a final assessment that was taped. In other cases accurate rating of the symptoms could not be done due to poor sound quality or technical problems. We randomly selected 35 of the 75 available audiotapes, and these were assessed by two independent blinded raters. It was a very strong correlation between the scores obtained by the blinded raters and the treating clinicians. This suggests that there was a low probability that the unblinded raters confounded the results. A similar approach to control for the lack of blinding was used in the Consortium for Research in Electroconvulsive Therapy trial [274]. This method to control for lack of blinding has not been validated. We still consider it a useful way to reduce the associated possible bias.

The randomization turned out to be satisfactory for sociodemographic factors, course of illness, and symptom severity, but not for baseline cognitive performance. ECT patients performed numerically better than patients in the APT group on all

cognitive measures (with exception of verbal learning). Since it is the interaction effect between group and time that is important for the analyses, the numerical differences in the baseline scores do not bias the main results.

5.2.3 Assessment

Besides the above-discussed bias associated with the unblinded assessments, several other aspects may have importance. The properties and the appropriateness of the rating scales and diagnostic interviews used in a multicenter study are probably the most prominent.

The diagnoses were made on the basis of a clinical interview and verified with the aid of the MINI-Plus or SCID-I, which involve the use of validated, standardized diagnostic interviews. Prior to the study all of the participating clinicians were trained in the use of one of the diagnostic instruments. However, the correlation between diagnoses performed by the clinicians at each study center was not assessed. We therefore cannot exclude the possibility that there were differences between the study centers that could have led to a selection bias, as discussed in Section 5.2.1. Patients with BD depression can be misdiagnosed as unipolar depressed or, vice versa, patients with unipolar depression or personality disorder can be misdiagnosed with BD, as was shown in a recent study [275]. Such possible misdiagnosis could have influenced the treatment efficacy. However, we find the possibility of inclusion of patients misdiagnosed with BD as unlikely due to the thorough diagnostic process. However, there are reasons to believe that patients evaluated to have a unipolar depression had a BD. This is due to the problems of getting reliable information from highly affected patients in the acute setting, as discussed in Section 5.2.2.

Depressive symptoms were mainly assessed using the MADRS. This scale was developed as an assessment tool to identify changes in depressive symptoms in clinical trials. It is documented to have good psychometric properties. It is better than the Hamilton Depression Rating Scale for differentiating between responders and nonresponders to AD treatment, and relies less on the presence of physical symptoms [238, 276]. Even though all of the participating raters underwent training in the use of

the MADRS and IDS-C30 and achieved an ICC of ≥0.7 for both the MADRS and IDS-C30 when rating at least 10 interviews, there might have been differences between the raters. These would have increased the variance in the depression symptom ratings and thus decreased the statistical power.

The MCCB has been developed for the assessment of cognitive functioning in schizophrenia and related disorders. It is a research tool designed to identify cognitive changes in clinical trials. It could thus be regarded to be an appropriate instrument for identifying cognitive changes in the current study. However, several aspects need to be addressed. Since there was no control group in the current study and there is no Norwegian norm sample, we based our results on the available US norms. While this is a potential source of error due to possible cultural and educational differences, the US norms of the MCCB were previously found to be suitable for assessing neurocognitive function in Norway [255]. Repeated testing might lead to a practice effect, which could have affected the current results and possibly masked an eventual underlying deterioration of test performance. We are not aware of any studies that have estimated the practice effects on MCCB tasks in a BD-depression sample. Data from an antipsychotic study [277] indicate a small practice effect on the MCCB in patients with schizophrenia. This battery is designed for repeated testing using alternate forms in the most affected tests (HVLT-R, BVMT-R, and NAB-Mazes), which would reduce the magnitude of the practice effect [257]. It is assumed that any practice effect, if present, would be similar in the ECT and APT groups. In the current study we found that the improvement of cognitive performance was equal in the two treatment groups. It is thus reasonable to exclude the possibility that the practice effect masked a potential deterioration of cognitive function due to ECT.

