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Long-term outcomes following electroconvulsive therapy for treatment-resistant depression

PhD thesis

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Declaration

I declare that this thesis has not been submitted as an exercise for a degree at this or any other university and it is entirely my own work.

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The work presented in this thesis comprises three studies:

Study 1: I designed this study with the help of my supervisor Prof Declan McLoughlin. I carried out data collection, data entry into statistical software, statistical analyses, interpretation of findings and write-up. As is recommended for data quality purposes in meta-analyses, a second rater also independently coded every study and extracted data from them. I am grateful to Dr Erik Kolshus who kindly assisted me with this.

Study 2 was a substudy of a larger study, the EFFECT-Dep Trial. I designed Study 2 under the supervision of Prof McLoughlin. The overall EFFECT-Dep Trial was designed by Prof McLoughlin and involved a large amount of patient recruitment and clinical and neuropsychological assessments before, during and after ECT by a ten-person clinical research team over a five-year period. I was a member of this team between October 2009 and May 2013. During that period I carried out patient recruitment and baseline assessments, intra-treatment and post-ECT follow-ups, data quality monitoring, training of research assistants and participant retention efforts. Dr Kolshus and I jointly re-evaluated every trial patient's clinical and/or research records for purposes of scoring of the primary outcome measures in Study 2 (ATHF and MSM). I entered the data for Study 2 into statistical software which was independently cross-checked by Dr Kolshus. I carried out statistical analyses, interpretation of findings and write-up for this study under the supervision of Prof McLoughlin.

Study 3: I designed this study with the help of Prof McLoughlin. Data were collected as part of routine clinical practice by Mr Shane McCarron and extracted from patients' clinical records by Ms Stephanie O'Connor and myself. The primary outcome measure (AMI) for each patient was scored independently Ms O'Connor and myself. I am grateful to Mr McCarron for his clinical work and Ms O'Connor for her assistance with data collection and her participation in the inter-rater reliability sessions on this project. I carried out data entry, statistical analyses, interpretation of results and write-up for this study under the supervision of Prof McLoughlin.

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Abstract

Background: Electroconvulsive therapy (ECT) is the most acutely effective treatment for depression but its use is limited by high rates of early relapse and retrograde amnesia of uncertain severity and duration.

Aims: The work presented in this thesis aimed to elucidate long-term clinical and cognitive outcomes of patients with moderate-to-severe, often medication-resistant depression treated with ECT. This thesis also aimed to examine the validity of several definitions of treatment-resistant depression and explore the effect of pre-ECT medication resistance on the likelihood of subsequent remission and relapse.

Methods: Study 1 was a systematic review and meta-analysis of 32 published studies on relapse following a successful course of ECT. Study 2 was a prospective one-year follow-up of patients treated with ECT as part of a randomised controlled trial of bitemporal vs. high-dose right unilateral ECT. Antidepressant Treatment History Form, Maudsley Staging Method, antidepressant medication count and clinical judgement of referring psychiatrists were examined for their utility in predicting short- and long-term ECT outcomes in a sample of 104 patients with unipolar depression. Medication resistance and other baseline clinical predictors of relapse were examined in a sample of 61 ECT remitters with unipolar or bipolar depression. Study 3 was a retrospective chart review of 48 patients treated with brief-pulse, mostly bitemporal ECT whose autobiographical memory was tested before, immediately after and three months following ECT using the recent life section of the Kopelman et al. Autobiographical Memory Interview.

Results: Study 1 found that long-term outcomes of patients who initially responded to ECT were currently suboptimal with half of such patients relapsing within the first year. Younger patients and those without psychotic features were more likely to relapse. Medication failure prior to ECT was not predictive of relapse. Six-month relapse rates have approximately doubled over the decades of ECT use.

Study 2 found that ECT is an effective treatment option for patients who are resistant to pharmacological therapies for depression. The studied measures of treatment-resistant depression showed little to no convergent validity in unipolar depression. Medication resistance, however defined, was not predictive of inferior short-term or long-term ECT outcomes. Of the 61 patients with unipolar or bipolar depression who remitted after ECT in this trial, approximately 40% relapsed during the one-year follow-up. Clinical features other than medication resistance, in particular younger age, non-psychotic depression, recurrent depression and bipolar II disorder were significant predictors of relapse. Continuation therapy with lithium during the naturalistic follow-up phase appeared to be significantly protective against relapse.

Study 3 found that autobiographical memory function of ECT patients is characterised by abnormal recall of personal episodic memories before ECT, immediately after the course and at three-month follow-up. Marked deficits in episodic memory recall persisted despite a significant improvement in mood state following ECT. Recall of semantic information about one's life was within normal range at all three assessment points. The recent life section of the Autobiographical Memory Interview was not sensitive to retrograde amnesia in this sample treated with brief-pulse, mostly bitemporal ECT.

Conclusions: Post-ECT maintenance of wellbeing in patients with depression needs to be improved. Reliable and valid assessment of episodic and semantic domains of autobiographical memory in this patient population remains a clinical and scientific challenge. Optimisation of assessment tools for treatment-resistant depression requires further study.

Tables

Figures

Abbreviations

ACC – anterior cingulate cortex

AI – Autobiographical Interview

AMI-SF – Columbia University Autobiographical Memory Interview—Short Form

ATHF – Antidepressant Treatment History Form

BDNF – brain-derived neurotrophic factor

C-ECT – continuation ECT

CBF – cerebral blood flow

CBT – cognitive behavioural therapy

CGI – Clinical Global Impression

CGI-I – Clinical Global Impression—Improvement

CGI-S – Clinical Global Impression—Severity

CI – confidence interval

CORE – Consortium for Research in Electroconvulsive Therapy

DBS – deep brain stimulation

DLPFC – dorsolateral prefrontal cortex

DSM-III – Diagnostic and Statistical Manual of Mental Disorders—3rd Edition

DSM-III-R – Diagnostic and Statistical Manual of Mental Disorders—3rd Edition Revised

DSM-IV – Diagnostic and Statistical Manual of Mental Disorders—4th Edition

DSM-5 – Diagnostic and Statistical Manual of Mental Disorders—5th Edition

ECT – electroconvulsive therapy

EEG – electroencephalogram

FDA – Food and Drug Administration

GABA – gamma-aminobutyric acid

HPA axis – hypothalamic-pituitary-adrenal axis

HRSD – Hamilton Rating Scale for Depression

HRSD-24 – Hamilton Rating Scale for Depression—24-item version

HSE – Health Service Executive

ICD-10 – International Classification of Diseases—10th Revision

IDO – indoleamine-2,3-dioxygenase

IL-6 – interleukin-6

IFN-α – interferon-alpha

IPT – interpersonal therapy

IQ – intelligence quotient

Kopelman AMI – Kopelman et al. Autobiographical Memory Interview

MAOI – monoamine oxidase inhibitor

MDD – major depressive disorder

MDE – major depressive episode

MGH-SM – Massachusetts General Hospital staging method

MMSE – Mini-Mental State Examination

MRI – magnetic resonance imaging

MSM – Maudsley Staging Method

NART – National Adult Reading Test

NCS-R – National Comorbidity Survey—Replication

NICE – National Institute for Health and Care Excellence

NIMH – National Institute of Mental Health

NMDA – *N*-methyl-D-aspartate

OGM – overgeneral autobiographical memory

RCT – randomised controlled trial

RDC – Research Diagnostic Criteria

RIMA – reversible inhibitor of monoamine oxidase A

RUL ECT – right unilateral electroconvulsive therapy

SSRI – selective serotonin reuptake inhibitor

SNRI – serotonin-noradrenaline reuptake inhibitor

ST – seizure threshold

STAR*D – Sequenced Treatment Alternatives to Relieve Depression

TCA – tricyclic antidepressant

TMS – transcranial magnetic stimulation

TNF-α – tumour necrosis factor-alpha

TRD – treatment resistant depression

TR-SM – Thase and Rush staging model

T_3 – triiodothyronine

VNS – vagus nerve stimulation

WHO – World Health Organisation

Table of Contents

1. Introduction

1.1. Major depressive disorder

1.1.1. Burden of depression

Major depressive disorder (MDD) is a psychiatric illness affecting approximately 300 million people across the globe (Ferrari et al., 2013). According to the Global Burden of Disease study, unipolar depression is currently the second leading cause of disability worldwide (Vos et al., 2012). In the large, nationally representative National Comorbidity Survey—Replication (NCS-R) study in the United States, lifetime prevalence rate of MDD was estimated at 16.2% (95% confidence interval [CI], 15.1-17.3%), which translates into 32.6 to 35.1 million American adults who will experience an episode of major depression at some point in their lives, with a median age at onset of 30 years (Kessler et al., 2003). In Ireland, a primary diagnosis of depression was the most common documented reason for psychiatric inpatient admission (122.3 per 100,000 population), accounting for 29.5% of all inpatient admissions in Irish psychiatric units and hospitals in 2011 (Daly & Walsh, 2012).

People living with depression experience equal or worse impairment in functioning and well-being compared to people affected by medical illnesses such as diabetes, hypertension, recent myocardial infarction, and congestive heart failure (Hays, Wells, Sherbourne, Rogers, & Spritzer, 1995). According to the World Health Organisation's (WHO) World Health Survey, depression results in greater decrements in overall health compared to chronic medical conditions such as angina, arthritis, asthma, and diabetes (Moussavi et al., 2007). In addition to causing significant personal distress and functional impairment, depression results in considerable economic burden (Mrazek, Hornberger, Altar, & Degtiar, 2014) and is linked to excess mortality in community-dwelling individuals (Cuijpers et al., 2014), with no significant difference in mortality rates between major and subthreshold depression (Cuijpers et al., 2013).

1.1.2. Diagnosis and clinical features of depression

MDD is a heterogeneous clinical syndrome characterised by the core features of depressed mood and/or loss of interest or pleasure (anhedonia) as well as several additional cognitive and neurovegetative symptoms. The Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) (American Psychiatric Association, 2013) diagnostic criteria for a major depressive episode require five or more of the following nine symptoms to be present during the same two-week period and must include at least one of either 1) depressed mood or 2) loss of interest or pleasure:

1) depressed mood most of the day nearly every day
2) markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
3) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day
4) insomnia or hypersomnia nearly every day
5) psychomotor agitation or retardation nearly every day
6) fatigue or loss of energy nearly every day
7) feelings of worthlessness or excessive or inappropriate guilt (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
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

1.1.3. Aetiology of depression

Defined using such broad modern diagnostic criteria as the DSM-5 criteria cited above, major depression is a heterogeneous syndrome exhibiting a highly variable longitudinal course, an inconsistent response to treatment and no clearly established pathophysiological mechanisms (Belmaker & Agam, 2008). Although the aetiology of depression remains unclear, genetic factors are known to play an important role in the

development of the disorder (Ebmeier, Donaghey, & Steele, 2006). In a meta-analysis of studies of genetic epidemiology of MDD, the commonly observed familial aggregation of this illness appeared to be primarily attributable to additive genetic effects (37% of variance, 95% CI 31-42%), while individual-specific environmental effects and measurement error explained the remaining 63% of variance (95% CI 58-67%) (Sullivan, Neale, & Kendler, 2000). The influence of shared environmental effects (i.e. environmental influences common to all family members, such as socioeconomic status, local environmental qualities, etc.) was estimated at 0% (95% CI 0-5%). Early life stress and trauma are strongly associated with the development of major depression and suicidal behaviour (Frodl & O'Keane, 2012; Mann & Currier, 2010). Demographic risk factors for developing MDD include female gender, being unemployed or disabled, and living in or near poverty (Kessler et al., 2003).

MDD itself is a risk factor for, and highly comorbid with, other psychiatric and medical disorders. The majority of lifetime cases of MDD (72.1%) in the NCS-R also had a comorbid DSM-IV disorder, particularly anxiety, substance use and impulse control disorders, with MDD rarely being the primary disorder (Kessler et al., 2003). Depression is common in medical illness and is associated with the metabolic syndrome, a constellation of risk factors for the development of type 2 diabetes mellitus, cardiovascular and cerebrovascular disease. A recent meta-analysis of epidemiological studies found a reciprocal relationship between depression and the metabolic syndrome (Pan et al., 2012). Other meta-analyses have shown that MDD is a significant risk factor for cardiovascular and cerebrovascular disease (Van der Kooy et al., 2007), type 2 diabetes mellitus (Knol et al., 2006) and dementia (Diniz, Butters, Albert, Dew, & Reynolds, 2013). This overlap between depression and the diseases linked to the metabolic syndrome suggest common aetiological mechanisms such as obesity, chronic inflammation and immune dysregulation, insulin and leptin resistance, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, autonomic dysfunction, mitochondrial dysfunction, vascular damage, etc. (Pan et al., 2012; Penninx, Milaneschi, Lamers, & Vogelzangs, 2013).

1.1.4. Neurobiology of depression

The neurobiology of depression remains unclear and our knowledge of the underlying pathophysiology is rudimentary even compared to other chronic multifactorial diseases (Krishnan & Nestler, 2008). Multiple pathophysiological mechanisms have been proposed but no single clear biomarker has yet emerged (Schmidt, Shelton, & Duman, 2011). In contrast with other neuropsychiatric disorders such as Alzheimer's, Parkinson's or Huntington's disease, there is no identifiable brain lesion responsible for the pathology of depression and the neural circuitry involved in this disorder is complex and includes numerous brain areas, including the prefrontal and cingulate cortex, hippocampus, striatum, amygdala and thalamus, among others (Nestler et al., 2002). A crucial role in the regulation of mood is played by a network of cortico-limbic pathways and these brain circuits likely play a role in the pathogenesis of depression (Mayberg, 1997). Consistent with this, magnetic resonance imaging (MRI) studies of patients with unipolar depression find volume reductions in brain areas involved in emotional processing, such as the frontal cortex, orbitofrontal cortex, cingulate cortex, hippocampus and striatum, as well as pituitary gland enlargement and an increased presence of white matter hyperintensities (Arnone, McIntosh, Ebmeier, Munafo, & Anderson, 2012).

A brain region of particular interest in depression is the hippocampus, a subcortical structure involved in a variety of functions, most crucially in learning and memory consolidation. A meta-analysis of MRI studies found significant reductions in hippocampal volume in both hemispheres of depressed patients compared to normal controls, with a mean of 10% on the right side and 8% on the left (Videbech & Ravnkilde, 2004). Hippocampal volume reduction is already present in first-episode patients as shown in a meta-analysis of MRI studies where a mean volume reduction of 4.5% on the right and 4.0% on the left was found (Cole, Costafreda, McGuffin, & Fu, 2011). Decreased hippocampal volume has been shown to be present also in high-risk individuals prior to the onset of depressive symptoms and has been found to be further reduced with repeated depressive episodes (MacQueen & Frodl, 2011).

The hippocampus is the primary neural binding site for glucocorticoids (Sapolsky, 2000). A dysregulation of the hypothalamic-pituitary-adrenal axis (HPA axis) has for decades been known to play a key role in the pathophysiology of depression. A significant percentage of depressed patients have increased levels of salivary, plasma and urinary cortisol, as well as increased size and activity of the pituitary and adrenal glands (Pariante & Lightman, 2008). Individuals exposed to early life stress are particularly vulnerable to HPA axis dysregulation and hippocampal alteration via epigenetic changes (Frodl & O'Keane, 2012). Prolonged exposure to stress and thus elevated levels of glucocorticoids has a deleterious impact on the hippocampus, resulting in impaired neurogenesis and atrophy (Sapolsky, 2000). Chronic glucocorticoid exposure leads to decrements in neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), that regulate neuroplasticity (Duman & Li, 2012). Glucocorticoids are therefore positioned at the interface between stress and the brain via their role in regulation of neurogenesis, neuronal survival, determination of size of complex brain structures (such as the hippocampus), acquisition of memories and emotional appraisal of events (Pariante & Lightman, 2008).

These negative neuroplastic changes in depression appear to be reversible with successful treatment (Duman & Li, 2012). Antidepressant drugs used in routine clinical practice today modulate monoaminergic neurotransmission. Although they produce immediate increases in monoamine availability in the synaptic cleft, they nonetheless require weeks to exert an antidepressant effect which suggests that other factors are involved in their clinical action (Nestler et al., 2002). A classic hypothesis stated that depression is caused by a deficiency of monoaminergic function in the brain (Wong & Licinio, 2004). This hypothesis originated from early clinical observations and the serendipitous discovery of iproniazid and imipramine, two structurally unrelated antidepressant compounds that alter serotonergic and noradrenergic neurotransmission; however, it is now commonly accepted that chronic administration of antidepressants also produces neuroplastic changes involving transcriptional and translational factors that mediate molecular and cellular plasticity (Krishnan & Nestler, 2008). In a landmark study,

it was shown that a blockade of hippocampal neurogenesis inhibited the therapeutic effect of fluoxetine, a selective serotonin reuptake inhibitor (SSRI), in a rodent model of depression (Santarelli et al., 2003), a finding subsequently replicated in non-human primates (Perera et al., 2011). Several studies have recently also shown that ketamine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, a rapidly-acting antidepressant with a novel mechanism of action, induces synaptogenesis and reverses atrophy in rodent prefrontal cortex produced by chronic stress (Duman & Li, 2012).

There is now compelling evidence that chronic inflammation is implicated in the pathophysiology of depression and many other chronic illnesses. A high degree of comorbidity is found between depression and other inflammatory conditions such as infectious, autoimmune and neurodegenerative diseases (Zunszain, Anacker, Cattaneo, Carvalho, & Pariante, 2011). The similarity between depression and “sickness behaviour” induced by pro-inflammatory cytokines is remarkable (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008). A clinical model that supports the role of pro-inflammatory cytokines in the pathophysiology of depression comes from therapeutic use of the cytokine interferon-alpha (IFN-α) for conditions such as hepatitis C infection and some malignancies. IFN-α treatment induces a depressive syndrome characterised by low mood, anxiety and cognitive symptoms, as well as neurovegetative symptoms of fatigue, anorexia, pain and psychomotor slowing in as many as half of studied patients (Raison, Demetrashvili, Capuron, & Miller, 2005). Pre-treatment with an SSRI significantly reduces the development of MDD during IFN-α treatment (Musselman et al., 2001), suggesting an overlap between serotonergic and inflammatory pathways in depression. Meta-analytic findings show reliable elevations in two pro-inflammatory cytokines in depression, tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) (Dowlati et al., 2010). Although glucocorticoids are potent anti-inflammatories, the findings of chronic elevation of cortisol and concurrent increase in inflammation can be reconciled. Sustained elevations in cortisol result in glucocorticoid resistance via a compensatory downregulation of the glucocorticoid receptor and activation of the pro-inflammatory cytokine pathways (Zunszain et al., 2011). Increased inflammation is also consistent with the classic

monoamine hypothesis of depression. Inflammation alters serotonin metabolism by increasing the activity of the metabolic enzyme indoleamine-2,3-dioxygenase (IDO), which results in degradation of tryptophan to kynurenine which is subsequently metabolised to quinolinic acid (Raison, Capuron, & Miller, 2006). Quinolinic acid is associated with lipid peroxidation, oxidative stress, excitotoxicity and neurodegenerative diseases via its ability to bind to the NMDA receptor which leads to the release of glutamate (Haroon, Raison, & Miller, 2012).

1.1.4.1. Neurobiology of late-life depression

The notable association between depression, vascular risk factors and cerebrovascular disease in older adults (Valkanova & Ebmeier, 2013) had led to the "vascular depression" hypothesis (Alexopoulos et al., 1997a; Taylor, Aizenstein, & Alexopoulos, 2013), also termed "subcortical ischaemic depression" (Krishnan et al., 2004), which posits that cerebrovascular disease may predispose, precipitate or perpetuate a subset of late-life depression. Clinical presentation of these patients includes executive dysfunction (Alexopoulos et al., 1997b) and MRI evidence of increased volume of white matter hyperintensities (Krishnan, Hays, & Blazer, 1997). Diffusion tensor imaging shows abnormalities, particularly in frontal regions, in white matter that appears normal on the standard T2-weighted MRI of patients with late-life depression, suggesting that white matter hyperintensities on standard MRI represent just the tip of the iceberg of actual structural brain abnormalities in this illness (Shimony et al., 2009).

White matter hyperintensities occurring in late-life depression appear to be ischaemic in origin and are concentrated in the frontal lobes. In a post-mortem study (Thomas et al., 2002) all white matter lesions in deceased patients with late-life MDD (without DSM-IV comorbidities) were found to be ischaemic, whereas in controls who died of other causes, there was a mixture of non-ischaemic and ischaemic white matter lesions, with non-ischaemic predominating. In addition, all white matter lesions in MDD patients were frontal, showing a marked specificity for the dorsolateral prefrontal cortex

(DLPFC), occurring less frequently in the anterior cingulate cortex (ACC). Meanwhile, in control subjects, all ischaemic frontal lesions occurred in the ACC and none in the DLPFC. Two ischaemic lesions were found in the occipital cortex in controls, while the majority of lesions (over two-thirds in total) were non-ischaemic in origin. The latter kind occurred in the DLPFC, ACC and the occipital cortex in controls. These findings are consistent with meta-analytic neuropsychological findings in MDD (Snyder, 2013) showing impairments on executive tests reliant on the integrity of the DLPFC and the ACC, among other brain regions, as well as meta-analytic findings of decreased activation in these areas in neuroimaging studies of MDD (Fitzgerald, Laird, Maller, & Daskalakis, 2008).

Patients with “vascular depression” also have diminished acute response to standard pharmacological treatment for depression (Kalayam & Alexopoulos, 1999), as well as worse long-term outcomes characterised by higher probability of relapse and recurrence (Alexopoulos et al., 2000). A recent study (Sheline et al., 2010) found that neuropsychological impairment, the volume of white matter hyperintensities on the MRI and the Framingham Stroke Risk Score (Wolf, D'Agostino, Belanger, & Kannel, 1991) predicted clinical outcome during three-month treatment with sertraline for late-life depression. The high degree of correlation between cognitive risk factors and severity of white matter hyperintensities on the MRI on the one hand and the Framingham Stroke Risk Score on the other suggests a common aetiological vascular component to all observed abnormalities.

1.1.5. Neuropsychological impairment in depression

In addition to disturbances of mood and neurovegetative functions, depression is associated with neuropsychological impairment across a range of cognitive domains including psychomotor speed, attention, memory and executive function (Austin, Mitchell, & Goodwin, 2001; Beblo, Sinnamon, & Baune, 2011; Snyder, 2013; Veiel, 1997; Zakzanis, Leach, & Kaplan, 1998). Observed neuropsychological deficits in MDD point to a global-

diffuse impairment of brain function, with particular involvement of the frontal lobes (Veiel, 1997).

Executive dysfunction is a key aspect of cognitive impairment in MDD. In a recent meta-analysis (Snyder, 2013) MDD was shown to be associated with broad, generalised impairments across all aspects of executive function (inhibition, shifting, updating, verbal working memory, visuospatial working memory, planning, verbal fluency), with effect sizes ranging between 0.32 and 0.97, the largest effect size being observed for a measure of inhibition. Decreased processing speed alone could not account for these findings. Although severity of executive dysfunction correlated with depression severity, patients in remission were still significantly impaired on the majority of components of executive function compared to normal controls. On some measures of executive function, remitted and currently depressed patients did not differ in severity of impairment, suggesting that at least some of these executive deficits are stable, enduring traits of this illness that persist following the resolution of mood symptoms.

Other systematic reviews and meta-analyses have also found deficits across a range of neuropsychological tasks in subsets of MDD patients such as first-episode (Lee, Hermens, Porter, & Redoblado-Hodge, 2012) and currently euthymic patients (Bora, Harrison, Yucel, & Pantelis, 2012; Hasselbalch, Knorr, & Kessing, 2011). Degree of cognitive impairment is positively associated with current severity of depression in the domains of episodic memory, executive function and processing speed, though not semantic or visuospatial memory (McDermott & Ebmeier, 2009). In this meta-analysis, patients exhibited similar deficits on timed and untimed neuropsychological tasks suggesting that greater psychomotor retardation in more severe depression was not solely responsible for the positive relationships between cognitive impairments and depression severity.

Although correlated with depression severity, these neuropsychological deficits do not appear to be mere state-related epiphenomena of low mood and lack of motivation. In a recent meta-analysis, healthy controls outperformed euthymic depressed patients

across all studied cognitive domains, with effect sizes generally in the small-to-moderate range (0.39–0.59) (Bora et al., 2012). The greatest deficits occurred in the executive function domain, with the largest effect size observed on the Stroop interference task that measures inhibition. More pronounced deficits were generally observed in late-onset depression with effect sizes ranging between 0.42 and 1.10, especially in the domains of verbal memory, processing speed and executive function. These mood state-independent cognitive deficits likely represent consequences of structural and functional brain abnormalities found in MDD (Bora et al., 2012).

These findings of persisting neuropsychological deficits have major clinical implications for remitted patients with MDD who may expect or be expected to return to premorbid level of functioning following the resolution of a depressive episode. This may not be achievable for all patients and such expectations may lead to frustration, low self-esteem, feelings of worthlessness and potentially even increase the likelihood of relapse (Hammar & Ardal, 2009). Discussions about the reality of enduring cognitive deficits in depression should form part of clinical practice (Hammar & Ardal, 2009). This information is of particular relevance to patients treated with electroconvulsive therapy (ECT) whose illness tends to be particularly severe, recurrent or indeed chronic and where risk for enduring cognitive impairment is thus expected to be the greatest. Disentangling the relative contributions of depressive illness and ECT treatment on persisting cognitive impairment in this patient population has thus far proven challenging.

1.1.5.1. Autobiographical memory impairment in depression

A hallmark aspect of neuropsychological dysfunction in depression of particular importance in the context of study of ECT-treated patients with depression is autobiographical memory impairment. While traditional laboratory experiments of neuropsychological function in neuropsychiatric disorders typically involve learning of new stimuli such as word lists (thus measuring abilities like encoding, retention and retrieval of material), such tasks are only capable of tapping into one aspect of memory which is

concerned with “what” is being remembered (Tulving, 2002). Episodic memory, on the other hand, which refers to the recollection of events occurring in the context of a particular time and place, is concerned not only with the “what” but also with the “where” and “when” (Tulving, 2002). “Episodic memory is a recently evolved, late-developing, and early-deteriorating past-oriented memory system, more vulnerable than other memory systems to neuronal dysfunction, and probably unique to humans. It makes possible mental time travel through subjective time, from the present to the past, thus allowing one to re-experience, through autonoetic awareness, one’s own previous experiences” (Tulving, 2002, p. 5). Autobiographical memory, a subset of episodic memory, is crucial to the sense of self, the experience of personhood and the feeling of existence as an individual in a culture over time, contributing to one’s sense of identity and continuity (Conway & Pleydell-Pearce, 2000; Piolino, Desgranges, & Eustache, 2009). The defining characteristic of episodic memory is “autonoetic consciousness, which is a *sine qua non* of episodic memory [and] is defined by a sense of self in time and the mental reliving of subjective experiences arising from the encoding context” (Piolino et al., 2009, p. 2315).

Over the past several decades, there has been an accumulating body of research demonstrating autobiographical memory impairment in patients with depression. The phenomenon of so-called “overgeneral autobiographical memory” (OGM) is a robust finding in the literature and appears to be a stable trait or cognitive style present in depression rather than an epiphenomenon of low mood (King et al., 2010). First observed in a study of suicide attempters (Williams & Broadbent, 1986), OGM refers to the tendency to recall a nonspecific summary of a *category* of events (e.g. “I don’t like parties”) rather than a description of a *specific* event situated in time and place (e.g. “the party I went to at my friend’s house on Saturday night”) when asked to recall a specific event in response to a cue word (e.g. “party”). OGM is a consistent finding in MDD patient samples compared to healthy controls, with a mean effect size of 1.12 across 11 studies (Williams et al., 2007). There is also a significant association between history of trauma and OGM with an effect size of 1.13 (Williams et al., 2007). A recent meta-analysis also showed that the number of specific and categorical/overgeneral memories generated by

depressed individuals at baseline significantly predicted the long-term clinical course of depression, albeit with small effect sizes (Sumner, Griffith, & Mineka, 2010). The greater the number of specific memories and the smaller the number of overgeneral memories generated at baseline, the fewer depressive symptoms were found at follow-up (Sumner et al., 2010). Interestingly, depressed patients are not only less able to generate specific autobiographical memories from their past but are also less capable of imagining specific future events, suggesting a generalised impairment in working memory and executive processing which are believed to underpin autonoetic consciousness (King, MacDougall, Ferris, Herdman, & McKinnon, 2011).

Autobiographical memory impairment of varying severity and duration occurs following ECT (Fraser, O'Carroll, & Ebmeier, 2008; Ingram, Saling, & Schweitzer, 2008; Rose, Fleischmann, Wykes, Leese, & Bindman, 2003; Sackeim, 2000; Sackeim, 2014; Semkovska & McLoughlin, 2013). The available evidence on the extent of autobiographical memory impairment and methodological factors complicating the study of this phenomenon in the specific context of ECT treatment for major depression are discussed in section 1.4.7 of this chapter.

1.2. Treatments

1.2.1. Existing therapeutic options for depression

Pharmacotherapy with antidepressant medication is the cornerstone of medical management of depression (Thase & Rush, 1997). Several somatic treatments are also available, such as ECT, transcranial magnetic stimulation (TMS), vagus nerve stimulation (VNS), deep brain stimulation (DBS), light therapy, as well as evidence-based psychotherapeutic approaches, such as cognitive behavioural therapy (CBT) and interpersonal therapy (IPT), among others.

1.2.2. Limitations of pharmacotherapy

Antidepressant medications in use today act on the monoaminergic system, targeting neurotransmission of serotonin, noradrenaline, and, to a lesser extent, dopamine. All existing pharmaceutical treatments for depression exhibit limited effectiveness, delayed onset of action and considerable side effects. The treatments available today are no more effective than those introduced over half a century ago and there is a scarcity of conceptually novel treatments with superior efficacy and a more rapid and safe mechanism of action in the pipeline (Wong & Licinio, 2004).

According to the best available evidence from the large Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, in real-world treatment settings in patients presenting with a major depressive episode (MDE), frequently comorbid with other psychiatric and/or medical conditions and a past history of depression, acute remission rates are as low as 36.8% and 30.6% for the first and second treatment step respectively, and remarkably low for third or fourth successive treatment, 13.7% and 13.0% respectively (Rush et al., 2006b). Theoretically, even if all patients had stayed in the treatment protocol, a third would still fail to remit following four treatment steps. However, despite researchers' best efforts and free care provided, large numbers of

patients still dropped out of treatment at each step, as many as 42.3% after step 3, highlighting the poor tolerability of existing antidepressants and combinations thereof.

It is evident that the effectiveness of current treatments for depression is suboptimal. Given that residual depressive symptoms are one of the few reliable predictors of relapse and recurrence, current guidelines for researchers and clinicians recognise remission (i.e. the full resolution of depressive symptoms) rather than response (i.e. a 50% reduction from baseline depression severity that may still leave significant residual symptoms) as the valid therapeutic goal (Rush et al., 2006a). This is analogous to treatment goals in other areas of medicine such as in the treatment of hypertension, for instance, where the goal is not to be "less hypertensive" but to have normal blood pressure (Rush, 2007). Nonetheless, authorities recognise that remission is not achievable for all depressed patients (Rush et al., 2006a). In cases of refractory depression, treatment options are limited.

1.2.3. Long-term clinical course of depression

As previously discussed, depression is characterised by neuronal atrophy and loss and could be characterised as a mild neurodegenerative disorder (Banasr, Dwyer, & Duman, 2011). Some patients with MDD display a longitudinal course characteristic of a progressive neurodegenerative illness with poor treatment outcomes, greater functional impairment and an increasing number, frequency and duration of depressive episodes (Moylan, Maes, Wray, & Berk, 2012). Although traditionally characterised as an episodic illness with a remitting-relapsing course, it is recognised that a subset of patients display a chronic course that leads to significant inter-episodic symptomatology and psychosocial impairment (Kennedy & Foy, 2005). For patients who fail or only partially respond to pharmacological treatment, long-term outcomes are poor (Fekadu et al., 2009b). Even for patients who achieve symptomatic remission, recurrence is the rule not the exception (Holtzheimer & Mayberg, 2011). In a 15-year prospective follow-up study by the US National Institute of Mental Health (NIMH), 85% of the 350 patients who initially recovered

from the index MDE subsequently experienced a recurrence (Mueller et al., 1999). Similarly, in a British cohort, of the 60 patients who recovered during the 8-11 year follow-up, two-thirds subsequently experienced a recurrence (Kennedy, Abbott, & Paykel, 2003).

Residual symptoms following an acute episode of major depression (i.e. subsyndromal depression) are associated with functional disability, poor quality of life, higher risk of suicide and are predictive of greater risk of short-term relapse and long-term chronic course of illness (Fekadu et al., 2009b; Kennedy & Foy, 2005). Residual depressive symptoms are a powerful predictor of poor long-term outcome even after the first lifetime MDE. A 12-year prospective naturalistic study of 96 first-episode MDD patients showed that incomplete recovery from first lifetime MDE portends a severe, relapsing, chronic course of illness (Judd et al., 2000). Patients with residual symptoms in this study had faster relapse and more recurrences of major depression, minor depression and dysthymia compared to those who had a full recovery from their first MDE.

1.3. Treatment-resistant depression

1.3.1. Burden of treatment-resistant depression

Treatment-resistant depression (TRD) is a major public health problem causing significant personal suffering, considerable social and economic costs, as well as premature death. Of the disease burden attributed to depression, a large portion of it is likely due to TRD (Fekadu et al., 2009b). As many as two-thirds of depressed patients do not remit following treatment with the current first-line treatment option: SSRI monotherapy (Rush et al., 2006b). In the broadest sense, therefore, the majority of patients treated for depression display some degree of treatment resistance (Sackeim, 2001).

A recent systematic review of long-term outcomes in TRD identified only nine eligible studies and found that TRD is a highly recurrent disorder with a tendency towards chronicity, exhibiting modest short-term remission rates (as low as 20% within the first two

years of treatment) and poor long-term outcomes with up to 80% of treatment responders relapsing within the first year (Fekadu et al., 2009b). Subsyndromal treatment resistance (i.e. treatment response but failure to achieve complete clinical remission without residual depressive symptoms) was predictably found to portend worse long-term outcomes.

1.3.2. Defining treatment-resistant depression

Significant conceptual and methodological difficulties in the existing literature have hampered our understanding of the pathophysiology and treatment of TRD. The most important methodological factor is likely to be the heterogeneity of the studied patient populations (Fava, 2003). There is no convincing evidence to suggest that TRD is a distinct subtype of depression (Fagiolini & Kupfer, 2003). Given that most patients with TRD have a recurrent illness that responded to standard monoaminergic antidepressant treatments in the past, rather than being a distinct syndrome, it is more likely that TRD represents a malignant transformation of the same illness over time whereby the same biological treatments that were once effective are no longer capable of producing and especially sustaining remission in the same patient (Holtzheimer & Mayberg, 2011).

A recent systematic review of randomised controlled trials (RCTs) of biological treatments for TRD found that trials used six different definitions of TRD (ranging from non-response to just one antidepressant to non-response to multiple trials of antidepressants from distinct pharmacological classes), did not tend to use systematic methods of gathering information regarding previous treatment history, and also found that there were significant differences between doses and durations of antidepressant trials deemed minimally acceptable by various investigators (Berlim & Turecki, 2007b). There is currently no agreement in the literature on the minimum number of failed antidepressant trials required for a “diagnosis” of TRD. In this systematic review, the majority of RCTs used two failed antidepressant trials as the cut-off point for treatment resistance, which appears to be the emerging consensus in the field. However, expert opinion still differs on whether failed trials need to be from distinct pharmacological

classes or not. Of the reviewed RCTs, the majority did not specify how the adequacy of previous antidepressant trials was evaluated or what the minimum required doses were for treatment to be deemed adequate. On average, investigators required the duration of previous antidepressant trials to be approximately five weeks, with most trials requiring a minimum of four weeks, and a minority requiring more than eight weeks of treatment.

Additionally, there is currently no consensus on what constitutes minimum adequate doses of failed antidepressant trials for a patient to be deemed treatment resistant. Traditionally, under-dosing of antidepressants has been a major problem in clinical practice both in the community and in academic treatment centres, leading to the phenomenon of “pseudoresistance” which is a major barrier to achieving remission in the real world (Sackeim, 2001). It is also unclear why simply minimum or average doses of antidepressants should be considered sufficient for a patient to be declared treatment resistant. Some experts have argued that maximum nontoxic doses of antidepressants should be used before declaring TRD, advocating doses as high as 300 mg of imipramine, 90 mg of phenelzine or equivalent for as long as eight weeks and with verifiable compliance before a major depressive episode can be truly considered treatment resistant (Souery et al., 1999). However, the real-world feasibility of such therapeutic strategies is limited due to poor tolerability of such robust doses of antidepressants, especially in older adults.

Duration of treatment is a problematic topic in light of pressures on clinicians to change pharmacotherapeutic strategy early if it does not appear to be working, particularly during inpatient admissions. However, evidence shows that the standard four-week trials used in most RCTs as the minimum cut-off for adequate length of treatment may be insufficient and that trials of as long as 10 weeks may be required to elicit a clinical response in some cases, especially in older adults where 12 weeks or more of treatment may be required (Berlim & Turecki, 2007b).

1.3.3. Staging methods for treatment-resistant depression

Several formal staging methods for TRD have been proposed in the literature and systematically reviewed in recent years (Berlim & Turecki, 2007a; Ruhe, van Rooijen, Spijker, Peeters, & Schene, 2012). The advantages and disadvantages of the most commonly used ones will be briefly discussed here.

1.3.3.1. Thase and Rush staging model

The Thase and Rush staging model (TR-SM) (Thase & Rush, 1997) is a widely used five-level model for rating the level of treatment resistance in depression. Treatment resistance rating progresses in a hierarchical fashion from failure to respond to one antidepressant (Stage I), to failure to respond to two or more antidepressants from distinct pharmacological classes, progressing from more commonly used SSRIs to less frequently used tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) (Stages II to IV), and, ultimately, resistance to ECT (Stage V). The main advantage of TR-SM lies in its ease of application. However, a limitation of this model is that it does not specify criteria for adequacy of antidepressant trials in terms of dosing and duration. In addition, it implies a hierarchy of efficacy of antidepressant treatments, ranging from SSRIs to TCAs to MAOIs to ECT, a questionable assumption which does not have sufficient empirical support (Berlim & Turecki, 2007a). The TR-SM assumes that between-class switching is more effective than within-class switching, a debatable assumption, at least in the case of SSRIs. Findings from the STAR*D, for instance, showed no significant difference in effectiveness comparing within- and between-class switching for SSRI-resistant patients (Rush et al., 2006b). The TR-SM also does not take into account augmentation strategies or combination trials, or indeed illness characteristics such as duration or severity of episode.

1.3.3.2. Massachusetts General Hospital staging method

The Massachusetts General Hospital staging method (MGH-SM) (Fava, 2003) was proposed as a modification of the TR-SM, addressing the aforementioned criticisms of the earlier method. The MGH-SM formally defines adequate doses and duration of antidepressant trials. It also considers optimisation and augmentation strategies. In addition, no assumptions are made regarding differential effectiveness of various antidepressant classes, with each adequate trial of any antidepressant class receiving a score of 1. However, ECT (regardless of dose or electrode placement) is somewhat arbitrarily assigned a score of 3.

With the exception of two other models discussed below, commonly used staging TRD methods such as TR-SM and MGH-SM have been devised on the basis of expert opinion alone and in the absence of validation studies to demonstrate their usefulness in predicting short- or longer-term outcomes in depression. Empirical support for these staging methods is currently scarce (Ruhe et al., 2012). This is in contrast to other medical specialties such as oncology, for instance, where there is empirical evidence available that models used for staging the illness are useful in selecting next-step treatments and predicting long-term outcome of the illness. One retrospective chart review has contrasted the predictive validity of TR-SM and MGH-SM in a sample of 115 patients and found that although the two staging methods yielded scores that were significantly correlated (r=0.84), only the MGH-SM scores were predictive of non-remission (Petersen et al., 2005). Interestingly, when the MGH-SM method was modified so that an additional 0.5 points was added to failure of a separate medication class (in order to more closely resemble the hierarchical nature of TR-SM), its predictive validity was eliminated.

1.3.3.3. Antidepressant Treatment History Form

The most widely used instrument in the ECT literature to determine the adequacy of prior antidepressant trials is the Antidepressant Treatment History Form (ATHF) (Sackeim, 2001). Devised in the 1980s (Sackeim et al., 1990), the strength of each

antidepressant trial is rated on a 0-5 scale on the basis of dose and duration of treatment. A score of 3 or above is the cut-off for an adequate trial. In ECT trials where the ATHF has been used, the failure to respond to one adequate trial of any antidepressant has been deemed sufficient for a categorical designation of TRD.

The ATHF has been found to predict acute (Dombrovski et al., 2005; Prudic, Sackeim, & Devanand, 1990) and long-term (Sackeim et al., 1990; Sackeim et al., 2000) outcomes following ECT. Patients who had failed at least one adequate medication trial prior to ECT tended to have a lower likelihood of remission and/or staying in remission during the follow-up. However, a different group of investigators from the Consortium for Research in Electroconvulsive Therapy (CORE) group found that baseline medication resistance as measured by the ATHF did not predict either remission or relapse in their large sample of ECT patients (Rasmussen et al., 2007; Rasmussen et al., 2009). The most recent relapse prevention study from the Columbia University group, the authors of the ATHF, also did not show any predictive value for the ATHF while a simple antidepressant count predicted the likelihood of relapse (Prudic et al., 2013). Some investigators have challenged the general notion that medication resistance is an important factor in influencing ECT outcome (Kellner, 2013).

1.3.3.4. Maudsley Staging Method

A recent methodological advance in the literature on quantifying TRD is the Maudsley Staging Method (MSM) (Fekadu et al., 2009a; Fekadu, Wooderson, Markopoulou, & Cleare, 2009c). This instrument has several advantages over existing ones, such as the incorporation of clinical characteristics of illness (episode duration and severity). It recognises that treatment resistance is a dimensional rather than a categorical phenomenon. Thus, the severity of treatment resistance is measured on a 15-point scale.

The authors conducted empirical validation studies where the MSM was found to have short- and long-term predictive validity both in terms of depressive symptomatology and functional impairment (Fekadu et al., 2012; Fekadu et al., 2009a; Fekadu et al.,

2009c). In comparison to the TR-SM, the MSM was more strongly predictive of future non-remission (Fekadu et al., 2009a). Neither antidepressant count alone nor the TR-SM predicted long-term outcome in a sample of 62 patients who were followed up for a mean of 30 months (Fekadu et al., 2009c).

1.3.4. Implications of medication resistance for patients treated with electroconvulsive therapy

As medication resistance is nowadays the leading indication for ECT in patients with depression, quantifying the extent to which it has an effect on ECT outcomes has important theoretical and clinical implications. First, if ECT is an effective treatment for medication resistant patients this may indicate a distinct mechanism of action compared to conventional monoaminergic antidepressants. Second, if medication resistance can be shown to reliably predict future resistance to ECT then an argument could be made for offering ECT as a treatment option earlier in the course a depressive episode than current treatment guidelines would suggest, at least for patients who have responded to it favourably in the past. Third, in the ECT field, currently only one instrument (ATHF) has been used to quantify TRD. This instrument assumes that the failure to respond to any one trial of even newer atypical compounds such as bupropion or reboxetine at the minimum adequate dose is equivalent (in terms of TRD designation) to failure of multiple courses of antidepressants from distinct pharmacological classes including TCAs and MAOIs and/or augmentation strategies such as lithium or triiodothyronine (T_3). In more practical terms, the ATHF requires a considerable amount of time to complete and is not suitable for routine clinical use. It remains to be seen how a simpler, most clinically useful measure of TRD such as medication count predicts ECT outcomes and to what extent the more formal research staging methods such as the ATHF and MSM correlate with clinicians' own judgement of medication resistance as a reason for referring a patient for ECT.

The issues surrounding the assessment of TRD and its impact on short- and long-term therapeutic effect of ECT are discussed in more detail in sections 1.4.2 and 1.5.2.5 of this chapter.

1.4. Electroconvulsive therapy (ECT)

1.4.1. Efficacy of ECT

Having once been used in diverse patient populations and following decades of debates over the nature and extent of its side effects, in Western industrialised nations ECT is nowadays generally reserved for patients with moderate depression refractory to pharmacological and psychological treatments and a minority of patients with severe depression that is life-threatening, requiring rapid clinical response for reasons such as acute suicidality, catatonia, severe agitation, inadequate intake of food or fluids and resulting physical deterioration etc. (The Royal College of Psychiatrists, 2013). Modern ECT is conducted under general anaesthesia, muscle relaxation and ventilation with oxygen and is a medically safe procedure (Lisanby, 2007; Tess & Smetana, 2009). A generalised tonic-clonic seizure is elicited by passing a small amount of electrical current through a patient's brain via the application of two hand-held electrodes to the scalp. The most commonly used electrode placements are bitemporal, right unilateral d'Elia, and bifrontal.

Decades of clinical research attest to the high acute efficacy of ECT. Recent systematic reviews and meta-analyses of the literature conducted by governmental organisations in the United Kingdom (Greenhalgh, Knight, Hind, Beverley, & Walters, 2005; National Institute for Clinical Excellence, 2010; The UK ECT Review Group, 2003) and the United States (US Food and Drug Administration Authority, 2011) show that ECT is an effective short-term antidepressant, more effective than pharmacotherapy and so-called sham ECT, a placebo procedure in which patients undergo all aspects of ECT treatment – anaesthesia, muscle relaxation, intensive clinical care and attention – except

inducement of a seizure which is believed to be the necessary, though not sufficient, condition for therapeutic efficacy.

Despite its unquestionable acute efficacy, these professional and governmental bodies concluded that randomised evidence for long-term benefits of ECT is lacking, with evidence particularly scarce beyond the first six months (Greenhalgh et al., 2005). In the United States, the Food and Drug Administration (FDA), in the process of reviewing the evidence pertinent to the risk reclassification of ECT devices, highlighted the lack of data on long-term efficacy and safety of this treatment as recently as January 2011 (US Food and Drug Administration Authority, 2011).

1.4.2. Impact of medication resistance on acute efficacy of ECT

A recent meta-analysis examined the efficacy of ECT in patients with established medication resistance on the ATHF and showed that such patients were significantly less likely to respond to an acute course of ECT compared to patients in whom medication resistance had not been established with an odds ratio of 0.52 (95% CI 0.39-0.69) (Heijnen, Birkenhager, Wierdsma, & van den Broek, 2010). Remission rates at the end of an acute course of ECT were 65% and 48% for medication non-resistant and medication resistant patients, respectively. Nonetheless, a remission rate of almost 50% in the medication resistant group is an encouraging finding given the generally low effectiveness of third or fourth step pharmacological treatments for depression unresponsive to initial medication steps (Rush et al., 2006b).

1.4.3. Mechanisms of action of ECT

The effects of ECT on the brain are manifold and the precise mechanism of its antidepressant action remains unclear. Early histopathological work from the late 1920s led Meduna, a pioneer of convulsive therapy, to hypothesise that there is an antagonistic relationship between epilepsy and psychosis based on autopsy findings of excessive

proliferation of glial cells in brains of deceased patients with epilepsy while the opposite appeared to be the case for brains of people with schizophrenia (Shorter & Healy, 2007). These observations led to the use of (first chemically, subsequently electrically induced) seizures in the treatment of major psychiatric disorders. ECT has not only a marked antidepressant and antipsychotic effect but is also efficacious for terminating acute episodes of mania and treatment-resistant seizure disorders such as status epilepticus (Post, Putnam, Uhde, & Weiss, 1986). Its efficacy against multiple conditions suggests that it possesses an anticonvulsant effect via biological mechanisms involved in the self-termination of induced seizures, such as an increase in seizure threshold, enhancement in gamma-aminobutyric acid (GABA) neurotransmission (enhancing the inhibitory tone of the brain), reduction in regional cerebral blood flow (CBF) and a marked increase in slow wave (delta and theta bands) activity on electroencephalogram (EEG) all taking place during a course of ECT (Sackeim, 1999; Sackeim, 2004).

In accordance with our current understanding of depression as relating to neuroplasticity and neurotransmitter systems, there is now accumulating evidence from human studies that a course of ECT raises BDNF (Haghighi et al., 2013; Marano et al., 2007), increases hippocampal volume on MRI (Joshi et al., 2015; Nordanskog et al., 2010; Tendolkar et al., 2013) and leads to both increases and decreases in grey matter volume in specific brain regions linked to mood disorders, with the magnitude of these changes associated with clinical outcome (Dukart et al., 2014). In addition to increases in neurotrophic factors, cell growth and synaptic connectivity, ECT also leads to alterations in hormonal and neurotransmitter status of patients, with significant changes to serotonergic, adrenergic, dopaminergic, GABAergic, glutamatergic and cholinergic neurotransmission, as well as increases in hypothalamic-pituitary hormones such as prolactin, endorphin and oxytocin (Wahlund & von Rosen, 2003).

1.4.4. Side effects of ECT

While modern ECT is a medically safe procedure with low morbidity and mortality (Tess & Smetana, 2009), it is known to produce some minor physical side effects such as nausea, headache and muscle ache which are transient and typically resolve within hours following a treatment session. The use of ECT, however, is limited by cognitive side effects of unclear severity and duration. Memory side effects are of major concern to many patients (Rose et al., 2003) as well as their treating clinicians. Further complicating the risk-benefit ratio of ECT and contributing to polarising views on its use is the lack of any clear relationship between patients' self-reports of cognitive impairment and objectively-measured neuropsychological functioning (National Institute for Clinical Excellence, 2010).

1.4.5. Efforts to reduce cognitive side effects of ECT

Over the past half-century, numerous modifications to ECT treatment have been attempted in order to reduce the cognitive side effects while preserving the robust clinical efficacy of standard bitemporal ECT. Most experimental work has focused primarily on optimising treatment parameters such as electrode placement, stimulus dose relative to seizure threshold, and pulse width to produce the best possible balance between clinical and neuropsychological outcomes. Right unilateral ECT is a form of ECT administration where both electrodes are placed over the non-dominant hemisphere. See Figure 1.1 below for the three most commonly used electrode placements: bitemporal, right unilateral (d'Elia) and bifrontal.

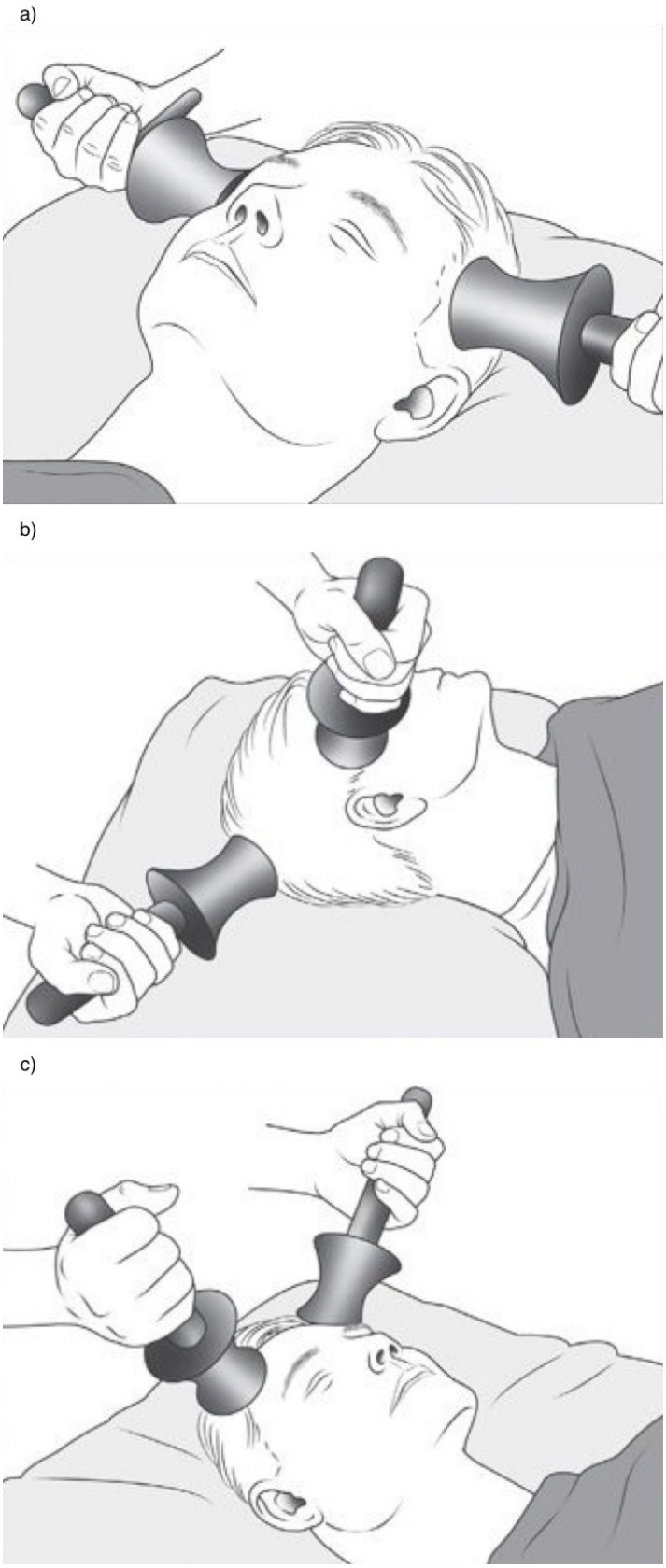

FIGURE 1.1. Three commonly used ECT electrode placements: a) bitemporal; b) right unilateral (d'Elia); c) bifrontal[1]

[1] Reproduced from Dunne, R. & McLoughlin, D.M. (2013). ECT prescribing and practice. *The ECT Handbook (3rd edition)*. Eds. J. Waite and A. Easton. London: Royal College of Psychiatrists.

The UK ECT Review Group's meta-analysis in 2003 concluded that right unilateral (RUL) ECT was less effective than bilateral ECT, with an effect size of 0.3 (The UK ECT Review Group, 2003). An update of this meta-analysis was carried out by the organisation now called National Institute for Health and Care Excellence (NICE) UK who downgraded this effect size to 0.2 in light of new data (National Institute for Clinical Excellence, 2010). However, many of the studies conducted prior to 2000 are biased against RUL ECT due to inadequate dosing. There is a strong dose-response relationship in RUL ECT (McCall, Reboussin, Weiner, & Sackeim, 2000) and this relationship is much more pronounced in RUL than in bitemporal ECT. Modern ECT stimulus dosing is titrated relative to each individual patient's seizure threshold (ST) which represents the minimum amount of electrical stimulation required to produce a generalised seizure. Low-dose RUL ECT (as a multiple of ST) is clinically ineffective, whereas the same dose relative to ST is highly effective (Sackeim, Decina, Kanzler, Kerr, & Malitz, 1987; Sackeim et al., 1993). Several RCTs conducted in recent years have demonstrated that high-dose RUL ECT administered at six times the patient's ST is clinically as effective as bitemporal ECT but may have fewer cognitive side effects (Kellner et al., 2010; McCall, Dunn, Rosenquist, & Hughes, 2002; Ranjkesh, Barekatain, & Akuchakian, 2005; Sackeim et al., 2009; Sackeim et al., 2000; Sackeim et al., 2008). Some of these studies, however, are limited by modest sample sizes and might thus have been statistically underpowered to detect a true difference between the treatments. In addition, these studies were designed as efficacy trials of ECT being administered under controlled research conditions (e.g. medication washout prior to first treatment, specified minimum number of treatments, treatment continuing until remission etc.) which may not reflect real-world effectiveness of ECT when used in less-than-ideal conditions of everyday clinical practice.

The largest RCT of ECT in depression to date, from the Consortium for Research in Electroconvulsive Therapy (CORE) group, randomised 230 patients to receive either bitemporal (1.5 x ST), right unilateral (6 x ST) or bifrontal (1.5 x ST) ECT and found no difference in efficacy between the three electrode placements, replicating earlier findings

of therapeutic equivalence of bitemporal and high-dose RUL ECT (Kellner et al., 2010). Unfortunately, approximately 25% of patients dropped out of each of the treatment groups by the end of acute treatment time point, limiting generalisability of findings. This study, however, did not replicate previous findings of superiority of RUL on any of the measured neuropsychological variables. Nonetheless, the high proportion of missing cognitive data (between 35-55% at the end-of-treatment time point) and the resulting need for large amount of data imputation limit the interpretation of this study's neuropsychological findings. On the other hand, the aforementioned trials that found the cognitive side-effect profile of high-dose RUL ECT to be more favourable than that of bitemporal ECT tended to have smaller samples, highlighting the need for replication in larger samples with high retention rates.

1.4.6. The nature of cognitive side effects of ECT

1.4.6.1. Subjective cognitive side effects following ECT

Cognitive side effects are nowadays the major limiting factor in the use of this treatment. A systematic review of the literature on patients' subjective experiences of ECT found that at least a third of patients report persisting memory deficits, particularly in the domain of retrograde amnesia for autobiographical events (Rose et al., 2003). However, a major limitation of much of this literature is the lack of objective neuropsychological assessment data against which to compare patients' self-reports.

Most studies from 1980 onwards consistently fail to find a correlation between subjective cognition and neuropsychological performance following ECT (Prudic, Peyser, & Sackeim, 2000; Sackeim, 2000). Subjective memory complaints tend to be heavily influenced by current depressed mood (Coleman et al., 1996). Oddly, patients often rate their memory as improved immediately after a course of ECT despite objective evidence of cognitive impairment (Coleman et al., 1996). There is emerging evidence that patients' memory self-evaluation is contingent upon the method of assessment; self-report checklist scales typically show no relationship with objective cognition while more direct methods of

questioning on the global impact of the treatment are more in line with objective performance as well as ECT treatment parameters (Berman, Prudic, Brakemeier, Olfson, & Sackeim, 2008; Brakemeier, Berman, Prudic, Zwillenberg, & Sackeim, 2011).

1.4.6.2. Objective cognitive side effects following ECT

Objectively measured adverse cognitive effects immediately after an ECT session are well-characterised and include disorientation and, less commonly, delirium (Lisanby, 2007). The length of postictal disorientation may be a predictor of short- and medium-term retrograde amnesia (Sobin et al., 1995). A recent systematic review and meta-analysis of nearly 3,000 patients from 84 studies found impairments across various domains of neuropsychological functioning which tended to resolve within two weeks following treatment (Semkovska & McLoughlin, 2010). More specifically, in the sub-acute period (0-3 days post-ECT), deficits were found on tests of verbal and visual anterograde memory and executive function. However, at short-term follow-up (4-14 days post-ECT) all but one cognitive variable showed return to baseline levels of functioning or indeed an improvement relative to baseline. At what was characterised as long-term follow-up (defined as beyond 15 days in this meta-analysis), no persisting cognitive deficits were found on any of the studied variables; in fact, most cognitive domains showed a small-to-medium improvement beyond baseline levels. However, a limitation of this meta-analysis is the inclusion of all assessment time points longer than 14 days after ECT (ranging between two weeks and two years after ECT) into the one category, a consequence of the scarcity of true long-term data in the primary literature. Most crucially, this systematic review failed to identify any studies using validated neuropsychological measures of retrograde amnesia, a surprising finding given the prominence of patients' concerns regarding this particular aspect of cognitive dysfunction following ECT.

1.4.6.3. Persistence of cognitive impairment following ECT

The duration and persistence of cognitive deficits remains a contentious issue. Further complicating matters is the well-established fact that depression itself is associated with a range of neuropsychological deficits (Zakzanis et al., 1998), some of which persist as trait markers during the remitted phase of the illness (Bora et al., 2012). It is unclear to what extent the detectable post-ECT cognitive impairment is due to the treatment itself or a feature of severe, chronic, treatment-resistant major depression. Existing ECT research has not made much use of control groups consisting of patients with MDD not treated with ECT or indeed healthy adults.

A large-scale naturalistic prospective study of ECT in community settings as practised in seven treatment centres in the New York state area found persisting retrograde amnesia at the six-month follow-up, more pronounced in bilateral ECT and sine-wave stimulation (Sackeim et al., 2007). In addition to poor cognitive outcomes, the study found worse clinical outcomes (remission rates in the range of 30-40%) in these treatment centres compared to those generally observed in RCTs (Prudic, Olfson, Marcus, Fuller, & Sackeim, 2004). The generalisability of these findings has been debated (Abrams, 2007a; Abrams, 2007b; Kellner, 2007). The study used the Columbia University Autobiographical Memory Interview—Short Form (AMI-SF) (McElhiney, Moody, & Sackeim, 2001), discussed in greater detail below, as a measure of retrograde amnesia.

1.4.7. Autobiographical memory impairment following ECT

1.4.7.1. Measuring consistency of autobiographical memory recall following ECT

Retrograde amnesia for autobiographical events is the major side effect of concern according to patient surveys (Rose et al., 2003). All the major RCTs of bitemporal vs. high-dose RUL ECT carried out over the past two decades (Kellner et al., 2010; Sackeim et al., 2009; Sackeim et al., 2000; Sackeim et al., 2008) assessed retrograde amnesia with the long or short form of the Columbia University Autobiographical Memory Interview

(McElhiney et al., 2001; McElhiney et al., 1995), used exclusively in the ECT literature. These studies reported significant decreases in consistency of autobiographical memory recall immediately after ECT and at longer-term follow-ups compared to pre-ECT baseline. The aforementioned largest-ever prospectively followed-up cohort of ECT-treated patients conducted in seven community hospitals found evidence of persisting retrograde amnesia for autobiographical events at six-month follow-up after ECT (Sackeim et al., 2007).

A conceptual difficulty in interpreting these studies is that autobiographical memory in the ECT literature has usually been measured as consistency of recall of information at follow-ups compared to answers provided at pre-ECT baseline (information which may have been missing or faulty to begin with). As such, these studies did not measure autobiographical memory performance per se but rather percentage agreement between answers provided at baseline and follow-ups. The AMI-SF does not examine relevant concepts found in the literature on autobiographical memory in major depression, in particular overgenerality of autobiographical memory (Liu, Li, Xiao, Yang, & Jiang, 2013; Sumner, 2012; Van Vreeswijk & De Wilde, 2004; Williams et al., 2007) and dissociation between episodic and semantic autobiographical memory recall (Soderlund et al., 2014). A recent study of depressed patients not treated with ECT and healthy controls has proposed a novel scoring system for the AMI-SF that would address some of the limitations of the existing scoring system, principally by allowing for separate assessment of semantic and episodic components of autobiographical memory (Semkovska, Noone, Carton, & McLoughlin, 2012).

An additional problem with testing and retesting of the same episodic memories at pre-ECT baseline and post-ECT follow-ups is highlighted by a very recent study from the Netherlands that examined the effect of ECT on reconsolidation of memories in humans (Kroes et al., 2014). Reconsolidation refers to a process whereby already consolidated memories can enter a temporarily labile state after their reactivation, leaving them susceptible to disruption (Nader & Hardt, 2009). Pre-ECT reactivation of episodic

memories during baseline neuropsychological testing may thus leave them temporarily more open to disruption than they otherwise would be had no testing taken place.

In the aforementioned study (Kroes et al., 2014), 42 patients with unipolar depression referred for ECT were randomised into three groups: A, B and C. All patients underwent an experimental learning task of two emotionally aversive stories, each presented using a slide-show accompanied by an auditory narrative. One week later, the memory for one of the two stories was reactivated. Patients in groups A and B then immediately received ECT after memory reactivation, while patients in group C did not receive ECT. In group A, memory was retested one day after memory reactivation and ECT. In group B, retesting was done immediately after recovery from ECT. Patients in group C (who did not receive ECT) were retested a week after memory reactivation. ECT patients received either high-dose bitemporal ECT at 2.5 x ST or high-dose RUL ECT at 6 x ST. The experiment showed three key findings:

1. A single session of ECT was able to disrupt the reactivated memory. This happened only in group A where patients were retested a day after ECT. In group B where patients were retested immediately after ECT, no effect of memory reactivation was seen and recall accuracy was the same for reactivated and non-reactivated memory.
2. Non-reactivated memories were unaffected by ECT in both groups that received ECT. Recall of non-reactivated memory did not differ between the two groups that received ECT and the control group that did not.
3. The control group that did not receive ECT benefitted from memory reactivation. Recall at follow-up was significantly improved for reactivated memory compared to non-reactivated memory.

These findings, if replicated, would have very significant implications for how we conceptualise the problem of retrograde amnesia following ECT and how we approach its assessment in the future to avoid unwittingly exposing the patients to iatrogenic harm by

reactivating their autobiographical memories just prior to treatment and thus making those memories more vulnerable to forgetting. This study also suggests that comparisons between ECT and non-ECT control groups are fraught with difficulty. A control group of patients not treated with ECT who are tested and retested at the same time intervals as ECT patients would likely benefit from repeated testing and show improved performance due to repeated accessing of the same memories, whereas in the ECT group, the pre-ECT baseline reactivation of memories would leave those memories more susceptible to forgetting during treatment due to disrupted reconsolidation and therefore lead to artificially worse performance at follow-up testing.

1.4.7.2. Measuring autobiographical memory performance following ECT using standardised neuropsychological tests

In the wider literature on neurological and neuropsychiatric disorders several standardised measures of autobiographical memory are commonly used. Among these are the Autobiographical Interview (AI) (Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002), the Autobiographical Memory Interview (Kopelman AMI) (Kopelman, Wilson, & Baddeley, 1989; Kopelman, Wilson, & Baddeley, 1990) and the Autobiographical Memory Test (AMT) (Williams & Broadbent, 1986). An advantage of standardised scales such as the Kopelman AMI is availability of published norms facilitating clinical interpretation of the severity of a patient's autobiographical memory impairment compared to the range of normal performance.

A handful of studies have been conducted where the Kopelman AMI scale was administered to ECT patients, all in the past several years. In one recent RCT, autobiographical memory was found to be improved relative to baseline at six-week follow-up after ECT (Sienaert, Vansteelandt, Demyttenaere, & Peuskens, 2010). However, in this study patients were receiving ultrabrief pulse bifrontal or RUL ECT, forms of ECT administration not in routine clinical use in Ireland and many other countries. Ultrabrief pulse stimulus waveform had previously been shown to produce significantly less

cognitive side effects than standard brief pulse ECT (Sackeim et al., 2008). While certainly intriguing, the findings of improved autobiographical memory following ECT in this study are of limited clinical utility at the present time due to the fact that the majority of patients worldwide still routinely receive brief pulse bitemporal ECT (Leiknes, Jarosh-von Schweder, & Hoie, 2012).

In another recent RCT, brief pulse was compared to ultrabrief pulse high-dose RUL ECT (Spaans et al., 2013). A non-significant improvement in Kopelman AMI score of 0.8 points in both treatment groups was observed immediately after the ECT course relative to pre-ECT baseline. In a third recent RCT, also comparing brief pulse and ultrabrief pulse RUL ECT (Mayur, Byth, & Harris, 2013), a statistically significant decline in semantic autobiographical memory was found in the brief pulse group, with no deterioration in the ultrabrief pulse group. Small number of participants (N=20 per group), significant attrition and large number of uncorrected comparisons render the results difficult to interpret. All in all, the total score on the 90-point Kopelman AMI declined from pre- to post-ECT by 8.3 points in the brief pulse group and increased by 1.3 points in the ultrabrief pulse group (Dr. P. Mayur, personal communication).

Finally, two other non-randomised studies investigated performance on the Kopelman AMI in ECT patients. The first, a retrospective chart review, assessed autobiographical memory on average 1.8 years after a course of ECT and found no difference in performance on the Kopelman AMI in patients treated with a combination of ECT and pharmacotherapy compared to a control group of patients treated with pharmacotherapy only (Kho, VanVreeswijk, & Murre, 2006). However, a major limitation of this study is the lack of pre-ECT baseline data. Similarly, in another recent report, this one prospective, no baseline data were collected in a sample of older adults treated with either bitemporal or RUL ECT (O'Connor, Gardner, Eppingstall, & Tofler, 2010). In this study, patients treated with bitemporal ECT showed significant decrease in autobiographical memory retrieval after five or six ECT sessions compared to their performance after one or two ECT sessions. No significant decrease was observed in the RUL group.

In summary, the studies carried out to date using a standardised neuropsychological test of autobiographical memory, the Kopelman AMI, have found no evidence of the large decrements in autobiographical memory performance typically observed in studies where the AMI-SF was used. Given patient and clinician concerns about autobiographical memory side effects of ECT, these discrepant findings are of major scientific and clinical interest and further research is warranted.

1.5. Long-term clinical outcomes after ECT

> Electroconvulsive therapy practitioners of a certain age recall a time when the norm was for patients to remit with ECT and remain well for years thereafter, even on no continuation treatment at all. What has changed? Is the illness different? Is contemporary ECT different? Is the ubiquitous use of antidepressants a factor? Some believe that depression itself is becoming a more prevalent and pernicious illness, one that is harder to treat. One of the classical hallmarks of the natural history of mood disorders, their clearly episodic (as opposed to chronic or continuous) nature, may be changing. Some ECT practitioners believe that modern ECT is a watered down version of a previously more robust treatment, one that was more likely to correct the underlying abnormalities of the depressed brain (particularly the dysregulation of the hypothalamic-pituitary-adrenal axis) (Kellner, 2013, p. 1).

1.5.1. The problem of relapse following ECT

As noted previously, ECT is a highly effective acute treatment for major depression, more effective than sham ECT and antidepressant medication (The UK ECT Review Group, 2003). Although remission rates in clinical trials of ECT tend to be higher compared to medication trials, high rates of relapse, especially early relapse, are typically found and are acknowledged to be a significant clinical problem (Kellner et al., 2006; Prudic et al., 2013; Sackeim et al., 2001).

A course of ECT per se has little to no lasting effectiveness against depression. In the absence of active continuation therapy, up to two-thirds of modern-day ECT remitters are expected to relapse within three months (Lauritzen, Odgaard, Clemmesen, & Lunde, 1996; Sackeim et al., 2001; Yildiz et al., 2010) and 75-85% within six months (Lauritzen et al., 1996; Sackeim et al., 2001; van den Broek, Birkenhager, Mulder, Bruijn, & Moleman,

2006). With the use of vigorous continuation therapy such as nortriptyline-lithium or venlafaxine-lithium combination therapy for unipolar depressed patients or continuation ECT (C-ECT; i.e. the continued administration of ECT following the acute course at a reduced frequency with the aim of preventing the return of depressive symptoms), 40-50% of ECT remitters in modern studies will still relapse within six months (Kellner et al., 2006; Prudic et al., 2013; Sackeim et al., 2001). In contrast, a meta-analysis of antidepressant medication trials found a six-month relapse rate of 15% on continuation pharmacotherapy and 34% on placebo, while 12-month relapse rate was 16% and 40% respectively (Geddes et al., 2003).

The Geddes et al. (2003) meta-analysis of antidepressant trials thus found much better long-term outcomes than seen in ECT studies or indeed in the STAR*D trial (Rush et al., 2006b). It should be borne in mind, however, that post-ECT relapse rate would be expected to be substantially higher than in medication trials since ECT patients tend to be the most severely and chronically ill and/or treatment resistant, whereas antidepressant medication trials carried out nowadays often exclude the most severely ill and suicidal patients, precisely the demographic that tends to be treated with ECT. A comparison with the STAR*D trial thus appears more apt. STAR*D was designed with the purpose of including “real world” patients with complex, comorbid, recurrent major depression rather than the “cleaner” populations studied in most RCTs designed for FDA registration purposes (Ghaemi, 2008). Thus, while in RCTs of antidepressants only a fifth of patients relapsed according to the Geddes et al. (2003) meta-analysis, in STAR*D 33.5% of those who remitted following the first treatment step (citalopram monotherapy) relapsed within the first year. For treatment-resistant patients in STAR*D, i.e. those who failed to respond to one or more treatment steps but subsequently remitted following two or more steps, relapse rates were between 42.9% and 50% at 12 months. These figures for treatment-resistant STAR*D patients are essentially the same as relapse rates in studies of ECT remitters maintained on long-term pharmacotherapy where relapse rates tend to range between 40-50%. Nonetheless, early relapse after ECT is high and its prevention is a key clinical challenge surrounding the use of this otherwise highly effective treatment.

1.5.2. Relapse prevention strategies following ECT

1.5.2.1. Continuation ECT

The problem of relapse prevention, while not as widespread at the time as in modern-day patients, has nonetheless been recognised since the earliest days of ECT use which predated the discovery of modern psychopharmacology. Continuation ECT (C-ECT) was the only method of relapse prevention available at the time. Proposed in the 1940s (Geoghegan & Stevenson, 1949), in a five-year follow-up study of C-ECT published in 1951 patients who had been successfully treated with a course of ECT were invited to take part in a five-year study of monthly single ECT administrations (Stevenson & Geoghegan, 1951). In the treatment group which consisted of 13 patients, no patient had relapsed during the first three years of follow-up, two patients relapsed in the fourth year and one in the fifth year. On the other hand, all 11 patients who refused C-ECT relapsed.

C-ECT has continued to be used to the present day. It is generally indicated in cases where continuation pharmacotherapy has already proven ineffective or intolerable due to side effects (American Psychiatric Association, 2001). Despite over 70 years of clinical experience to support its use, C-ECT is an underused and under-researched treatment modality (Petrides, Tobias, Kellner, & Rudorfer, 2011). For the majority of its history, the evidence base for it was remarkably poor, with only case series and expert opinion available to support it. Particularly lacking are randomised high-quality studies on the efficacy and safety of this treatment (van Schaik et al., 2012).

The first RCT of C-ECT, used with a fixed-dosing schedule, was published in 2006 and found it to be equally as effective in relapse prevention as continuation pharmacotherapy with nortriptyline-lithium combination therapy during the six-month follow-up (Kellner et al., 2006). Perhaps surprisingly, almost 40% of patients relapsed on C-ECT by six months. However, a limitation of this study was its use of C-ECT at a fixed dosing schedule which does not reflect routine clinical practice where patients tend to be treated with a flexible schedule to deal with exacerbations of depressive symptoms and signs of early relapse. In addition, this study used C-ECT without concomitant

continuation pharmacotherapy. The latter tends to be used in conjunction with C-ECT in routine clinical practice and might reasonably be expected to augment its efficacy. These are some of the possible explanations for such high relapse rate observed in this trial.

Two small subsequent RCTs, one from 2008 (Navarro et al., 2008) and another from 2013 (Nordenskjold et al., 2013), with a 24-month and 12-month follow-up respectively, studied a combination of C-ECT and antidepressant medication and compared it to antidepressant continuation therapy alone. In these two trials, C-ECT and medication combination treatment was significantly more effective at preventing relapse than antidepressants alone. Nonetheless, even with C-ECT + individualised pharmacotherapy combination treatment, 32% of patients still relapsed within the first year in the Swedish trial (Nordenskjold et al., 2013). These relapse rates on C-ECT or C-ECT + antidepressant combination therapy in the three trials from the past decade are markedly worse compared to those reported in early research cited previously.

It has been noted that, according to clinical impressions at least, in decades past it was the norm for many patients to be treated with a course of ECT and stay symptom-free for years afterwards on no continuation treatment (Kellner, 2013). Long-term outcomes appear to have significantly worsened over time (Sackeim, 1994). In fact, as will be shown in the following brief historic overview, patients treated nowadays with the most vigorous antidepressant therapy available relapse at the same rates as untreated or placebo-treated patients in the 1960s.

1.5.2.2. Continuation antidepressant medication monotherapy

Following the discovery of the first effective antidepressant classes, monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs), three key early trials carried out in the United Kingdom in the 1960s demonstrated the efficacy of these agents over placebo in relapse prevention after ECT, with relapse rates at six months in TCA- or MAOI-treated patients in the region of 20% compared with 40-70% in untreated or benzodiazepine-only treated patients (Imlah, Ryan, & Harrington, 1965; Kay, Fahy, & Garside, 1970; Seager & Bird, 1962). These three early trials not only demonstrated the efficacy of post-ECT prophylactic treatment with antidepressants, but also provided some of the strongest evidence at the time for the long-term benefit of these then-novel agents in the treatment of depressive illness (Sackeim, 1994).

In the first of the three key early studies, Seager and Bird (1962) compared the efficacy of imipramine to placebo in a randomised double-blind trial with a six-month follow-up. Patients were randomised prior to the ECT course to concomitantly receive either imipramine or placebo. Following the end of ECT treatment, some patients continued receiving either imipramine (150 mg/d for the first month, 75 mg/d subsequently) or placebo (equivalent number of inert tablets) they were already on, while others were crossed over from imipramine to placebo and vice versa in a random fashion. Overall, the results showed that of the 28 successfully followed-up patients, 17% relapsed on imipramine (2/12) whereas 69% (11/16) did so on placebo. Of the four possible treatment combinations, the group that had initially received imipramine during the ECT course and was switched to placebo after ECT fared the worst in terms of relapse (88% or 7/8 of such patients relapsed). The group that had been on placebo during ECT treatment and continued with placebo during follow-up relapsed at the rate of 50% (4/8 patients). The two groups that were treated with imipramine during follow-up fared equally well with relapse rate standing at 17%, regardless of whether they had been treated with imipramine or placebo during the course of ECT. This early study of maintenance pharmacotherapy for depression therefore suggested that abrupt discontinuation of an

antidepressant greatly increases vulnerability to early relapse compared to continuous antidepressant or continuous placebo treatment.

Imlah et al. (1965) compared phenelzine, imipramine and placebo in a randomised, though apparently non-blind, trial. Once again, patients were randomised to the three groups prior to ECT treatment as the study aimed to investigate a possible synergistic effect of combining ECT with pharmacotherapy. Patients were discharged on the same medication they were on in hospital, either imipramine 75 mg/d or phenelzine 45 mg/d. Patients who had been on placebo were discharged without medication. Of the 150 randomised patients, 111 completed the six-month follow-up. At six months, both active treatments more than halved the relative risk of relapse compared to those on no maintenance treatment (21% relapse for imipramine, 22% for phenelzine, 51% for no treatment). These findings extended the existing evidence base to now include an MAOI and replicated Seager and Bird's (1962) findings for imipramine from three years previously.

In the final of the three key early trials which informed clinical practice in subsequent decades, Kay et al. (1970) randomised 132 patients under double-blind conditions to either amitriptyline or diazepam to be taken both during ECT treatment and the subsequent six-month follow-up. Diazepam was used instead of placebo as the study psychiatrists deemed the use of placebo in patients with depression of such severity as to necessitate the use of ECT treatment unethical. The doses of the two drugs were variable and up to the discretion of the treating psychiatrist. Drugs were dispensed in identical-looking tablets containing either 25 mg of amitriptyline or 2 mg of diazepam. Doses allowed were between two to six tablets daily, translating into 50-150 mg/d of amitriptyline or 4-12 mg/d of diazepam. Three patients committed suicide during the six-month follow-up, all in the diazepam group. Of the 115 patients who completed the trial, 15% relapsed on amitriptyline (8/52) while 38% did on diazepam (24/63, including the three suicides). Overall, the group not treated with an antidepressant fared somewhat better than the placebo-treated group in the Seager and Bird (1962) trial (69% relapse rate) and the no

treatment group in the Imlah et al. (1965) study (51% relapse rate). This may be due to the anxiolytic effect of diazepam. However, the three suicides led the authors to discuss the existing clinical impressions linking diazepam to suicide in depressed patients and to caution against its use in ECT-treated patients, at least when not administered in conjunction with an antidepressant. The possible role of benzodiazepines in disinhibited and self-injurious behaviour continues to be studied (Berman, Jones, & McCloskey, 2005).

These three early studies were characterised by numerous methodological shortcomings, the most important of which is that they were primarily designed to test the efficacy of TCA or MAOI augmentation of ECT and hence patients were randomised prior to ECT to receive either antidepressants or placebo in conjunction with ECT. Failure to re-randomise patients after the ECT course skews the results in favour of those who were responsive to antidepressants in the first place (Sackeim, 1994). Very little is known about the ECT treatment parameters or patients' clinical characteristics in these studies. Patients in these trials were treated with the now-outmoded sine-wave ECT as was standard clinical practice in the United Kingdom and elsewhere in the 1960s. Most importantly, the changing nature of ECT patient populations over the subsequent decades renders these findings non-applicable to present-day clinical practice. Interestingly, these studies found very low relapse rates in patients maintained on antidepressant medication, despite what would nowadays be considered suboptimal dosing and compliance. Untreated patients appeared to fare as well as modern patients treated with optimised antidepressant + lithium continuation therapy.

1.5.2.3. Continuation pharmacotherapy with lithium

In the following decades, the use of ECT in the Western world declined with increased reliance on medication for management of mental illness and unfavourable public as well as professional perceptions towards the treatment. Little research was published during the 1970s and 1980s addressing the problem of relapse after ECT. As the rates of ECT use declined, ECT began to be reserved for patients who were most

severely ill and/or treatment resistant whereas this was not the case in earlier decades when ECT would have often been used as first-line treatment for inpatients with endogenous depression. Nonetheless, the work that was carried out extended the existing evidence base to now include lithium monotherapy in post-ECT prophylaxis for patients with unipolar depression.

Perry and Tsuang (1979) conducted a retrospective study where ECT-treated unipolar patients who were subsequently treated with either imipramine or lithium were identified by means of a chart review and interviewed six months following ECT (Perry & Tsuang, 1979). Relapse rates in the two groups were essentially the same (20% and 21% for imipramine and lithium, respectively) and were also essentially the same as the relapse rates of actively-treated patients from the three trials from the 1960s discussed above. The findings of efficacy of lithium monotherapy were replicated in a randomised double-blind trial of 38 unipolar depressed patients treated with either lithium or placebo in post-ECT prophylaxis with a one-year follow-up (Coppen et al., 1981). In this study, patients on lithium monotherapy spent significantly fewer weeks in an episode of depression than those on placebo, although the trial failed to detect an effect during the first six months of continuation treatment, the period with the greatest risk of relapse, perhaps due to small sample size. In a more recent study of post-ECT lithium monotherapy (Shapira, Gorfine, & Lerer, 1995), six-month relapse rate was 33% (8/24 patients). Notably, seven of the eight patients who relapsed met ATHF criteria for treatment resistance (failing at least one adequate medication trial before ECT) while only six of the 16 who did not relapse were treatment resistant. No studies of continuation lithium monotherapy have been published in the last 20 years (Rasmussen, 2014).

1.5.2.4. Predictors of relapse following ECT

Beginning in the early 1980s, Harold Sackeim and colleagues at Columbia University and the New York State Psychiatric Institute undertook a series of NIMH-funded studies of ECT as used in the modern era, culminating in a 30-year research

programme which included several RCTs and a large prospective observational study aimed at answering various unresolved questions surrounding the use of ECT. The first in a series of key papers from this group studying relapse following ECT was a report (Sackeim et al., 1990) on the long-term outcomes of a subset of patients who had taken part in two of their RCTs of different ECT modalities (Sackeim et al., 1987; Sackeim et al., 1993). The patients (N=58) were followed-up naturalistically for one year and their long-term antidepressant therapy was up to the discretion of the treating psychiatrist. Relapse rate in this study was 50%. The risk of relapse was greater in medication resistant patients than in those who had not received an adequate medication trial prior to ECT. Interestingly, the adequacy of post-ECT pharmacotherapy was only weakly related to the likelihood of relapse. Adequate post-ECT pharmacotherapy (as determined by doses and duration of treatment stipulated by an early version of the ATHF) appeared to be beneficial only for the patients who had not failed an adequate medication trial at pre-ECT baseline whereas adequacy of post-ECT pharmacotherapy made no difference to those who were medication resistant to begin with. The only clinical variable that was predictive of relapse was greater number of previous episodes. Although patients who relapsed did not have a longer duration of illness compared to those who stayed well, they had a greater number of previous episodes in the same timeframe, indicating a more rapidly recurrent, malignant form of illness.

Following the publication of this seminal study which for the first time demonstrated modern relapse rates of roughly 50% in the first year following ECT, the Columbia group subsequently replicated these findings in two other RCTs with one-year naturalistic follow-ups (Sackeim et al., 2000; Sackeim et al., 2008). In a 2000 study with a one-year naturalistic follow-up, which otherwise found a 53% relapse rate at 12 months, the adequacy of continuation therapy was again unrelated to the likelihood of relapse, although there was a suggestion that TCA + lithium combination therapy may have been more effective than other strategies, though patients in this study were not randomised to maintenance treatments (Sackeim et al., 2000). The notion that lithium augmentation may be especially beneficial in preventing post-ECT relapse was empirically tested in a

landmark 2001 placebo-controlled RCT of post-ECT continuation therapy which showed that nortriptyline + lithium combination was indeed more effective than nortriptyline monotherapy or placebo (Sackeim et al., 2001). Relapse rates in the nortriptyline monotherapy group were very high (60%), above the original projections for placebo, compared to 39% in the nortriptyline + lithium group. The authors hypothesised that the abrupt discontinuation of ECT and the institution of post-ECT continuation therapy only after the ECT course has finished may be contributing to these poor outcomes. In all the major RCTs of ECT carried out in the United States, patients underwent medication washout prior to the ECT course, leaving them without effective treatment in the early days or weeks after the ECT course has ended but before the effect of medication(s) has set in.

To test this hypothesis, a large RCT was undertaken to address the question of whether concomitant pharmacotherapy during ECT would enhance its acute effectiveness and/or prevent early relapse. While there was evidence of enhanced acute effectiveness of ECT administered with concomitant pharmacotherapy compared to placebo (Sackeim et al., 2009), concomitant pharmacotherapy during the ECT course had no protective effect on six-month relapse rates (Prudic et al., 2013). Overall, 60% of the completer sample relapsed during the six-month follow-up. Patients who had been treated with nortriptyline or venlafaxine during the ECT course relapsed at the same rate as those treated with placebo despite vigorous post-ECT pharmacotherapy with either nortriptyline + lithium or venlafaxine + lithium. These disappointing results once again highlight the limited efficacy of all existing treatments for refractory depression and the urgent need for more effective relapse prevention strategies for ECT patients.

1.5.2.5. Medication resistance as a predictor of relapse following ECT

Such high rates of relapse in recent decades could at least in part be accounted for by the historical changes in ECT patient populations (Sackeim, 1994). ECT is nowadays reserved for a minority of patients with severe, chronic, difficult-to-treat

depression where several treatment steps have usually been attempted without success. Such treatment-resistant patients may be less likely to achieve full remission and, when they do, they may be especially prone to relapse and recurrence (Fekadu et al., 2009b).

The negative impact of prior medication resistance on ECT outcomes had been noted as early as 1960 in a study where imipramine-resistant patients appeared to also be more likely to fail to improve with ECT, although outcomes were measured and reported in a largely impressionistic fashion (Bruce et al., 1960). In a 1974 study with a three-month follow-up, Hamilton observed the same negative effect of imipramine (150 mg/d or above) resistance on subsequent response to ECT (Hamilton, 1974). Interestingly, patients who had failed a trial of phenelzine (45 mg/d or above) in this study did not exhibit worse ECT outcomes at one or three months post-ECT, raising the possibility that resistance to different classes of antidepressant medication (TCAs vs. MAOIs) exerts a differential influence on ECT outcome.

The detrimental impact of medication resistance on ECT outcomes was more conclusively shown in a series of studies where patients with established medication-resistance as defined by the ATHF had worse acute (Prudic et al., 1996; Prudic et al., 1990) and longer-term (Sackeim et al., 2001; Sackeim et al., 1990; Sackeim et al., 2000) outcomes compared to patients who did not meet strict research criteria for medication resistance. However, a recent large RCT failed to find any relationship between the ATHF and relapse (Prudic et al., 2013) as did an earlier trial by the CORE group where ATHF was predictive of relapse only in the interim week between final ECT and randomisation to continuation treatment but not during the six-month follow-up (Rasmussen et al., 2009). It is unclear whether prior medication resistance truly predicts relapse or to what extent this effect might stem from the use of this particular set of research criteria for TRD.

1.5.2.6. Outstanding clinical questions surrounding relapse following ECT

Currently, there is no agreement on what constitutes optimal post-ECT relapse prevention treatment. Prior medication resistance appears to portend subsequent relapse but many patients continue to be treated with the same medication regimen after ECT that they had previously failed to respond to, a counterintuitive strategy (Sackeim, 1994). The American Psychiatric Association guidelines on ECT, now over a decade old, recommend continuation therapy with either pharmacotherapy or continuation ECT (C-ECT) for virtually all patients, beginning as soon after the acute treatment as possible but no specific guidelines are provided and clinicians are advised to take into account past history of treatment and consider C-ECT where response to ECT has been previously good but was followed by multiple recurrences on pharmacotherapy (American Psychiatric Association, 2001). The Royal College of Psychiatrists in their ECT practice guidelines do not offer any specific recommendations on optimal relapse prevention strategy beyond noting that at least six months of continuation pharmacotherapy should be prescribed and that antidepressant-lithium combination may reduce the risk of relapse, adding that C-ECT is an option for patients with frequent relapses and non-responders to pharmacotherapy (The Royal College of Psychiatrists, 2013).

To help address these unresolved questions, in Chapter 3 an up-to-date systematic review and meta-analysis of all existing evidence, randomised and observational, is reported in order to provide an overview of the state-of-the-art and to attempt to determine what, if any, relapse prevention strategies have thus far been shown to be most effective.