An important issue is whether the MCCB measures the cognitive functions assumed to be affected by ECT. Speed of processing, verbal memory, and working memory measured by the MCCB are relevant cognitive domains to assess since impairments have been found after ECT [225, 267, 268]. However, the main impairment after ECT reported from patients is retrograde and especially autobiographical memory. The MCCB does not measure retrograde memory. Thus,

the MCCB had to be supplied by an assessment of autobiographical memory. Assessing autobiographical memory constitutes a methodological challenge, since it is both complex and highly individual.

Although being the most-used instrument for assessing autobiographical memory in ECT-studies, the AMI-SF has several weaknesses. The most prominent is the lack of normative data in either healthy or depressed samples that could be compared directly with our results or used to estimate the normal change in autobiographical memory consistency [231, 278]. The current study did not include a healthy control group, and the extent to which a healthy population would have been able to give consistent answers in the AMI-SF after a six-week period remains unclear. It was thus impossible to differentiate between normal, mood-, and treatment-associated loss of autobiographical memory over time. This is a limitation of the current study.

The interval between the last ECT session and posttreatment assessment differed between patients. This is a limitation of the study. However, we found no correlation between any of the MCCB scores and time from the last ECT session to posttreatment assessment. We cannot exclude that this is due to the small sample. Previous research has found the resolution of ECT-induced neurocognitive impairments to be time dependent [279]. Further, we did not assess the inter-rater reliability for the neuropsychological assessments. However, all tests were performed by trained neuropsychologists or test assistants, and the MCCB consists of well-known and frequently used tests. All tests were reviewed by a single highly experienced test assistant, and this should have reduced any possible assessment bias.

The possible effects of the previous and current use of medications on cognitive performance could not be evaluated. This constitutes a confounding factor and thus limits the generalizability of the results. However, the medication at study entry did not differ significantly between the two groups. At the posttreatment cognitive assessment there were no significant group differences in the number of patients receiving each class of medications, with the exception of ADs—more

patients in the APT group received ADs. We cannot totally exclude that this has biased the results.

Another possible confounding factor is the impact of comorbid psychiatric conditions such as anxiety on cognitive performance. Sleep disturbances or lack of motivation might also impact test performance [253], but such effects would presumably apply to both treatment groups.

5.2.4 Treatment

There are methodological considerations regarding both treatment alternatives. The APT group used an algorithm rather than a specific medication or combination of medications. The use of an algorithm made it possible to include patients with treatment resistance to several medications. There could be a concern that the current algorithm might be outdated, since it was taken from a textbook published in 2007 [10]. When the study was planned the algorithm was one of the most up-to-date. Additionally, it gave separate recommendations for treating BD I and BD II depression. Although there have been several new studies on treatments for BD depression since 2007, they have produced only minor changes to the available treatment alternatives. For example, there are only minor differences in the pharmacological treatment recommendations between the current algorithm and one of the most up-to-date treatment guidelines, the CANMAT guideline [140]. Both guidelines take into account the controversial status regarding the effect and safety of ADs, which are suggested to be used in combinations with mood stabilizers only. There is a paucity of data concerning the treatment of treatment-resistant BD depression [133]. Thus, the use of any specific medication or combination of medications in the pharmacological arm of the study would have been difficult to justify.

The electrode placement and the dosing regimen might affect the results of ECT. Some authors have considered RUL electrode placement to be inferior to BL electrode placement, since it has been shown to be less effective in some studies. This is reflected in the meta-analysis performed by the UK ECT Review Group [154],

which found BL ECT to be moderately more effective than unilateral ECT. However, the efficacy of RUL ECT has been shown to be especially sensitive to dosage. It is not effective at low stimulus intensities (near the seizure threshold) [218], and the UK ECT Review Group meta-analysis included studies with ineffective low-dose RUL treatment. Later studies support the use of high-dosage RUL ECT, since it has been shown to be as effective as BL treatment with less severe and persistent cognitive effects [152, 219]. Therefore, we assume that the modest remission rate in the current study was probably not due to the use of RUL electrode placement, but rather to the selection of patients with a low potential for remission.