1.6. Aims of the present studies

The work presented in this thesis aims to contribute to the existing body of knowledge on ECT by clarifying some of the outstanding questions surrounding the long-term clinical outcomes and cognitive sequelae of this important treatment modality for severe, treatment-resistant MDD. In particular, the main objectives of this thesis are to:

i. perform a systematic review and meta-analysis of the existing literature on long-term clinical outcomes following a successful course of ECT;
ii. characterise the nature of baseline medication resistance in a sample of ECT patients, examine the validity of various definitions of treatment resistance, identify the most parsimonious and clinically useful among several measures of treatment resistance and explore the effect of baseline medication resistance on the likelihood of remission and relapse/recurrence after ECT;
iii. characterise the long-term clinical course of depression following ECT, with a particular emphasis on the rates, temporal patterns and clinical predictors of relapse/recurrence in ECT remitters;
iv. measure autobiographical memory functioning before, after and at long-term follow-up after ECT using a standardised neuropsychological instrument capable of separating theoretically and clinically relevant components of autobiographical memory (semantic vs. episodic recall) and compare the performance of ECT-treated patients to normative data of healthy control subjects.

The work presented here consists of three separate yet thematically linked studies. Study 1, the results of which are presented in Chapter 3, is a systematic review and meta-analysis of relapse following a successful course of ECT. All prospective studies appearing in the peer-reviewed literature beginning with the earliest published reports on the topic were quantitatively synthesised. Historical trends in relapse rates were examined. The main focus was on relapse in modern-day studies. The relative efficacy of

different relapse prevention strategies such as pharmacotherapy with various classes of antidepressants or C-ECT was examined where such data were available.

Study 2 was an RCT of bitemporal vs. high-dose RUL ECT with a one-year naturalistic follow-up. The results of Study 2 are presented in Chapters 4 and 5. In Chapter 4, a comparison of four measures of antidepressant treatment resistance (two research instruments and two clinical estimates) was carried out on patients with unipolar MDD who took part in Study 2. In Chapter 5, relapse/recurrence rates, baseline clinical predictors of relapse/recurrence and the effect of post-ECT lithium continuation therapy were studied in all ECT remitters who were followed up prospectively for a year as part of Study 2.

In Chapter 6, the results of Study 3 are presented. Study 3 was a retrospective chart review of patients who received a course of brief pulse, predominantly bitemporal ECT and who had their semantic and episodic autobiographical memory function examined before, after and three months following a course of ECT as part of routine clinical practice in an Irish inpatient psychiatric service.

2. Materials and Methods

2.1. Study 1: Systematic review and meta-analysis of relapse following a successful course of ECT for major depression

2.1.1. Systematic reviews and meta-analyses in evidence-based medicine

Evidence-based medicine is the "conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research" (Sackett, Rosenberg, Gray, Haynes, & Richardson, 1996, p. 71). Randomised controlled trials (RCTs) are nowadays considered the best methodology for evaluating medical treatments. However, the exceedingly large volume of health-related information makes it impossible for healthcare providers, patients, researchers and policymakers to individually appraise all studies related to a topic (Higgins, Green, & Cochrane Collaboration, 2008). A systematic review therefore "attempts to collate all empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question" (Higgins et al., 2008). Systematic reviews of RCTs are considered the gold standard for judging the merits and harms of medical treatments (Sackett, Rosenberg, Gray, Haynes, & Richardson, 1996). Systematic reviews, however, are not confined to appraisal of medical treatments but are being increasingly used in other disciplines such as the allied health professions (nursing, physiotherapy, occupational therapy etc.), psychology, education, sociology, etc.

Systematic reviews often, though not always in cases where this is not possible, utilise meta-analysis to provide a quantitative synthesis of results from primary studies using statistical methods. According to one definition (Egger, Smith, & Phillips, 1997), meta-analysis is a "statistical procedure that integrates the results of several independent studies considered to be combinable" (p. 1533). It has become the cornerstone of evidence-based medicine. A quantitative approach is believed to provide a more objective

appraisal of evidence than traditional narrative reviews, as well as allowing for a more precise estimate of treatment effect size and sources of heterogeneity between the included studies (Egger et al., 1997). Heterogeneity refers to a situation where there are genuine differences underlying the results of meta-analysed studies which are not explainable by chance alone (Higgins, Thompson, Deeks, & Altman, 2003). The assessment of heterogeneity is therefore of utmost importance in a meta-analysis (Higgins et al., 2003). The quality of any meta-analysis naturally depends on the quality of the systematic review on which it is based and the quality of the primary studies themselves. In the evidence-based medicine literature, the quality of primary studies is categorised according to a common hierarchy of "levels of evidence" such as shown in Figure 2.1 below.

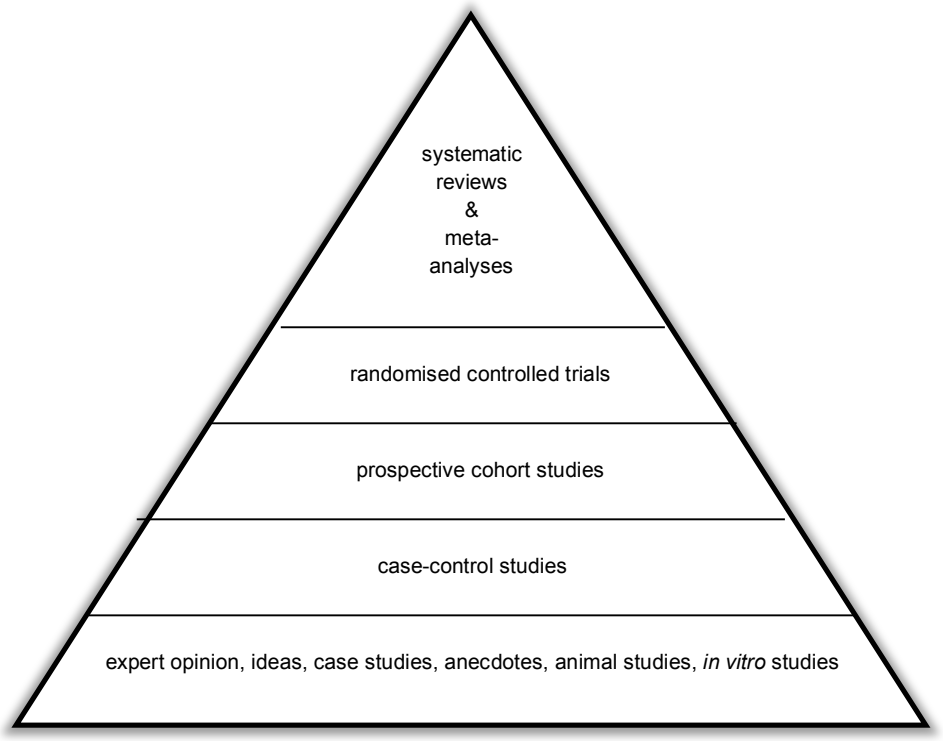

FIGURE 2.1. Levels of evidence in evidence-based medicine[2]

[2] Adapted from the Guide to Research Methods - The Evidence Pyramid (2004) accessed March 30, 2014 at http://library.downstate.edu/EBM2/2100.htm

2.1.2. Systematic review of long-term clinical outcomes in ECT patients with major depression

A systematic review of the entire span of the published research evidence on this topic was undertaken in May 2011 using keyword searches of the following electronic databases: PubMed, EMBASE, CINAHL, PsycINFO and Cochrane Library. The electronic database search was updated in January 2013. For specific details about the search strategy, study inclusion and exclusion criteria, and coding of outcomes of interest, see Chapter 3.

Literature searches could not identify any previous published meta-analyses on the topic of relapse following ECT. Two unpublished and non-peer reviewed meta-analyses of RCTs of post-ECT continuation therapies commissioned by British governmental agencies were found (National Institute for Clinical Excellence, 2010; The Royal College of Psychiatrists, 2005). These meta-analyses compared the relative efficacy of continuation pharmacotherapy with placebo, another pharmacological intervention or continuation ECT in RCTs of post-ECT continuation therapies. As only a small number of such RCTs have been published, these reviews thus excluded the majority of the available evidence on post-ECT relapse. These meta-analyses, as well as published systematic reviews and/or meta-analyses about acute clinical efficacy of ECT in general or in specific patient populations were hand-searched for additional references (Dunne & McLoughlin, 2012; Greenhalgh et al., 2005; Heijnen et al., 2010; Janicak et al., 1985; Kho, van Vreeswijk, Simpson, & Zwinderman, 2003; Pagnin, de Queiroz, Pini, & Cassano, 2004; Stek, van der Wurff, Hoogendijk, & Beekman, 2009; The UK ECT Review Group, 2003; van Schaik et al., 2012). Previously published narrative reviews and editorials about post-ECT relapse were also hand-searched for additional citations (Abou-Saleh & Coppen, 1988; Bourgon & Kellner, 2000; Sackeim, 1994).

2.1.3. Meta-analyses of relapse in ECT patients with major depression

A series of meta-analyses were conducted using the Comprehensive Meta Analysis Version 2.2 software (Borenstein, Hedges, Higgins, & Rothstein, 2011). The conduct and reporting followed the PRISMA guidelines (Moher, Liberati, Tetzlaff, Altman, & Prisma Group, 2009) and the MOOSE guidelines for meta-analyses of observational studies (Stroup et al., 2000). Data were pooled using a random-effects model (DerSimonian & Laird, 1986) due to anticipated substantial differences in study designs and patient populations. Heterogeneity was assessed using the I^2 statistic (Higgins et al., 2003). Where different continuation therapies were compared in RCTs either against one another or against placebo, relative risks (RR) with 95% CIs and numbers needed to treat (NNT) were calculated. Publication bias was assessed by visual inspection of funnel plots. See section 3.2.4 for further details.

2.2. Study 2: Medication resistance and other clinical predictors of relapse of major depression after ECT: a prospective one-year follow-up

2.2.1. Study design

The present study is divided into two substudies reported in Chapters 4 and 5. This was a prospective investigation of medication resistance and other baseline clinical predictors of long-term clinical outcomes of patients with major depression who were treated with a course of ECT as part of a randomised controlled trial with a one-year follow-up, the EFFECT-Dep Trial (Enhancing the Effectiveness of Electroconvulsive Therapy in Severe Depression [trial registration: ISRCTN23577151]) conducted at St. Patrick's University Hospital and Trinity College Institute of Neuroscience between May 2008 and October 2012.

The EFFECT-Dep Trial was a randomised, patient- and rater-blind, non-inferiority trial of low-dose bitemporal ECT administered at 1.5 x seizure threshold (ST) and high-dose right unilateral (RUL) ECT at 6 x ST. The aim of the trial was to compare the clinical effectiveness and the side-effect profile of high-dose RUL ECT to standard bitemporal ECT. The design of the trial was pragmatic, aiming to reflect real-world treatment conditions. Patients continued to receive concomitant pharmacological treatment for depression during the course of ECT (i.e. no drug washout) in line with routine clinical practice in many countries. The length of treatment course was determined by the referring consultant psychiatrist. Patients were ideally treated until remission (i.e. a ≥60% decrease in Hamilton Rating Scale for Depression, 24-item version, score from baseline and a score of ≤10 for two consecutive weeks) or until they had received a full course of 12 ECT sessions. These treatment conditions make the results of the present trial more pertinent to Irish, British and several other European countries' psychiatric practice than other currently available RCT evidence from the United States.

Following the randomised treatment phase, all participants (regardless of remission status) were assessed at a number of pre-specified time points over the course of a one-year naturalistic follow-up. Antidepressant continuation/maintenance treatment during the follow-up phase was chosen by the treating physician(s).

2.2.2. Ethics and consent

The EFFECT-Dep Trial received ethical approval from the St. Patrick's University Hospital Research Ethics Committee (protocol number: 12/07) and the St. James' Hospital-Adelaide and Meath & National Children's Hospital Research Ethics Committee (protocol number: 2008/05/04). All consultant psychiatrists referring patients to St. Patrick's University Hospital's ECT clinic provided written consent prior to study commencement for their patients to be approached by the researchers for recruitment to the trial. All prospective participants were given a full verbal and written description of the study by the researchers. All participants provided written informed consent prior to taking part.

2.2.3. Participants

All patients referred for a course of ECT at St. Patrick's University Hospital's ECT clinic during the study period were screened for eligibility and, if eligible, approached by one of the researchers to discuss the nature of the study and obtain consent for participation.

Study inclusion criteria were: diagnosis of major depressive episode confirmed by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First, Spitzer, Gibbon, & Williams, 1996) and the 24-item Hamilton Rating Scale for Depression (HRSD-24) (Beckham & Leber, 1985; Hamilton, 1960) score of 21 or above.

Exclusion criteria were: dementia or another Axis I comorbidity, any medical condition rendering the patient unfit for general anaesthesia, ECT in the previous six

months, alcohol or substance abuse in the previous six months, inability or refusal to consent.

2.2.4. Randomisation and blinding

Patients were randomly allocated to either treatment. Patients and raters were blind to treatment allocation. Randomisation was stratified according to:

1. whether the patient had received ECT in the past or not;
2. source of referral:
    a. St. Patrick's University Hospital (including St. Edmundsbury Hospital)
    b. St. James' Hospital
    c. Other Health Service Executive (HSE) hospital

All patients referred from these three sources received ECT treatment at St. Patrick's University Hospital's ECT Clinic. Patients referred for ECT from other HSE hospitals were admitted to St. Patrick's University Hospital as inpatients for the duration of the ECT course.

Allocation concealment was ensured through the use of an off-site independent randomisation service at the Clinical Trials Unit, Institute of Psychiatry, London, United Kingdom. Success of blinding was measured at the end of the entire course of ECT.

2.2.5. Treatment parameters

ECT was administered in accordance with the Royal College of Psychiatrists' guidelines (The Royal College of Psychiatrists, 2005). Treatments were delivered twice weekly (Tuesdays and Fridays) with hand-held electrodes using a MECTA 5000M device (MECTA Corporation, OR, USA) which delivers a brief-pulse (1.0 msec) stimulus. Each patient's ST (i.e. the minimum electrical charge required to produce a generalised seizure lasting at least 25 seconds as determined by electroencephalogram [EEG] monitoring or at least 15 seconds on observation of the motor seizure) was established during the first

ECT session using an empirical titration method. The dose at subsequent treatments was administered relative to the ST; 1.5 x ST for bitemporal ECT and 6 x ST for RUL ECT. For bilateral ECT, the bitemporal electrode placement was used, for RUL the d'Elia placement (see Figure 1.1 above). Seizure duration was measured by EEG. Methohexitone (0.75-1.0 mg/kg) was used for anaesthesia and suxamethonium (0.5-1.0 mg/kg) for muscle relaxation.

2.2.6. Study procedures

Patients were assessed at baseline, after every two ECT treatments, at the end of ECT course, and at several follow-up time-points (2 weeks, 4 weeks, 6 weeks, 8 weeks, 3 months, 4 months, 6 months, 9 months and 12 months). All baseline assessments were carried out prior to randomisation and the first ECT treatment. The baseline clinical and neuropsychological assessment battery was extensive and typically took up to three hours to complete in full. Some participants were unable to complete every scheduled assessment, or part thereof, due to inability (stemming from illness severity), refusal or because they could not be contacted in time to arrange an appointment. In such cases, assessments were administered in the order of priority. To enter the study, a participant had to at the very least complete the SCID-I and HRSD-24 as these two measures determined study eligibility in conjunction with information from clinical case-notes. During the ECT course, participants were assessed on the HRSD-24 after every two treatment sessions (i.e. typically once a week). This "intra-treatment" assessment was used to track depression severity and response to ECT treatment. The full assessment battery was carried out at the end of ECT course (i.e. "end of treatment" assessment), and at 3 months, 6 months and 12 months after ECT. At other time-points (2 weeks, 4 weeks, 6 weeks, 8 weeks, 4 months and 9 months), only the HRSD-24 was administered. If a patient refused one or more follow-up assessments, they were still contacted at each subsequent scheduled follow-up unless they specifically stated that they wished to withdraw from the study. In some cases, patients were not reachable in time to complete a

particular follow-up assessment. In those cases, patients were contacted again when the next scheduled assessment was due.

2.2.7. Baseline demographic and diagnostic assessments

2.2.7.1. Participant background information

A form was developed prior to study commencement to collect baseline demographic information about each participant. This included: participant's name and address, date of birth, contact telephone number, marital status, educational attainment, occupation and socioeconomic group, height, weight, smoking status, recent average weekly alcohol intake, source of referral (St. Patrick's University Hospital, St. James' Hospital, other HSE hospital), previous ECT, date of last ECT (if applicable), and information regarding any family history of mental illness. The name of next-of-kin, their address, and telephone contact details were also recorded for those participants who consented to having their next-of-kin contacted by the researchers. A separate form was developed for collecting information regarding the participant's medical comorbidities to capture the extent of medical burden.

2.2.7.2. Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)

The research version of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First et al., 1996) was used to confirm a diagnosis of a major depressive episode. The SCID is a semi-structured interview used to diagnose psychiatric disorders in line with DSM criteria. The research edition of the SCID-I is the gold standard diagnostic tool used to confirm the presence of DSM-IV Axis I disorders in research studies.

The full SCID contains an overview section (covering demographic and employment history of the patient, current complaint, history of psychiatric illness, treatment history and current functioning) and nine diagnostic sections (Mood Episodes,

Psychotic Symptoms, Psychotic Disorders Differential, Mood Disorders Differential, Substance Use, Anxiety, Somatoform Disorders, Eating Disorders, and Adjustment Disorders). The diagnostic sections may be used alone or in conjunction with others. In this study, only the Current Major Depressive Episode subsection of the Mood Episodes section was administered.

The interviewer administers the SCID by posing probe and supplemental questions to the patient for each of the nine diagnostic criteria for major depression. This is followed by additional questions for ascertaining diagnostic subtypes such as melancholic, atypical, catatonic or postpartum depression, and the presence of psychotic features including various types of delusions and hallucinations. Each criterion is scored on a scale of 1-3, 1 indicating "absent or false", 2 indicating "subthreshold symptoms" and 3 indicating "threshold or true".

The majority of evidence for the reliability of the SCID is based on studies of DSM-III diagnosed samples. The largest of these (N=592) showed fair test-retest reliability with a kappa (κ) coefficient of 0.64 for patients with MDD (Williams et al., 1992). The kappa statistic corrects for chance agreement between scores. For DSM-IV samples, one study found fair test-retest (κ=0.61) and good inter-rater (κ=0.80) reliability for the SCID in MDD patients (Zanarini et al., 2000). A more recent study (N=151) of DSM-IV SCID-I found fair level of inter-rater reliability (κ=0.66) for MDD (Lobbestael, Leurgans, & Arntz, 2011).

2.2.7.3. Treatment review

A form for collecting information about each patient's current treatment at each major follow up (baseline, end of treatment, 3-month, 6-month and 12-month follow-ups) was developed for the purposes of this study. The information collected was names of all medications currently taken, dosages, duration of treatment with each of these medications and compliance.

2.2.7.4. National Adult Reading Test

The National Adult Reading Test (NART) (Nelson & Willison, 1991) was used as an estimate of premorbid intelligence quotient (IQ). The version of the NART used in the present study (Nelson & Willison, 1991) is an updated version of the original test (Nelson, 1982). It consists of 50 words with “irregular” spellings. The words vary in frequency of usage, starting with more common ones (e.g. chord) and progressing to more difficult, obscure ones (e.g. demesne). The patient is instructed to try to pronounce each word. If the patient is unfamiliar with the word, guessing is encouraged. Each response (even if incorrect) is reinforced with phrases such as “that’s good” or “that’s fine” to reduce test anxiety. Correct pronunciations of these words cannot be arrived at by guesswork since an attempt at pronunciation based on common rules of phonemic decoding would result in an incorrect pronunciation. Hence, the test measures prior knowledge of the words. The total number of correctly pronounced words is converted into an estimated IQ score using criteria laid out in the test manual (Nelson & Willison, 1991).

Vocabulary tests are commonly used to estimate premorbid mental ability in adult patients with neurological/neuropsychiatric diseases where deterioration in intellectual function is suspected. The NART shows strong correlations with other measures of IQ such as the Wechsler scales (Lezak, Howieson, & Loring, 2004; Strauss, Sherman, & Spreen, 2006). Performance is unaffected by age (Nelson & Willison, 1991). The NART has previously been shown to be valid in depression where performance was unaffected compared to matched healthy controls (Crawford, Besson, Parker, Sutherland, & Keen, 1987). Inter-rater and test-retest reliability is high (>0.90) (Nelson & Willison, 1991).

2.2.8. Baseline antidepressant treatment history evaluation

Extensive information regarding prior treatment for the index episode was collected at baseline using case-note reviews, patient interview, and contact with the patient’s next-of-kin and/or pharmacy, as required, and with the patient’s permission. Baseline medication resistance was assessed in four ways:

i. the Antidepressant Treatment History Form (ATHF) (Sackeim, 2001);
ii. the Maudsley Staging Method (MSM) (Fekadu et al., 2009a);
iii. clinical judgement of referring physician (each consultant psychiatrist indicated whether they deemed the patient to be treatment resistant on the clinical ECT treatment booklet which is completed for every patient referred for ECT);
iv. antidepressant count (i.e. the number of antidepressant medication trials attempted during index episode regardless of dose, duration or compliance).

2.2.8.1. Antidepressant Treatment History Form (ATHF)

The ATHF was used to determine if the index depressive episode met strict research criteria for treatment resistance. The ATHF was originally developed in the 1980s by Dr. Sackeim and colleagues at Columbia University, New York, United States, and first published in 1990 (Sackeim et al., 1990). Its subsequent revision was published in 2001 (Sackeim, 2001). Detailed scoring procedures for each licensed antidepressant drug are provided by the authors (Sackeim, 2001). The latest version of the scoring procedures (see Appendix 1) that includes the newest antidepressants such as duloxetine and escitalopram was kindly provided by the authors in 2012 (Dr. J. Prudic, personal communication). As per the authors, the cut-off dose of each antidepressant agent that defines adequacy corresponds to the minimal dose determined to be effective in RCTs and generally represents two-thirds of the maximum safe dose recommended by the Physicians' Desk Reference. This amounts to a minimum of four weeks at 200 mg/d of imipramine or equivalent for tricyclic antidepressants (TCAs) or 20 mg/d of fluoxetine or equivalent for selective serotonin reuptake inhibitors (SSRIs). Blood levels take precedence over daily dose for lithium and TCAs. Scoring procedures are also provided for ratings of ECT courses. For psychotic depression, in addition to four weeks of antidepressants at these doses, a minimum of concurrently administered three weeks of 400 mg/d of chlorpromazine or equivalent for typical antipsychotics and 20 mg/d of olanzapine or equivalent for atypicals is required. Combination trials include concomitant administration of lithium or T_3 (triiodothyronine) and antidepressants for non-psychotic or psychotic depression, or antipsychotics and antidepressants for psychotic depression.

Other combination trials, such as concurrent use of two antidepressants (e.g. venlafaxine + mirtazapine or SSRI + bupropion), are scored as separate trials.

The ATHF documents the following information: date of onset of current episode, episode duration, SCID diagnosis (unipolar or bipolar and psychotic or non-psychotic depression), sources of information (patient interview, case notes, prescribing physician, pharmacy, relative etc.), the names of all medications attempted, blood levels (if measured), daily dosages, dates of each dosage change, duration of treatment at each dosage, reason for change (including side-effects) and clinical outcome.

The strength of each antidepressant trial is rated on a 0-5 scale depending on the dose and duration of treatment. A score of ≥3 constitutes an adequate trial. Each antidepressant medication has to be administered for a minimum of four weeks at full therapeutic dose in order for the trial to be considered adequate. If a patient experienced prior episode(s) of depression and was on maintenance treatment when they suffered a recurrence, the maintenance medication they were on when the symptoms re-emerged is taken into account in the scoring of the current episode since the patient clearly experienced depressive breakthrough on this regimen and can now be said to be resistant to this drug. All other psychopharmacological treatments such as benzodiazepines, mood stabilisers, antipsychotics etc. are recorded but do not contribute to scoring of antidepressant trials with the following exceptions:

i. in bipolar depression, lithium, carbamazepine and lamotrigine, administered at adequate dose/blood level for an adequate length of time count as antidepressant trials;
ii. lithium and T_3 are considered augmenting agents and may increase the rating of the antidepressant trial if administered at an adequate dose for at least two weeks concurrent with an antidepressant medication trial at a full therapeutic dose;
iii. antipsychotics must be administered at an adequate dose for at least three weeks to patients with psychotic depression in conjunction with an antidepressant drug at a full therapeutic dose for the antidepressant trial to be deemed adequate.

Among several possible ways of scoring the ATHF (sum score of all trials, score of most potent trial, categorical classification into TRD or not TRD), the outcome that is used by far the most frequently in the ECT literature is a categorical classification of TRD or not. To be designated treatment resistant, the patient had to have failed to respond to at least one adequate trial of any antidepressant from any class. In practice, this leads to some problems with classification not necessarily being congruent with clinical reality as illustrated in two hypothetical case vignettes below:

Patient A is a 35-year-old mother of two presenting to her general practitioner (GP) with a two-month history of fatigue, low mood, hypersomnia, weight gain and feelings of worthlessness and rejection. She states that her symptoms started during an acrimonious separation from her partner of two years. She continues to work on a part-time basis, albeit with difficulty, as getting out of bed in the morning is a struggle. She requires help from her mother with child care. She denies any previous history of depression or thoughts of self-harm. Her GP prescribes 10 mg of escitalopram. On follow-up visit six weeks later, the patient reports no improvement in her condition. Her dose is increased to 20 mg. According to the ATHF classification, Patient A has treatment-resistant depression (reason: no response to ≥4 weeks of adequate dose of an SSRI).

Patient B is a 67-year-old housewife with a longstanding history of recurrent unipolar MDD with seven previous admissions which, among many antidepressant medication trials, included two courses of ECT. Her most recent admission was nine months ago when she received a course of seven bitemporal ECT treatments and was discharged fully remitted on a maintenance treatment of clomipramine 100 mg and lithium 400 mg (most recent blood level was 0.5 mmol/l four weeks ago). She relapsed on this regimen two weeks ago and was readmitted due to taking an overdose of paracetamol. On admission her clomipramine was increased to 125 mg but this was poorly tolerated due to postural hypotension and urinary retention and had to be reduced back to 100 mg. Rather than attempting a medication switch in light of an extensive past history of failed medication trials (including an MAOI during the previous episode which ultimately

necessitated a course of ECT), her consultant psychiatrist is recommending another course of ECT given past history of favourable response. According to the ATHF, Patient B does not have treatment-resistant depression (reason: insufficient dose of TCA).

The ATHF has high inter-rater reliability with an intraclass correlation coefficient (ICC) of 0.90 for the most potent antidepressant trial score, and 0.94 for the total score which sums up the potency of all antidepressant trials a patient received during the episode (Sackeim et al., 1990). Good predictive validity for acute (Dombrovski et al., 2005; Prudic et al., 1990; Sackeim et al., 2000) and longer-term (Sackeim et al., 2001; Sackeim et al., 1990) ECT outcomes has been found in prospective studies conducted by the scale's authors. Patients who had failed one or more adequate medication trials on the ATHF prior to ECT tended to have lower remission and higher relapse rates in these studies by the Columbia group.

2.2.8.2. Maudsley Staging Method (MSM)

The information collected regarding antidepressant treatment history was also used to quantify the extent of treatment resistance on the recently developed Maudsley Staging Method (MSM) (Fekadu et al., 2009a). This novel instrument was designed as a multidimensional model for determining the severity of treatment resistance by incorporating not only the number of attempted antidepressant trials, augmentation trials and ECT but also clinical characteristics of illness (episode duration and symptom severity). The severity of treatment resistance is measured on a 15-point scale (see Table 2.1 below). Possible scores on the MSM range between 3 and 15; 3-6 points indicating a mild degree of treatment resistance, 7-10 moderate and 11-15 severe.

TABLE 2.1. Maudsley Staging Method parameters and scoring system[3]

Parameter/Dimension	Parameter Specification	Score
Duration		
	Acute (≤12 months)	1
	Sub-acute (13-24 months)	2
	Chronic (>24 months)	3
Symptom severity at baseline		
	Subsyndromal	1
	Syndromal	
	Mild	2
	Moderate	3
	Severe without psychosis	4
	Severe with psychosis	5
Treatment failures		
Antidepressants	Level 1: 1-2 medications	1
	Level 2: 3-4 medications	2
	Level 3: 5-6 medications	3
	Level 4: 7-10 medications	4
	Level 5: >10 medications	5
Augmentation	Not used	0
	Used	1
Electroconvulsive therapy	Not used	0
	Used	1
Total		(15)

According to the recent published report on the MSM (Fekadu et al., 2012), the authors determined the minimum adequate dose and duration of an antidepressant trial using the Maudsley Prescribing Guidelines (Taylor, Paton, & Kapur, 2009), supplemented by the ATHF (Sackeim, 2001) and the British National Formulary (British Medical Association, 2012). However, the ATHF criteria differ quite significantly from the Maudsley guidelines (and indeed standard clinical practice in the United Kingdom and Ireland) in terms of what they consider to be the minimum effective dose of various antidepressants. For example, for TCAs, four weeks of 200 mg/d of imipramine or equivalent is required on the ATHF, whereas according to the Maudsley guidelines, six weeks is required and the minimum effective dose is said to be "unclear"; 75–100 mg/d, possibly 125 mg/d. The difference in tolerability, especially in older adults who are the majority of patients treated with ECT nowadays, between 75-125 mg and 200 mg is clinically significant. In fact, 200 mg would be approaching the upper boundary of safety according to the British National Formulary. For a commonly used newer antidepressant venlafaxine, the difference

[3] Adapted from Fekadu et al., 2009a

between the two sets of guidelines is again quite large (ATHF: four weeks at 225 mg/d, Maudsley: six weeks at 75 mg/d). Given these discrepancies, the authors were contacted and they kindly provided their in-house scoring sheets with dosing criteria for each antidepressant (Dr. A. Cleare, personal communication; see Appendix 2). Another major difference between the two instruments is that the MSM does not require psychotic depression to be treated with an antipsychotic in addition to an antidepressant as the Maudsley guidelines are equivocal on this matter. What both models have in common, however, is that they omit the role of psychotherapy in determining treatment resistance in depression.

The MSM has good short- and long-term predictive validity. In a validation study (Fekadu et al., 2009a) of 88 inpatients treated at a unit specialising in treatment-resistant mood disorders, the MSM predicted failure to achieve remission at discharge with an odds ratio of 1.67 ($p<0.001$). All three factors in the model (duration of illness, symptom severity and treatment failures) independently predicted non-remission. In a follow-up study (Fekadu et al., 2009c) where 62 of the original 88 patients were interviewed at a median of 29.5 months after discharge, the MSM predicted depressive symptomatology and functional impairment during the follow-up, while antidepressant count and the Thase and Rush Staging Model did not.

2.2.9. Clinical outcome measures

2.2.9.1. Hamilton Rating Scale for Depression, 24-item (HRSD-24)

The primary clinical outcome measure in this study is the Hamilton Rating Scale for Depression, 24-item (HRSD-24) (Hamilton, 1960; Hamilton, 1967) administered using the Structured Interview Guide for the HRSD (SIGH-D) (Williams, 1988). The 24-item HRSD version used in this study (Beckham & Leber, 1985) contains the original 21 items, plus three additional items on helplessness, hopelessness and worthlessness commonly encountered in the literature but the exact origin of which is not known (Williams, 2001). First developed in the late 1950s, the HRSD is the most commonly used clinician-rated

measure in clinical trials of depression (Williams, 2001). Its psychometric properties and the merits of its continued use have been extensively debated in recent years (Bagby, Ryder, Schuller, & Marshall, 2004; Bagby, Schuller, Ryder, & Marshall, 2005; Bech et al., 2005; Carroll, 2005; Corruble & Hardy, 2005; Hsieh & Hsieh, 2005; Licht & Bech, 2005).

Although widely used, the lack of standardised procedures for administration and scoring, and the use of various modified versions with additional items have led to concerns regarding the validity and reliability of this instrument. A systematic review (Bagby et al., 2004) of studies examining the psychometric properties of the HRSD published since 1979 found that it has acceptable internal reliability (Cronbach α ranging from 0.46 to 0.97 in published studies), acceptable inter-rater reliability (Pearson r ranging from 0.82 to 0.98 and intraclass correlation coefficient (ICC) ranging from 0.46 to 0.99) and good test-retest reliability (Pearson r ranging from 0.81 to 0.98). However, inter-rater reliability for individual items is poor. In an effort to address this problem, studies such as this one frequently use the Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D) (Williams, 1988) which contains probe questions and anchor descriptors corresponding to each item on the scale in order to maintain a high level of inter-rater reliability. The systematic review also found acceptable levels of convergent, discriminant and predictive validity. However, poor content validity and a multidimensional scale structure were observed, with a notable absence of some symptoms included in current conceptualisations of depression such as concentration difficulties and reverse vegetative symptoms, while other symptoms which are not diagnostic of depression according to modern criteria such as anxiety, hypochondriasis and loss of insight are featured. Nonetheless, in the absence of broad consensus on a superior alternative, the HRSD remains the current preferred method of assessment of depression severity in clinical trials.

2.2.9.2. Remission, relapse and recurrence

This study investigated three categorical clinical outcomes operationally defined as follows:

i. Remission was defined as a ≥60% decrease in HRSD-24 score relative to baseline and a score of ≤10 on a minimum of two consecutive testing occasions separated by one week.

ii. Relapse and recurrence were defined as a ≥10-point increase in HRSD-24 compared to end-of-treatment score and a HRSD-24 score of ≥16. In addition, this increase in HRSD-24 score had to be maintained one week later (if indicated, additional follow-ups were arranged to confirm relapse). Hospital admission, further ECT, and deliberate self-harm/suicide also constituted relapse regardless of HRSD-24 score. If these criteria were met at any point during the first six months of follow-up, the patient was deemed to have relapsed. If, however, relapse criteria were met from the beginning of the seventh through to the end of the twelfth month of follow-up, this was considered a recurrence. This distinction is in accordance with theoretical conceptualisations of relapse and recurrence of MDD; relapse represents a return of the index major depressive episode, while recurrence is deemed to be the formation of a new major depressive episode after a period of sustained remission (Frank et al., 1991; Nierenberg & DeCecco, 2001; Rush et al., 2006a).

Like all proposed criteria for depression outcomes, these are acknowledged to be somewhat arbitrary in nature. These specific criteria for remission and relapse/recurrence were chosen to correspond with those used in the recent major trials of bitemporal vs. high-dose RUL ECT (Kellner et al., 2010; Sackeim et al., 2009; Sackeim et al., 2000; Sackeim et al., 2008) in order to facilitate comparisons of the present study's findings with the existing literature.

2.2.10. Data quality assurance

All clinical raters underwent extensive training prior to their involvement in patient assessments. Training on the primary outcome measure (HRSD-24) involved conducting, watching and scoring of videotaped interviews, observing an experienced clinician conducting live interviews, administering and scoring of live interviews under supervision, and inter-rater reliability sessions which took place prior to study commencement and subsequently every six months. For these inter-rater sessions, each rater recorded several HRSD-24 interviews with patients in St. Patrick's University Hospital who provided written consent to be videotaped for educational purposes. Videotaped interviews were watched and scored by all raters and an intraclass correlation coefficient (ICC) was computed to measure inter-rater agreement. At every session, the ICC exceeded 0.85, indicating high inter-rater reliability for the primary outcome measure in this study.

Training on the diagnostic and clinical assessments other than the HRSD-24 (i.e. SCID-I, treatment history review, medical history review) was provided by an experienced research registrar in psychiatry. This involved observing live interviews of trial patients by the psychiatrist and then administering the SCID-I under supervision and with corrective feedback until supervision was no longer required. Training on the neuropsychological test battery was provided by a postdoctoral research neuropsychologist. The training involved explanation of all tests by the neuropsychologist, reading of test manuals, watching trained staff administering the tests to patients, administering and scoring the entire test battery to a healthy control, videotaped recording of the session with the healthy control and corrective feedback from the clinical neuropsychologist, and finally administering the full test battery to one of the trial participants under supervision, with corrective feedback. The administration of tests under supervision was repeated, if required, until tests were administered and scored without errors.

Five levels of quality control checks were instituted to ensure the correct scoring of all clinical and neuropsychological measures and to minimise administrative errors in paper and electronic data entry:

i. each team member scored the assessments they had carried out;
ii. each team member was paired with another team member. Once every two or three weeks, each pair cross-checked each other's scorings for errors;
iii. every month the team leader double-checked all scores. A team discussion regarding any discrepancies or unresolved issues was held;
iv. every month a team member entered the data into SPSS Data Entry Builder programme;
v. a team member periodically cross-checked the SPSS data file with paper records for electronic data entry errors.

2.2.11. Statistical analyses

All statistical analyses used a two-tailed $p<0.05$ level of significance and were carried out using SPSS version 21 software (IBM Corp., 2012). The primary method of analysis of depressive relapse/recurrence was survival analysis. The following variables were modelled as potential predictors of relapse: electrode placement, age, presence of psychotic symptoms at baseline, depression polarity, HRSD score at end of acute phase of treatment, baseline medication resistance and number of previous depressive episodes. See sections 4.2.5 and 5.2.5 for further details regarding specific statistical analyses carried out in each of the two substudies.

2.3. Study 3: Autobiographical memory specificity before and after ECT with a three-month follow-up: a retrospective casenote study

2.3.1. Study design

As part of routine clinical practice in St. Patrick's University Hospital, in July 2011 the ECT clinic began to routinely assess cognitive function in all patients (apart from those participating in the EFFECT-Dep Trial) before, immediately after and at three-month follow-up after completing a course of ECT, in line with clinical guidelines on the use of ECT (National Institute for Clinical Excellence, 2010). This study was a retrospective chart review of autobiographical memory of those patients who received an acute course of ECT for a major depressive episode at St. Patrick's University Hospital between August 2011 (when routine memory testing began) and January 2014.

2.3.2. Ethics and consent

This study received ethical approval from St. Patrick's University Hospital Research Ethics Committee (protocol number: 06/13). All information used in this retrospective case-note review was collected as part of routine clinical practice by the patient's clinical team and a clinical nurse specialist from the ECT clinic who administered the HRSD-24 and Kopelman AMI. The study involved no direct patient contact from the researchers.

2.3.3. Inclusion and exclusion criteria

The inclusion criterion for this study was an International Classification of Diseases-10 (ICD-10) clinical diagnosis of a major depressive episode. The following exclusion criteria were applied: dementia, another Axis I disorder, taking part in the

EFFECT-Dep Trial, substance abuse in the previous year, and being unable or unwilling to undergo neuropsychological assessment.

2.3.4. Study procedures

Eligible patients were identified from the St. Patrick's University Hospital ECT Clinic's clinical logbook. Eligible patients' case-notes were requested from the hospital's medical records.

The following demographic and clinical information was extracted from case-notes:

- age
- gender
- educational level
- International Classification of Diseases-10 (ICD-10) diagnoses
- medical comorbidities
- duration of index episode
- number of previous episodes
- number of previous ECT courses
- medication status before and after ECT course
- number of ECT treatments received
- ECT treatment parameters (electrode placement, dose, anaesthetic and muscle relaxant used)

The following clinical outcome information was also extracted from case-notes:

- Hamilton Depression Rating Scale (24-item) score before, after the full course of ECT and at three-month follow-up;
- Mini-Mental State Examination (MMSE) score before the ECT course.

Hardcopies of all Autobiographical Memory Interview (AMI) questionnaires with verbatim records of patient answers to each question were obtained from the ECT Clinic's records.

2.3.5. Clinical outcome measures

2.3.5.1. Hamilton Rating Scale for Depression, 24-item

The Hamilton Rating Scale for Depression, 24-item (HRSD-24) (Hamilton, 1960; Hamilton, 1967) was administered using the Structured Interview Guide for the HRSD

(SIGH-D) (Williams, 1988). See section 2.2.9.1 for details regarding the psychometric properties of this scale.

2.3.5.2. Clinical Global Impression scale

Referring psychiatrists rated their patients' symptoms on the Clinical Global Impression (CGI) scale (Guy, 1976). The CGI is a quick and easy-to-administer clinician-rated global estimate of severity and change in a patient's condition. It was originally developed for use in National Institute of Mental Health (NIMH) trials of schizophrenia (Guy, 1976) but can be applied to any psychiatric disorder.

In the present study, at pre-ECT baseline the patient's physician assessed, based on his/her clinical experience, the severity of a patient's mental illness on the following seven-point scale: 1 = normal, shows no signs of illness; 2 = borderline ill; 3 = slightly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill patients. This clinical judgement yielded a pre-ECT CGI-Severity (CGI-S) score. At the end of the ECT course, the Clinical Global Impression-Improvement (CGI-I) scale was used to assess how much the patient's illness had improved or worsened relative to pre-ECT baseline. Treating psychiatrists indicated the extent of the patient's improvement or deterioration on the following seven-point scale: 1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; 7 = very much worse.

The CGI is used extensively in psychiatry research but its psychometric properties have infrequently been examined directly, with published information particularly lacking for reliability (Zaider, Heimberg, Fresco, Schneier, & Liebowitz, 2003). One major criticism of the CGI-I is that at the end of a treatment trial it essentially tests the clinician's memory of the patient's condition at the beginning of the trial (Forkmann et al., 2011). Nonetheless, meta-analytic studies have demonstrated its concurrent validity with other measures and sensitivity to treatment effects in depression (Spielmans & McFall, 2006), schizophrenia

(Leucht & Engel, 2006) and social anxiety disorder (Hedges, Brown, & Shwalb, 2009) treatment trials.

2.3.5.3. Autobiographical Memory Interview

The Autobiographical Memory Interview (AMI) (Kopelman et al., 1989; Kopelman et al., 1990) is a semi-structured interview designed to assess the semantic and episodic components of autobiographical memory, retrograde amnesia and its temporal gradient. The test assesses autobiographical memories from three time periods of an individual's life (childhood, early adult life and recent past). It is divided into two components: the "personal semantic schedule", used to assess semantic memory of facts of one's life (addresses, dates, locations, names of friends, neighbours, relatives, hospital staff members etc.), and the "autobiographical incidents schedule", a measure of episodic memory for specific events located in a time and place.

The AMI was administered as instructed by the test manual (Kopelman et al., 1990). The examiner, a clinical nurse specialist trained on the administration of the scale by a clinical neuropsychologist, read the written interview questions. The nature and number of permissible follow-up prompts were pre-specified in the interview guide. All answers were recorded on the scoring sheet as close to verbatim as practicable. Scoring procedures are detailed in the manual. In brief, questions on the personal semantic schedule are scored 1-3 depending on the completeness of the answer. Partial scores are allowed. The episodic memories on the autobiographical incidents schedule are scored depending on the specificity and descriptive richness of the answer, as follows: 3 = the memory is clear and specific, situated in time and place; 2 = the memory is specific but time and place are not recalled *or* the memory is less specific but time and place are recalled; 1 = vague personal memory; 0 = no response or response solely based on general knowledge about oneself (i.e. semantic memory). Examples of patient answers and corresponding scores are provided by the scale's authors.

The full AMI takes up to half an hour to administer and is therefore, in its totality, unsuitable for routine clinical use with moderately or severely depressed, generally older adult ECT patients. In a previous multicentre study (McLoughlin et al., 2007) of a similar patient population referred for ECT in South London, randomised to receive either ECT or transcranial magnetic stimulation (mean age in the ECT group was 68.3 years; 72.7% female), the completion rates for the AMI were too low to allow for statistical analyses. This is not surprising given the nature of depressive illness and the typically short time window between referral for ECT and the first ECT session during which the required medical workup must be completed. A lengthy neuropsychological examination on all ECT patients is therefore unfeasible. For these reasons, only the recent life section of the AMI was administered clinically in St. Patrick's University Hospital. A drawback of administering only the recent life section is the inability to assess the temporal gradient of retrograde amnesia. However, although the literature on this is not entirely clear, several studies that have examined the temporal gradient of retrograde amnesia following ECT have found that memories most proximal to the ECT course may be more affected than more remote memories (Lisanby, Maddox, Prudic, Devanand, & Sackeim, 2000; McElhiney et al., 1995; Squire, Slater, & Miller, 1981). Therefore, given the clinical realities of limited time, staff and patient cooperativeness, it seems sensible to focus on assessment of recent life memories in the hope of capturing the memories most liable to disruption from ECT and carry out this assessment on as many patients as possible by maximising compliance due to the brief and, relatively speaking, not very challenging or elaborate nature of the task.

In a normative sample of healthy adults (N=34, age range 20-78), demographic variables such as age and premorbid intelligence were not found to influence scores (Kopelman et al., 1990). The inter-rater reliability between three raters scoring the answers from the normative sample was high, with correlation coefficients ranging between 0.83 and 0.86 between pairs of raters. In light of this, the authors suggest that for clinical purposes, a score by a single rater is sufficient, whereas for research purposes, two raters should independently score each question, and where they disagree by more

than one point, the scoring should be discussed, whereas if the discrepancy is one point or less, the mean score of the two ratings can be used. In the present study, a clinical nurse specialist who received training from a clinical neuropsychologist, administered and scored the AMI for clinical purposes. For research purposes, the present author who also received training on AMI administration and scoring from a clinical neuropsychologist re-scored all the questionnaires. Inter-rater reliability with a second trained rater, a masters-level psychologist, was measured. Where scores differed by more than one point, the discrepancies were resolved by joint re-evaluation of the answers, discussion and consensus. Otherwise, mean scores of the two raters were used in statistical analyses.

The AMI shows moderate correlations with other tests of remote memory such as the Crovitz Test (which uses the cue-word paradigm for assessment of autobiographical memory), the Prices Test and the Famous Personalities Test (Kopelman, 1989; Kopelman et al., 1989). It is capable of discriminating between healthy controls and amnesic patients such as those diagnosed with Alzheimer's dementia and Korsakoff's syndrome (Kopelman, 1989), as well as patients with focal lesions to diencephalic, temporal and frontal lobe structures (Kopelman, Stanhope, & Kingsley, 1999). The AMI also allows for separate assessment of semantic and episodic autobiographical memory, two correlated yet dissociable components of autobiographical memory. For instance, in a study of patients with unilateral temporal lobe epilepsy, the scores on the AMI were impaired for personal episodic memory but intact for personal semantic memory (Viskontas, McAndrews, & Moscovitch, 2000), suggesting that the two constructs are underpinned by different brain areas. An important advantage of the AMI is that it allows for assessment of specificity of episodic autobiographical memory, a central aspect of cognitive impairment in patients with MDD (Sumner et al., 2010; Van Vreeswijk & De Wilde, 2004; Williams et al., 2007).

Among the measures of remote memory that have been used in research studies and clinical practice, public events questionnaires are prevalent (Strauss et al., 2006). In the ECT literature, several studies have used such questionnaires to study retrograde

amnesia (Lisanby et al., 2000; Meeter, Murre, Janssen, Birkenhager, & van den Broek, 2011; Squire, 1975; Weiner, Rogers, Davidson, & Squire, 1986). A drawback of such tests is that public events memory is significantly influenced by the subject's interest in current affairs, reading newspapers, watching television, as well as demographic variables such as age, gender and education (Meeter et al., 2011). The AMI does not suffer from such limitations as the test content is provided by each individual patient drawing from the reservoir of their life experiences which all people have and thus the performance does not depend on having previously acquired any particular knowledge from the news media (Strauss et al., 2006). Public events questionnaires also become out of date quickly and therefore require frequent updating with the latest content, as described recently by colleagues (Noone et al., 2014). This poses logistical challenges in obtaining timely normative data for each new updated version. Additionally, in longitudinal studies where participants need to be re-tested several times, there is a danger of practice effects, with participants potentially learning answers to questions with repeated administration of the same questions. The AMI does not require the participant to retrieve the same episodic memories repeatedly at each testing session which reduces practice effects.

2.3.5.4. Mini-Mental State Examination

The Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) is one of the most extensively used cognitive assessment tools in medicine. It is a brief and simple bedside screening tool for global cognitive impairment and dementia. It is also useful for tracking changes in cognitive function over time. The test takes 5-10 minutes to administer and covers the following domains: orientation in time and place, registration and recall of verbal information, attention and calculation, language, and visual construction (copying). Performance is scored on a 30-point scale. A score of 23 or below is generally considered abnormal (Tombaugh & McIntyre, 1992). The MMSE was administered as part of routine pre- and post-ECT assessment of global cognitive function

on patients in this study. For purposes of this research, the pre-ECT MMSE score was used to control for baseline global cognitive function in analyses of AMI performance.

The MMSE has moderate-to-high internal and test-retest reliability (Tombaugh & McIntyre, 1992). Test-retest reliability generally fell between 0.80 and 0.95 in a review of published studies (Tombaugh & McIntyre, 1992), dipping below that in samples where one would expect to see marked day-to-day variation in scores. For instance, in one study of reliability and validity of the MMSE, patients with delirium had a test-retest correlation coefficient of 0.56 (Anthony, LeResche, Niaz, von Korff, & Folstein, 1982). This actually shows that the MMSE is sensitive to the fluctuating course of a condition like delirium. Meanwhile, in the same study, scores attained by cognitively intact hospital patients and patients with dementia on two testing occasions separated by a day had high test-retest reliability (0.85 and 0.90, respectively).

Regarding the validity of the MMSE, it is important to note that it is not intended as a diagnostic instrument for any particular nosological category. Instead, it provides an estimate of global cognitive impairment and can thus help determine where further workup is necessary. The common cut-off score of 23 shows good sensitivity and specificity for detecting dementia and good predictive validity for longitudinal decline in cognitive function (Tombaugh & McIntyre, 1992). The MMSE also shows good correlations with other neuropsychological tests and activities of daily living in this patient population (Tombaugh & McIntyre, 1992).

Performance on the MMSE is influenced by demographic factors, particularly age and education, and population-based norms (N=18,056) have been developed to address this (Crum, Anthony, Bassett, & Folstein, 1993). Patients with MDD underperform on the MMSE compared to normal controls. In a meta-analysis, the mean effect size across six studies was 1.03 (Zakzanis et al., 1998).

2.3.6. Statistical analyses

All statistical analyses used a two-tailed $p<0.05$ level of significance and were carried out using SPSS version 21 software (IBM Corp., 2012). Intraclass correlation coefficients were used to assess the inter-rater reliability of the AMI total, semantic and episodic scores. To test for the effect of time (baseline, after final ECT, three-month follow-up) on three AMI scores (total, semantic and episodic) while controlling for covariates (age, gender, years of education, baseline MMSE score, baseline HRSD-24 score), a repeated measures analysis of covariance (ANCOVA) for used for each of the three dependent variables. See section 6.2.6 for further details regarding statistical analyses.

3. Systematic review and meta-analysis of relapse following a successful course of ECT for major depression

3.1. Introduction

ECT is a unique treatment in psychiatry that predates modern psychopharmacology. Once used as first-line treatment for severe depression in often medication-naïve patients, its use nowadays is reserved for a minority of patients with severe, chronic, difficult-to-treat depression where several treatment steps have usually been unsuccessful. Such treatment-resistant patients are generally less likely to achieve full remission and when they do are prone to relapse and recurrence (Fekadu et al., 2009b). Although acute remission rates exceed those seen with other somatic treatments (Ren et al., 2014; The UK ECT Review Group, 2003), high rates of relapse, especially early relapse, are observed and acknowledged as a major clinical problem (Kellner et al., 2006; Prudic et al., 2013; Sackeim et al., 2001). Consolidating and prolonging remission is a key clinical challenge surrounding ECT use (Kellner, 2013).

Following introduction of the first effective antidepressants, continuation antidepressant monotherapy after ECT appeared to minimise the likelihood of relapse. Early research conducted in the United Kingdom in the 1960s demonstrated the efficacy of antidepressants over placebo with six-month relapse rates in tricyclic antidepressant (TCA) or monoamine oxidase inhibitor (MAOI) treated patients of about 20% compared with 40-70% in untreated or benzodiazepine-only treated patients (Imlah et al., 1965; Kay et al., 1970; Seager & Bird, 1962). However, more recent studies show considerably less favourable outcomes, with relapse rates typically about 40-50% at six months despite vigorous continuation therapy such as antidepressant-lithium combination or continuation ECT (Kellner et al., 2006; Prudic et al., 2013; Sackeim et al., 2001). Of note, in a more recent trial where patients were randomised to either TCA monotherapy with nortriptyline,

TCA-lithium combination or placebo, TCA monotherapy was not significantly more effective than placebo in preventing relapse (Sackeim et al., 2001).

Higher rates of relapse in recent decades may be due to historical changes in ECT patient populations with medication-resistant patients now being the majority of those referred for ECT (Sackeim, 1994). The negative impact of medication resistance on ECT outcomes had been suggested decades ago (Bruce et al., 1960; Hamilton, 1974) and was subsequently demonstrated by studies showing that patients with established medication resistance have worse acute (Prudic et al., 1996; Prudic et al., 1990) and longer-term (Sackeim et al., 1990) outcomes. A recent meta-analysis confirmed that acute remission rates with ECT are lower in treatment-resistant patients (48%) compared to those in whom medication resistance had not been established (65%) (Heijnen et al., 2010).

Currently there is no agreement on what constitutes optimal post-ECT relapse prevention treatment. The American Psychiatric Association guidelines on ECT, now over a decade old, recommend continuation therapy with either pharmacotherapy or continuation ECT for virtually all patients (American Psychiatric Association, 2001). The Royal College of Psychiatrists guidelines recommend a minimum of six months of continuation pharmacotherapy (The Royal College of Psychiatrists, 2013). The NICE guidelines state that antidepressant pharmacotherapy should be initiated or continued in patients who have responded to a course of ECT and advise to consider lithium augmentation (National Institute for Clinical Excellence, 2010). However, no specific guidelines on choice of agent (or combination thereof) or duration of treatment exist. Given that relapse following ECT is a key clinical problem surrounding the use of this treatment, an up-to-date systematic review of all existing evidence, randomised and observational, was carried out to provide an overview of current knowledge on this important question.

3.2. Materials and Methods

3.2.1. Search strategy

An electronic literature search of PubMed, Embase, CINAHL, PsycINFO and Cochrane Library databases was performed up to January 2013 with no time, language or other restrictions. Keywords used were (ECT OR electroconvulsive therapy OR convulsive therapy) AND (depression OR depressive OR mood disorder OR bipolar disorder OR affective disorder OR melancholi*) AND (long term OR follow up OR relapse OR prognosis OR mortality OR maintenance OR continuation). Hand-searches of reference sections of previous reviews and included studies were carried out.

Following exclusion of database duplicates and clearly ineligible reports, judging by title and abstract screening, two reviewers (the present author and Dr. Erik Kolshus, senior registrar in psychiatry) independently evaluated for eligibility all studies retained for full-text screening. Where studies met inclusion criteria (described below), the two reviewers independently extracted data from reports. Information regarding study design, ECT treatment parameters, sample characteristics, type of continuation therapy, type of outcome measure, definition of relapse, valid sample size at each follow-up, cumulative number of relapses at each time point and cumulative number of dropouts at each time point was extracted. Discrepancies were resolved by joint re-evaluation of reports.

When extracting relapse proportions from reports, preference was given to information in the body of texts and tables. Where the study explicitly reported relapse rates only for the study endpoint but where patients were assessed at multiple intermediate time points, survival curves were examined; where it was deemed that the number of relapses could be extracted from graphs, this was done jointly by the two reviewers. Where studies met inclusion criteria but data were reported in a non-extractable format, original authors were contacted. Given the literature age span, this was not always possible as authors were sometimes untraceable or deceased.

3.2.2. Study eligibility criteria

The following inclusion criteria were applied:

(1) prospective study reported in a peer-reviewed publication

(2) participant age ≥18

(3) an acute course of ECT was administered for treating a major depressive episode (unipolar or bipolar) diagnosed by clinical judgement or formal diagnostic criteria (e.g. DSM-IV)

(4) those deemed to be ECT responders or remitters were prospectively followed-up and monitored for relapse

(5) relapse was operationally defined by the original investigators and reported in a categorical fashion (i.e. as the percentage of the initial responder or remitter sample who relapsed)

(6) relapse was ascertained on the basis of clinical judgement or by using formal diagnostic criteria and/or pre-specified cut-off scores on clinician-rated depression severity rating scales (e.g. Hamilton Depression Rating Scale)

(7) clinical outcome assessment was carried out three months or more following the last ECT session

Exclusion criteria:

(1) case studies or series with N<10

(2) retrospective studies

(3) prospective studies where relapse was not established directly via patient interview but instead on the basis of proxy measures (e.g. rehospitalisation rates), mailed self-report questionnaires or information obtained from third-parties (e.g. patients' relatives or treating physicians)

(4) presence of non-affective psychosis, dementia, neurological disease or unstable medical conditions in the sample

(5) unmodified ECT

3.2.3. Outcomes

Relapse rate was defined as the proportion of the original ECT responder or remitter sample that subsequently experienced a return of depressive symptoms deemed to be significant enough to merit the designation of relapse by the original investigators. Specific criteria for relapse varied between the studies; original investigators' definitions were retained. Relapse criteria used in each individual study are described in Table 3.1

below. Studies using inadequate measures of relapse likely to underestimate its true prevalence (e.g. rehospitalisation rates only) were excluded.

The primary outcome was cumulative relapse proportion at the six-month follow-up after last ECT for which we expected most data would be available. In all primary analyses, only samples treated with antidepressant pharmacotherapy were included because virtually all ECT patients today receive long-term prophylactic therapy which is most commonly administered in the form of medication. Secondary analyses of relapse rates on continuation ECT (C-ECT) (which is used less frequently than medication) were also carried out. C-ECT is a form of relapse prevention where the patient continues to receive ECT after the acute course at a reduced schedule. It is indicated in patients with a past history of good ECT response where antidepressant continuation therapy was either ineffective or could not be tolerated at therapeutic doses (American Psychiatric Association, 2001). C-ECT has a long clinical history. Its use predates the discovery of antidepressant medication but it remains an under-researched treatment (The Royal College of Psychiatrists, 2005). NICE guidelines conclude that prospective evidence for the efficacy (and safety) of C-ECT is lacking and make no treatment recommendation beyond recognising that it "will continue to be used in exceptional circumstances" (National Institute for Clinical Excellence, 2010, p. 526).

Other secondary analyses investigated relapse rates on placebo or no maintenance treatment. Additional secondary outcomes were relapse rates at three, twelve and twenty-four months after last ECT, again in patients receiving antidepressant medication. Finally, to investigate the relative efficacy of different relapse prevention strategies, we aimed to calculate relative risks of relapse in randomised controlled trials (RCTs) of different continuation therapies at three, six and twelve months where at least two studies comparing the same strategy were available.

3.2.4. Statistical analyses

All analyses were based on study completers. Attrition rates for each study were recorded (see Table 3.1). Mean relapse proportions with 95% confidence intervals (CIs) were calculated by pooling samples using a random-effects model (DerSimonian & Laird, 1986) as we expected substantial differences in study designs and patient populations. Heterogeneity was assessed using the I^2 statistic (Higgins et al., 2003). Where substantial heterogeneity was observed and where sufficient data were available, random-effects meta-regression analyses with unrestricted maximum likelihood estimation were carried out to explore possible sources of heterogeneity. Pre-specified covariates investigated were mean age, proportion of psychotic patients and proportion of medication-resistant patients. Planned subgroup analyses compared study designs (trial vs. observational), relapse criteria (standardised symptom rating scale vs. clinical judgement), and whether concomitant pharmacotherapy was allowed during the index ECT course. To investigate the possibility of changes in relapse rates over time, a cumulative meta-analysis was carried out for the primary endpoint (six months).

For head-to-head comparisons of different continuation therapies, relative risks (RR) with 95% CIs and numbers needed to treat (NNT) were calculated.

Publication bias was assessed by visual inspection of funnel plots where more than 10 studies were available. All statistical analyses were carried out using Comprehensive Meta Analysis Version 2.2 software (Borenstein et al., 2011).

3.3. Results

3.3.1. Search results

The computerised search retrieved 4,198 results (see Figure 3.1). Hand-searches identified four additional eligible studies. Following exclusion of database duplicates and initial exclusion of ineligible studies, 194 titles were retained for full-text screening. Of the

194 full-text studies screened, 32 met inclusion criteria and provided extractable data either from published reports or contact with original authors (see Table 3.1 below for details regarding study characteristics).

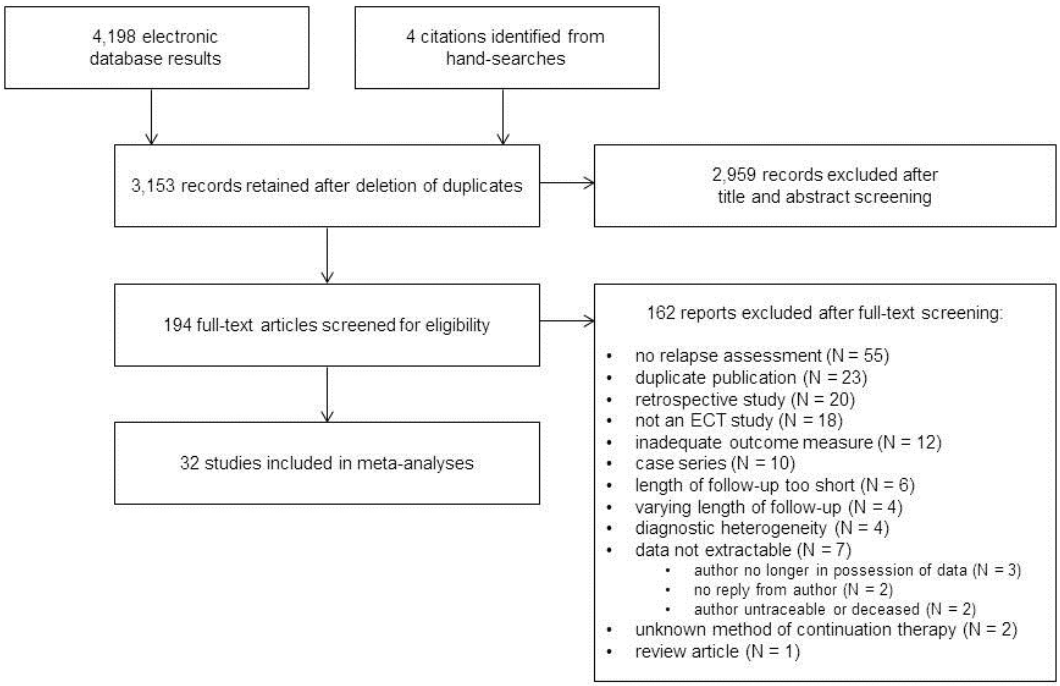

FIGURE 3.1. Study flow diagram

TABLE 3.1. Characteristics of included studies

Study	Design	ECT treatment parameters	Diagnostic criteria	Relapse criteria	Method of post ECT continuation therapy	Length of follow-up	Samples	N responders/ remitters from ECT at the start of continuation phase	N (%) of completer subsample that relapsed by study endpoint	N (%) dropout at study endpoint
Arfwidsson 1973	RCT of ECT + chlorpromazine vs. ECT + placebo during acute phase no antidepressants during 3-month follow-up	BL electrode placement threshold stimulation variable frequency of treatment concomitant chlorpromazine or placebo	clinical judgement of "endogenous or mixed endogenous-psychogenic depression"	double-blind rating on the Cronholm-Ottosson Depression Scale + global clinical rating	none (except hypnotics and sedatives)	3 months	total sample	47	23/46 (50%)	1 (2%)
Barton 1973	RCT of ECT until remission vs. ECT until remission + two extra sessions no antidepressants during 3-month follow-up	BL electrode placement 2 x weekly no concomitant medication	clinical judgement of "primary depressive illness [...] endogenous pattern"	"even minimal return of true depressive symptoms" according to clinical judgement	none (except hypnotics)	3 months	total sample	54	23/50 (46%)	4 (7%)
Birkenhager 2004	part prospective part retrospective cohort (prospective subsample from author-supplied data reported here)	brief-pulse mixture of RUL (d'Elia) and BL electrode placement age dosing method 2 x weekly medication washout prior to ECT; continuation pharmacotherapy started during the last two weeks of ECT course	DSM-III-R unipolar MDD mood-congruent delusions only where psychotic	monthly clinical evaluation by psychiatrist	TAU	12 months	prospectively followed-up subsample	28	10/28 (36%)	0 (0%)
Birkenhager 2005	prospective cohort	brief-pulse RUL d'Elia 2.5 x ST, crossed over to BL 1.5 x ST if inadequate response after 6 sessions 2 x weekly	DSM-IV unipolar MDD mood-congruent delusions only where psychotic	met DSM-IV criteria for MDD for at least one week and had a HRSD-17 score of ≥16	mostly TAU (except 18 patients who were followed-up as part of an RCT of imipramine continuation therapy)	12 months	total sample	59	23/55 (42%)	4 (7%)

Cosgriff 1990	prospective cohort	unknown	unknown	clinical judgement	TAU	3 months	total sample	13	4/13 (31%)	0 (0%)
Dannon 2002	RCT of ECT vs. rTMS naturalistic follow-up	RUL d'Elia 2.5 x ST crossed over to BL if no response after 6 sessions	DSM-IV MDD	met DSM-IV criteria for MDD and had a HRSD-17 score of ≥16	TAU	6 months	ECT-treated sample	20	4/20 (20%)	0 (0%)
Eranti 2007	RCT of ECT vs. rTMS naturalistic follow-up	brief-pulse BL at 1.5 x ST or RUL at 2.5 x ST 2 x weekly	DSM-IV MDE unipolar or bipolar	clinical judgement	TAU	6 months	ECT-treated sample	13	6/12 (50%)	1 (8%)
Flint 1998	prospective cohort	brief-pulse fixed high-dose RUL switched to BL if inadequate response after 5 sessions 3 x weekly	DSM-III-R unipolar psychotic MDD	met DSM-III-R criteria for MDD and had a HRSD-17 score of ≥16	nortriptyline	24 months	ECT-treated sample	15	8/15 (53%)	0 (0%)
Grunhaus 1994	prospective cohort	brief-pulse dose-titrated relative to ST mixture of BL and RUL (clinician's choice)	RDC MDD	met RDC criteria for MDD and GAS <50	TAU	6 months	total sample	20	11/20 (55%)	0 (0%)
Grunhaus 2001	RCT of fluoxetine + melatonin vs. fluoxetine + placebo post ECT continuation therapy	mixture of RUL at 2.5 x ST and BL dose-titrated relative to ST	DSM-IV unipolar MDD	return of five or more DSM-IV criteria for MDD and had a HRSD-17 score of ≥16	fluoxetine + melatonin vs. fluoxetine + placebo	3 months	1) fluoxetine + melatonin 2) fluoxetine + placebo	1) 21 2) 18	1) 5/20 (25%) 2) 5/15 (33%)	1) 1 (5%) 2) 3 (17%)
Imlah 1965	RCT of ECT + phenelzine vs. ECT + imipramine vs. ECT + placebo during acute phase medications continued during follow-up phase; patients on placebo discharged on no medication	2 x weekly	clinical judgement of "depressive illness of a sufficient degree to warrant the use of ECT"	clinical judgement	phenelzine vs. imipramine vs. no medication	6 months	1) phenelzine 2) imipramine 3) no medication	1) 42 2) 39 3) 43	1) 8/37 (22%) 2) 7/33 (21%) 3) 21/41 (51%)	1) 5 (12%) 2) 6 (15%) 3) 2 (5%)
Kay 1970	RCT of ECT + amitriptyline vs. ECT + diazepam (diazepam used as placebo as placebo was deemed unethical by study psychiatrists) medications continued during follow-up phase	unknown	clinical judgement of "affective disorders uncomplicated by organic brain disease, schizophrenia or subnormality"	treatment "failure" defined as relapse, lack of satisfactory progress, serious side-effects or need for administration of TCAs or MAOIs	amitriptyline vs. diazepam	6 months	1) amitriptyline 2) diazepam	1) 52 2) 63	1) 8/52 (15%) 2) 24/63 (38%)	1) 0 (0%) 2) 0 (0%)

Kellner 2006	RCT of C-ECT vs. nortriptyline + lithium continuation therapy	brief-pulse BL at 1.5 x ST 3 x weekly	DSM-IV unipolar MDD	two consecutive HRSD-24 ratings ≥16 with a minimum 10 point increase from post ECT HRSD-24 score	C-ECT vs. nortriptyline + lithium	6 months	1) C-ECT 2) nortriptyline + lithium	1) 89 2) 95	1) 33/74 (45%) 2) 30/74 (41%)	1) 15 (17%) 2) 21 (22%)
Krog-Meyer 1984	Group 1 (predicted good response) prospective cohort given continuation placebo Group 2 (predicted poor response) RCT of placebo or amitriptyline continuation therapy	unknown	ICD-8 endogenous depression	increase in dose of amitriptyline or placebo or a change to another antidepressant medication	amitriptyline vs. placebo	6 months	1) placebo group 1 2) placebo group 2 3) amitriptyline	1) 15 2) 13 3) 11	1) 3/15 (20%) 2) 9/13 (69%) 3) 2/11 (18%)	1) 0 (0%) 2) 0 (0%) 3) 0 (0%)
Lauritzen 1996	Group A: RCT of ECT + paroxetine vs. ECT + placebo Group B: RCT of ECT + paroxetine vs. ECT + imipramine medications continued during follow-up phase	brief-pulse 3 x weekly BL for first 3 sessions, followed by RUL d'Elia	DSM-III-R MDE	HRSD-17 score of ≥18 and/or Bech Melancholia Scale score of ≥15 maintained for a week	paroxetine vs. imipramine vs. placebo	6 months	1) paroxetine group A 2) placebo group A 3) paroxetine group B 4) imipramine group B	1) 15 2) 16 3) 21 4) 22	1) 6/13 (46%) 2) 9/12 (75%) 3) 2/18 (11%) 4) 8/17 (47%)	1) 2 (13%) 2) 4 (25%) 3) 3 (14%) 4) 5 (23%)
Martinez-Amoros 2012	prospective cohort	brief-pulse BL "half age" dosing method	DSM-IV unipolar MDD	met criteria for a major depressive episode	C-ECT + TAU pharmacotherapy vs. TAU pharmacotherapy	24 months	1) C-ECT + TAU pharmacotherapy 2) TAU pharmacotherapy	1) 44 2) 83	1) 26/44 (59%) 2) 40/83 (48%)	1) 0 (0%) 2) 0 (0%)
Meyers 2001	RCT of nortriptyline + perphenazine vs. nortriptyline + placebo continuation therapy	unknown	DSM-IV unipolar psychotic MDD	met DSM-IV criteria for MDD or development of delusional ideation	nortriptyline + placebo vs. nortriptyline + perphenazine	6 months	1) nortriptyline + placebo 2) nortriptyline + perphenazine	1) 13 2) 16	1) 2/13 (15%) 2) 5/15 (33%)	1) 0 (0%) 2) 1 (6%)
Navarro 2008	RCT of C-ECT + nortriptyline vs. nortriptyline continuation therapy	brief-pulse BL 3 x weekly	DSM-IV unipolar psychotic MDD	met DSM-IV criteria for MDD and HRSD-17 score of ≥16	nortriptyline vs. C-ECT + nortriptyline	24 months	1) nortriptyline 2) C-ECT + nortriptyline	1) 17 2) 16	1) 8/13 (62%) 2) 1/12 (8%)	1) 4 (24%) 2) 4 (25%)
Nordenskjold 2013	RCT of C-ECT + individualised pharmacotherapy vs. individualised pharmacotherapy continuation therapy	ultrabrief-pulse RUL 6 x ST	MDE unipolar or bipolar verified by MINI-PLUS	MADRS ≥20 or psychiatric rehospitalisation or suicide or suspected suicide	C-ECT + individualised pharmacotherapy vs. individualised pharmacotherapy	12 months	1) C-ECT + individualised pharmacotherapy 2) individualised pharmacotherapy	1) 28 2) 28	1) 7/18 (39%) 2) 16/25 (64%)	1) 10 (36%) 2) 3 (11%)

Prudic 2004	prospective cohort	mixture of electrode placements (BL and RUL), wave form (brief-pulse and sine-wave) and dosing (titrated and fixed high dose)	DSM-IV MDE unipolar, bipolar or schizoaffective	HRSD-24 score of ≥16 for two consecutive weeks and an absolute increase of at least 10 points for two consecutive weeks relative to post ECT score or rehospitalisation with depression, psychotic symptoms or suicidal intent	TAU; however, "use of continuation ECT was frequent but equally represented among patients who did (43.9%) and did not relapse (49.0%)"	6 months	total sample	162	99/145 (68%)	17 (10%)
Prudic 2013	RCT of nortriptyline + lithium vs. venlafaxine + lithium continuation therapy	brief-pulse RUL 6 x ST BL 1.5 x ST concomitant pharmacotherapy with nortriptyline, venlafaxine or placebo	DSM-IV MDE unipolar or bipolar	HRSD-24score of ≥16 for two consecutive weeks and an absolute increase of at least 10 points for two consecutive weeks relative to post ECT score; also, if rated considerably worse on the CGI for two consecutive weeks and the study psychiatrist deemed it was in the patient's best interest to exit the protocol due to emergence of suicidal ideation or intent, psychotic symptoms, hypomania or mania, or significant functional impairment (GAF <50)	nortriptyline + lithium vs. venlafaxine + lithium	6 months	total sample	122	61/102 (60%)	20 (16%)
Sackeim 1993	RCT of RUL 1.5 x ST vs. BL 1.5 x ST vs. RUL 2.5 x ST vs. BL 2.5 x ST naturalistic follow-up	brief-pulse RUL 1.5 x ST BL 1.5 x ST RUL 2.5 x ST BL 2.5 x ST	RDC MDE unipolar or bipolar	met RDC criteria for MDD, had a HRSD-24 score increase of ≥50% from post ECT score and HRSD-24 score of ≥14 maintained for a week	TAU	12 months	total sample	73	41/70 (59%)	3 (4%)

Sackeim 2000	RCT of RUL 1.5 x ST vs. RUL 2.5 x ST vs. RUL 6 x ST vs. BL 2.5 x ST naturalistic follow-up	brief-pulse RUL 1.5 x ST RUL 2.5 x ST RUL 6 x ST BL 2.5 x ST	RDC MDE unipolar or bipolar	met RDC criteria for MDD, had a HRSD-24 score increase of ≥50% from post ECT score and HRSD-24 score of ≥14 maintained for a week	TAU	12 months	total sample	64	33/62 (53%)	2 (3%)
Sackeim 2001	RCT of nortriptyline vs. nortriptyline + lithium vs. placebo continuation therapy	brief-pulse mixture of BL and RUL d'Elia electrode placement (clinician's choice)	RDC unipolar MDE	HRSD-24 score of ≥16 for two consecutive weeks and an absolute increase of at least 10 points for two consecutive weeks relative to post ECT score	nortriptyline vs. nortriptyline + lithium vs. placebo	6 months	1) nortriptyline 2) nortriptyline + lithium 3) placebo	1) 27 2) 28 3) 29	1) 15/25 (60%) 2) 9/23 (39%) 3) 21/25 (84%)	1) 2 (7%) 2) 5 (18%) 3) 4 (14%)
Sackeim 2008	RCT of brief-pulse RUL 6 x ST vs. brief-pulse BL 2.5 x ST vs. ultrabrief-pulse RUL 6 x ST vs. ultrabrief-pulse BL 2.5 x ST naturalistic follow-up	brief-pulse RUL 6 x ST brief-pulse BL 2.5 x ST ultrabrief-pulse RUL 6 x ST ultrabrief-pulse BL 2.5 x ST	RDC and DSM-IV MDE unipolar or bipolar	HRSD-24 score of ≥16 for two consecutive weeks and an absolute increase of at least 10 points for two consecutive weeks relative to post ECT score or rehospitalisation with symptom worsening, psychotic symptoms or suicidal intent	TAU	12 months	total sample	68	34/60 (57%)	8 (12%)
Seager 1962	RCT of ECT + imipramine vs. ECT + placebo patients continued to receive the same medications during follow-up phase or were randomised to crossover treatment	unknown	clinical judgement of "depressive illness warranting electrical treatment"	clinical judgement	imipramine vs. placebo	6 months	1) imipramine 2) placebo	1) 12 2) 16	1) 2/12 (17%) 2) 11/16 (69%)	1) 0 (0%) 2) 0 (0%)
Shapira 1995	RCT of ECT 2 x weekly vs. 3 x weekly open trial of continuation lithium monotherapy	brief-pulse BL 1.5 x ST 2 x weekly or 3 x weekly	RDC endogenous MDD	HRSD-21 ≥18, 50% increase in HRSD-21 score from post ECT score and sufficient clinical severity to warrant additional antidepressant medication or hospitalisation	lithium	6 months	total sample	28	8/24 (33%)	4 (14%)

Spiker 1985	prospective cohort	brief-pulse mostly RUL	RDC primary MDD, psychotic subtype	readmitted for depression or another course of ECT or "clear consensus among the patient, the patient's family, and the therapist that the patient had suffered a relapse"	TAU	12 months	total sample	32	16/32 (50%)	0 (0%)
Tew 2007	prospective naturalistic follow-up of those who refused randomisation to Sackeim 2001	see Sackeim 2001	RDC unipolar MDD	HRSD-24 ≥16 or an increase in score >10 points	TAU	6 months	total sample	75	27/53 (51%)	22 (29%)
van den Broek 2006	RCT of continuation imipramine vs. placebo	brief-pulse RUL d'Elia 2.5 x ST, crossed over to BL 1.5 x ST if inadequate response after 6 sessions patients in "critical condition" received BL from the start	DSM-IV unipolar MDD	at least "moderately worse" compared to post ECT on the CGI	imipramine vs. placebo	6 months	1) imipramine 2) placebo	1) 12 2) 15	1) 2/11 (18%) 2) 12/15 (80%)	1) 1 (8%) 2) 0 (0%)
Wijkstra 2000	prospective cohort	brief-pulse BL dose determined by age method	DSM-IV MDD	met DSM-IV MDD criteria and ≥50% increase in HRSD-17 score and HRSD-17 ≥14 maintained for at least a week	C-ECT	6 months	total sample	12	6/12 (50%)	0 (0%)
Yildiz 2010	RCT of continuation sertraline vs. placebo	brief-pulse BL dose determined by age method 2 x weekly	DSM-IV unipolar MDD	MADRS ≥16 maintained over two consecutive visits	sertraline vs. placebo	3 months	1) sertraline 2) placebo	1) 26 2) 6	1) 6/23 (26%) 2) 4/6 (67%)	1) 3 (12%) 2) 0 (0%)

Abbreviations: BL – bilateral; CGI – Clinical Global Impression scale; C-ECT – continuation ECT; ECT – electroconvulsive therapy; GAF – Global Assessment of Functioning scale; GAS – Global Assessment Scale; HRSD-17 – Hamilton Rating Scale for Depression (17-item version); HRSD-21 – Hamilton Rating Scale for Depression (21-item version); HRSD-24 – Hamilton Rating Scale for Depression (24-item version); ICD-8 – International Classification of Diseases 8th Revision; MADRS – Montgomery-Asberg Depression Rating Scale; MAOI – monoamine oxidase inhibitor; MDD – major depressive disorder; MDE – major depressive episode; MINI-PLUS – Mini-International Neuropsychiatric Interview Plus; RCT – randomised controlled trial; RDC – Research Diagnostic Criteria; rTMS – repetitive transcranial magnetic stimulation; RUL – right unilateral; ST – seizure threshold; TAU – treatment as usual; TCA – tricyclic antidepressant

3.3.2. Relapse rate at six months

By six months following ECT, 34.0% (95% CI=27.2-41.5%, I^2=76%) of patients (N=844) treated with continuation pharmacotherapy had relapsed. Because long-term outcomes are believed to have worsened over the many decades of ECT use, a cumulative meta-analysis was performed with each study added to the previous ones in chronological order (Figure 3.2). Beginning with the first controlled studies of continuation pharmacotherapy in the 1960s, relapse rates held at around 20%. As modern studies of more treatment-resistant patients and clearer reporting of methodology began to be conducted, relapse rates rose towards present-day levels. It should be noted that following the publication of three important early trials (Imlah et al., 1965; Kay et al., 1970; Seager & Bird, 1962), with the exception of one small trial in 1984 (Krog-Meyer, Kirkegaard, & Kijne, 1984), no other prospective long-term follow-up studies of continuation pharmacotherapy meeting inclusion criteria were found between 1970 and the early 1990s, perhaps coinciding with diminishing use of ECT. Given this gap in evidence, it is unclear when precisely the shift in relapse rates might have occurred.

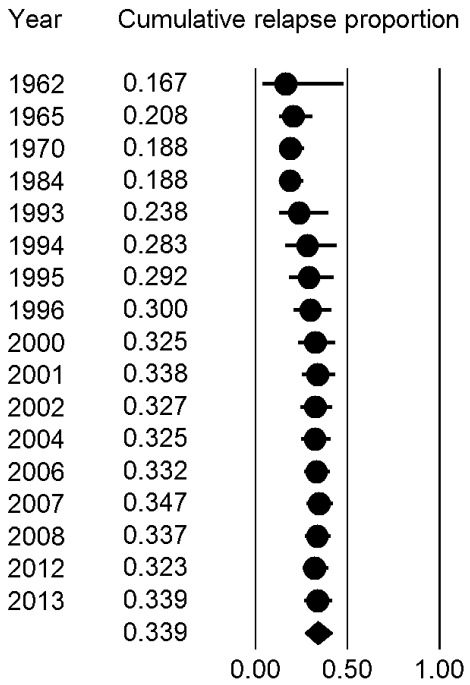

FIGURE 3.2. Cumulative meta-analysis showing the progression of six-month relapse rate from 1962 to 2013

Due to the historical trend observed in the data, a sensitivity analysis was carried out where only modern post-DSM-III studies of pharmacologically-treated patients (N=710) were included in the meta-analysis (Birkenhager, Renes, & Pluijms, 2004; Dannon, Dolberg, Schreiber, & Grunhaus, 2002; Eranti et al., 2007; Grunhaus et al., 1994; Kellner et al., 2006; Krog-Meyer et al., 1984; Lauritzen et al., 1996; Martinez-Amoros et al., 2012; Meyers et al., 2001; Navarro et al., 2008; Prudic et al., 2013; Sackeim et al., 2001; Sackeim et al., 1993; Sackeim et al., 2000; Shapira et al., 1995; Tew et al., 2007; van den Broek et al., 2006). Relapse rate across these 17 studies was 37.7% (95% CI=30.7-45.2%, I^2=70%) (Figure 3.3).

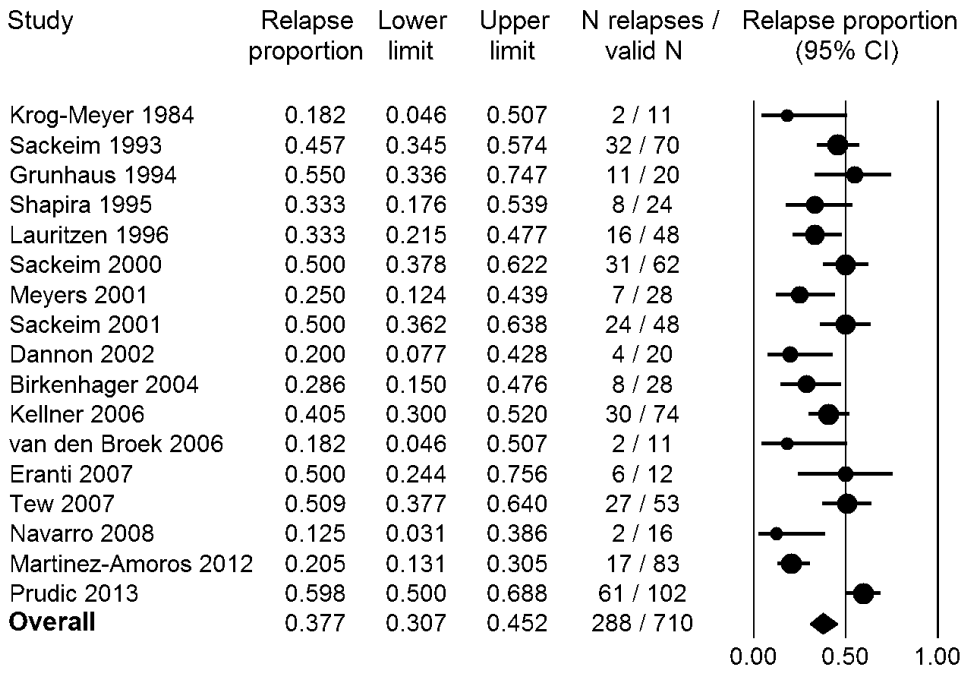

FIGURE 3.3. Forest plot showing six-month relapse rate in modern post-DSM-III studies

Due to remaining high heterogeneity, random-effects meta-regressions were performed to investigate the possible contribution of study characteristics on outcome. Since only a small number of studies reported relevant moderators, multivariate analyses could not be conducted; hence, each moderator was modelled separately. In modern studies, there was no effect of baseline medication-resistance on likelihood of relapse

(p=0.429). However, there was a suggestion of lower relapse rates in samples with a greater percentage of psychotic patients (p=0.004) and a higher mean age (p=0.038).

Methodological factors appeared to influence outcome. In subgroup analyses, studies using clinical judgement to determine relapse reported lower rates (28.3%, 95% CI=17.1-43.1%) than studies using cut-off scores on depression rating scales (41.7%, 95% CI=34.8-48.9%). Studies where concomitant pharmacotherapy was permitted during the ECT course had lower relapse rates (29.2%, 95% CI=18.0-43.6%) than those where maintenance pharmacotherapy was begun after the course (41.6%, 95% CI=35.0-48.6%). Naturalistic studies (39.1%, 95% CI=29.2-50.0%) and controlled trials (36.1%, 95% CI=26.9-46.4%) of continuation pharmacotherapy did not differ in relapse rates.

3.3.3. Relapse rates at three, twelve and twenty-four months

By three months following ECT, 27.1% of patients (N=350) on continuation pharmacotherapy had relapsed (95% CI=20.5-34.8%, I^2=48%) based on a meta-analysis of 11 studies (Cosgriff, Abbott, Oakley-Browne, & Joyce, 1990; Dannon et al., 2002; Grunhaus, Hirschman, Dolberg, Schreiber, & Dannon, 2001; Grunhaus et al., 1994; Lauritzen et al., 1996; Meyers et al., 2001; Navarro et al., 2008; Sackeim et al., 2001; Sackeim et al., 1993; Shapira et al., 1995; Yildiz et al., 2010) (Figure 3.4).

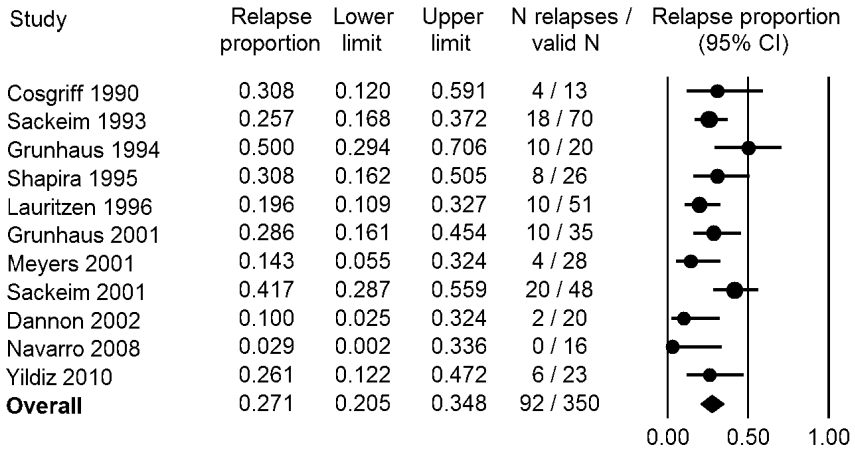

FIGURE 3.4. Forest plot showing three-month relapse rate

By one year following ECT, 51.1% (95% CI=44.7-57.4%, I^2=27%) of patients (N=348) had relapsed across eight included samples of patients treated with continuation pharmacotherapy (Birkenhager et al., 2004; Birkenhager, van den Broek, Mulder, & de Lely, 2005; Navarro et al., 2008; Nordenskjold et al., 2013; Sackeim et al., 1993; Sackeim et al., 2000; Sackeim et al., 2008; Spiker, Stein, & Rich, 1985) (Figure 3.5).