The lack of dose titration in the study might be a further limitation. In order to make the current multicenter study feasible, we followed the usual clinical practice at the study centers, which did not involve dose titration but instead employed an age-based approach. However, the appropriateness of dosage was determined at each treatment, which we assume outweighs the lack of initial dose titration. Dose adjustments were made at subsequent treatments after evaluating the seizure duration, δ-waves, seizure ending, postictal suppression, postictal reorientation time, and clinical effect.

Prior to the start of the treatment patients in both groups had to stop medications not approved by the study protocol. The discontinuation of psychoactive drugs might have led to withdrawal symptoms [280], possibly complicating the assessment of depressive symptoms.

5.2.5 Statistical considerations

The sample size is a limitation of the study. It limits both the usefulness of regression models (Paper I) and the probability of detecting any significant differences in MCCB scores between the BD subtypes (Paper I) or the treatment groups (Papers II and III) (type II error). Therefore, future studies should attempt to replicate the findings of the current study.

The high dropout rates also limit the statistical power of the analysis and may be a source of type II errors. In the efficacy analysis we applied an LME model approach rather than a *t*-test to group means at the endpoint. This approach has the advantage of taking into account the full longitudinal profile of the MADRS without requiring imputation of missing values. We therefore assume that missing data due to subjects dropping out of the study were managed appropriately.

A formal power analysis of changes in cognitive measures was not performed, since there were no published results about the cognitive changes and variances after ECT applied to treatment-resistant BD depression. Post hoc calculation of power is not recommended [281]. To discuss if clinical significant differences may have gone undetected in a nonsignificant statistical test we studied the 95% CI for the effect measure. It did not include clinical significant effect sizes.

The use of standardized *T* scores rather than raw scores was necessary to calculate the MCCB composite score and to make it possible to compare test scores between patients of different genders and ages (since the *T* scores are corrected for both age and gender), and between the different MCCB tests. The use of composite scores rather than multiple single test measures usually increases the power. On the other hand, the transformation into *T* scores might have reduced the power of the longitudinal analyses. We therefore performed additional analyses of the differences in raw scores rather than the differences in *T* scores—these yielded similar results that did not change the conclusion.

Multiple comparisons, which were performed between neuropsychological variables and treatment, increase the risk of false-positive results (type I error). A post-hoc adjustment using the Bonferroni method could have been performed, but this increases the risk of losing true associations. The use of composite scores instead of the rather conservative Bonferroni approach is assumed to have increased the reliability of the results.

6 Conclusions

In conclusion, this first RCT of ECT in BD depression has produced the following findings:

1. Patients with treatment-resistant BD depression show global neurocognitive impairments.
2. The severity of neurocognitive impairment increases with age.
3. ECT is more effective than APT in treating treatment-resistant BD depression.
4. The response rate is higher in the ECT than in the APT group. The remission rates are modest, with no differences between the treatment groups.
5. Autobiographical memory consistency is reduced in patients treated with ECT compared to those receiving APT.
6. General neurocognitive function is unaffected shortly after RUL ECT.

7 Future perspectives

From the present study three future research questions arise. First, the low remission rates reflect the need for research focusing on more efficient treatment options for the challenging condition of BD depression. Other stimulation techniques, such as DBS, might be worth investigating, as well as the combination of multiple treatment strategies. The ECT patients included in this study received no pharmacological treatment other than concomitant medication, which is contrary to clinical practice. The use of ECT as an add-on to pharmacological treatment might have enhanced the remission rate. Controlled studies of the impact of pharmacological treatment on the efficacy and side effects of ECT on BD depression are needed.

Second, BD is a lifelong illness. The efficacy of acute treatment is not directly transferable to efficacy in maintenance therapy. Preventing future affective episodes is important, and studies of the efficacy of ECT maintenance treatment in BD are warranted. The outcome variable in the current study was symptom severity, as measured with the MADRS. The goal of treating depression is not only reducing depressive symptoms. It is also important to assess how the treatment affects quality of life and occupational and psychosocial functioning.

Finally, the present study underlines the need for further research on the effects of ECT on autobiographical memory, compared to normal forgetting and the effects of depression. This includes follow-up assessments of the currently included patients after six months and two years.

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