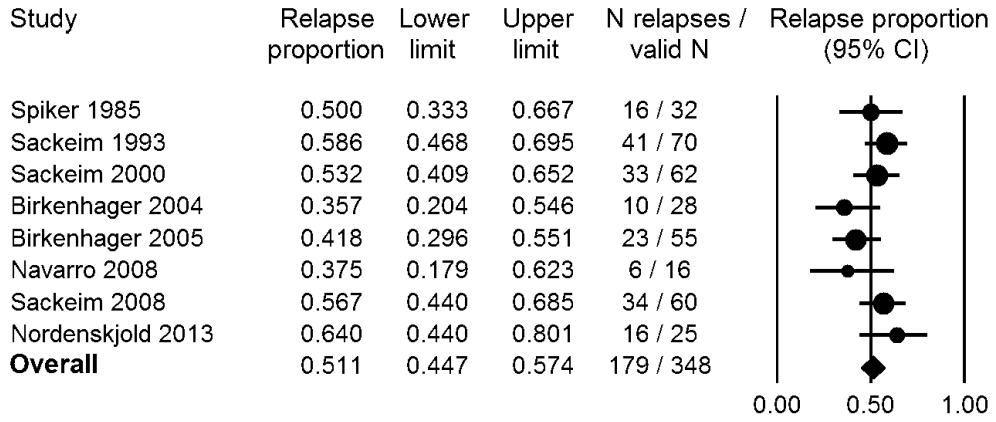

FIGURE 3.5. Forest plot showing 12-month relapse rate

Visual inspection of the funnel plot of studies reporting 12-month outcomes did not indicate presence of publication bias (Figure 3.6).

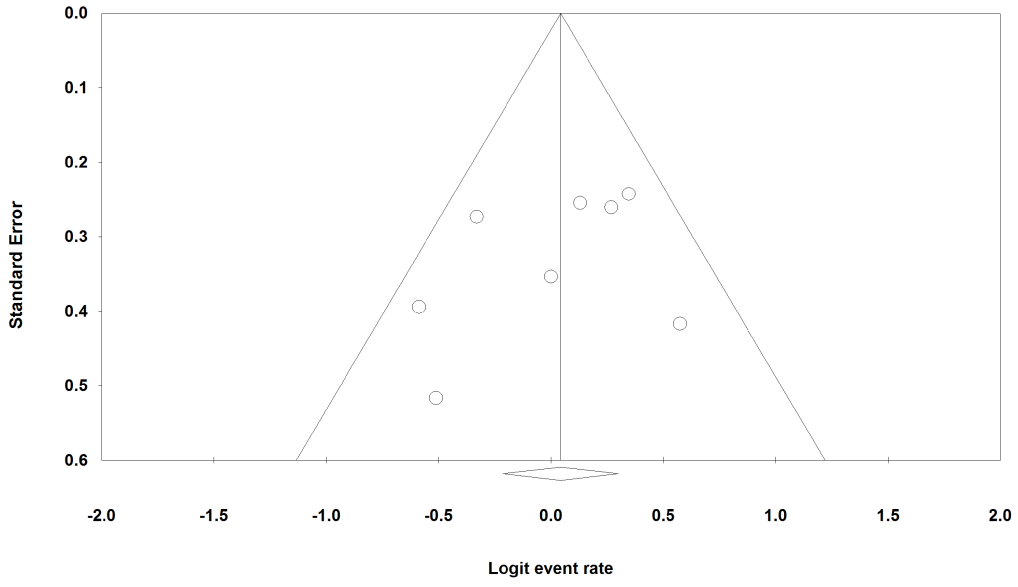

FIGURE 3.6. Funnel plot for 12-month relapse rate

Only three prospective studies with a two-year follow-up were found: two investigating outcomes in psychotic elderly patients (N=28) treated with nortriptyline monotherapy (Flint & Rifat, 1998; Navarro et al., 2008) and one in a general adult sample (N=83) maintained on treatment-as-usual pharmacotherapy (Martinez-Amoros et al., 2012). Relapse rate at two years was 50.4% (95% CI=41.2-59.6%, I^2=0) (Figure 3.7).

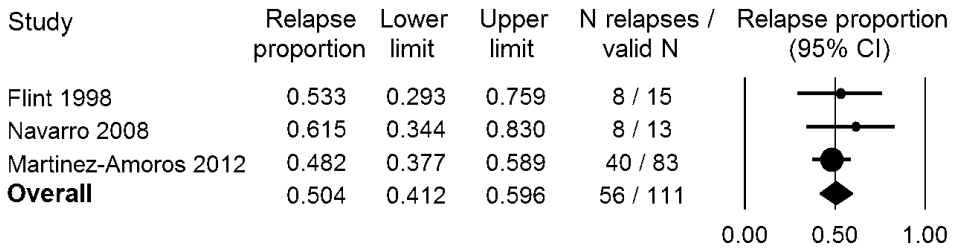

FIGURE 3.7. Forest plot showing 24-month relapse rate

3.3.4. Relapse rates with continuation ECT (C-ECT)

At the six-month follow-up, relapse rate across the four eligible C-ECT samples (N=146) was 37.2% (95% CI=23.4-53.5%, I^2=57%) (Kellner et al., 2006; Martinez-Amoros et al., 2012; Navarro et al., 2008; Wijkstra, Nolen, Algra, van Vliet, & Kahn, 2000), a virtually identical relapse rate to the figure for modern-era pharmacologically-treated patients presented above (37.7%). Given the similarity in six-month relapse rates in medication and C-ECT samples, a meta-analysis was carried out of all eligible modern-era studies where patients were treated with any form of recognised continuation therapy, pharmacological or C-ECT. Across 19 eligible studies (N=1001), 39.5% of patients had relapsed (95% CI=31.9-47.7%, I^2=81%) (Birkenhager et al., 2004; Dannon et al., 2002; Eranti et al., 2007; Grunhaus et al., 1994; Kellner et al., 2006; Krog-Meyer et al., 1984; Lauritzen et al., 1996; Martinez-Amoros et al., 2012; Meyers et al., 2001; Navarro et al., 2008; Prudic et al., 2013; Prudic et al., 2004; Sackeim et al., 2001; Sackeim et al., 1993; Sackeim et al., 2000; Shapira et al., 1995; Tew et al., 2007; van den Broek et al., 2006; Wijkstra et al., 2000).

When the two studies (Kellner et al., 2006; Wijkstra et al., 2000) where patients (N=86) were treated with C-ECT only and where no concomitant medication was permitted were analysed separately, relapse rate at six months rose to 45.4% and heterogeneity was eliminated (95% CI=35.2-55.9%, I^2=0).

For one and two-year follow-ups, only two studies at each time point met inclusion criteria. Patients in these studies were treated with C-ECT and pharmacotherapy combination therapy. Relapse rate at 12 months (N=33) was 20.5% (95% CI=3.0-68.1%, I^2=73%) (Navarro et al., 2008; Nordenskjold et al., 2013). At 24 months (N=56) it was 30.3% (95% CI=2.9-86.4%, I^2=85%) (Martinez-Amoros et al., 2012; Navarro et al., 2008). In addition to very small sample size and number of studies, high levels of heterogeneity were present in the analyses.

3.3.5. Relapse rates in untreated samples

To examine the long-term efficacy of a course of ECT in the absence of continuation treatment, studies reporting outcomes in unmedicated patients were meta-analysed. Two studies published in 1973, both with a three-month follow-up, reported relapse in ECT responders not permitted to take antidepressant medication during follow-up (Arfwidsson, Arn, & Beskow, 1973; Barton, Mehta, & Snaith, 1973). By three months after ECT, 47.9% had relapsed (95% CI=38.1-57.9%, I^2=0). No modern studies featuring entirely untreated (i.e. including no placebo) samples were found.

Next, relapse rates were analysed in placebo-treated samples where some non-specific benefit can be expected. Three RCTs (Lauritzen et al., 1996; Sackeim et al., 2001; Yildiz et al., 2010) provided extractable data at three months and seven RCTs (Imlah et al., 1965; Kay et al., 1970; Krog-Meyer et al., 1984; Lauritzen et al., 1996; Sackeim et al., 2001; Seager & Bird, 1962; van den Broek et al., 2006) provided six-month data. Relapse rates were 62.7% (95% CI=47.6-75.8%, I^2=0) at three months and 65.5% (95% CI=49.7-78.5%, I^2=72%) at six months. As with active continuation therapy, relapse rates were substantially lower in placebo samples from an earlier era. When only modern-

day post-DSM-III RCTs (Krog-Meyer et al., 1984; Lauritzen et al., 1996; Sackeim et al., 2001; van den Broek et al., 2006) are considered (N=65), relapse rate on placebo reached 78.0% (95% CI=66.1-86.5%, I^2=0) at six months.

3.3.6. Relative risk of relapse on continuation antidepressant pharmacotherapy vs. placebo

Relative risks of relapse in RCTs of active relapse prevention strategies vs. placebo were investigated at three and six months after ECT.

For the three-month follow-up, three placebo-controlled RCTs (N=128) provided extractable data: two (Lauritzen et al., 1996; Yildiz et al., 2010) evaluating selective serotonin reuptake inhibitor (SSRI) monotherapy vs. placebo and the other (Sackeim et al., 2001) comparing TCA monotherapy and TCA-lithium combination to placebo. The first meta-analysis measured relative risk of relapse in patients treated with any antidepressant pharmacotherapy vs. placebo. Relative risk of relapse on medication was 0.56 (95% CI=0.38-0.81, p=0.002, NNT=3.5, I^2=0) (Figure 3.8).

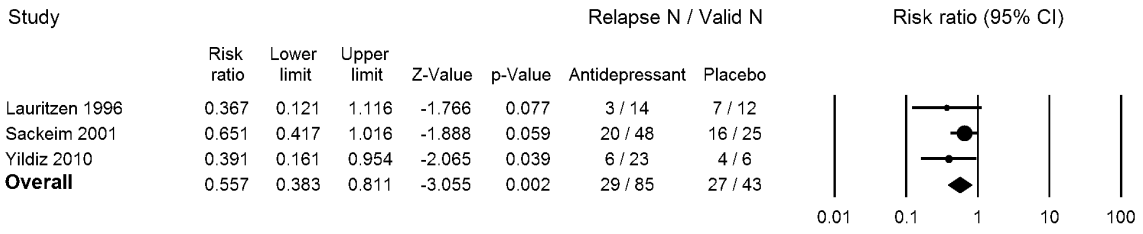

FIGURE 3.8. Forest plot showing relative risk of relapse on pharmacotherapy vs. placebo at three months

Next, the two studies (N=55) comparing SSRI monotherapy vs. placebo were separately analysed. One study used paroxetine (Lauritzen et al., 1996), the other sertraline (Yildiz et al., 2010). Pooled analysis showed SSRI monotherapy to be significantly more effective than placebo in preventing relapse at three months (RR=0.38, 95% CI=0.19-0.77, p=0.007, NNT=2.7, I^2=0).

At six months, two meta-analyses could be carried out: one featuring any antidepressant pharmacotherapy vs. placebo; another featuring tricyclic antidepressant monotherapy vs. placebo. No meta-analyses of other medication classes or combination strategies vs. placebo could be carried out for the six-month time point as only one study evaluated efficacy of an MAOI vs. placebo (Imlah et al., 1965), one study compared an SSRI to placebo (Lauritzen et al., 1996), while one study featured a TCA-lithium combination treatment group vs. placebo (Sackeim et al., 2001). Across the seven included studies (Imlah et al., 1965; Kay et al., 1970; Krog-Meyer et al., 1984; Lauritzen et al., 1996; Sackeim et al., 2001; Seager & Bird, 1962; van den Broek et al., 2006) (N=402), continuation pharmacotherapy halved the risk of relapse compared to placebo at six months (RR=0.49, 95% CI=0.39-0.62, p<0.0001, NNT=3.3, I^2=0) (Figure 3.9).

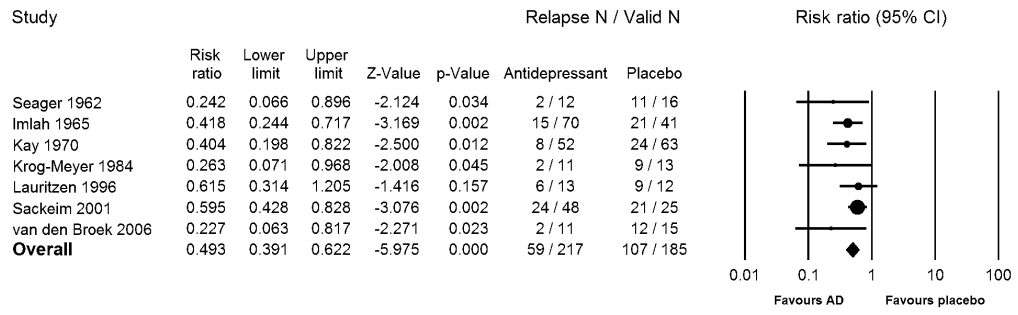

FIGURE 3.9. Forest plot showing relative risk of relapse on pharmacotherapy vs. placebo at six months

Patients in these studies were predominantly treated with TCAs. When TCA monotherapy samples are considered separately, this strategy was found to reduce the relative risk of relapse slightly further (RR=0.44, 95% CI=0.29-0.66, p<0.0001, NNT=3.2, I^2=36%). In all included studies where TCAs were used, with the exception of one trial that compared nortriptyline with placebo (Sackeim et al., 2001), TCA monotherapy was significantly more effective than placebo. Other included studies used either imipramine (Imlah et al., 1965; Seager & Bird, 1962; van den Broek et al., 2006) or amitriptyline (Kay et al., 1970; Krog-Meyer et al., 1984) monotherapy.

No placebo-controlled RCTs of continuation pharmacotherapy with a one-year (or longer) follow-up were identified. No meta-analyses of head-to-head comparisons of

different active relapse prevention strategies could be carried out as only one study contained the same comparison.

3.4. Discussion

3.4.1. Summary of key findings

Relapse rates following ECT are disappointingly high and appear to have increased over time. In patients treated with continuation pharmacotherapy, the main focus of this investigation, relapse was highest in the first six months, plateauing afterwards. In present-day clinical practice, nearly 40% of ECT responders can be expected to relapse in the first six months and roughly 50% by the end of first year.

A course of ECT, in the absence of active continuation therapy, does not appear to have much lasting effect. In early trials where no continuation therapy was permitted, half of all patients who responded to ECT relapsed within three months (Arfwidsson et al., 1973; Barton et al., 1973). This suggests that the natural course of depressive illness severe enough to warrant ECT is a prompt return to depression in the absence of long-term treatment. When modern placebo samples were analysed, relapse rates were even higher, approaching 80% at six months. In current ECT practice, therefore, it is recommended that initial gains are consolidated with vigorous maintenance therapy.

3.4.2. Outcomes after ECT vs. pharmacotherapy for major depression

Nonetheless, these findings need to be interpreted in the context of superior acute remission rates with ECT compared to other existing treatments for treatment-resistant depression. Meta-analyses investigating acute outcomes found ECT to be more effective than other somatic therapies for major depression such as pharmacotherapy (The UK ECT Review Group, 2003) and transcranial magnetic stimulation (Ren et al., 2014). Although this systematic review did not identify any studies directly comparing long-term outcomes in ECT vs. medication-treated patients, when these results are compared to the

existing literature on short- and longer-term antidepressant effectiveness in refractory MDD, similar outcomes are observed. In the STAR*D study (Rush et al., 2006b), relapse rates were predictably higher in patients entering follow-up after more previous failed treatment steps. During the one-year follow-up, remitters from the third and fourth successive treatment steps relapsed at rates of 43% and 50% respectively. These long-term outcomes in medication-treated patients with similar degree of treatment resistance to modern ECT samples are very similar to the present findings of a 51% relapse rate one year following ECT. Acute remission rates for every treatment step in STAR*D, however, were much lower compared to those typically observed in ECT trials, hence more patients overall can be expected to benefit from ECT.

3.4.3. Predictors of relapse after ECT

Exploratory moderator analyses on the main outcome of interest, relapse rate at six months following ECT, suggest that older age and presence of psychotic symptoms at baseline are associated with a more favourable long-term outcome. These findings are consistent with existing research evidence as well as clinical impressions of higher acute efficacy of ECT among older adults and patients with psychotic depression (Sackeim, 2005). On the other hand, baseline medication resistance which has been found to have a detrimental impact on the acute efficacy of ECT (Heijnen et al., 2010) was not found to influence long-term outcomes in this meta-analysis, a surprising finding. One possibility is that our failure to detect an effect of medication resistance on relapse may be a methodological artefact of the particular instrument for assessing medication resistance, the Antidepressant Treatment History Form (ATHF) (Sackeim, 2001), which was used in most of the studies that reported this variable. In addition, the only studies that reported the prevalence of medication resistance in their samples are from the last two decades, a time during which ECT has tended to be used predominantly in medication-resistant patients. The early long-term follow-up studies from the 1960s in which, presumably, more medication-naïve patients were sampled, did not report how many of their patients failed

previous medication trials. The concept of treatment-resistant depression as we know it today was not widely recognised until more recent times and was rarely, if ever, systematically reported in the early psychiatric literature. Given that medication resistance is nowadays the leading indication for ECT, further research on its impact on the likelihood of relapse and recurrence of depression after remission from ECT is needed.

3.4.4. Optimising post-ECT continuation therapy

This systematic review unfortunately cannot offer clear guidance on what type of continuation therapy works best and for which patients. Many ECT patients routinely receive continuation therapy with the same medication(s) that failed to elicit a clinical response prior to ECT, a counterintuitive strategy (Sackeim, 1994). No evidence is available to suggest this practice might be effective, although no particular evidence to the contrary exists either. This meta-analysis suggests that continuation pharmacotherapy is significantly more effective than placebo at both three- and six-month follow-ups. Most available evidence consists of trials of older antidepressants such as imipramine and amitriptyline. The search of the published literature could not identify any placebo-controlled trials of some of the most commonly used newer-generation antidepressants such as serotonin-norepinephrine reuptake inhibitors (SNRIs), mirtazapine or popular augmentation strategies with mood stabilisers (other than lithium) or atypical antipsychotics. Even for SSRIs, now in their third decade of clinical use, published evidence is scant (only two studies). ECT research has favoured use of TCAs; however, since TCAs produce many undesirable side-effects, carry an overdose risk and cannot be tolerated at adequate doses by many patients (especially older adults for whom ECT tends to be used most), efficacy of newer antidepressants with more favourable side-effect profiles merits further investigation. Also requiring future study is the optimisation of treatment schedules for C-ECT which has thus far tended to be used with fixed dosing schedules in prospective studies. This may have underestimated its true efficacy when

using more flexible, symptom-titrated dosing schedules currently under investigation (Lisanby et al., 2008).

Other non-medical approaches such as psychotherapy may also have a place in the treatment of this refractory patient population. A recent RCT published after this meta-analysis was completed, the first prospective study to examine the efficacy of psychotherapy in post-ECT relapse prevention, found that when standard medical management of ECT responders (individualised pharmacotherapy) is used either alone or in combination with cognitive behavioural therapy (CBT) or C-ECT, sustained clinical response is significantly more likely in the group that received CBT in conjunction with pharmacotherapy compared to pharmacotherapy alone or pharmacotherapy + C-ECT combination, with benefits of psychotherapy add-on treatment persisting for the entire duration of the one-year follow-up (Brakemeier et al., 2013). Unfortunately, in this study ultrabrief pulse right unilateral ECT was used in conjunction with propofol anaesthesia (which has known anticonvulsant properties), perhaps explaining the unusually diminished effectiveness of C-ECT (Youssef & McCall, 2015).

3.4.5. Limitations

When interpreting results of this meta-analysis, certain limitations should be borne in mind. Much of the available evidence comes from small, underpowered, predominantly observational studies. There was substantial variability between the included studies in design, quality and patient selection criteria that appeared to influence outcomes. Very few RCTs of continuation therapies with long-term follow-up exist, with evidence particularly lacking for outcomes beyond six months. Data from prospective controlled studies are particularly lacking for certain important clinical outcomes such as suicide and indeed all-cause mortality in this severely ill and treatment-resistant patient population.

3.4.6. Conclusions and future directions

In summary, this systematic review found that up to half of all patients who respond to ECT relapse within the first year, the period of highest risk being the first six months. Continuation pharmacotherapy or C-ECT significantly reduces the risk of relapse. However, many questions remain unanswered. Future studies should clarify which patient characteristics might predict relapse and what the optimal post-ECT continuation treatment or combination thereof entails. More focus is required on treatments other than TCAs, including psychotherapy and indeed optimisation of treatment schedules for C-ECT, preferably in conjunction with concomitant pharmacotherapy. Such research is required to keep ECT patients in remission for as long as possible and with the fewest side effects.

Chapter 5 examines various clinical predictors of relapse in a sample prospectively followed up for 12 months as part of an RCT of bitemporal vs. high-dose right unilateral ECT. Factors predicting relapse highlighted by this meta-analysis (age and psychosis) were modelled in addition to other theoretically-informed variables previously identified as important in the ECT and wider depression literature. The equivocal previous findings of the role of medication resistance are a particular focus of the upcoming Chapter 4 where an attempt is made to clarify the impact on TRD on ECT outcomes using several research and clinical criteria for defining and quantifying TRD.

4. Convergent and predictive validity of staging methods for treatment-resistant depression

4.1. Introduction

Treatment-resistant depression (TRD) is a relapsing condition associated with significant morbidity, disability and a tendency toward chronicity (Fekadu et al., 2009b). Although it is a major social and economic public health problem (Mrazek et al., 2014), there are no universally agreed upon definitions, staging methods or treatment algorithms. Surprisingly few studies have investigated the reliability and validity of various proposed TRD staging methods (Ruhe et al., 2012).

Antidepressant medication resistance is nowadays the leading indication for ECT referral in the Western world. It had been noted half a century ago that poor response to antidepressants portends a less favourable subsequent response to ECT (Bruce et al., 1960; Hamilton, 1974; Medical Research Council, 1965). Interestingly, in a prospective sample drawn from a nationwide audit of ECT in Scotland, there was no agreement between the referring psychiatrists' clinical judgement of treatment resistance and any of the four studied research definitions of TRD (Husain, Kevan, Linnell, & Scott, 2005), which included the Antidepressant Treatment History Form (ATHF) (Sackeim, 2001).

In the modern ECT literature, the ATHF has served as the gold standard for quantification of TRD since first proposed 25 years ago (Prudic et al., 1990; Sackeim et al., 1990). The ATHF assesses the adequacy of antidepressant treatment trials during the index episode according to published criteria for dosing and duration (Sackeim, 2001), classifying patients as treatment resistant if adequacy criteria are met for one or more of the attempted antidepressant trials (described in greater detail in Chapter 2.2.8.1). In addition to ECT studies, it has been used in investigations of other somatic therapies for TRD such as transcranial magnetic stimulation (George et al., 2010), vagus nerve stimulation (Bajbouj et al., 2010), deep brain stimulation (Schlaepfer, Bewernick, Kayser, Madler, & Coenen, 2013) and psychosurgery (Christmas et al., 2011). The ATHF has

excellent inter-rater reliability (Sackeim et al., 1990) and has shown predictive validity in some (Prudic et al., 1996; Prudic et al., 1990; Sackeim et al., 2001; Sackeim et al., 1990; Sackeim et al., 2000; Sackeim et al., 2008; Shapira et al., 1995) but not all (Heijnen, van den Broek, & Birkenhager, 2008; Husain, Kevan, Linnell, & Scott, 2004; Pluijms, Birkenhager, Huijbrechts, & Moleman, 2002; Rasmussen et al., 2007; Rasmussen et al., 2009; van den Broek, de Lely, Mulder, Birkenhager, & Bruijn, 2004) studies investigating the association between TRD and short- and longer-term ECT outcomes. It has also shown predictive validity in some studies of treatments for depression other than ECT (Joel et al., 2014; Tew et al., 2006). The scale's convergent validity with other TRD staging methods has not been examined.

In recent years, a novel method for quantifying TRD, the Maudsley Staging Method (MSM) (Fekadu et al., 2009a; Fekadu et al., 2009c), has begun to be used in ECT research (Loo et al., 2014; Trevino, 2011). The MSM differs from the ATHF in that it is a dimensional model of the degree of treatment resistance and incorporates a wider range of clinical information such as episode duration and severity (described in more detail in Chapter 2.2.8.2). The extent of its predictive utility in ECT samples is yet to be determined.

The aim of the present study was to assess the convergent and predictive validity of two research definitions (ATHF and MSM) and two clinical measures (number of attempted antidepressant trials during the index episode and clinical judgement of referring psychiatrist) of TRD. In addition, the ATHF was used to classify patients according to the emerging preferred definition of TRD in the depression research literature (Berlim & Turecki, 2007a; Berlim & Turecki, 2007b; McIntyre et al., 2014) as well as regulatory bodies (European Medicines Agency, 2013) where TRD is defined as failure of at least two adequate antidepressant medication trials. Since there are no universally accepted criteria for antidepressant trial adequacy, the ATHF criteria were used for this purpose in the present study.

4.2. Materials and Methods

4.2.1. Study design and participants

Patients with unipolar major depressive disorder (MDD) meeting Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First et al., 1996) criteria for current major depressive episode (MDE), with or without psychotic features, referred for a course of ECT were included in this study. Patients were treated with low-dose bitemporal or high-dose right unilateral ECT as part of a randomised controlled trial, the EFFECT-Dep Trial (ISRCTN23577151), with a one-year naturalistic follow-up (see Chapter 2.2 for details regarding trial design, treatment parameters, participants, follow-up procedures and outcome measures).

Patients with a clinical diagnosis of bipolar disorder who took part in the trial were excluded from this analysis. The rationale for exclusion of bipolar depression comes from the uncertainties surrounding recommendations for optimal treatment of depressive episodes in the context of bipolar disorder (Pacchiarotti et al., 2013). Mood stabilisers and atypical antipsychotics, with or without concomitant antidepressants, are the mainstay of bipolar depression treatment nowadays, whereas antidepressant monotherapy is generally discouraged. There are, in fact, only four Food and Drug Administration (FDA) approved treatments for bipolar depression: olanzapine-fluoxetine combination, quetiapine, lurasidone monotherapy, and lurasidone in combination with lithium or valproate (Tohen & Abbott, 2015). While the ATHF (Sackeim et al., 2000; Sackeim et al., 2008) and the MSM (Fekadu et al., 2012) have been applied to bipolar depression previously, a more homogeneous sample was deemed preferable for the purposes of this validation study.

Other exclusion criteria were: score of <21 at pre-ECT baseline on the 24-item Hamilton Rating Scale for Depression (Beckham & Leber, 1985; Hamilton, 1960), dementia or other Axis I diagnosis, any medical condition rendering the patient unfit for

general anaesthesia, ECT in the previous six months, alcohol or substance abuse in the previous six months and inability or refusal to consent.

4.2.2. Ethics

The study received approval from the St. Patrick's University Hospital Research Ethics Committee (protocol number: 12/07) and the St. James' Hospital-Adelaide and Meath & National Children's Hospital Research Ethics Committee (protocol number: 2008/05/04). All participants provided written informed consent.

4.2.3. Baseline assessment of treatment resistance

Information regarding treatment of the index episode was collected at pre-ECT baseline using multiple sources of information: medical records, patient interview, contact with next-of-kin, treating clinical team and dispensing pharmacy. Gathered clinical information regarding names, dosages and duration of attempted antidepressant medication and augmentation trials, duration and severity of current episode, and presence of psychotic features formed the basis for assessment of TRD using the two research tools for quantifying TRD: the Antidepressant Treatment History Form (ATHF) (Sackeim, 2001) and the Maudsley Staging Method (MSM) (Fekadu et al., 2009a) (see Chapters 2.2.8.1. and 2.2.8.2. for detailed descriptions of these instruments, scoring criteria and information regarding their psychometric properties). There are no universally accepted criteria for antidepressant trial adequacy. Two sets of criteria were used here to determine adequacy:

i. for the ATHF, published criteria (Sackeim, 2001) were used in conjunction with the latest unpublished update incorporating antidepressants approved in the interceding years;
ii. for the MSM, the Maudsley Prescribing Guidelines (Taylor et al., 2009) were used in conjunction with the MSM's original authors' in-house scoring sheets (Dr. A Cleare, personal communication) since the Maudsley guidelines are equivocal on some matters.

These two instruments were chosen over other existing staging methods for TRD (described in Chapter 1.3.3) as they have the most published evidence regarding their validity. The ATHF defines TRD as the failure of at least one antidepressant trial of adequate dose and duration according to pre-specified criteria (Sackeim, 2001) while the MSM does not categorise patients into TRD vs. not TRD categories, instead providing a dimensional score denoting the degree of treatment resistance. Possible scores on the MSM range between 3 and 15; 3-6 points indicating mild degree of treatment resistance, 7-10 moderate and 11-15 severe. In the present study, the ATHF was also modified to define TRD as two or more failed antidepressant trials in line with the current standard definition of TRD in the literature (Berlim & Turecki, 2007a; Berlim & Turecki, 2007b).

Two clinical indicators of TRD were also used: antidepressant count (i.e. the number of antidepressant medication trials attempted during the index episode regardless of dose, duration or compliance), a frequently used simple measure of treatment resistance previously shown to predict relapse following ECT (Prudic et al., 2013), and clinical judgement of the referring consultant psychiatrist (this information was available for all patients referred for ECT as part of standardised pre-ECT workup by the referring clinical team).

4.2.4. Outcome measures

Clinical outcomes in this study were assessed using the HRSD-24 (see Chapter 2.2.9.1 for a description of its content and psychometric properties). Treatment response was defined as a ≥60% decrease in HRSD-24 from baseline and a score of ≤16. Remission was defined as a ≥60% decrease in HRSD-24 score relative to baseline and a score of ≤10 on a minimum of two consecutive testing occasions separated by one week. Relapse was defined as a ≥10 point increase in HRSD-24 compared to end-of-treatment score and a HRSD-24 score of ≥16 at any time during the one-year follow-up. In addition, this increase in HRSD-24 score had to be maintained a week later (if indicated, additional follow-ups were arranged to confirm relapse). Hospital admission, further ECT, and

deliberate self-harm/suicide also constituted relapse regardless of HRSD-24 score. Similar criteria for these clinical outcomes were used in all recent major trials of bitemporal vs. high-dose right unilateral ECT.

4.2.5. Statistical analyses

Convergent validity of two or more scales which are supposed to measure the same theoretical construct is established when a high degree of correlation between them is shown. The strength of association between the TRD assessment tools studied here was measured using Pearson's correlation coefficient *r* (for two continuous measures), point-biserial correlation coefficient r_{pb} (for one continuous and one categorical measure) and the chi-square (χ^2) test (for two categorical measures). Logistic regression was also used to predict group membership on the ATHF (TRD vs. not TRD) based on scores on the other studied measures of TRD (MSM, number of antidepressant trials and clinical judgement of referring psychiatrist).

Predictive validity of a measure can be demonstrated by showing a significant association between said measure and a relevant future outcome. As treatment resistance "breeds" future treatment resistance in depression, in this study predictive utility of TRD measures was examined using logistic regression where each TRD measure served as a predictor variable in univariate models, with the two treatment outcomes (non-remission and relapse after ECT) serving as dichotomous outcome variables. Odds ratios (OR) with 95% confidence intervals (CI) were computed for these outcomes. Odds refers to the ratio of the number of participants experiencing the outcome to the number of participants not experiencing the outcome. An odds ratio is the ratio of the odds in the experimental group to the odds in the control group. Odds should not be confused with risks (the latter being the more intuitive measure of probability). Table 4.1 below illustrates computation of event risks, odds and ratios thereof in a hypothetical sample of patients.

The threshold for statistical significance was set at two-tailed $p<0.05$. All statistical analyses were carried out in SPSS Version 21.0 (IBM Corp., 2012).

TABLE 4.1. Measuring probability in a hypothetical sample of patients

Group	N	Number of participants experiencing the outcome	Number of participants NOT experiencing the outcome
Treatment	20	12	8
Placebo	20	7	13
Statistics			
Outcome **rate** in the treatment group	12/20 = 0.6 or 60%		
Outcome **rate** in the placebo group	7/20 = 0.4 or 40%		
Relative risk (RR)	0.6 / 0.4 = 1.5		
Odds of outcome in the treatment group	12/8 = 1.5		
Odds of outcome in the placebo group	7/13 = 0.5		
Odds ratio (OR)	1.5 / 0.5 = 3.0		
Absolute risk increase (or reduction)	0.6 – 0.4 = 0.2 or 20%		
Number needed to treat (NNT)	1 / (0.6 – 0.4) = 5		

4.3. Results

4.3.1. Sample characteristics

Of the 138 randomised patients in the EFFECT-Dep Trial, 106 had unipolar depression. Of these, 104 (98.1%) had complete medication treatment histories on which subsequent analyses were conducted. Table 4.2 below presents the demographic and clinical characteristics of the sample evaluated for TRD.

TABLE 4.2. Demographic and clinical characteristics of the sample

Variable	Unipolar MDD (N=104)
Age, years	57.4 (14.5)
Female gender	68 (65.4%)
Education, years	13.3 (3.2)
Premorbid IQ[a]	107.8 (0.7)
Marital status (N=102)	
Single	25 (24.5%)
Married	63 (61.8%)
Divorced or widowed	14 (13.7%)
Psychosis	20 (19.2%)
Electrode placement	
Right unilateral	52 (50%)
Bitemporal	52 (50%)
History of previous ECT	35 (33.7%)
Pre-ECT HRSD-24 score	29.7 (6.3)
Pre-ECT CGI-S score[b]	5.4 (0.7)
Duration of index episode, weeks, median (range)	19 (4-520)
Number of previous episodes, median (range)	4 (0-23)

All data are presented as mean (SD) or n (%) unless otherwise specified.
[a]N=82; IQ estimated by the National Adult Reading Test (NART).
[b]As indicated by the referring psychiatrist.

Abbreviations: CGI-S = Clinical Global Impression - Severity scale; ECT = electroconvulsive therapy; HRSD-24 = Hamilton Rating Scale for Depression (24-item); IQ = intelligence quotient; MDD = major depressive disorder; NART = National Adult Reading Test

4.3.2. Patterns of antidepressant medication use

All antidepressant trials during the index episode were recorded (Table 4.3 below). Patients received a mean of 2.8 (SD=1.5, range 0-12) antidepressant trials prior to ECT referral. Trials varied substantially in terms of duration, dosage and compliance. Patients received a mean of 1.4 (SD 1.3, range 0-9) adequate trials on the ATHF criteria and 1.7 (SD 1.2, range 0-9) on the MSM criteria.

By far the most frequently used antidepressants were venlafaxine and mirtazapine, often used in combination. The most popular medication class was serotonin-noradrenaline reuptake inhibitors (SNRIs), followed by selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs). Monoamine oxidase inhibitors (MAOIs) were used only three times. Notably, when SSRIs and SNRIs were used, the majority of trials were rated adequate (between approximately two-thirds and three-quarters, depending on criteria used), whereas only a minority of TCA trials (approximately 10-30%, depending on criteria) were administered at what was deemed to be an adequate dose and duration.

To aid interpretation of Table 4.3 below, adequacy criteria for the ATHF and MSM antidepressant trials are summarised here (full sets of criteria are presented in Appendix 1 and 2, respectively). On the ATHF, trials must be of at least four weeks' duration to be considered adequate. ≥200 mg of imipramine or equivalent for TCAs, ≥20 mg of fluoxetine or equivalent for SSRIs, ≥225 mg of venlafaxine or equivalent for SNRIs, and ≥60 mg of phenelzine or equivalent for MAOIs is considered the minimum adequate dose. For psychotic depression, concomitant administration of at least three weeks' duration of ≥400 mg of chlorpromazine or equivalent for typical antipsychotics and ≥20 mg of olanzapine or equivalent for atypical antipsychotics must be achieved alongside an antidepressant trial of adequate dose and duration in order for the antidepressant trial to be deemed adequate overall.

On the MSM, antidepressant trials must be of at least six weeks' duration to be deemed adequate. Required doses are: ≥125 mg of imipramine or equivalent for TCAs,

≥20 mg of fluoxetine or equivalent for SSRIs, ≥75 mg of venlafaxine or equivalent for SNRIs, and ≥45 mg of phenelzine or equivalent for MAOIs. There is no requirement for antipsychotic augmentation of antidepressants in psychotic depression.

TABLE 4.3. Adequacy of antidepressant trials during index depressive episode according to ATHF and MSM criteria

Antidepressant	Number of attempted trials	Number (%) of adequate trials (ATHF criteria)	Number (%) of adequate trials (MSM criteria)
SSRI	65	50 (76.9%)	44 (67.7%)
Citalopram	10	6 (60.0%)	6 (60.0%)
Escitalopram	29	25 (86.2%)	22 (75.9%)
Fluoxetine	9	7 (77.8%)	8 (88.9%)
Paroxetine	7	6 (85.7%)	6 (85.7%)
Sertraline	10	6 (60.0%)	2 (20.0%)
SNRI	90	56 (62.2%)	63 (70.0%)
Duloxetine	22	21 (95.5%)	17 (77.3%)
Venlafaxine	68	35 (51.5%)	46 (67.6%)
TCA	48	5 (10.4%)	14 (29.2%)
Amitriptyline	18	2 (11.1%)	8 (44.4%)
Clomipramine	14	2 (14.3%)	4 (28.6%)
Dosulepin	1	0	0
Lofepramine	7	1 (14.3%)	2 (28.6%)
Nortriptyline	6	0	0
Trimipramine	2	0	0
MAOI & RIMA	3	2 (66.7%)	2 (66.7%)
Moclobemide	1	1 (100%)	1 (100%)
Tranylcypromine	2	1 (50.0%)	1 (50.0%)
Other			
Agomelatine	8	n/a	7 (87.5%)
Bupropion	5	1 (20.0%)	1 (20.0%
Mianserin	1	0	0
Mirtazapine	61	41 (67.2%)	35 (57.4%)
Reboxetine	2	1 (50.0%)	1 (50.0%
Trazodone	7	0	3 (42.9%)
ECT	1	1 (100%)	1 (100%)
VNS	1	1 (100%)	n/a

Abbreviations: ATHF – Antidepressant Treatment History Form; ECT – electroconvulsive therapy; MAOI – monoamine oxidase inhibitor; MSM – Maudsley Staging Method; RIMA – reversible inhibitor of monoamine oxidase A; SNRI – serotonin-noradrenaline reuptake inhibitor; SSRI - selective serotonin reuptake inhibitor; TCA – tricyclic antidepressant; VNS – vagus nerve stimulation

In addition to antidepressants, patients were also commonly treated with various augmentation strategies and other psychotropic medications such as anxiolytics and hypnotics. Only medications with known antidepressant activity (and recognised as such by the ATHF and/or MSM criteria) were recorded (Table 4.4 below). Recognised augmentation strategies for unipolar depression on the ATHF are lithium and triiodothyronine (T_3). Antipsychotics are required for treatment of psychotic depression on the ATHF but are not otherwise considered augmenting agents. Recognised augmentation strategies on the MSM are mood stabilisers (lithium, carbamazepine, lamotrigine and pregabalin), anxiolytics (buspirone), thyroid hormone (T_3), beta blockers (pindolol), dopamine agonists and stimulants (dexamphetamine, methylphenidate, modafinil and pramipexole), as well as miscellaneous compounds (dexamethasone, metyrapone, ketoconazole, tryptophan and yohimbine). Table 4.4 below shows the frequency of use of various augmentation strategies in this unipolar sample referred for ECT. Medications were included in the table when at least one patient received a trial of the medication in question.

4.3.3. Patterns of antidepressant medication resistance

Based on the clinical judgement of referring consultant psychiatrists, 70.8% (75/104) of this sample with unipolar depression referred for ECT were deemed treatment resistant. ATHF criteria (i.e. ≥1 failed antidepressant medication trials) categorised 75% (78/104) of the sample as having TRD; the remaining 25% (26/104) received zero adequate medication trials prior to being referred for ECT. 40 (38.5%) patients met the more stringent (but also more widely accepted) TRD definition of two or more failed adequate trials. The MSM does not dichotomise patients into TRD vs. not TRD but instead provides a dimensional score of treatment resistance severity. Mean MSM score was 6.5 (SD 1.4, range 4-13) indicating mild-to-moderate degree of treatment resistance.

TABLE 4.4. Adequacy of augmentation strategies during index depressive episode according to ATHF and MSM criteria

Augmenting agent	Number of attempted trials	Number (%) of adequate trials (ATHF criteria)	Number (%) of adequate trials (MSM criteria)
Mood stabilisers			
Carbamazepine	1	n/a	0
Lamotrigine	11	n/a	8 (72.7%)
Lithium	45	19 (42.2%)	23 (51.1%)
Pregabalin	3	n/a	1 (33.3%)
Antipsychotics[a]			
Aripiprazole	11	n/a	6 (54.5%)
Olanzapine	28	n/a	10 (35.7%)
Quetiapine	15	n/a	3 (20.0%)
Risperidone	1	n/a	0
Ziprasidone	1	n/a	1 (100%)
Other			
Buspirone	1	n/a	1 (100%)
Pramipexole	2	n/a	0
Triiodothyronine (T_3)	2	2 (100%)	2 (100%)
Tryptophan	1	n/a	0

[a]Concomitant treatment with an antipsychotic at an adequate dose for a minimum of three weeks is required for an antidepressant trial for psychotic depression to be deemed adequate on the ATHF. Antipsychotics, however, are not considered as augmenting agents for depression in general on the ATHF and are therefore not counted here.

Abbreviations: ATHF – Antidepressant Treatment History Form; MSM – Maudsley Staging Method

4.3.4. Convergent validity of TRD assessment tools

Surprisingly, using point-biserial correlation, there was no significant correlation between the MSM score and the ATHF dichotomous classification of treatment resistance (r_{pb}=0.14, p=0.147). Total MSM score did not significantly differ between the groups classified treatment resistant (mean=6.63, SD=1.44) vs. not treatment resistant (mean=6.15, SD=1.41) on the ATHF (t(102)=1.46, p=0.147). Using logistic regression, the MSM score did not predict categorical TRD classification status on the ATHF (OR=1.31, 95% CI 0.91-1.88, p=0.149).

When the ATHF criteria were tightened to make two failed adequate medication trials the cut-off for TRD, statistically significant differences emerged on the MSM score between TRD and non-TRD groups ($t(102)=2.23$, $p=0.028$). However, absolute differences in mean MSM score between the TRD (mean=6.90, SD=1.71) and non-TRD (mean=6.27, SD=1.20) groups were small; only 0.63 points on the 15-point MSM scale. Logistic regression showed that the MSM score predicted TRD classification status if two failed medication trials according to ATHF criteria for trial adequacy was used as the cut-off for determining TRD (OR=1.38, 95% CI 1.02-1.86, $p=0.036$).

As stated previously, patients received a mean of 2.8 (SD=1.5, range 0-12) antidepressant trials (not including augmentation strategies or other psychotropic medications) prior to ECT referral. A simple count of all antidepressant medications administered during the index episode irrespective of duration or dosing adequacy was statistically significantly associated with the total MSM score ($r=0.39$, $p=0.00004$) and the ATHF TRD classification ($r_{pb}=0.26$, $p=0.009$). Antidepressant medication count also significantly associated with TRD status when using a more stringent cut-off on the ATHF of two or more failed trials ($r_{pb}=0.35$, $p=0.0003$). There was, however, no significant association between antidepressant count and the referring psychiatrist's clinical impression of treatment resistance ($r_{pb}=0.09$, $p=0.367$).

There was also no association between the referring psychiatrist's clinical judgement of treatment resistance and MSM score ($r_{pb}=0.03$, $p=0.791$), nor was there a relationship between the referring psychiatrist's clinical judgement and the ATHF TRD classification ($\chi^2=1.24$, $p=0.265$; OR=1.70, 95% CI 0.67-4.32). However, there was a significant association between the referring psychiatrist's judgement of treatment resistance and treatment resistance defined as ≥2 failed antidepressant medication trials on the ATHF ($\chi^2=4.71$, $p=0.030$; OR=2.83, 95% CI 1.08-7.39).

In summary, the two research staging methods for TRD, the ATHF and the MSM, showed no convergent validity. There was a weak but statistically significant association between the ATHF and MSM only when the ATHF was modified to classify treatment

resistance as failure of ≥2 adequate antidepressant trials. The latter definition of TRD was also the only one showing significant association with referring psychiatrists' clinical judgement of treatment resistance while none of the other TRD definitions did. The simplest numerical estimate of TRD, antidepressant medication count, showed significant associations with both of the more complex research staging methods.

4.3.5. Predictive validity of TRD assessment tools

4.3.5.1. Remission after ECT

Overall, of the 104 unipolar MDD patients with complete medication treatment histories who took part in the EFFECT-Dep Trial, 59 (56.7%) met response criteria and 46 (44.2%) met the stricter remission criteria. Response and remission rates for patients with varying degrees of treatment resistance as per ATHF criteria are presented in Table 4.5. below. Although there was a numerical trend toward somewhat lower response and remission rates with increasing number of failed antidepressant trials, being classified as medication resistant (≥1 failed adequate antidepressant trials) on the ATHF at baseline did not significantly predict non-remission following a course of ECT (OR=1.68, 95% CI 0.69-4.10, p=0.257). Even using more stringent criteria for treatment resistance (≥2 failed medication trials on the ATHF) there was no significant association with non-remission status after ECT (OR=1.57, 95% CI 0.70-3.51, p=0.276).

TABLE 4.5. Response and remission rates in the unipolar MDD sample (N=104) stratified by the number of failed antidepressant trials as per ATHF criteria

Number of adequate antidepressant trials, ATHF criteria	Number of patients	Response rate	Remission rate
0	26	18 (69.2%)	14 (53.8%)
1	38	22 (57.9%)	17 (44.7%)
≥2	40	19 (47.5%)	15 (37.5%)
Total sample	104	59 (56.7%)	46 (44.2%)

As can be seen in Figure 4.1 below, there was no significant association between baseline MSM score and non-remission after ECT (OR=1.19, 95% CI 0.89-1.57, p=0.251). There was also no significant relationship between either the number of attempted antidepressant trials during the index episode (OR=1.10, 95% CI 0.84-1.43, p=0.497) or referring psychiatrist's clinical judgement of treatment resistance (OR=0.60, 95% CI 0.25-1.42, p=0.244) and non-remission after ECT.

In summary, none of the five studied definitions of TRD predicted lower odds of remission after ECT.

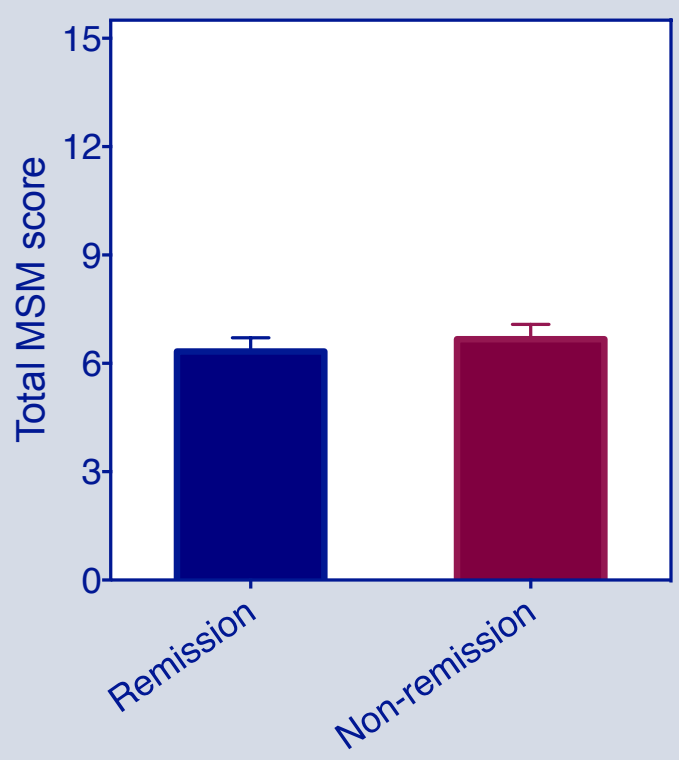

FIGURE 4.1. Mean total MSM score with 95% CIs in ECT remitters (N=46) and non-remitters (N=58)

4.3.5.2. Relapse after successful ECT

The 46 unipolar MDD patients who met remission criteria were followed up for up to a year after the ECT course. Of these, 32.6% (15/46) met relapse criteria within the one-year follow-up. Relapse rates for patients with varying degrees of treatment resistance as per ATHF criteria are presented in Table 4.6 below.

TABLE 4.6. Relapse rates in the unipolar MDD remitter sample (N=46) stratified by the number of failed antidepressant trials as per ATHF criteria

Number of adequate antidepressant trials, ATHF criteria	Number of patients	Relapse rate
0	14	4 (28.6%)
1	17	5 (29.4%)
≥2	15	6 (40.0%)
Total sample	46	15 (32.6%)

Remitters who met ATHF criteria for medication resistance at pre-ECT baseline were not significantly more likely to subsequently relapse (OR=1.31, 95% CI 0.33-5.15, p=0.700). The same applied to those patients who met more stringent criteria for TRD of ≥2 failed medication trials on the ATHF (OR=1.63, 95% CI 0.45-5.93, p=0.459). Equally, there was no significant association between baseline MSM total score and post-ECT relapse (OR=0.68, 95% CI 0.40-1.16, p=0.154) (Figure 4.2.).

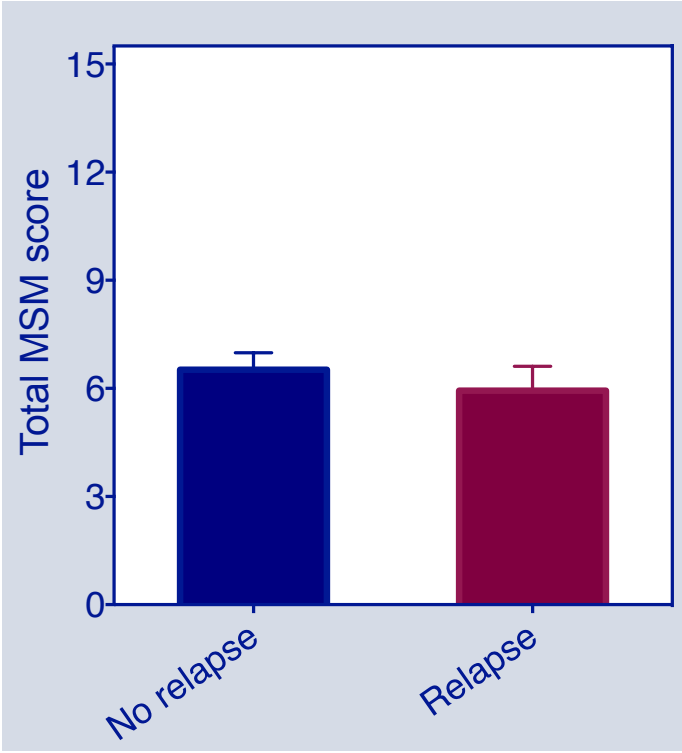

FIGURE 4.2. Mean total MSM score with 95% CIs in non-relapsers (N=31) and relapsers (N=15)

Likewise, there was no association between either the number of failed antidepressant trials (OR=0.78, 95% CI 0.47-1.29, p=0.333) or the referring psychiatrist's clinical impression of treatment resistance (OR=1.39, 95% CI 0.31-6.23, p=0.666) and subsequent relapse.

In summary, none of the five methods of defining TRD showed significant associations with relapse following a successful course of ECT.

4.4. Discussion

4.4.1. Summary of key findings

This study offered an in-depth characterisation of antidepressant medication resistance in an inpatient sample with moderate-to-severe unipolar depression referred for ECT using two sets of research criteria and two simple clinical estimates of treatment resistance. The chief conclusions were as follows: a) TRD staging methods show little to no convergent validity; b) the cut-off point at two failed antidepressant trials appears to be more valid than one; and c) treatment-resistant depression, however defined, does not significantly diminish acute or longer-term outcome after ECT.

The question of what treating psychiatrists mean when they designate a patient treatment resistant for purposes of ECT referral remains open. This matter is of considerable clinical importance given that the majority of patients treated in modern ECT trials meet criteria for medication resistance. Neither of the research criteria for TRD studied here corresponded with clinical judgement, in line with previous findings (Husain et al., 2005). A significant association between clinical judgement of treating psychiatrists and other TRD definitions was observed only in the instance where TRD was categorised into two or more vs. one or no failed adequate antidepressant trials. This is perhaps unsurprising considering the fact that this definition of TRD also happens to be the emerging consensus in the field of depression research (Berlim & Turecki, 2007a).

4.4.2. Challenges in defining and staging of TRD

Unexpectedly, no significant association between the two research staging methods, ATHF and MSM, was found. Only when the ATHF criteria were modified to fit the emerging standard definition of TRD in clinical trials (i.e. ≥2 failed antidepressant trials, as opposed to just one), was there a significant association with the MSM estimate of TRD severity. These results raise the question of whether these scales are measuring different constructs or whether the construct of TRD is currently too obscure or inherently unstable to measure in a robust fashion. It is possible that the construct of TRD is more robust, and the tools used to "measure" it more valid, in individuals with antidepressant failure in the context of recurrent depression as opposed to first-episode depression. To my knowledge, no previous literature has directly examined this question. The results of the present study would seem to suggest a lack of validity of TRD assessment tools in a patient population with recurrent depression. Only two of the 104 patients studied here had first-episode depression; the remaining 102 had a median of four previous episodes and a third of them had received one or more previous ECT courses.

Naturally, any attempt to establish construct validity of TRD staging methods is hampered by the absence of an objective criterion against which to compare the performance of these scales. Due to our limited understanding of the underlying disease process and lack of an objective biological marker for TRD these scales were developed on the basis of expert opinion. Empirical support for their validity is still preliminary (Ruhe et al., 2012). It is not at all clear whether TRD represents a biologically meaningful subtype of depression or whether it is merely a clinical subgrouping that, by the virtue of previous poor response to currently available treatments, portends future non-response to other antidepressants of similarly limited effectiveness. In addition to their lack of predictive utility, it should also be borne in mind that the quickest and simplest estimate of treatment resistance (antidepressant trial count during the index episode) correlated significantly with the complex research scales requiring significant time and effort to

complete (up to several hours per patient, depending on complexity of previous history), further questioning their utility from a purely practical point of view.

Another area of conceptual confusion relates to the staging model of TRD adopted from other areas of medicine without sufficient empirical validation. One of the "staging methods" examined in the present study is the MSM which was designed to predict relevant future treatment outcomes in depression (i.e. nonremission and relapse/recurrence) based on dimensional severity of TRD as measured by a 15-point scale. This is broadly similar to the concept of staging in oncology. The earliest and perhaps most influential model of TRD is the Thase and Rush Staging Method (discussed in Chapter 1.3.3.1) which argues that patients progress from resistance to SSRI, to resistance to TCA, to resistance to MAOI, to, finally, resistance to ECT; again, this is somewhat analogous to the cancer staging model. To my knowledge, there is no evidence that such a hierarchical staging model of TRD is valid and there is some evidence that is not (see Petersen et al. [2005] where the hierarchical staging model was directly examined and refuted). "Staging", however, remains the standard terminology used in the TRD literature for now.

4.4.3. The role of TRD in ECT outcomes

The lack of utility of TRD in predicting subsequent remission and relapse after ECT is at odds with the existing meta-analysis showing reduced acute response rates in ATHF-defined medication resistant patients (Heijnen et al., 2010) but in line with the meta-analysis showing no association between baseline medication resistance and relapse after a successful course of ECT (Jelovac, Kolshus, & McLoughlin, 2013). Interestingly, in the Heijnen et al. (2010) meta-analysis of seven studies, the four studies showing an effect for ATHF (Dombrovski et al., 2005; Prudic et al., 1996; Prudic et al., 1990; Sackeim et al., 2000) were conducted by the group who originally devised the scale while the three independent replications from the Netherlands (Heijnen et al., 2008; van den Broek et al., 2004) and the United States (Rasmussen et al., 2007) found no significant association

between ATHF rating and acute ECT response. One of the four samples (Prudic et al., 1996) in which an effect of ATHF was detected was in fact a subsample of a larger one (Dombrovski et al., 2005) included in the same meta-analysis. In the present study, an attempt was made to measure TRD using several methods to circumvent the issue of the ATHF usually being the only tool used in the modern ECT literature to quantify TRD. Despite this, no significant association was found between TRD – defined by the ATHF or otherwise – with clinical outcomes. The more recently developed MSM did not show an advantage over the ATHF in this study. The use of MSM in the ECT literature is only starting; one recent trial (Loo et al., 2014) showed a non-significant statistical trend toward higher baseline MSM score predicting higher depression rating scores after ECT.

One possibility is that an effect of treatment resistance was not detected due to insufficient sample size. This explanation seems unlikely when comparing this study's size to previous research on the topic. In the present study, 104 patients were evaluated for short-term and 46 for long-term ECT outcomes. The original MSM validation studies included 88 patients for evaluation of its predictive utility for short-term treatment outcomes (Fekadu et al., 2009a), and 62 (Fekadu et al., 2009c) and 118 (Fekadu et al., 2012) patients for long-term outcomes. The latter study included patients with bipolar depression.

In the original ATHF validation studies, 53 patients were evaluated for acute non-response to ECT (Prudic et al., 1990) and 58 for subsequent relapse (Sackeim et al., 1990). These studies found that ATHF resistance rating predicted both outcomes. A subsequent very large study (N=328) by the same authors found a statistically significant but weak association between the ATHF rating and non-remission after ECT (OR=1.67, 95% CI 1.05-2.67, p=0.03) (Dombrovski et al., 2005). A large study by a different group, however, which included 216 patients with complete medication treatment histories, found no association between ATHF rating and non-remission after ECT (Rasmussen et al., 2007). Two studies by a third group, one with 86 participants (Heijnen et al., 2008) and the

other with 85 (van den Broek et al., 2004) found no association between medication resistance on the ATHF and acute ECT outcomes.

4.4.4. Limitations

In addition to modest sample size, limitations of this study include the fact that all patients were referred for ECT, yielding a sample older than typical depression samples and a restricted range of illness severity. More importantly, a third of the sample received one or more previous lifetime courses of ECT. This of course raises the possibility that some patients who were not prescribed any adequate courses of antidepressants during the index episode were fast-tracked to ECT owing to past favourable response to ECT. There is also a minority of patients who are not administered adequate trials of antidepressants due to a rapid deterioration in their physical condition or acute suicidality necessitating urgent referral for ECT. This may have rendered some patients not treatment resistant, technically speaking, but if a more longitudinal view of their illness were to be taken, they could be considered treatment resistant due to the non-response to adequate pharmacotherapy during previous depressive episodes necessitating repeated courses of ECT. It should also be borne in mind that medication courses during the index episode were assessed retrospectively at the time of ECT referral, thus relying on potentially imperfect medical records and patient recall.

4.4.5. Conclusions

In conclusion, various TRD measures showed surprisingly weak agreement with one another. Treatment-resistant depression, however defined, was not shown to be useful in predicting poorer future outcomes with ECT. In the following Chapter 5, other potential clinical predictors of relapse after ECT will be examined for their predictive utility.

5. Predictors of relapse following a successful course of electroconvulsive therapy: a prospective one-year follow-up

5.1. Introduction

Despite the excellent acute efficacy of electroconvulsive therapy (ECT) (The UK ECT Review Group, 2003), relapse is a common problem (Kellner, 2013; Prudic et al., 2013). The meta-analysis reported in Chapter 3 and elsewhere (Jelovac et al., 2013) indicated that half of all remitters relapse during the first year despite maintenance treatment with antidepressants. Older age and presence of psychotic features at baseline were associated with a more favourable long-term prognosis, whereas medication resistance prior to ECT was surprisingly not predictive of relapse. In accordance with the latter finding, in Chapter 4 of this thesis it was also shown that none of the five studied definitions of medication resistance predicted subsequent relapse after ECT in a sample of remitters with unipolar depression.

Its higher efficacy in older adults makes ECT an unusual treatment in medicine in that regard. It is unclear why older age confers greater benefit from ECT but this is a well-replicated finding (O'Connor et al., 2001; Rhebergen et al., 2015; Sackeim, 2005; Tew et al., 1999). There may be a lower rate of comorbid personality disorders in older adults treated with ECT (Sackeim, 2005). At the same time, older age is a risk factor for greater cognitive impairment after ECT (Sackeim et al., 2007). Another well-replicated finding in the ECT literature is that once remission has been achieved, the modality of ECT used to achieve is uninformative in terms of predicting future likelihood of relapse (Prudic et al., 2013; Sackeim et al., 1993; Sackeim et al., 2000; Sackeim et al., 2008).

In the wider depression literature, other clinical features of affective disorders have received attention as predictors of long-term illness trajectory. Residual symptoms at the end of acute treatment phase are a potent predictor of future relapse/recurrence (Fava,

Fabbri, & Sonino, 2002; Judd et al., 2000; Kennedy & Foy, 2005; Nierenberg et al., 2010; Paykel et al., 1995). Not surprisingly, increasing number of prior depressive episodes, indicating a more recurrent course of illness, is also associated with future relapse/recurrence (Bockting et al., 2006; Bulloch, Williams, Lavorato, & Patten, 2014; Keller, Lavori, Lewis, & Klerman, 1983). Unipolar and bipolar depression tend to follow a different long-term course, with bipolar II disorder in particular associated with a greater risk of recurrences, chronicity, and inter-episodic symptomatology (Akiskal et al., 1995; Ayuso-Gutierrez & Ramos-Brieva, 1982; Judd et al., 2003a). While ECT is an effective acute treatment for bipolar depression (Dierckx, Heijnen, van den Broek, & Birkenhager, 2012; Schoeyen et al., 2015; Tohen & Abbott, 2015), information regarding long-term post-ECT outcomes in bipolar disorder (Medda et al., 2013) is scarce.

Selecting optimal post-ECT continuation treatment remains a clinical challenge. No evidence exists that any particular antidepressant class or continuation ECT is more effective than others (Jelovac et al., 2013). Cognitive behavioural therapy has thus far been studied in only one prospective study with encouraging results (Brakemeier et al., 2013). There is some suggestion that lithium augmentation may be uniquely protective against relapse in ECT patients (Rasmussen, 2014) but the evidence for this comes from largely uncontrolled studies. Only two randomised controlled trials (RCTs) have compared lithium to placebo in post-ECT relapse prevention; in one lithium was used as monotherapy (Coppen et al., 1981), a practice not recommended in unipolar depression today, and in the other as an augmenting agent to nortriptyline (Sackeim et al., 2001). Both found lithium to be superior to placebo in reducing relapse.

In the present study, the aforementioned clinical features (electrode placement, age, psychotic features, baseline medication resistance, polarity, residual depressive symptoms at the end of ECT course and number of previous depressive episodes) were modelled as prospective predictors of relapse in a sample of remitters from ECT. The aim of the study was to help elucidate a profile of an ECT patient most susceptible to relapse.

5.2. Materials and Methods

5.2.1. Study background

This study was an investigation of predictors of depressive relapse in patients who remitted following a course of ECT for a major depressive episode. Patients were receiving ECT as part of a randomised controlled trial, the EFFECT-Dep Trial (ISRCTN23577151), conducted at St. Patrick's University Hospital between 2008 and 2013 (see Chapter 2.2. for details regarding trial design, participants, treatment parameters and outcome measures). In brief, following the randomised treatment phase in which patients received either twice-weekly brief-pulse bitemporal ECT at 1.5 x seizure threshold (ST) or high-dose right unilateral ECT at 6 x ST, all participants, regardless of remission status, were assessed at a number of pre-specified time points over the course of a one-year naturalistic follow-up. For the purposes of the present study, the subsample of trial participants who remitted after ECT were studied. Antidepressant continuation/maintenance treatment during the follow-up phase was chosen on an individualised basis by the treating physician(s).

5.2.2. Ethics

The EFFECT-Dep Trial received ethical approval by the St. Patrick's University Hospital Research Ethics Committee (protocol number: 12/07) and the St. James' Hospital-Adelaide and Meath & National Children's Hospital Research Ethics Committee (protocol number: 2008/05/04). All participants provided written informed consent.

5.2.3. Participants

Study inclusion criteria were: diagnosis of a major depressive episode confirmed by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First et al., 1996); 24-item Hamilton Rating Scale for Depression (HRSD-24) (Beckham & Leber,

1985; Hamilton, 1960) score of ≥21 at pre-ECT baseline; meeting remission criteria after the course of ECT (defined as a ≥60% decrease in HRSD-24 score relative to baseline and a score of ≤10 on a minimum of two consecutive testing occasions separated by one week).

Exclusion criteria were: dementia or another Axis I comorbidity, any medical condition rendering the patient unfit for general anaesthesia, ECT in the previous six months, alcohol or substance abuse in the previous six months and inability or refusal to consent.

5.2.4. Assessments

The clinical measures used in this study were described in detail in Chapter 2.2. The diagnosis of a major depressive episode and presence of psychotic features were confirmed using the SCID-I (First et al., 1996). Diagnosis of bipolar disorder was made clinically; occurrence of past manic or hypomanic episodes was recorded based on i) the referring psychiatrist's clinical diagnosis and ii) chart review and discussion by the EFFECT-Dep Trial research team. Depression severity was measured using the HRSD-24 (Beckham & Leber, 1985; Hamilton, 1960) and the Clinical Global Impression (CGI) scale (Guy, 1976). The HRSD-24 score was used to derive the two categorical clinical outcomes operationally defined as follows: relapse and recurrence of depression were defined as a ≥10 point increase in HRSD-24 compared to end-of-treatment score and a HRSD-24 score of ≥16. This increase in HRSD-24 score had to be maintained one week later (if indicated, additional follow-ups were arranged to confirm relapse). Hospital admission, further ECT, and deliberate self-harm/suicide also constituted relapse regardless of HRSD-24 score. If these criteria were met at any point during the first six months of follow-up, the patient was coded as relapsed. If these criteria were met from the beginning of the seventh through to the end of the twelfth month of follow-up, this was considered a recurrence. This somewhat arbitrary distinction is in accordance with theoretical conceptualisations of relapse and recurrence of MDD; relapse represents a

return of the index major depressive episode, while recurrence is the formation of a new episode after a period of sustained remission (Frank et al., 1991; Rush et al., 2006a).

5.2.5. Statistical methods

Patients who relapsed were compared to non-relapsers on demographic and clinical features using the chi-square test (or Fisher's exact test, where appropriate) for categorical variables and independent samples t-test (or Mann-Whitney U for non-normally distributed data) for continuous measures.

Unlike in the previous Chapter 4 where the outcome of interest was whether medication resistance at baseline predicted increased odds of an event occurring (in that study, the two events examined were non-remission and relapse), in the present study the outcome of interest was re-emergence of depressive symptoms during the 12-month follow-up. Such "time-to-event" outcomes take into account not only whether an event (in this case, relapse/recurrence) took place but also the timing of said event. Time-to-event analyses are appropriate in situations such as this where there is no known cure for a disease (in this case, major depression), hence the main goal of continuation therapy is to extend as long as possible the time period of remaining well (i.e. free of depressive symptoms).

As is standard in analyses of longitudinal time-to-event data, the primary method of analysis of time-to-relapse data in this study was survival analysis for right-censored data. Right-censoring indicates a special type of missing data occurring in the specific context of survival analysis. Right-censoring arises for the following possible reasons:

i. a participant exits the study before experiencing the studied event for reasons such as voluntarily dropping out of the study or dying of an unrelated cause;

ii. the study follow-up period is completed before all participants have experienced the studied event.

This is a very important feature of survival analysis since many participants will not have experienced the event in question during the study follow-up and must therefore still be incorporated into the analysis.

The main method of survival analysis in this study was the Cox proportional hazards model (Cox, 1972). The semi-parametric Cox proportional hazards regression is a highly popular method of multivariate analysis of time-to-event data in the medical literature. Its main advantage over fully parametric models is that it makes no assumptions regarding the shape of the survival curve and therefore does not require it to match one of several known probability distributions (e.g. exponential, normal, log-normal, Weibull etc.). Cox proportional hazards was used here to model the following seven a priori specified covariates: electrode placement, age, presence of psychotic features at baseline, polarity, baseline medication resistance, HRSD-24 score after the final ECT session and the number of previous depressive episodes. Covariates were chosen based on the existing literature (see section 5.1). Each covariate was initially analysed separately in univariate models to examine its individual utility in predicting relapse. Univariate analyses were followed by a multivariate model featuring all seven aforementioned variables in order to examine the contribution of each one while controlling for the remaining covariates.

In survival analysis, the main outcome of interest is the hazard ratio. Unlike odds ratios used in Chapter 4 which do not take into account when an event occurs, only that it did occur, the hazard of an event represents the instantaneous risk of an individual who has survived event-free until time *t* experiencing the event at time *t*. For a categorical covariate, a hazard ratio (HR) indicates the ratio of hazard rate in one group vs. the other group. In Cox proportional hazards regression, a key assumption of the model is that the HR is proportional (i.e. constant) over time. The data must meet this assumption.

The other widely used method of survival analysis is the non-parametric Kaplan-Meier method (Kaplan & Meier, 1958). As is standard in survival analyses, for categorical predictors of relapse the Kaplan-Meier method was used to graphically plot survival

functions for each group which were then compared statistically using the log-rank (Mantel-Cox) test.

All statistical analyses used a two-tailed $p<0.05$ significance level and were carried out using SPSS version 21 software (IBM Corp., 2012).

5.3. Results

5.3.1. Sample characteristics

The demographic and clinical characteristics of relapsers and non-relapsers are presented in Table 5.1 below. Patients who remained well during the 12-month follow-up were, as a group, significantly older than those who relapsed by an average of 8.0 years (mean 65.4 vs. 57.4; p=0.043), had fewer previous depressive episodes (median 3 vs. 4.5; p=0.033), were more likely to be have had psychotic features at baseline (37.8% [14/37] vs. 4.2% [1/24]; p=0.003) and less likely to have a bipolar diagnosis (13.5% [5/37] vs. 37.5% [9/24]; p=0.030). There were no statistically significant differences between relapsers and non-relapsers on any of the other recorded clinical characteristics.

TABLE 5.1. Demographic and clinical characteristics of the sample

	Total group (N=61)	Relapse (N=24)	No relapse (N=37)	Statistics[a]		
	mean (SD)	**mean (SD)**	**mean (SD)**	**t**	**df**	**p**
Age, years	62.3 (13.3)	57.4 (17.2)	65.4 (8.9)	2.1	31.1	0.043
Education, years	12.9 (3.7)	12.0 (3.3)	13.4 (3.9)	1.5	58	0.141
Premorbid IQ[b]	107.4 (7.4)	107.8 (7.2)	107.1 (7.7)	0.3	47	0.760
HRSD-24 score at pre-ECT baseline	29.6 (6.1)	29.4 (5.8)	29.7 (6.4)	0.1	59	0.921
HRSD-24 score at the start of post-ECT continuation treatment	4.7 (2.7)	5.0 (2.5)	4.5 (2.8)	0.6	59	0.530
Pre-ECT CGI-S score	5.4 (0.7)	5.4 (0.8)	5.4 (0.7)	0.1	59	0.900
Post-ECT CGI-I score	1.2 (0.5)	1.3 (0.4)	1.2 (0.5)	0.5	59	0.611
	median (range)	**median (range)**	**median (range)**	**U**		**p**
Duration of index episode, weeks	16 (2-111)	19 (4–57)	14 (2-111)	431.0		0.988
Number of previous depressive episodes	3 (0-23)	4.5 (2-23)	3 (0-21)	301.0		0.033
	n (%)	**n (%)**	**n (%)**	χ^2	**df**	**p**
Female gender	39 (63.9)	17 (70.8)	22 (59.4)	0.8	1	0.366
Polarity				4.7	1	0.030
Unipolar	47 (77.0)	15 (62.5)	32 (86.5)			
Bipolar	14 (23.0)	9 (37.5)	5 (13.5)			
Psychotic features	15 (24.6)	1 (4.2)	14 (37.8)			0.003[c]
Electrode placement				0.7	1	0.404
Bitemporal	29 (47.5)	13 (54.2)	16 (43.2)			
Right unilateral	32 (52.5)	11 (45.8)	21 (56.8)			
Medication resistant[d]	40 (66.7)	17 (70.8)	23 (63.9)	0.3	1	0.576
History of previous ECT	22 (36.1)	9 (37.5)	13 (35.1)	0.04	1	0.851

[a]Statistical analyses comparing relapse and no relapse groups
[b]N=49; estimated by the National Adult Reading Test (NART)
[c]Fisher's exact test
[d]N=60; medication resistance defined as failure of ≥1 adequate medication trials (as per ATHF criteria) during the index episode

Abbreviations: ATHF = Antidepressant Treatment History Form; CGI-I = Clinical Global Impression – Improvement scale; CGI-S = Clinical Global Impression – Severity scale; df = degrees of freedom; ECT = electroconvulsive therapy; HRSD-24 = Hamilton Rating Scale for Depression (24-item); IQ = intelligence quotient; NART = National Adult Reading Test; SD = standard deviation

5.3.2. Patterns of relapse and recurrence during the 12-month follow-up

Overall, of the 61 remitters, 24 (39.3%) experienced a return of major depression within the 12-month follow-up period, one (1.6%) withdrew from the study at four weeks while still in remission (represented by a vertical line at four weeks on the survival curves indicating a censored observation), and the remaining 36 (59.0%) completed the follow-up phase without a return of depressive symptoms (Figure 5.1). Of the 24 patients who relapsed, the majority of relapses (79.2%; 19/24) occurred within the first six months (resulting in a cumulative relapse rate of 31.1% at six months), while only five patients (constituting 20.8% of all instances of reappearance of depressive symptoms) experienced a recurrence of depression in the subsequent six months. No manic/hypomanic relapses or suicides occurred during the follow-up phase. Due to the small number of recurrences, relapse and recurrence of depression during the 12-month follow-up was merged into a unitary outcome henceforth referred to as “relapse”.

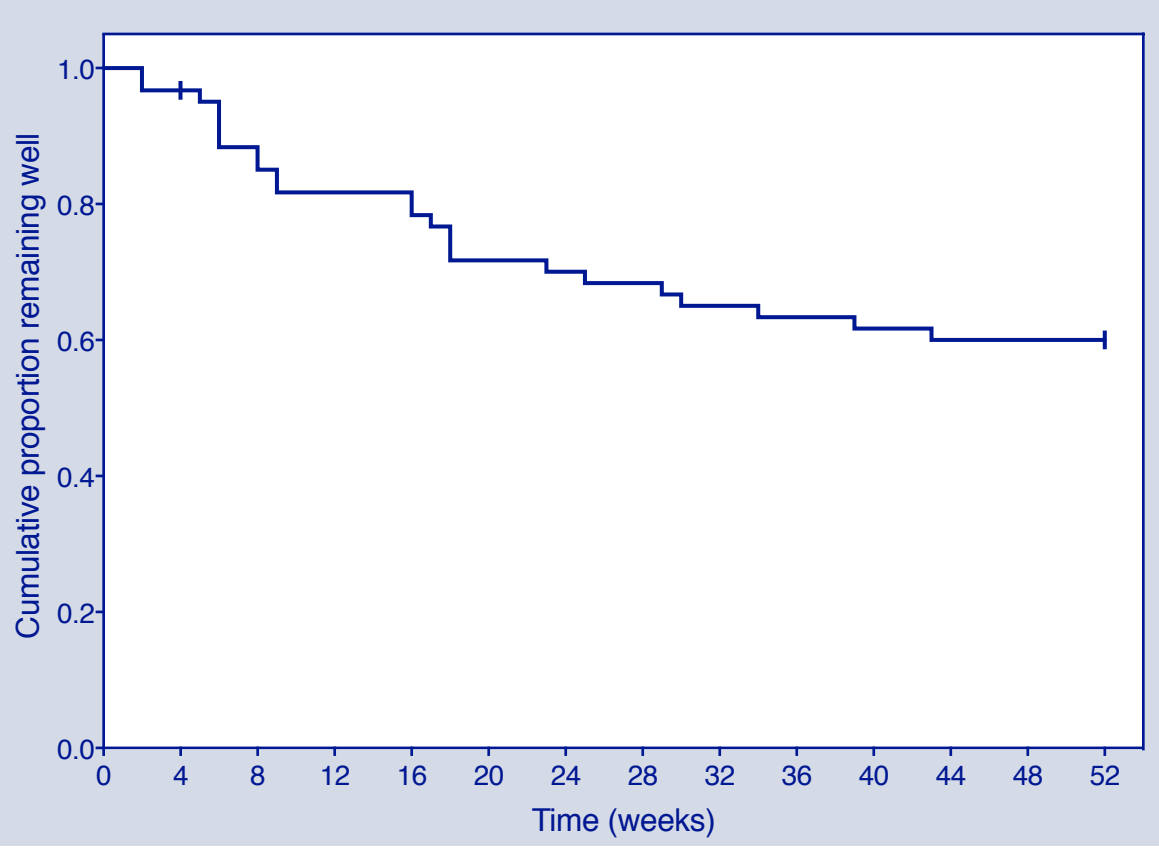

FIGURE 5.1. Kaplan-Meier survival curves showing cumulative proportion of patients remaining depression-free during the 12-month follow-up

5.3.3. Baseline clinical predictors of relapse

5.3.3.1. Electrode placement

Electrode placement has not been shown in any of the previous RCTs of bitemporal vs. high-dose right unilateral ECT to affect subsequent relapse rates. However, because patients were followed up as part of an RCT, the effect of treatment allocation was examined. In the bitemporal group, 13/29 (44.8%) patients relapsed while 11/32 (34.4%) did so in the right unilateral group, an absolute risk reduction of 10.4%.

The Kaplan-Meier survival distributions for the two electrode placements are shown in Figure 5.2 below; there was no statistically significant difference between them (log-rank test, χ^2=1.26, p=0.262). Using Cox proportional hazards, there was no significant association between electrode placement and hazard of relapse (HR=0.67, 95% CI 0.29-1.42, p=0.271).

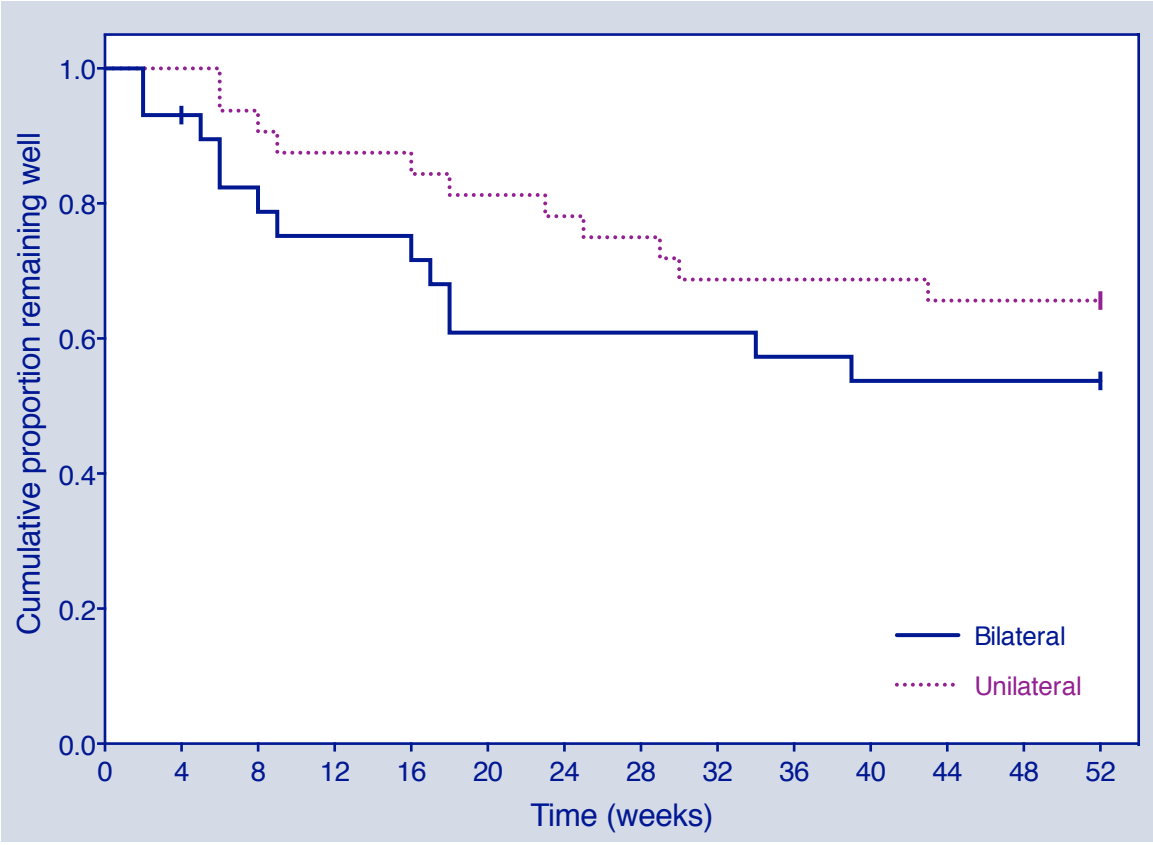

FIGURE 5.2. Kaplan-Meier estimates of the cumulative proportion of patients remaining well during the 12-month follow-up stratified by electrode placement

5.3.3.2. Medication resistance

Next, the effect of pre-ECT baseline medication resistance as measured by the ATHF was examined. Analysed in greater detail in Chapter 4, medication resistance, however defined, did not predict relapse following a successful course of ECT in the subsample of remitters with unipolar depression (N=46) who took part in the EFFECT-Dep Trial (see section 4.3.5.2). Here, remitters with either unipolar or bipolar depression for whom complete medication treatment history for the index episode was available (60/61; 98.4% of the remitter sample) were analysed.

Patients who had received no adequate antidepressant medication trials during the index episode relapsed at a rate of 35.0% (7/20), whereas those who received at least one adequate medication trial as per ATHF criteria (thus fulfilling ATHF criteria for treatment resistance) relapsed at a rate of 42.5% (17/40), a risk difference of 7.5%.

As shown in Figure 5.3 below, the was no statistically significant difference in the Kaplan-Meier survival distributions between the medication resistant and non-resistant groups (log-rank test, χ^2=0.56, p=0.455). Using Cox proportional hazards, patients classified as treatment resistant on the ATHF were not significantly more likely to relapse during the 12-month follow-up (HR=1.39, 95% CI 0.58-3.36, p=0.462).

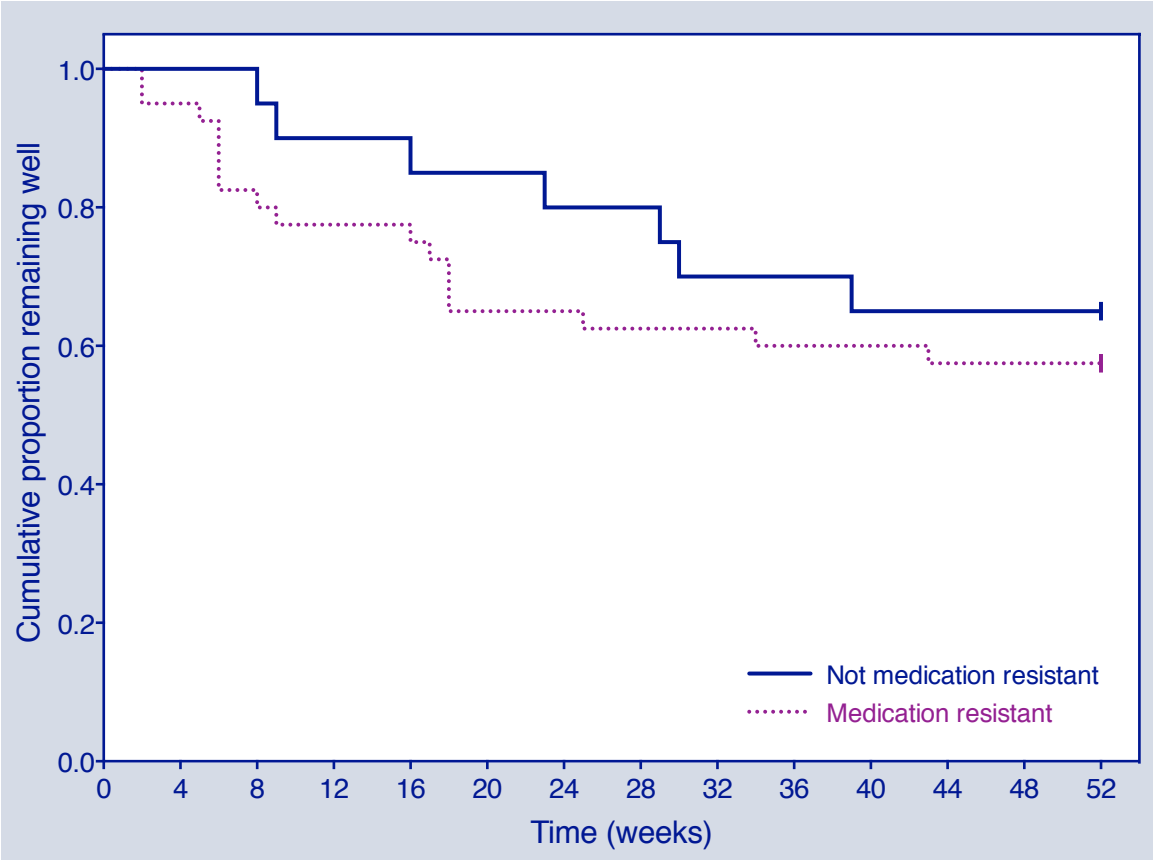

FIGURE 5.3. Kaplan-Meier estimates of the cumulative proportion of patients remaining well during the 12-month follow-up stratified by ATHF classification of medication resistance

5.3.3.3. Age

Next, other hypothesised predictors of post-ECT relapse were examined, starting with variables showing significant associations with relapse in the meta-analysis reported in Chapter 3: age and psychotic features. Increasing age conferred significantly lower hazard of relapse (HR=0.96, 95% CI 0.93-0.99, p=0.006). For each year increase in age, there was a 4% reduction in the hazard of relapse.

5.3.3.4. Psychotic features

Kaplan-Meier survival functions were plotted for psychotic vs. non-psychotic depression (Figure 5.4 below). Of the 15 patients with psychotic depression only one relapsed (6.7%); meanwhile, 23 out of 46 (50%) of patients without psychotic symptoms at pre-ECT baseline relapsed, a very large absolute risk reduction of 43.3% favouring the

psychotic depression group. Presence of psychotic features at baseline significantly reduced the hazard of relapse (HR=0.11, 95% CI 0.01-0.79, p=0.028); patients with psychotic depression had an 89% reduction in hazard of relapse compared to the non-psychotic group.

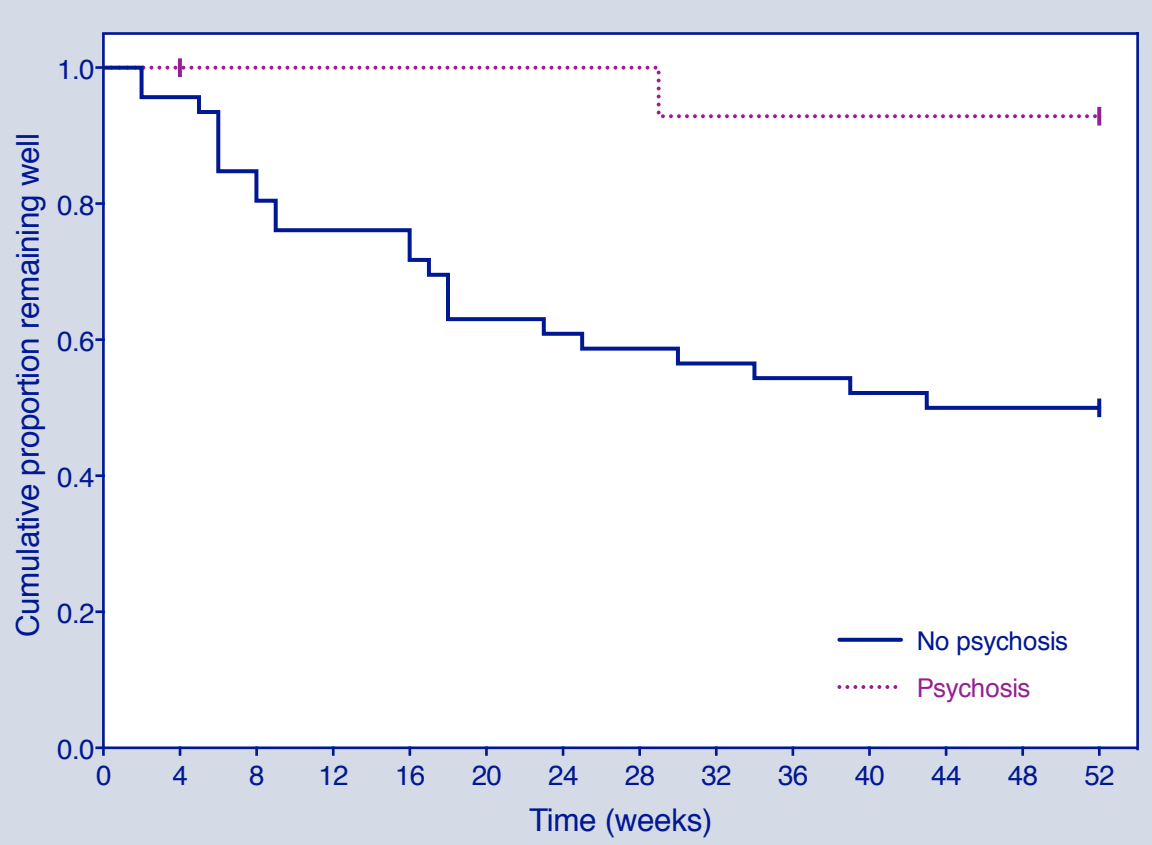

FIGURE 5.4. Kaplan-Meier estimates of the cumulative proportion of patients remaining well during the 12-month follow-up stratified by psychosis

5.3.3.5. Polarity

Next, polarity of depression was examined as a predictor of relapse. Kaplan-Meier survival functions for unipolar and bipolar depression shown in Figure 5.5 below were significantly different (log-rank test χ^2=4.96, p=0.003). Of the 47 patients with unipolar depression, 15 (31.9%) relapsed compared to 9/14 (64.3%) in the bipolar disorder group. Compared to patients with unipolar MDD, patients with bipolar disorder had a nearly 2.5 times greater hazard of relapse (HR=2.47, 95% CI 1.08-5.66, p=0.033).

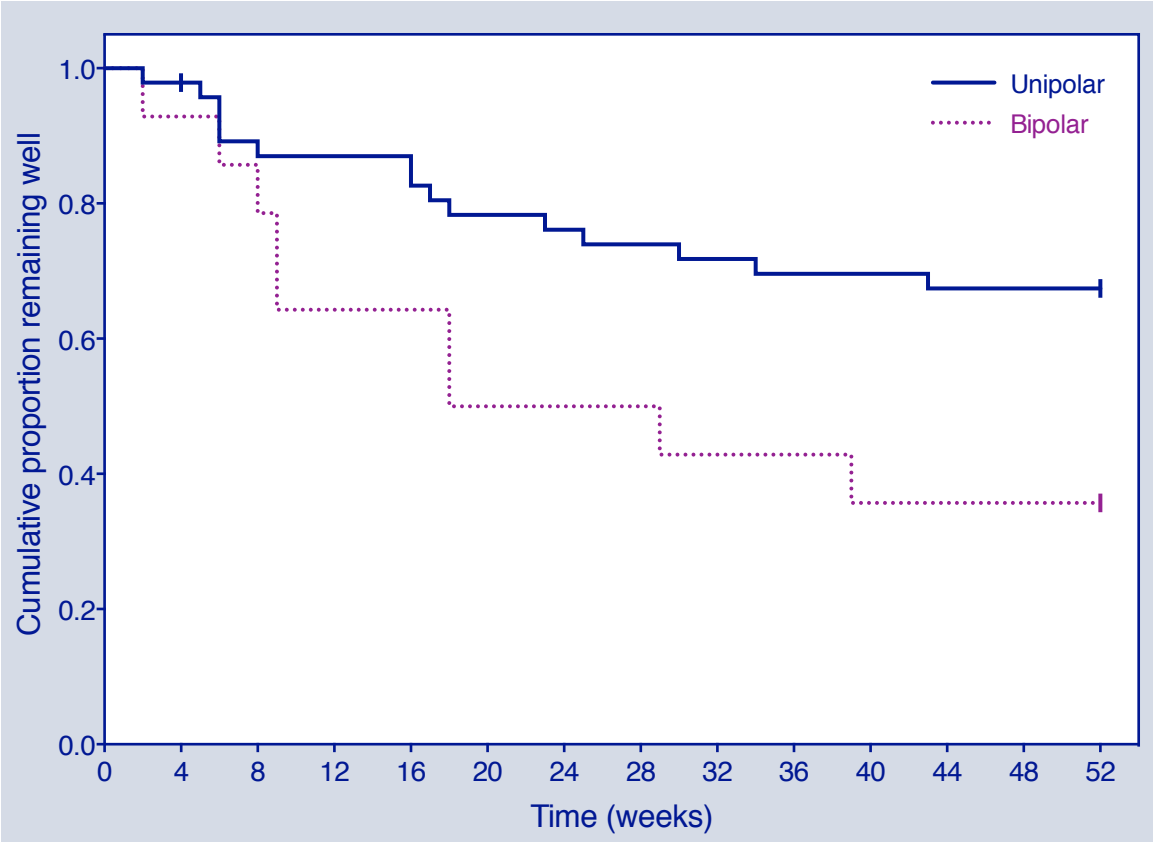

FIGURE 5.5. Kaplan-Meier estimates of the cumulative proportion of patients remaining well during the 12-month follow-up stratified by polarity

To further explore this relationship between polarity of depression and relapse, patients with bipolar disorder were subdivided into bipolar I and bipolar II categories, depending on whether they had a previous history of one or more manic or hypomanic episodes, respectively. Kaplan-Meier survival curves for the three diagnostic groups were plotted in Figure 5.6 below. Of the 47 patients with unipolar depression, 15 (31.9%) relapsed. A similar percentage relapsed in the bipolar I group (2/6; 33.3%). In the bipolar II group, however, all but one patient relapsed (7/8; 87.5%). As the unipolar and bipolar I survival curves crossed, the proportional hazards assumption of Cox regression was violated. Given that these two groups relapsed at similar rates (31.9% vs. 33.3%), they were merged into one group and compared to patients with a bipolar II diagnosis as the data now met assumptions of Cox regression. Patients treated with ECT for a major depressive episode in the context of bipolar II disorder were over four times more likely to

relapse than the group consisting of the other two diagnoses (HR=4.29, 95% CI 1.75-10.51, p=0.001).

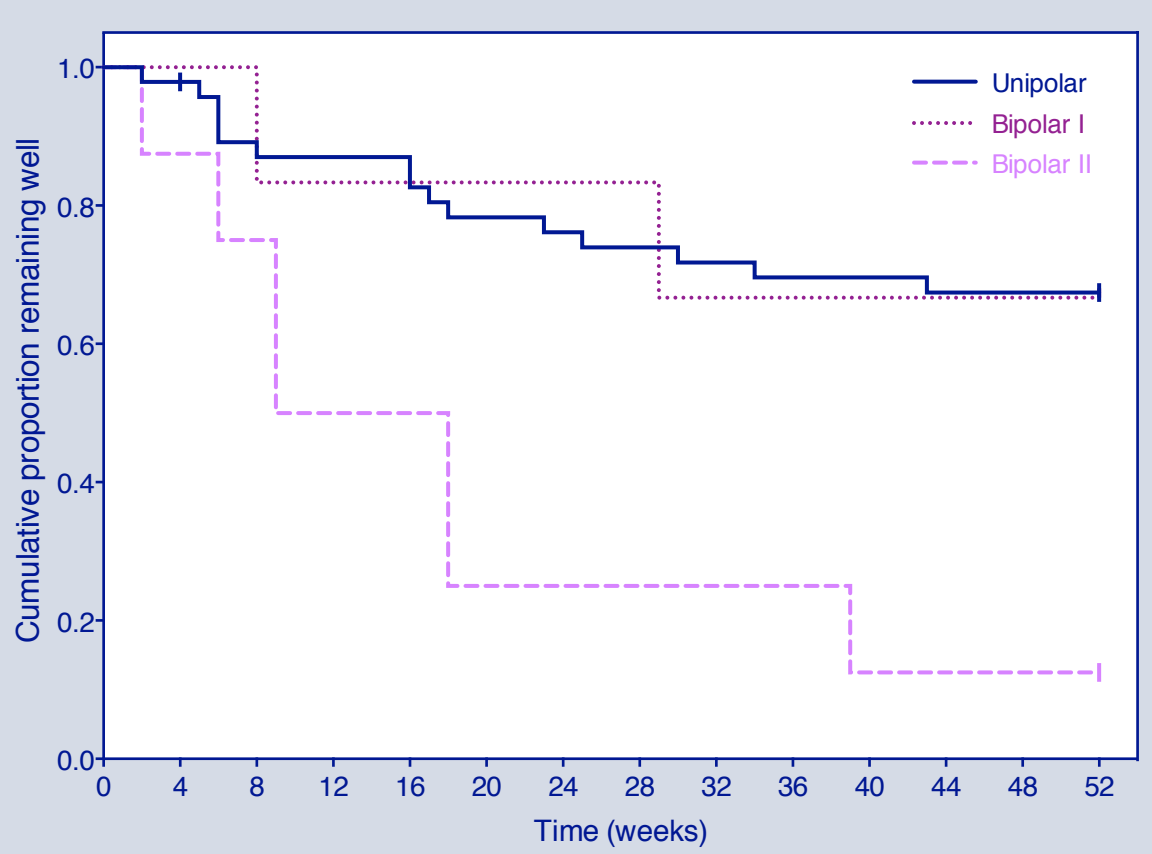

FIGURE 5.6. Kaplan-Meier estimates of the cumulative proportion of patients remaining well during the 12-month follow-up stratified by unipolar MDD vs. bipolar subtypes

5.3.3.6. Residual depressive symptoms at the end of ECT course

Next, the impact of residual depressive symptoms (as measured by the HRSD-24 score after final ECT treatment) on the subsequent clinical course was studied. Mean HRSD-24 score at the end of ECT course in the remitter group was 4.7 (SD 2.7, range 0-10). Surprisingly, no relationship was found between HRSD-24 score at the start of follow-up phase and likelihood of relapse (HR=1.05, 95% CI 0.91-1.22, p=0.478).

5.3.3.7. Number of previous depressive episodes

As the number of previous depressive episodes variable was non-normally distributed, logarithmic transformation was applied. Log-transformed number of previous

depressive episodes was a significant predictor of post-ECT relapse in a Cox proportional hazards model (HR=2.95, 95% CI 1.04-8.41, p=0.043).

5.3.3.8. Multivariate model

A multivariate Cox regression model (Table 5.2 below) featuring the seven a priori specified covariates (electrode placement, ATHF medication resistance, age, psychosis, polarity, HRSD-24 score at the end of ECT course and number of previous depressive episodes) showed that the predictors of relapse identified as statistically significant in univariate models (age, psychosis, polarity and number of previous episodes) remained significant when modelled simultaneously and after adjustment for the remaining three covariates (electrode placement, medication resistance and HRSD-24 score at the end of ECT course). Adjusting for covariates, increasing age was still associated with a decreased hazard of relapse (HR=0.96, 95% CI 0.926-0.998, p=0.041), as was the presence of psychotic features at baseline (HR=0.11, 95% CI 0.01-0.89, p=0.038). Bipolar II diagnosis was associated with a greater hazard of relapse (HR=2.89, 95% CI 1.08-7.76, p=0.035) compared to the reference category of unipolar and bipolar I groups combined. Higher number of previous depressive episodes also conferred significantly greater hazard of relapse in the multivariate model (HR=3.30, 95% CI 1.10-9.90, p=0.033). Adjusting for covariates, the hazard of relapse was actually halved in the ATHF medication resistant group compared to non-resistant group, though this difference did not reach statistical significance (p=0.226).

TABLE 5.2. Multivariate Cox proportional hazards model for relapse

	HR	95% CI for HR	p value
Right unilateral electrode placement[a]	0.96	0.41-2.23	0.924
Medication resistant	0.53	0.19-1.49	0.226
Age	0.96	0.926-0.998	0.041
Psychotic features at pre-ECT baseline	0.11	0.01-0.89	0.038
Bipolar II diagnosis[b]	2.89	1.08-7.76	0.035
HRSD-24 score at the end of ECT course	1.04	0.87-1.24	0.666
Number of previous depressive episodes[c]	3.30	1.10-9.90	0.033

[a]compared to the reference category of bitemporal electrode placement
[b]compared to the reference category of unipolar and bipolar I groups combined
[c]log-transformed
Abbreviations: ECT = electroconvulsive therapy; HR = hazard ratio; HRSD-24 = 24-item Hamilton Rating Scale for Depression

5.3.4. Effectiveness of post-ECT lithium therapy

The post-ECT follow-up phase was naturalistic; the choice of continuation antidepressant treatment(s) was up to the discretion of the treating psychiatrist. None of the 61 remitters received continuation/maintenance ECT; all received pharmacotherapy. Due to the large number of combinations of antidepressants and augmentation strategies, no meaningful statistical analyses were possible due to small sample sizes for each treatment strategy. In any case, no evidence exists for superiority of any particular antidepressant over others in preventing post-ECT relapse (see meta-analysis in Chapter 3). Some, mostly uncontrolled, evidence (recently reviewed in Rasmussen, 2014) suggests that lithium may be protective against relapse in ECT patients.

In the present study, of the 61 remitters, 27 (44.3%) were already receiving lithium during the course of ECT. All of them (plus one additional patient who was commenced on lithium at the end of the ECT course) embarked on the follow-up phase on lithium. Thus, 28 of the 61 (45.9%) remitters were receiving lithium for the majority of the follow-up period. Of the 28 patients on lithium, 21 (75%) had a diagnosis of unipolar depression and were using it to augment an antidepressant while the remaining seven (25%) were using it as a mood stabiliser in the context of bipolar disorder. As shown above, patients with unipolar and bipolar disorder relapsed at different rates. Given that patients were not

randomised to lithium therapy, it is also possible, indeed probable, that the patients with unipolar depression who were prescribed lithium were clinically judged to be at a greater risk of relapse to begin with. Therefore, an adjustment was made for risk factors for relapse identified above (age, psychotic features, bipolarity and number of previous depressive episodes). A multivariate Cox proportional hazards model (Figure 5.7 below) showed a significant reduction in the hazard of relapse in the lithium group (HR=0.37, 95% CI 0.14-0.97, p=0.044).

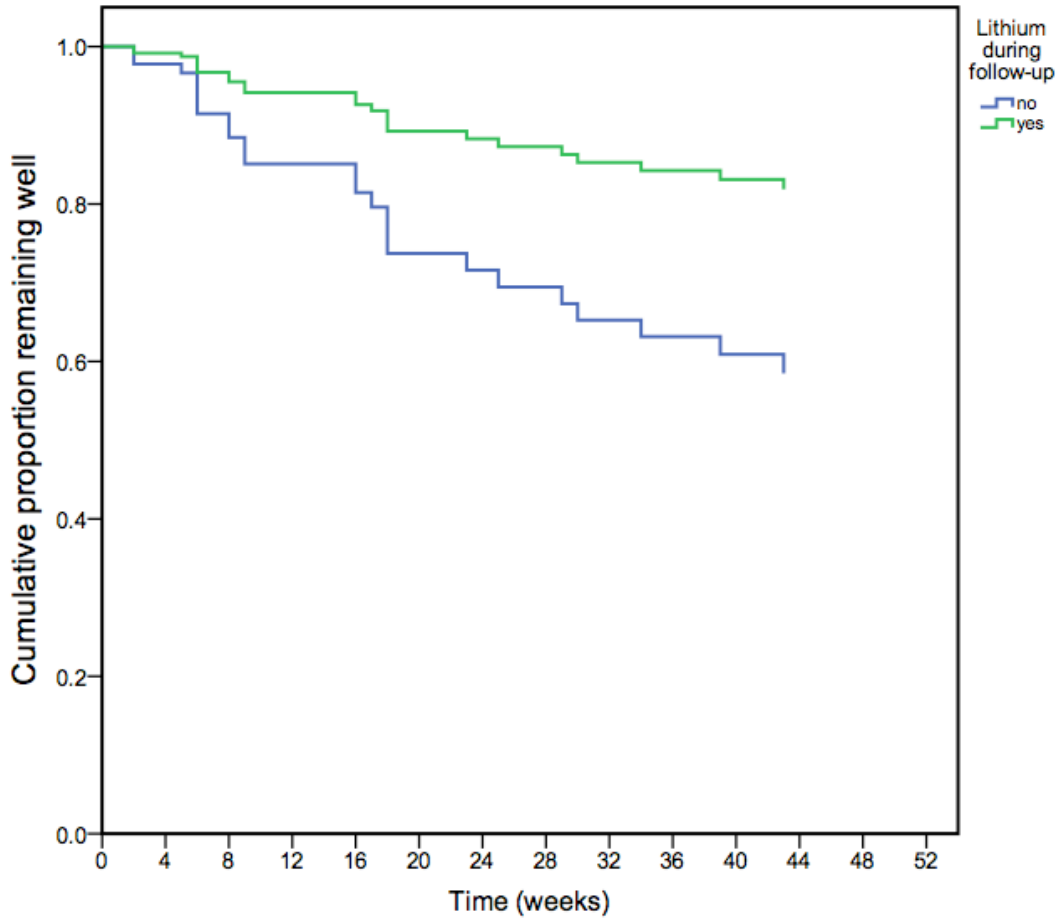

FIGURE 5.7. Cox proportional hazards estimates of the cumulative probability of remaining well during the 12-month follow-up stratified by lithium augmentation continuation therapy; adjusted for age, psychosis, polarity and number of previous depressive episodes

5.4. Discussion

5.4.1. Summary of key findings

The principal findings of this study were that older adults and patients with psychotic depression had a more favourable long-term prognosis following a successful course of ECT while medication-resistant patients did not have inferior outcomes compared to those who had not received adequate antidepressant pharmacotherapy prior to ECT. These results are aligned with those of the meta-analysis reported in Chapter 3 and elsewhere (Jelovac et al., 2013). A markedly low relapse rate of 6.7% observed in patients with psychotic depression in the present study offers support for the view that psychotic depression may represent a distinct diagnostic entity especially responsive to ECT (Petrides et al., 2001). Overall, the relapse rates at six and twelve months in this study, approximately 30% and 40% respectively, were approximately 10% lower than the estimates derived from the aforementioned meta-analysis of ECT studies in the modern era, perhaps reflecting the fact that almost half of the sample received lithium during and after the ECT course. During the non-randomised follow-up phase of this study, lithium continuation therapy was significantly protective against relapse. Several uncontrolled studies (Atiku, Gorst-Unsworth, Khan, Huq, & Gordon, 2015; Nordenskjold, von Knorring, & Engstrom, 2011; Sackeim et al., 2000) and one randomised trial (Sackeim et al., 2001) have demonstrated an advantage for lithium augmentation over antidepressants alone or antidepressants combined with other augmentation strategies in post-ECT continuation therapy. Unsurprisingly, patients in this study who had a more recurrent course of illness prior to index ECT course were especially prone to relapse.

5.4.2. Medication resistance and long-term outcome after ECT

Despite some reports showing increased relapse rates in patients meeting ATHF criteria for treatment resistance (Sackeim et al., 1990; Sackeim et al., 2000; Sackeim et al., 2008; Shapira et al., 1995), two large recent RCTs of six-month post-ECT continuation therapy showed no significant effect of ATHF rating on the subsequent risk of relapse

(Prudic et al., 2013; Rasmussen et al., 2009). In the present study, in a multivariate survival analysis adjusting for relevant covariates, pre-ECT medication resistance was in fact associated with a non-significant *reduction* in the hazard of subsequent relapse. Conflicting results notwithstanding, these results represent good news for patients with treatment-resistant depression which is a major public health problem and the leading indication for ECT referral nowadays. ECT is an effective treatment option for this difficult-to-treat, refractory patient population. Although it is possible that a detrimental effect of treatment resistance was not detected due to sample size, an unlikely explanation given virtually the same (Sackeim et al., 1990; Sackeim et al., 2000; Sackeim et al., 2008) or smaller (Shapira et al., 1995) sample sizes in previous studies showing a significant effect, it is worth keeping in mind that even if an effect were demonstrable in a very large sample, this would not necessarily translate into a clinically meaningful effect.

5.4.3. ECT treatment parameters as a predictor of outcomes

This study found no significant difference in relapse rate in patients treated with high-dose right unilateral ECT compared to low-dose bitemporal ECT. In the past three decades, a considerable amount of research effort has focused on elucidating the impact of variations in ECT treatment technique on clinical and cognitive outcomes. While treatment parameters such as electrode placement (Dunne & McLoughlin, 2012; The UK ECT Review Group, 2003), stimulus dosage (Kellner et al., 2010; McCall et al., 2000; Sackeim et al., 1987; Sackeim et al., 1993), pulse width (Loo et al., 2014; Spaans et al., 2013), concomitant pharmacotherapy (Sackeim et al., 2009) and treatment frequency/schedule (Charlson et al., 2012) have been robustly shown to affect acute clinical and cognitive outcomes, there is no evidence for persisting differential effects of ECT technique on the long-term course of depressive illness. Of the six published RCTs investigating clinical efficacy of bitemporal vs. high-dose (6 x ST) right unilateral ECT, two followed-up remitters for a year (Sackeim et al., 2000; Sackeim et al., 2008). These studies found no difference between the two electrode placements on subsequent pattern

of relapse once remission had been achieved by whichever means. These results were confirmed in the present study. In terms of cognitive outcomes, while some studies have shown advantage for unilateral ECT on various cognitive measures at long-term follow-up, a recent meta-analysis found that these differences between unilateral and bilateral electrode placements disappeared when cognitive testing took place more than three days after the final ECT session (Semkovska, Keane, Babalola, & McLoughlin, 2011). There is evidence of persistent advantage for unilateral ECT on autobiographical memory at long-term follow-up according to a large prospective community study (Sackeim et al., 2007), although assessment of this cognitive domain is fraught with methodological difficulties (Kessler et al., 2014; Semkovska & McLoughlin, 2013). In summary, three RCTs with one-year follow-up have now demonstrated that right unilateral ECT administered at 6 x ST compared to standard bitemporal ECT does not lead to worse acute or long-term clinical outcomes but is advantageous from the viewpoint of less autobiographical memory impairment.

5.4.4. Longitudinal course of bipolar disorder following ECT

An interesting but preliminary finding suggested that patients with bipolar II diagnosis have a poorer long-term prognosis after ECT than patients with unipolar MDD and bipolar I disorder. In the present study, the latter two groups relapsed at virtually the same rate (approximately one-third in each group) while patients with bipolar II disorder had a markedly worse outcome with all but one relapsing during the study period. This is an unexpected finding in light of a recent meta-analysis showing ECT to be equally effective in unipolar and bipolar depression when examining acute remission rates (Dierckx et al., 2012). In this meta-analysis, bipolar disorder outcomes were not broken down by bipolar subtype as only one of the included studies (Medda, Perugi, Zanello, Ciuffa, & Cassano, 2009) reported separate outcomes for bipolar I vs. bipolar II disorders and found that remission rates (defined as post-treatment HRSD score of <8) were significantly lower in both bipolar groups compared to unipolar depression. Taking a

broader view of the longitudinal course of affective disorders, however, the results of the present study are less surprising. Although bipolar II is a less severe form of bipolar illness in terms of symptom severity, it is more severe than bipolar I in terms of chronicity, number of episodes, rapidity of cycling and temperamental instability (Akiskal et al., 1995; Ayuso-Gutierrez & Ramos-Brieva, 1982; Judd et al., 2003a; Judd et al., 2003b; Mantere et al., 2008; Vieta, Gasto, Otero, Nieto, & Vallejo, 1997). Due to the small number of remitted patients with bipolar disorder (N=14) in the present study, these results must be interpreted with caution.

5.4.5. Limitations

In addition to modest sample size, other limitations of this study include reliance on clinical diagnosis of past (hypo)manic episodes. Differential diagnosis of bipolar II disorder from other causes of affective instability, such as borderline personality disorder, can be challenging. Previous studies have found that patients with MDD comorbid with borderline personality disorder were less likely to respond to ECT compared to patients with MDD with or without other personality disorders (Feske et al., 2004). Patients with comorbid personality disorders appear to have higher relapse rates after ECT (Prudic et al., 2004; Sareen, Enns, & Guertin, 2000). It would have been better had all bipolar diagnoses been confirmed using the SCID. Additionally, it would have been useful to administer the personality disorders section of the SCID to explore the previously under-researched relationship between personality and long-term illness trajectory following ECT. This was not practically feasible, however, due to the short time interval (typically less than 48 hours) available between patient referral and the first ECT session during which recruitment took place and a large amount of baseline clinical information had to be collected, including taxing neuropsychological assessments. Age-at-onset of depressive illness should have been recorded. As it stands, it cannot be determined which patients had late- vs. early-onset depression. It is conceivable that late-onset depression is a stronger predictor of ECT outcome than the patient's current age. Incorporation of these

measures into future studies would help elucidate some of the outstanding questions. Especially needed is further research into optimisation of relapse prevention by means of pharmacotherapy, continuation/maintenance ECT and psychotherapy.

5.4.6. Conclusions

In summary, this prospective study of post-ECT relapse found that approximately 40% of patients initially successfully treated with ECT relapsed during the subsequent year. Younger age, non-psychotic depression, bipolar II disorder and greater number of previous depressive recurrences predicted a less favourable outcome while medication resistance and residual depressive symptoms after the ECT course did not worsen prognosis. In the upcoming Chapter 6, focus is shifted away from long-term clinical outcomes to long-term cognitive sequelae of ECT, specifically autobiographical memory, an area of continuing uncertainty and concern among patients, their families, clinicians and the general public alike.

6. Autobiographical memory specificity before and after ECT with a three-month follow-up: a retrospective casenote study

6.1. Introduction

Electroconvulsive therapy (ECT) is a highly effective treatment for severe depression but its use is limited by cognitive sequelae. According to patient surveys, retrograde amnesia for autobiographical memories is the side-effect of greatest concern (Rose et al., 2003). Routine neuropsychological testing predominantly measures anterograde memory function (i.e. the ability to learn new information) and thus fails to adequately capture ECT patients' subjective complaints, which mostly relate to difficulties with retrieving personal memories from past life (Semkovska & McLoughlin, 2013). While anterograde memory function tends to return to or indeed improve beyond pre-ECT baseline levels within two weeks following a treatment course (Semkovska & McLoughlin, 2010), retrograde amnesia can persist at long-term follow-up (Sackeim et al., 2007). Despite considerable research (Sackeim, 2014), the nature, extent and duration of autobiographical memory impairment have not yet been fully elucidated.

Over the past three decades, there has been an accumulating body of evidence demonstrating autobiographical memory impairment in patients with depression. The phenomenon of so-called overgeneral autobiographical memory (OGM) is a robust finding in the depression literature (Sumner, 2012; Sumner et al., 2010; Van Vreeswijk & De Wilde, 2004; Williams et al., 2007). First observed in a study of survivors of a suicide attempt (Williams & Broadbent, 1986), OGM refers to the tendency to provide a generic summary of a category of events (e.g. "I never enjoy going to parties") rather than a description of a specific event situated in time and place (e.g. "the party at my friend's house I went to last Saturday") when asked to recall an event in response to a cue word (e.g. "party"). One meta-analysis of 11 studies found a mean effect size (Cohen's d) of

1.12 for severity of OGM in patients with depression compared to healthy controls (Williams et al., 2007), while another found OGM to predict the longitudinal course of illness with fewer specific and more overgeneral/categorical memories at baseline being associated with greater depressive symptoms at follow-up (Sumner et al., 2010). OGM is also present in at-risk individuals (Kuyken & Dalgleish, 2011; Young, Bellgowan, Bodurka, & Drevets, 2013), suggesting that it may be an underlying cognitive vulnerability factor for the development of depression.

OGM has not been extensively studied in ECT patients. The preponderance of modern ECT research has focused on the quantification of retrograde amnesia and the extent to which it is influenced by variations in treatment parameters such as dose, electrode placement and pulse width (Sackeim, 2014). These studies, the majority of which have used the short or long form of the Columbia University Autobiographical Memory Interview (McElhiney et al., 2001; McElhiney et al., 1995), have found significant decreases in consistency of autobiographical memory recall at short- and long-term follow-ups compared to pre-ECT baseline (Kellner et al., 2010; Sackeim et al., 2009; Sackeim et al., 2000; Sackeim et al., 2007; Sackeim et al., 2008). These studies focused on overall percentage consistency between answers provided at baseline and follow-ups as an estimate of retrograde amnesia, irrespective of any pre-existing abnormalities in autobiographical memory function such as overgenerality.

One previous study examining OGM in ECT patients, using the cue-word Autobiographical Memory Test (Williams & Broadbent, 1986) discussed above, found that worse OGM at baseline predicted incipient relapse in the first week following cessation of treatment (Raes et al., 2008). Another study (Soderlund et al., 2014), using a different instrument, the Autobiographical Interview (Levine et al., 2002), showed an impairment in episodic but not semantic autobiographical memory in a sample of 21 patients with depression referred for ECT. The Autobiographical Interview comprises both free recall and a structured interview involving specific probes designed to assess the effect of retrieval support on recall of event, time, place, perceptual, thought and emotional details

of memories, thus reducing the contribution of executive dysfunction to observed deficits in episodic autobiographical memory retrieval. This is an important contribution to the literature since the majority of studies finding reduced specificity of episodic autobiographical memory in depression used the cue-word Autobiographical Memory Test, a technique that places high demand on executive function. This is problematic because executive function is impaired in depression (Snyder, 2013) so it is unclear to what extent poor performance on the Autobiographical Memory Test reflects executive deficits. Both of the aforementioned studies examining specificity of autobiographical memory in patients referred for ECT, however, reported autobiographical memory specificity only at pre-ECT baseline.

The first study to show a dissociation between episodic and semantic autobiographical memory in depression found a selective impairment in episodic and good performance on semantic autobiographical memory (Soderlund et al., 2014). The term "dissociation" in neuropsychology refers to the following concept (Dunn & Kirsner, 2003):

> Dissociations are used to infer the existence of separate mental processes. There are two main types, single and double. Let *A* and *B* be two tasks and let *a* and *b* be two manipulations, variables or factors. A single dissociation is observed if *a* affects performance on *A* but not on *B*. A double dissociation is observed if, in addition, *b* affects performance on *B* but not on *A*. In cognitive neuropsychology, manipulation *a* would usually correspond to a comparison between a patient or group of patients who are impaired on *A* but not *B*, and normal controls, who are unimpaired on both *A* and *B*. Similarly, manipulation *b* would correspond to a comparison between another patient or group of patients impaired on *B* but not *A* and normal controls. Both single and double dissociations invite the inference that there is an underlying mental function required by *A* but not by *B*. In addition, a double dissociation invites the converse inference, that there is an underlying mental function required by *B* but not by *A* (p. 1).

In other words, if two cognitive functions which are strongly correlated under normal circumstances (in this instance, two components of autobiographical memory – semantic and episodic) are shown to be dissociable in some disease process (in this case, major depression), this implies that the two memory components in question are underpinned by different neural networks even though one would not realise this by simply looking at performance in normal controls or people with neurological/neuropsychiatric diseases which do not specifically affect one of the two memory components. If the brain

is capable of defective performance on one of these cognitive processes at the same time as the other remaining unaffected (or at least largely spared), this has important theoretical implications for our understanding of organisation of the brain's structure and/or function.

A standardised neuropsychological instrument, the Kopelman et al. Autobiographical Memory Interview (AMI) (Kopelman et al., 1990), is commonly used in neurological samples and increasingly used in the ECT literature to measure semantic and episodic autobiographical memory. In patients with some forms of amnesia and normal control samples, episodic and semantic components show strong correlations (0.60-0.77) (Kopelman et al., 1990). The scale's authors found that while in general performance on both components of the AMI (and other remote memory tests) shows strong correlations, some patients do badly on one component but well on the other, highlighting the need for assessment of both components given that they are not measuring the same underlying construct.

To make a case for dissociation of episodic and semantic autobiographical memory (single dissociation in this instance; to demonstrate a double association one would need to also find a patient group with normal episodic but impaired semantic autobiographical memory) one needs to find a disease process that produces defective performance on one component while allowing for normal performance on the other within the same patient (preferably of course a group of patients). The best way to show this is by comparing performance of individuals affected by this disease process to normal performance on each of the two autobiographical memory components. Major depression appears to be one such disease process.

The present study aimed to assess episodic and semantic autobiographical memory of patients treated with ECT using the Kopelman AMI (Kopelman et al., 1990), before, immediately after the course and at long-term follow-up and compare it to published norms. The aim was to study the previously under-researched dissociation between episodic and semantic autobiographical memory in patients with depression and

to examine the possible differential effect of ECT on these two components of memory. The aim was to also explore the relationship between specificity of episodic autobiographical memory at baseline and the subsequent clinical course of depressive illness after ECT.

6.2. Materials and Methods

6.2.1. Study design

The study was conducted at St. Patrick's University Hospital, a non-profit independent-sector psychiatric facility where Ireland's largest ECT clinic is located. As part of routine clinical practice and in line with current treatment guidelines advising monitoring of cognitive status before, during and after a course of ECT (National Institute for Clinical Excellence, 2010), autobiographical memory of patients receiving ECT at St. Patrick's University Hospital's ECT clinic was monitored at baseline, end of ECT course and three-month follow-up. This study was a retrospective chart review of all patients who were successfully followed-up during a period of 2.5 years between August 2011 (when routine autobiographical memory testing began) and January 2014.

6.2.2. Ethics

This study received ethical approval from St. Patrick's University Hospital Research Ethics Committee (protocol number: 06/13). All information used in this retrospective case-note review was collected as part of routine clinical practice by the patient's clinical team and a clinical nurse specialist from the ECT clinic.

6.2.3. Participants

Adult inpatients aged 18 or over with an ICD-10 clinical diagnosis of a major depressive episode (in the context of unipolar major depressive disorder or bipolar disorder) referred for a course of ECT were assessed for study eligibility. Patients were

eligible for the study if they completed the three-month follow-up. Exclusion criteria were: dementia, another Axis I disorder and substance abuse in the past year.

6.2.4. Treatment parameters

Brief-pulse (1.0 msec) ECT was delivered twice weekly with hand-held electrodes using a MECTA 5000M device (MECTA Corporation, OR, USA) in accordance with the Royal College of Psychiatrists' guidelines (Dunne & McLoughlin, 2013). Each patient's seizure threshold (ST) was established during the first ECT session using an empirical titration method. Subsequent treatments were administered at 1.5 x ST for bitemporal ECT or 4 x ST for right unilateral (d'Elia placement) ECT. Electrode placement was chosen by the referring psychiatrists in consultation with patients. Methohexitone (0.75–1.0 mg/kg) or thiopentone (1.5-2.5 mg/kg) were used for anaesthesia and suxamethonium (0.5–1.0 mg/kg) for muscle relaxation. Seizure duration was monitored by observation of motor activity and electroencephalogram (EEG). Treatment was continued until satisfactory clinical response was achieved as judged by the referring clinician or the patient received 12 treatment sessions, which is the maximum duration of an ECT course set by the Irish Mental Health Commission.

Patients received their regular concomitant pharmacotherapy during the ECT course as is standard clinical practice in Ireland and many other countries. Post-ECT individually-tailored continuation treatment with antidepressants and other psychotropic medications was prescribed to all patients by their treating psychiatrist.

6.2.5. Outcomes

Clinical outcomes were evaluated using the 24-item Hamilton Rating Scale for Depression (HRSD-24) (Beckham & Leber, 1985; Hamilton, 1960) and the Clinical Global Impression (CGI) (Guy, 1976) scale. Treatment response was defined as a decrease in HRSD-24 score of ≥60% and an end-of-treatment score of ≤10. Relapse was defined as

an increase in HRSD-24 score of at least 10 points relative to end-of-treatment score and a score of ≥16.

Global cognitive status was assessed using the Mini-Mental State Examination (Folstein et al., 1975) (see Chapter 2.3.5.4 for a description of this scale and its psychometric properties). Autobiographical memory was measured by the recent life section of the Kopelman et al. Autobiographical Memory Interview (AMI) (Kopelman et al., 1990) (see Chapter 2.3.5.3 for a more detailed description of this scale and its psychometric properties). Although initially developed for use in neurological populations (Kopelman, 1989; Kopelman et al., 1989), the AMI has previously been found to successfully discriminate between depressed patients and normal controls (Warren & Haslam, 2007). Its use in clinical practice is facilitated by published normative data based on 34 controls aged 20-78 years (Kopelman et al., 1990), allowing clinicians to compare their patients' performance to that of healthy adults.

The AMI is a semi-structured interview consisting of the "personal semantic schedule" measuring memory for facts about one's life and the "autobiographical incidents schedule" measuring recall of specific episodic events from one's past life. The full AMI covers three time periods: childhood, early adulthood and recent life. Only the recent life section was administered here in order to maximise compliance. In a previous ECT trial (McLoughlin et al., 2007), severely depressed participants found the complete AMI too onerous to complete in full. The aim was also to focus on memories more proximal to the time of treatment as they may be more vulnerable to the effect of ECT than more remote memories (Lisanby et al., 2000; Squire, Slater, & Chace, 1975).

In the present study, specificity of autobiographical memory was operationally defined as the score on the autobiographical incidents schedule of the AMI. Each episodic memory is scored on a 0-3 scale depending on the level of descriptive richness and specificity in time and place. Three episodic memories are probed in the recent life section of the AMI, yielding a possible range of performance of 0-9 points. Lower scores on this subscale indicate worse specificity of episodic autobiographical memory.

The AMI was administered to patients by a clinical nurse specialist, Shane McCarron, who was trained on the administration of the scale by a clinical neuropsychologist. Two raters (this author and a masters-level psychologist Stephanie O'Connor) independently scored verbatim transcripts of interviews with all patients. Inter-rater reliability was high, with intraclass correlation coefficients exceeding 0.90 for the total score, personal semantic schedule and the autobiographical incidents schedule. Means of the two raters' scores were used in subsequent statistical analyses as recommended by the AMI's testing manual when using the scale for research purposes.

6.2.6. Statistical analyses

Patients who completed the three-month follow-up were compared to non-completers on demographic and clinical characteristics using the chi-square (χ^2) test or Fisher's exact test for categorical variables and independent samples t-test for continuous variables. Change in mean HRSD-24 score over time was tested with a repeated measures analysis of variance (ANOVA). To test for the effect of time (baseline, after final ECT and three-month follow-up) on three dependent variables (AMI total score, personal semantic schedule score and autobiographical incidents schedule score), while controlling for covariates (age, gender, years of education, baseline HRSD-24 and baseline MMSE), a repeated measures analysis of covariance (ANCOVA) was carried out for each of the three measures of autobiographical memory. To measure the effect of baseline autobiographical memory specificity on depression outcomes after ECT, Pearson's r correlation coefficients were used to calculate correlations between baseline autobiographical incidents schedule scores and HRSD-24 scores after the final ECT session and at three-month follow-up. Binary logistic regressions were performed to measure the effect of baseline autobiographical incidents schedule score on the likelihood of response and relapse. Odds ratios (OR) were calculated for these categorical outcomes. Threshold for statistical significance was set at $p<0.05$. Statistical analyses were performed in SPSS version 22.0 (IBM Corp., NY, USA).

6.3. Results

6.3.1. Participant flow and sample characteristics

The chart review identified 221 new referrals for a course of ECT during the study period (excluding patients undergoing maintenance ECT and patients hospitalised elsewhere but receiving ECT at our clinic). Of those 221 referrals, 206 were for treatment of a major depressive episode. Of these 206, 129 were excluded from the study due to: being unable or unwilling to complete cognitive assessment (74 patients); participation in a concurrent randomised controlled trial in which autobiographical memory was already being assessed (28 patients); repeat course of ECT being administered to a patient already in this study (18 patients); and comorbid Axis I disorder or substance abuse (9 patients). Baseline assessments were completed by 77 patients, of which 29 (37.7%) were lost to three-month follow-up due to being uncontactable or refusing to complete the assessment. Long-term follow-up was completed by 48 patients.

There were no significant differences between study completers and non-completers in age ($t(42)=-0.09$, $p=0.930$), gender (χ^2 (1, $N=77)=2.29$, $p=0.130$), polarity (χ^2 (1, $N=76)=0.78$, $p=0.379$), baseline HRSD-24 ($t(75)=0.25$, $p=0.804$), presence of baseline medication resistance as an indication for ECT (Fisher's exact test $p=0.341$), number of ECT sessions received ($t(74)=-0.01$, $p=0.996$) or electrode placement (Fisher's exact test $p=0.704$). Subsequent analyses were carried out on the N=48 completer sample whose demographic and clinical characteristics and pharmacotherapy during the ECT course are presented in Tables 6.1 and 6.2 below.

TABLE 6.1. Demographic and clinical characteristics of the sample

Variable	Total sample (N=48)
Age, years	61.6 (12.6)
Female gender, n (%)	30 (62.5)
Education, years	13.6 (2.9)
Bipolar depression, n (%)	8 (16.7)
Psychotic features, n (%)	11 (22.9)
Duration of index episode, weeks, median (range)	8 (2-104)
History of previous ECT, n (%)[a]	25 (61.0)
Electrode placement, n (%)	
Bitemporal[b]	44 (91.7)
Right unilateral	4 (8.3)
Number of ECT sessions	7.9 (2.2)
Primary indication for ECT, n (%)[c]	
Medication resistant	37 (77.1)
Rapid response required	7 (14.6)
Acute suicidality	0
Physical deterioration	4 (8.3)
Number of concomitant psychotropic medications	3.8 (1.6)
HRSD-24 score at baseline	27.9 (9.3)
CGI-S score at baseline	5.4 (0.8)
MMSE score at baseline	27.1 (3.2)

All data are presented as mean (SD) unless otherwise specified.
[a] Information available for n=41.
[b] Bitemporal group includes 44 patients who received bitemporal ECT only and 4 patients who were either started on right unilateral and switched to bitemporal due to lack of clinical response or switched from bitemporal to right unilateral due to cognitive side effects.
[c] As indicated by the referring psychiatrist.
Abbreviations: HRSD-24 = 24-item Hamilton Rating Scale for Depression; CGI-S = Clinical Global Impression-Severity scale; MMSE = Mini-Mental State Examination

TABLE 6.2. Psychotropic medications administered during the ECT course

Medication type	n (%)[a]
SSRI	5 (11.4)
SNRI	21 (47.7)
TCA	8 (18.2)
MAOI	1 (2.3)
Mirtazapine	18 (40.9)
Agomelatine	3 (6.8)
Bupropion	1 (2.3)
Pramipexole	1 (2.3)
Lithium	18 (40.9)
T_3	3 (6.8)
Anticonvulsants	15 (34.1)
Antipsychotics	39 (88.6)
Benzodiazepines	14 (31.8)
Z-drug hypnotics	18 (40.9)

[a]Information available for 44 out of 48 patients.

Abbreviations: SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant; MAOI = monoamine oxidase inhibitor; T_3 = triiodothyronine

6.3.2. Depression outcomes after ECT

Mean HRSD-24 score (Figure 6.1) changed significantly over time ($F(2,92)=83.67$, $p<0.001$, partial $\eta^2=0.65$). Post hoc Bonferroni-adjusted paired t-tests indicated that the mean HRSD-24 end-of-treatment score was significantly lower compared to pre-ECT baseline ($p<0.0001$); meanwhile, there was a significant increase in mean HRSD-24 score from immediately after final ECT to three-month follow-up ($p=0.001$) but the latter score was still significantly lower than the pre-ECT baseline ($p<0.0001$). 37 (77.1%) patients were classified as treatment responders immediately after the course of ECT. End-of-treatment mean CGI-Improvement (CGI-I) score was 2.19 (SD=1.28). Of the 37 responders, 11 (29.7%) relapsed during the three-month follow-up period.

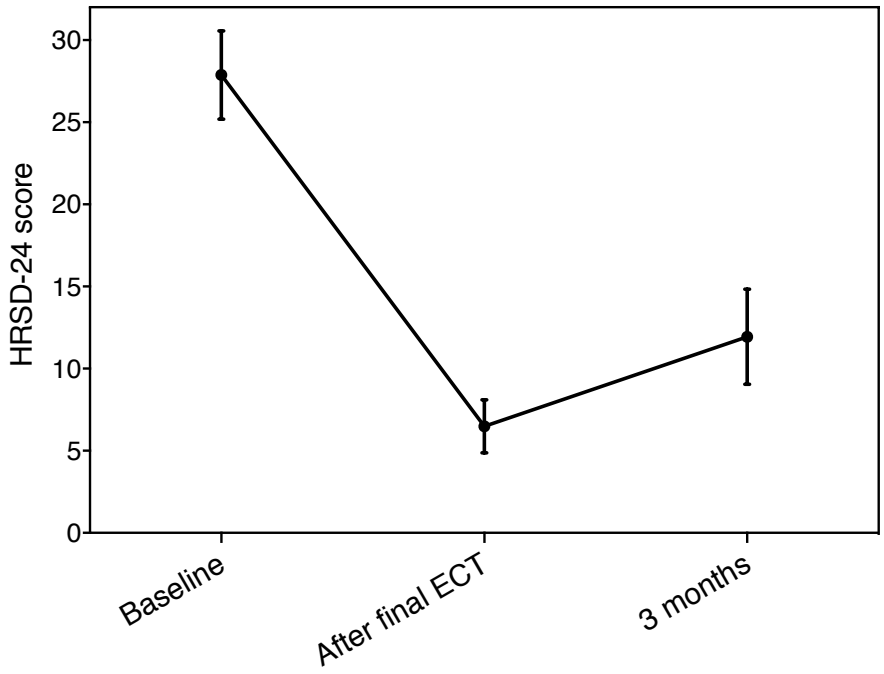

FIGURE 6.1. Mean depression rating scores with 95% CIs at pre-ECT baseline, end of ECT course and three-month follow-up. HRSD-24 = 24-item Hamilton Rating Scale for Depression

6.3.3. Semantic and episodic autobiographical memory before and after ECT

Figure 6.2 shows patients' uncorrected (raw) mean AMI total, personal semantic schedule and autobiographical incidents schedule scores with 95% confidence intervals (CIs) at baseline, end of ECT treatment and three-month follow-up, as well as the published range (Kopelman et al., 1990) of normal performance in healthy controls. On all three testing occasions, patients performed within the normal range on semantic personal memory but were in the "definitely abnormal" range (which refers to scores at or below which none of the controls scored in the normative sample) on episodic autobiographical memory. The patients' reduced total AMI score was therefore entirely accounted for by abnormalities in episodic memory retrieval. In the patient sample, scores on the semantic and episodic subscales showed statistically significant but weak correlations at baseline ($r=0.37$, $p=0.010$) and three-month follow-up ($r=0.39$, $p=0.006$), and no correlation after final ECT ($r=0.17$, $p=0.241$).

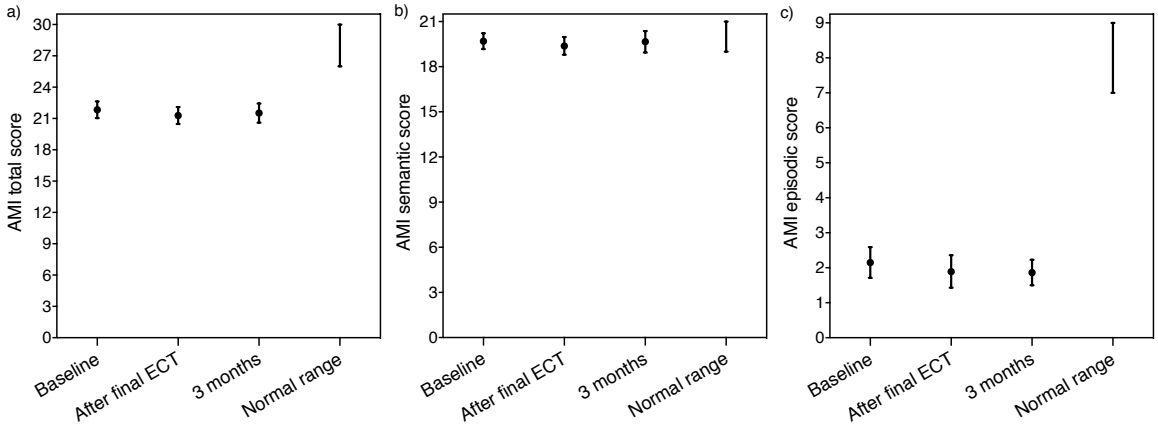

FIGURE 6.2. Recent life section Autobiographical Memory Interview (AMI) scores. a) Total AMI scores, b) AMI personal semantic schedule scores, c) AMI autobiographical incidents schedule scores. Scores are presented as means and 95% CIs at pre-ECT baseline, end of ECT course and three-month follow-up, along with the range of normal performance from published norms (Kopelman et al., 1990).

6.3.4. Retrograde amnesia after ECT

There was no significant effect of time on autobiographical memory performance while controlling for age, gender, years of education, baseline HRSD-24 and baseline MMSE, either on the AMI total score ($F(2,80)=0.78$, $p=0.460$), or semantic ($F(2,80)=0.71$, $p=0.494$) and episodic ($F(2,80)=0.46$, $p=0.633$) subscales. These results remained unchanged if the four patients who had received right unilateral ECT were excluded from analyses (data not shown). There was no significant correlation between the number of ECT sessions and scores on the AMI after final ECT, either for the total score ($r=0.07$, $p=0.633$), or for the semantic ($r=-0.04$, $p=0.781$) and episodic ($r=0.18$, $p=0.235$) subscales. The same lack of correlation was observed between the number of ECT treatments and AMI total ($r=-0.16$, $p=0.272$), semantic ($r=-0.16$, $p=0.289$) and episodic ($r=-0.10$, $p=0.492$) scores at three-month follow-up.

In order to address the possibility of reduced baseline performance on the AMI being due to long-term consequences of a previous lifetime ECT course, the subsample of those with no previous history of ECT was evaluated. Information regarding past ECT treatment was available for 41/48 (85.4%) of study participants. Between-subjects ANCOVAs (controlling for age, gender, years of education, baseline HRSD-24 and

baseline MMSE) showed that patients who were now receiving their first ECT course (n=16) did not differ from those who had previously received one or more courses (n=25) on AMI total ($F(1,34)=1.48$, $p=0.232$), semantic ($F(1,34)=2.03$, $p=0.163$) or episodic ($F(1,34)=0.18$, $p=0.675$) scores at pre-ECT baseline. In patients with no previous history of ECT, there was significant impairment in episodic autobiographical memory already present at pre-ECT baseline and persisting through long-term follow-up while their performance on semantic personal memory was normal at all three assessment points (data not shown). In other words, the same pattern of results was observed as for the whole sample.

6.3.5. Mood state as a moderator of autobiographical memory performance

Next, the effect of current depressive symptoms on autobiographical memory performance was investigated. There was no significant correlation between HRSD-24 score and any of the three AMI scores at any of the three time points. Correlation coefficients ranged between -0.15 and 0.23 and p-values exceeded 0.05 in all instances.

6.3.6. Specificity of episodic autobiographical memory at baseline as a predictor of post-ECT clinical outcomes

Finally, specificity of autobiographical memory at baseline, as measured by the autobiographical incidents schedule score, was examined as a predictor of clinical outcome immediately after the ECT course and at three-month follow-up. Episodic memory performance at baseline did not significantly correlate with either end-of-treatment HRSD-24 score ($r=0.15$, $p=0.306$) or three-month follow-up HRSD-24 score ($r=0.23$, $p=0.123$). Likewise, when treatment outcomes after the final ECT treatment were dichotomised into response vs. non-response, baseline episodic memory score did not predict clinical response (OR=1.11, 95% CI=0.68 to 1.79, $p=0.685$). In treatment responders, baseline episodic memory specificity did not significantly predict relapse status at three months (OR=1.56, 95% CI=0.93 to 2.61, $p=0.091$).

6.4. Discussion

6.4.1. Summary of principal findings

This study found a reduction in autobiographical memory specificity before, after and at three-month follow-up after ECT and a dissociation between episodic and semantic memory performance in patients with major depression. These results confirm and extend previously published findings (Raes et al., 2008; Soderlund et al., 2014) of reduced episodic autobiographical memory specificity in depressed patients referred for ECT. The present study shows for the first time that this impairment persists after ECT and at long-term follow-up. The phenomenon of reduced episodic autobiographical memory specificity has now been demonstrated in this patient group using three instruments (Kopelman AMI, Autobiographical Interview and Autobiographical Memory Test), which are dissimilar in a number of aspects, suggesting that the finding is robust to variations in assessment technique. The deficit was already present at pre-ECT baseline and could not be attributed to previous lifetime exposure to ECT. On the contrary, retrieval of personal semantic information (e.g. names of relatives, neighbours, addresses, locations, dates etc.) was normal, both before and after ECT.

6.4.2. Overgenerality of episodic autobiographical memory as a trait marker for depression

The present study showed longitudinal stability of impaired episodic autobiographical memory specificity over a three-month follow-up despite a significant improvement in mood state. This suggests that autobiographical memory specificity does not necessarily normalise with successful treatment and may thus represent a cognitive trait of depression. Several previous studies (Gallassi, Di Sarro, Morreale, & Amore, 2006; Nandrino, Pezard, Poste, Reveillere, & Beaune, 2002; Spinhoven et al., 2006; Young, Bellgowan, Bodurka, & Drevets, 2014), though not all (Semkovska et al., 2012), of remitted patients with major depression who were not receiving ECT found that they continued to

show reduced episodic autobiographical memory specificity compared to normal controls. In the present study, however, the possibility cannot be ruled out that an underlying improvement in autobiographical memory specificity arising from the resolution of the depressive episode was obscured by a deleterious impact of ECT. A control group of similarly ill depressed patients not treated with ECT assessed at the same time points would have been required to investigate this question.

6.4.3. Absence of post-ECT retrograde amnesia on the Kopelman AMI

The finding of no retrograde amnesia at either immediately after ECT or long-term follow-up is surprising given that over 90% of patients in this study received brief-pulse bitemporal ECT that has repeatedly been reported to affect autobiographical memory (Kellner et al., 2010; Sackeim et al., 2009; Sackeim et al., 2000; Sackeim et al., 2007; Sackeim et al., 2008). Inability to detect retrograde amnesia in a sample treated with a modality known to induce it likely indicates lack of sensitivity of the recent life section of the Kopelman et al. AMI to detect ECT-induced autobiographical memory dysfunction. In light of this, several recent randomised controlled trials (Mayur et al., 2013; Sienaert et al., 2010; Spaans et al., 2013) that have used this instrument and shown no retrograde amnesia following ultra-brief pulse high-dose right unilateral ECT need to be interpreted with caution as this may in part be a methodological artefact.

Notwithstanding its disadvantage in detecting retrograde amnesia in ECT patients (for which the instrument was not originally designed), the AMI allows for in-depth characterisation of the two theoretical components of autobiographical memory and successfully discriminates between the performance of patients with depression from that of healthy controls. The AMI is also capable of showing a clear dissociation between the episodic vs. semantic components of autobiographical memory in major depression, consistent with neuropsychological and functional neuroimaging evidence (Piolino et al., 2009) demonstrating that unique processes, as well as some commonalities, are involved in the storage and retrieval of these two types of autobiographical memory.

6.4.4. Limitations and future directions

This study has several important limitations, the most significant of which is retrospective design. These highly preliminary findings require further replication in prospectively studied samples. Fortunately, the sample studied here is representative of patients receiving ECT in clinical practice and taking part in recent ECT trials (Kellner et al., 2010; Sackeim et al., 2009; Sackeim et al., 2000) with respect to age, gender, baseline illness severity, acute response to treatment and relapse rates (Jelovac et al., 2013). The effect of electrode placement could not be investigated here, a known moderator of autobiographical memory performance, as only four patients received right unilateral ECT. These findings are therefore applicable mainly to bitemporal brief-pulse ECT, though this is advantageous from the perspective of its still being the most commonly used electrode placement and pulse width worldwide (Leiknes et al., 2012). Postictal time to reorientation, a variable previously shown (Sobin et al., 1995) to be a good predictor of retrograde amnesia at short- and longer-term follow-up, was also not measured.

More importantly, the effect of other relevant aspects of cognition, particularly executive dysfunction, on autobiographical memory recall was not studied here. It is unlikely that executive function deficits can account for these results since a domain-general impairment like executive dysfunction would be expected to result in impairment in recall of autobiographical information across the board, not a selective reduction in episodic autobiographical memory retrieval. In the Soderlund et al. (2014) study it was shown that the specific impairment on episodic but not semantic autobiographical memory could not be explained by executive dysfunction since the measure of autobiographical memory used in their study was specifically designed to minimise demands on executive function via specific retrieval cuing procedures. It is also known from previous research that executive functioning following ECT returns to or improves somewhat relative to pre-ECT baseline levels within a few weeks of finishing an ECT course (Semkovska & McLoughlin, 2010), whereas persistent autobiographical memory impairment has been

detected at six months following an ECT course (Sackeim et al., 2007) and beyond. It is unlikely that executive dysfunction can explain the totality of these findings, especially the reduction in specificity at three-month follow-up.

In light of these findings, it would be useful for future (preferably prospective) ECT research to provide separate measurements of semantic and episodic autobiographical memory, not just an overall score, as these two memory components appear to be differentially affected by depression and it is possible that a more sensitive measure of retrograde amnesia would be able to show a differential impact of ECT on the two. In addition, our understanding of overgenerality of autobiographical memory as a prominent aspect of cognitive dysfunction in depression needs to be incorporated into design of future instruments measuring retrograde amnesia after ECT. This study highlights the need for an instrument that would address the nature and extent of the problem in a robust way. Normative data for healthy controls, as well as patients with depression not receiving ECT, are required so that the effect of depressive illness on autobiographical memory can be controlled for when attempting to estimate the contribution of ECT to impaired performance. Simply controlling for current mood state is not sufficient since patients with a diagnosis of major depression who are currently in remission often continue to exhibit reduced autobiographical memory specificity. It would also be desirable for ECT studies to incorporate a qualitative assessment alongside objective neuropsychological testing to ascertain whether patients' subjective perception of the nature of their memory impairment also relates mostly to difficulties recalling events rather than personal semantic information.

6.4.5. Conclusions

In conclusion, this retrospective study showed markedly impaired episodic autobiographical memory specificity in depressed patients that is apparent before starting ECT but that does not deteriorate further after ECT, probably due to a lack of sensitivity of the recent life section of the Kopelman et al. AMI in detecting ECT-induced retrograde

amnesia. It remains to be seen whether this deficit can be successfully remediated (Dalgleish et al., 2014; Raes, Williams, & Hermans, 2009) and whether its resolution would enhance long-term clinical outcomes by reducing susceptibility to relapse and recurrence of depression.

7. General discussion

7.1. Summary of key findings

The work presented in this thesis contributes to the existing body of knowledge on long-term clinical outcomes and cognitive sequelae of ECT for treatment-resistant depression in the following key areas:

i. The first meta-analysis of the entire existing literature on relapse following a successful course of ECT (Chapter 3) showed that unlike in the early decades of ECT use when six-month relapse rates were in the region of 20%, modern ECT responders relapse at approximately double that rate. Half of all patients are nowadays expected to relapse within the first year despite maintenance treatment. There were no differences in relapse rates between studies using continuation pharmacotherapy or continuation ECT. There is no replicated randomised evidence for superiority of any particular antidepressant class or augmentation strategy over another with the exception of superiority of antidepressants over placebo; combinations of active treatments were infrequently compared in randomised trials and, where such evidence was available, only one trial had been conducted comparing the same treatments or combinations thereof.

ii. The systematic review identified key areas of knowledge deficit, namely optimisation of relapse prevention strategies such as individualised, symptom-titrated treatment protocols for continuation pharmacotherapy and continuation ECT, as well as supportive approaches such as psychotherapy.

iii. The systematic review also identified older age and psychotic depression as predictors of good long-term outcome. Although several individual studies showed an association between baseline medication resistance and relapse, no overall effect was found when all studies reporting this outcome were pooled.

iv. To explore the role of medication resistance further, a prospective study of 104 patients with unipolar depression participating in a clinical trial of bitemporal vs. high-dose right unilateral ECT was undertaken (Chapter 4). Several measures of treatment-resistant depression (TRD) were tested for their ability to predict acute and long-term ECT outcomes. This study found that TRD, however defined, was not associated with worse ECT outcomes. Furthermore, there was little to no agreement between various definitions of TRD.

v. In order to identify clinically useful predictors of depressive relapse in ECT patients, 61 remitters from the aforementioned trial were prospectively followed-up for a year following remission (Chapter 5). Approximately 40% of these patients experienced a re-emergence of depressive symptoms during the follow-up. In line with the meta-analysis, this study found that older age and psychotic features at baseline were associated with a lower likelihood of relapse while TRD showed no association with relapse. In addition, a greater number of previous depressive episodes and a diagnosis of bipolar II disorder were associated with worse long-term prognosis. Post-ECT continuation therapy with lithium was protective against relapse.

vi. Finally, in order to characterise long-term cognitive sequelae of ECT, autobiographical memory function was assessed before and after a course of ECT as well as at three-month follow-up using the Kopelman et al. Autobiographical Memory Interview, a standardised neuropsychological instrument for measuring theoretically and clinically relevant components of autobiographical memory (semantic and episodic recall). This retrospective naturalistic study assessed a sample of 48 patients undergoing brief-pulse, mostly bitemporal ECT as part of routine clinical practice (Chapter 6). The study showed that at all three assessment points episodic autobiographical recall was significantly impaired in ECT patients compared to norms while their semantic recall was spared. No retrograde amnesia after ECT was detected using this particular instrument.

7.2. Post-ECT outcomes in a historical context

As is the case with pharmacological antidepressant treatments, the effectiveness of ECT appears to have declined over time. The finding of worsening outcomes since the 1960s in the meta-analysis reported in Chapter 3 was expected. A narrative review from two decades ago (Sackeim, 1994) already signalled a deterioration in long-term ECT outcomes based on emerging data in the 1980s and the early 1990s.

In the wider literature on depression, the common and significant problem of decreasing drug-placebo differences encountered in clinical trials was confirmed in a recent meta-analysis of trials conducted over a thirty-year period (Undurraga & Baldessarini, 2012). Tricyclic antidepressants (TCAs) were found to be more effective than newer antidepressant agents; however, when placebo response rates from older trials of TCAs were substituted for those in modern trials of newer drugs, all antidepressants showed identical response rates. Therefore, the narrowing of the drug-placebo gap was mostly accounted for by increasing placebo responses rather than decreasing drug efficacy. In this important piece of meta-analytic work, the authors highlighted some of the problems inherent to modern clinical trials and called attention to some of the possible reasons for the apparent decline in antidepressant efficacy over time. These included: increasing size and complexity of often multisite trials; declining levels of training and expertise of personnel involved in diagnostic assessments and symptom ratings; greater diagnostic heterogeneity; changes in the types of patients recruited to trials such as less severely ill patients being willing to participate in placebo-controlled trials; regression to the mean; longer trials requiring more assessments and thus being at a greater risk of measurement variance and more clinical contact providing more opportunity for spontaneous remission and enhanced placebo response, etc. These issues affecting modern antidepressant drug trials are also applicable to a degree to modern ECT research.

One of the explanations that has been frequently offered for this apparent decline in effectiveness of ECT over time is the fact that failure to respond to antidepressant

medication is now the leading indication for ECT in Western countries. Given that treatment resistance "breeds" future treatment resistance, it seems logical to assume that the relegation of ECT to the "treatment of last resort" status in many countries has led to a profound change in the composition of ECT treatment populations over time, with patients least likely to respond to any treatment now constituting the majority of samples.

There is some empirical support for this view. A recent study by colleagues examining trends in use of ECT in South London over time found that in 2006, patients referred for ECT had failed to respond to an average of 6.5 medication trials, a dramatic increase from 1.7 in 1987 (Lambe et al., 2014). The authors offered the introduction of NICE guidelines in 2003 which emphasise the "treatment of last resort" status of ECT as a possible explanation for this finding.

The meta-regression analysis reported in Chapter 3 showed that the proportion of patients meeting TRD criteria in a sample did not predict the subsequent likelihood of relapse despite some reports to the contrary. However, a notable limitation of this analysis is the fact that the earliest ECT trials did not evaluate TRD; hence, the question of whether patients fared better after ECT because more treatment-naïve patients were referred for ECT in studies stretching further back in time to the heyday of ECT use in the 1950s and 1960s could not be investigated directly. The reason for that is that the concept of TRD was generally not yet on the radar. It was only in the early 1970s that this concept began to explicitly emerge in the psychiatric literature (Hamilton, 1974; Heimann, 1974; Lehmann, 1974). The first systematic attempts at defining TRD only began to be published in the 1980s (Souery & Pitchot, 2013).

Not only have ECT patient populations changed over time but the very concept of depressive illness has undergone significant evolution over the many decades of ECT use. It has been argued that the current conceptualisation of major depressive disorder, while initially serving to improve diagnostic reliability, has outlasted its utility because it results in such clinical heterogeneity of the syndrome that it has ultimately hindered progress in elucidating the underlying neurobiology, leading to a situation where despite

decades of intensive basic and clinical research, the treatments available today are no more effective than those available 50-70 years ago (Holtzheimer & Mayberg, 2011). Past research attempts at developing rating scales for assessment of profile of a good candidate for ECT based on “endogenous” or “melancholic” depressive subtypes have ultimately proven fruitless (Kellner, Popeo, Pasculli, Briggs, & Gamss, 2012). However, not knowing what to do because a patient has not responded to anything else is not necessarily a good indication for ECT. Unfortunately, such referrals do occasionally happen in clinical practice. Sound clinical judgement is essential for identifying suitable patients for ECT and avoiding, as far as possible, the worst possible outcome: no clinical response and newly added memory problems.

7.3. Treatment-resistant depression and ECT outcomes

Given that TRD is a major public health problem and an area of considerable clinical and scientific interest, its relationship with ECT outcomes was further investigated in a one-year prospective study reported in Chapter 4. This study showed that that TRD, defined in various ways, with applied definitions ranging from simple clinical judgement to complex research scoring methods, played no role in predicting either acute ECT remission rates or subsequent likelihood of relapse. This study represents a significant contribution to the literature on the role of TRD in subsequent outcomes since much of the previous research on the topic has tended to use only one or two sets of criteria for defining TRD in any given sample. Surprisingly, little to no agreement was found between the various TRD definitions in this study, bringing us essentially no closer to an understanding of what TRD is or how it might best be measured. Clinical assessment of TRD remains elusive for now, as does its neurobiology.

In the present study, defining TRD as the failure of two or more adequate antidepressant trials appeared to be somewhat more valid than the cut-off at one failed trial. Interestingly, this was also the only definition of TRD that showed significant

agreement with referring psychiatrists' own clinical judgement of medication resistance as the reason for ECT referral. Other lines of evidence also suggest that two failed antidepressants is a sensible demarcation line for TRD. Firstly, this is the emerging preferred definition in depression clinical trials literature (Berlim & Turecki, 2007a; Berlim & Turecki, 2007b). Secondly, the best available evidence, the STAR*D study (Rush et al., 2006b), showed that remission rates after the first two treatment steps were roughly the same (about one-third of the sample), dropping off precipitously to about 13% at third and fourth treatment steps, suggesting that a natural cut-off point at two failed antidepressant trials signifies the presence of something more difficult to treat and possibly more malignant.

A conceptual difficulty with modern TRD staging methods is that they evaluate the index episode and do not take into account the previous longitudinal course of illness. It is unclear whether past depressive episodes should be considered when assessing TRD. If viewed from a lifespan perspective, a more recurrent illness is surely a hallmark of treatment resistance. The study reported in Chapter 5 in fact showed that an increasing number of previous depressive episodes was a significant predictor of relapse after ECT while medication resistance during the index episode was not. This issue has major implications for how TRD is defined in the ECT literature due to the atypical patient population studied in ECT compared to most other depression trials. Many ECT patients who have exhibited poor response to pharmacological treatment during previous depressive episodes and who successfully responded to ECT in the past are more likely to be offered ECT earlier in the treatment of subsequent episodes, certainly earlier than suggested in treatment algorithms for depression where ECT is generally relegated to the final treatment step after all else has failed. Some patients who have failed to respond to numerous medication trials in the past may not receive any adequate trials during the current episode since the clinician and the patient may agree that ECT is indicated early on. Are such patients treatment resistant? According to currently available methods for staging TRD, such patients would not be classified as treatment resistant. From a clinical

perspective, however, the majority of patients who arrive at ECT display some degree of treatment resistance if a broader view of their illness is taken.

7.4. Predictors of long-term ECT outcomes

The two robust predictors of lower likelihood of relapse in the study reported in Chapter 5 were older age and psychotic features at baseline. These observations fit well with the totality of the existing literature on post-ECT relapse meta-analysed in Chapter 3. The data on psychotic depression were particularly striking in the present study: only 7% of patients with psychotic depression relapsed contrasted with 50% of the non-psychotic group. Psychotic depression appears to be particularly responsive to ECT (Avery & Lubrano, 1979; Birkenhager, Pluijms, & Lucius, 2003; Buchan et al., 1992; Petrides et al., 2001) and may be a distinct clinical syndrome rather than simply representing the severe end of the spectrum of depressive illness; converging findings of differences between psychotic and non-psychotic depression exist in terms of clinical features (Coryell, Pfohl, & Zimmerman, 1984; Parker et al., 1995), neuroendocrine abnormalities (Nelson & Davis, 1997), neuropsychological functioning (Gomez et al., 2006; Jeste et al., 1996; Schatzberg et al., 2000) and response to treatment (Parker, Roy, Hadzi-Pavlovic, & Pedic, 1992).

It is unclear what it is about older age that confers better ECT outcomes but there appears to be a nuanced interaction between age, medication resistance and personality disturbance. The literature on personality disorders and ECT outcomes has recently been reviewed (Rasmussen, 2015) and consists mostly of chart reviews. The best available evidence comes from a large prospective community study showing that patients with comorbid DSM-IV Axis II disorders had lower remission and higher relapse rates after ECT (Prudic et al., 2004). A seminal study on the topic of borderline personality disorder showed that only 22% of patients with major depression and comorbid borderline personality disorder remitted after ECT (Feske et al., 2004), a rate one might normally expect for sham (placebo) ECT or ineffective modalities such as low-dose right unilateral

ECT. Interestingly, patients with other personality disorders did not fare significantly worse than patients with no personality disorders (remission rates of 56% and 72%, respectively). In a noteworthy twist, once presence of borderline personality disorder was controlled for, medication resistance and younger age no longer predicted worse ECT response. 80% of patients with borderline personality disorder were rated medication resistant. This study therefore showed that a factor usually not assessed in most research studies (borderline personality disorder) may in fact be an underlying crucial factor accounting for the ostensible association between age and medication resistance on the one hand and ECT response on the other. Personality features or indeed presence of DSM-IV Axis II disorders were not measured in the present study, a limitation of this work. The role of personality disorders in ECT outcomes and how comorbid Axis II pathology interacts with medication resistance are important areas of future inquiry. It would have also been informative to measure the effect of another source of chronic psychopathology on relapse: chronic depression or dysthymia. Dysthymia is predictive of lower likelihood of acute remission after ECT (Dombrovski et al., 2005) and there is a suggestion that it may be associated with post-ECT relapse (Prudic, Sackeim, Devanand, & Kiersky, 1993).

7.5. Autobiographical memory function in ECT patients

Autobiographical memory impairment is almost universally acknowledged to be a clinical problem associated with some ECT modalities. It is also a source of negative public perceptions, polarised views and stigma associated with this treatment. A large amount of research effort over the past several decades has gone into assessment of retrograde amnesia and attempts at its amelioration via manipulation of ECT treatment parameters such as dosing, electrode placement and pulse width. Chapter 6 examined the utility of the recent life section of the Kopelman et al. Autobiographical Memory Interview (AMI) in the specific context of ECT treatment. This scale, as recently reviewed (Semkovska & McLoughlin, 2013), has recently begun to be used in ECT clinical trials

(Mayur et al., 2013; Sienaert et al., 2010; Spaans et al., 2013) and naturalistic studies (Kho et al., 2006; O'Connor et al., 2010).

The present study found that the recent life section of the AMI (which assesses recall of episodic and semantic details of personal memories from the past five years with a focus on the past year) detected no retrograde amnesia following ECT compared to pre-ECT baseline performance in patients undergoing brief-pulse bitemporal ECT under naturalistic conditions of routine clinical practice, a surprising finding. Crucially, recall of episodic events was very poor prior to ECT, even in patients with no lifetime exposure to ECT, and did not improve during the follow-up despite a significant improvement in mood state; meanwhile, semantic memory was within normal range at all three assessment points. These results, suggesting a dissociation between episodic and semantic autobiographical memory in depression, are in line with the sole previous study examining this question in patients with depression referred for ECT (Soderlund et al., 2014).

The most significant limitation of the present study is retrospective design. That said, this allowed for inclusion of many patients who are too ill or unwilling to take part in research studies. A proportion of patients taking part in this study were in fact those who had refused participation in the clinical trial reported in Chapters 4 and 5. Another limitation is that the age range in the ECT group (38-84 years) was somewhat shifted upward compared to the normative sample of healthy controls (20-78 years). There is no significant correlation between age and performance on the semantic or episodic subscales of the AMI (Kopelman et al., 1990); hence, the same norms are provided for all ages. However, on other more sensitive measures of autobiographical memory, episodic recall deteriorates with aging (Levine et al., 2002; Piolino, Desgranges, Benali, & Eustache, 2002). It is possible that the dissociation between episodic and sematic autobiographical memory observed in the present study would have been less dramatic had a somewhat older control group or different instrument been used.

It appears, therefore, that the recent life section of the AMI is not sensitive to retrograde amnesia usually shown following brief-pulse bitemporal ECT using the

Columbia University Autobiographical Memory Interview (McElhiney et al., 2001; McElhiney et al., 1995). Alternative measures of episodic and semantic components of autobiographical memory exist (Irish, Lawlor, O'Mara, & Coen, 2008; Levine et al., 2002; Piolino et al., 2002) but their administration and scoring are too lengthy and/or complex for routine use in an ECT clinic by staff who are not neuropsychologists. Similar problems are encountered in ECT research studies where a number of other baseline and outcome measures are usually being collected, all contributing to significant burden placed on participants in terms of time and effort during a difficult spell of severe illness. Researchers also face significant time pressures due to the typically fairly narrow window of opportunity for recruitment and assessment of participants between ECT referral and commencement of treatment.

Ideally, a novel instrument for assessment of autobiographical memory function and retrograde amnesia in ECT patients would be brief (15-20 minutes) and straightforward enough for staff from diverse backgrounds (nursing, psychiatry, psychology) to be able to administer and score. The measure would assess free and supported (cued) recall of episodic and semantic details of personally-experienced events. It would evaluate overgenerality of episodic autobiographical memory by classifying recalled memories as specific, extended or categorical in line with the wider literature on autobiographical memory in major depression. It would incorporate both re-testing of memories recalled at pre-ECT baseline (to measure consistency of recall at follow-ups) and assessment of autobiographical memory performance in general (permitting assessment of memories that were not recalled at baseline, thus allowing for detection of improvement in performance). Normative data for purposes of establishing the degree of impairment and its clinical significance would be required for two groups: healthy controls with no history of neuropsychiatric disorders and patients with a diagnosis of major depression who have never been treated with ECT. This is of crucial importance since overgenerality of autobiographical memory appears to be a trait phenomenon in major depression; patients often continue to exhibit it even during clinical remission. Therefore, a

reduction in performance in a group of ECT patients compared to a group of healthy controls with no history of depression cannot be said to equate to retrograde amnesia since impairments in the ECT group are likely to be a combination of ECT-induced retrograde amnesia and significant abnormalities in autobiographical memory function caused by the underlying depressive illness itself.

Biological underpinnings of autobiographical memory impairment in ECT patients and patients with major depression more generally remain unknown and require elucidation in future studies. Electroconvulsive stimulation results in hippocampal neurogenesis in animal models (Madsen et al., 2000; Perera et al., 2011; Scott, Wojtowicz, & Burnham, 2000) and increases hippocampal volumes in humans (Joshi et al., 2015; Nordanskog et al., 2010; Tendolkar et al., 2013). Hippocampal neurogenesis is a well-known correlate of antidepressant treatment efficacy but it is also true that generalised seizures result in aberrant remodelling of neuronal networks in the hippocampus (Cho et al., 2015; Jessberger et al., 2007; Parent et al., 1997) which may account for disruption of autobiographical memory and other hippocampus-dependent cognitive functions.

In an interesting parallel, a recent human study has demonstrated that recall of episodic but not semantic autobiographical memories is disrupted by generalised seizures in the absence of structural damage to the medial temporal lobes (Gascoigne, Barton, Webster, Gill, & Lah, 2015). In this study of children with idiopathic generalised epilepsy (i.e. children with generalised seizures in whom structural brain abnormalities had been ruled out by neuroimaging), a significant deficit in recall of episodic autobiographical memory details was found while semantic recall was normal compared to controls. Deficits in recall of personal episodic memories were present even when retrieval support was provided. Earlier age at epilepsy diagnosis was strongly predictive of impaired episodic recall suggesting a cumulative detrimental effect of seizures on autobiographical memory function. This is an important finding showing that autobiographical memory

abnormalities in epilepsy patients are not necessarily attributable to overt structural pathology of the medial temporal lobes.

In light of everything discussed above, therefore, it is important for future research on post-ECT retrograde amnesia to move beyond its current focus on overall scores on various scales since these conflate semantic information and semanticised memories with potentially vulnerable episodic memories.

7.6. Conclusions

In conclusion, the work presented in this thesis aimed to elucidate long-term clinical and cognitive outcomes of patients with moderate-to-severe, often treatment-resistant depression treated with ECT. The studies reported here found that ECT is an effective acute treatment option for patients who are resistant to drug therapies for depression. Medication resistance was not associated with inferior long-term outcomes. Other clinical features were found to be more important in predicting relapse, in particular younger age, non-psychotic depression, recurrent depression and bipolar II disorder. Long-term outcomes for patients who initially benefitted from ECT are currently suboptimal with up to half of such patients relapsing within the first year following treatment. Continuation therapy with lithium may be protective against relapse. Autobiographical memory function of ECT patients is characterised by poor recall of personal episodic memories and good recall of semantic information about one's life. Optimisation of assessment methods for treatment-resistant depression and autobiographical memory in ECT research calls for further study.

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Appendices

Appendix 1: Antidepressant Treatment History Form criteria for adequacy of antidepressant medication trial dosing and duration

Rating Medication Trials for Antidepressant Potency

TCA/Tetracyclics

I. Amitriptyline(Elavil, Endep), imipramine(Tofranil), desipramine(Norpramine, Pertofrane), trimipramine(Surmontil), clomipramine(Anafranil), maprotilene(Ludiomil), doxepin(Sinequan, Adapin), nomifensine.

By dosage:

1	any drug < 4 wks OR
	any drug < 100 mg/d
2	4 wks or more and 100-199 mg/d
3	4 wks or more and 200-299 mg/d
4	4 wks or more and ≥ 300 mg/d

By blood level: imipramine and desimipramine only; levels take precedence

4	4 wks or more and DMI level ≥ 125 ng/ml
4	4 wks or more and IMI + DMI ≥ 225 ng/ml

II. Nortriptyline(Pamelor, Aventyl)

By blood level: levels take precedence

1	NT < 4 wks
2	4 wks or more and level < 50 ng/ml
3	4 wks or more and level 50-99 ng/ml
4	4 wks or more and level 100-150 ng/ml

By dosage:

1	NT < 4 wks OR
	4 wks or more and NT < 50 mg/d
2	4 wks or more and NT 50-75 mg/d
3	4 wks or more and NT 76-100 mg/d
4	4 wks or more and NT > 100

III. Protriptyline(Vivactil)

1	drug < 4 wks OR
	4 wks or more and dosage ≤ 30 mg/d
2	4 wks or more and dosage 31-40 mg/d
3	4 wks or more and dosage 41-60 mg/d
4	4 wks or more and dosage > 60 mg/d

NOTES:For TCA-MAOI combinations: score each agent alone, as a separate trial
For TCA-paroxetine/fluoxetine combination trials: after one week on 20 mg of paroxetine or fluoxetine the dosage equivalent of the TCA should be doubled to determine resistance rating

SSRIs

I. Fluoxetine(Prozac), citalopram (Celexa), vilazodone (Viibryd)

1 drug < 4 wks OR
4 wks or more and dosage 1-9 mg/d

2 4 wks or more and dosage 10-19 mg/d

3 4 wks or more and dosage 20-39 mg/d

4 4 wks or more and dosage ≥ 40 mg/d

II. Fluvoxamine(Luvox)

1 drug < 4 wks OR
drug < 100 mg/d

2 4 wks or more and 100-199 mg/d

3 4 wks or more and 200-299 mg/d

4 4 wks or more and ≥ 300 mg/d

III. Paroxetine(Paxil)

1 less than 4 wks OR
4 wks or more and dosage 1-9 mg/d

2 4 wks or more and dosage 10-19 mg/d

3 4 wks or more and dosage 20-29 mg/d

4 4 wks or more and dosage ≥ 30 mg/d

IV. Sertraline(Zoloft):

1 drug < 4 wks OR
4 wks or more and dosage < 50 mg/d

2 4 wks or more and dosage 50-99 mg/d

3 4 wks or more and dosage 100-199 mg/d

4 4 wks or more and dosage ≥ 200 mg/d

V. Escitralopram (Lexapro):

1 drug < 4 wks OR
4 wks or more and dosage < 5 mg/d

2 4 wks or more and dosage 5-9 mg/d

3 4 wks or more and dosage 10-19 mg/d

4 4 wks or more and dosage ≥ 20 mg/d

Other Antidepressants

I. Bupropion(Wellbutrin)

1 drug < 4 wks OR
4 wks or more and dosage < 150 mg/d

2 4 wks or more and dosage 150-299 mg/d

3 4 wks or more and dosage 300-449 mg/d

4 4 wks or more and dosage ≥ 450 mg/d

II. Mirtazapine(Remeron)

1 less than 4 wks OR
4 wks or more and dosage < 15 mg/d

2 4 wks or more and dosage 15-29 mg/d

3 4 wks or more and dosage 30-44 mg/d

4 4 wks or more and dosage ≥ 45 mg/d

III. Nefazodone(Serzone)

1 drug < 4 wks OR
4 wks or more and dosage < 150 mg/d

2 4 wks or more and dosage 150-299 mg/d

3 4 wks or more and dosage 300-599 mg/d

4 4 wks or more and dosage ≥ 600 mg/d

IV. Trazodone(Desyrel), amoxapine(Ascendin)*

1 drug < 4 wks OR
4 wks or more and dosage < 200 mg/d

2 4 wks or more and dosage 200-399 mg/d

3 4 wks or more and dosage 400-599 mg/d

4 4 wks or more and dosage ≥ 600 mg/d

*Amoxapine will also receive an antipsychotic rating

V. Venlafaxine (Effexor and Effexor XR)

1 less than 4 wks OR

4 wks or more and dosage < 75 mg/d

2 4 wks or more and dosage 75-224 mg/d

3 4 wks or more and dosage 225-374 mg/d

5 4 wks or more and dosage ≥ 375 mg/d

VI. Reboxetine

1 less than 4 wks OR

4 wks or more and dosage 5< mg/d

2 4 wks or more and dosage 5-7 mg/d

3 4 wks or more and dosage ≥ 8 mg/d

4 4 wks or more and dosage ? mg/d

VII. Duloxetine

1 less than 4 wks OR

4 wks or more and dosage <20 mg/d

2 4 wks or more and dosage 20-39 mg/d

3 4 wks or more and dosage 40 – 60 mg/d

4 4 wks or more and dosage ≥60 mg/d

VIII. Desvenlafaxine (Pristiq)

1 drug < 4 wks OR

4 wks or more and dosage < 49 mg/d

2 4 wks or more and dosage up to 49 mg/d

3 4 wks or more and dosage 50-99 mg/d

4 4 wks or more and dosage ≥ 100 mg/d

VIII. Milnacipran (Savella)

1 drug < 4 wks OR

4 wks or more and dosage < 49 mg/d

2 4 wks or more and dosage up to 50-99 mg/d

3 4 wks or more and dosage 100 -199 mg/d

4 4 wks or more and dosage ≥ 2000 mg/d

MAOIs

I. Phenelzine(Nardil)

1 drug < 4 wks OR
4 wks or more and dosage ≤ 30 mg/d

2 4 wks or more and dosage 31-60 mg/d

3 4 wks or more and dosage 61-90 mg/d

4 4 wks or more and dosage 91 mg/d or greater

II. Moclobemide

1 less than 4 wks OR
4 wks or more and dosage < 150 mg/d

2 4 wks or more and dosage 150-299 mg/d (100-200=30 Nardil)

3 4 wks or more and dosage 300-599 mg/d (300=60 Nardil)

4 4 wks or more and dosage ≥ 600 mg/d (600 = 90 Nardil)

III. Selegiline(Eldepryl)

1 drug < 4 wks OR
4 wks or more and dosage ≤ 20 mg/d

2 4 wks or more and dosage 21 - 40 mg/d

3 4 wks or more and dosage 41 - 59 mg/d

4 4 wks or more and dosage ≥ 60 mg/d

5

IV. Tranylcypromine(Parnate), isocarboxazid(Marplan)

1 drug < 4 wks OR
4 wks or more and dosage ≤ 20 mg/d

2 4 wks or more and dosage 21-40 mg/d

3 4 wks or more and dosage 41-60 mg/d

4 4 wks or more and dosage ≥ 61 mg/d

NOTES:

MAOI inhibition: 80% inhibition will rate 4

For TCA-MAOI combinations, score each agent considered alone

TCA/SSRI and any other combinations, e.g. SSRI/bupropion, should be treated as

TCA/MAOI combinations: rate each medication separately

Lithium

I. Lithium alone

For bipolar patients: levels take precedence over dosage

1 drug < 4 wks OR
4 wks or more and level: ≤ 0.4 mEq/L OR
4 wks or more and dosage: < 600 mg/d for any duration

2 4 wks or more and level: 0.41-0.6 mEq/L OR
4 wks or more and dosage: 600- 899 mg/d

3 4 wks or more and level: > 0.6 mEq/L OR
4 wks or more and dosage: ≥ 900 mg/d

Unipolar patients can receive a maximum rating of 2 for Li alone

II. Lithium as an augmenting agent

4 antidepressant drugs I - IX rated level 3 and Li for at least 2 wks
CBZ rated level 3 and Li for at least 2 wks

5 antidepressant drugs I - IX rated level 4 and Li for at least 2 wks

ECT

I. Unknown technical parameters

1 1 - 3 ECT

2 4 - 6 ECT

3 7 - 9 ECT

4 10 - 12 ECT

5 13 or more ECT

II. Bilateral, bifrontal, or right unilateral (at 6x seizure threshold) ECT

1 1 - 3 bilateral ECT

2 4 - 6 bilateral ECT

4 7 - 9 bilateral ECT

5 10 or more bilateral ECT

NOTES:

If ECT and antidepressant medication are given simultaneously, this does not constitute a combination/ augmentation trial. Each should be rated separately.

Anticonvulsants

I. Carbamazepine(Tegretol); Trileptal

For bipolar patients:

1 CBZ < 4 wks OR

4 wks or more and level < 6

2 4 wks or more and level 6 - 7.9

3 4 wks or more and level ≥ 8

Unipolar patients can receive a maximum rating of 2 for CBZ alone

II. Lamotrigine (Lamictal)

For bipolar patients:

1 drug < 4 wks OR

4 wks or more and dosage < 50 mg/d

2 4 wks or more and dosage 50-199 mg/d

3 4 wks or more and dosage ≥ 200 mg/d

Unipolar patients can receive a maximum rating of 2 for Lamotrigine alone

III. Gabapentin (Neurontin), Clonazepam(Klonopin), valproic acid(Depakene), and topiramate (Topamax) can be rated 1 if used alone; they are not considered augmenting agents

Benzodiazepines

I. Alprazolam(Xanax)

1 alprazolam < 4 wks OR

4 wks or more and dosage < 4 mg/d

2 4 wks or more and dosage 4 mg/d or greater

II. Other benzodiazepines

1 any dosage for any duration

These drugs are not considered augmenting agents.

Miscellaneous

I. Stimulants, eg, D-amphetamine(Dexedrine), methylphenidate(Ritalin), pemoline(Cylert)

1 any dosage for any duration

These drugs are not considered augmenting agents.

II. Antipsychotics alone

1 any dosage for any duration

When used in nonpsychotic patients and should be rated together into one continuous trial, no matter how many different neuroleptics were given.

III Antipsychotics as augmenting agents

3.5 antidepressant drugs I - IX rated level 3 and antipsychotic for at least 2 wks

4.5 antidepressant drugs I - IX rated level 4 and antipsychotic for at least 2 wks

These drugs are not considered augmenting agents.

IV. Clonidine(Catapres), L-tryptophan, thyroid hormones (Cytomel, Synthroid, etc.), estrogen, fenfluramine

0 any dosage for any duration

These drugs are not considered augmenting agents.

V. Sedatives (buspirone, zolpidem, Benadryl, etc.)

1 any dosage for any duration when used as a psychotropic

If the patient uses different sedatives, with the exception of alprazolam, they should be rated as one continuous trial.

VI. Phototherapy in any form: 1

VII. Thyroid hormone

3.5 antidepressant drugs I - IX rated level 3 and thyroid hormone for at least 2 wks

4.5 antidepressant drugs I - IX rated level 4 and thyroid hormone for at least 2 wks

VI. Other Somatic Treatments (rTMS, VNS, DBS):

rTMS: 10Hz LDLPFC; 3000 pulses/session; 120% motor threshold

3 30 sessions

VNS

3 1 amp; 1 yr

DBS: currently experimental and not rated

Equivalent Doses of Antipsychotic Drugs*

Generic name (Trade names)	Equivalent Doses		
Phenothiazines			
Chlorpromazine(Thorazine)	100 mg	200 mg	400 mg
Thioridazine(Mellaril)	100 mg	200 mg	400 mg
Mesoridazine(Serentil)	50 mg	100 mg	200 mg
Trifluoperazine(Stelazine)	4 mg	8 mg	16 mg
Fluphenazine(Prolixin, Permitil)	1.5 mg	3 mg	6 mg
Fluphenazine decanoate	0.25 cc/mo	0.5 cc/mo	1 cc/mo
Perphenazine(Trilafon)	10 mg	20 mg	40 mg
Prochlorperazine(Compazine)	15 mg	30 mg	60 mg
Thioxanthenes			
Thiothixene(Navane)	5 mg	10 mg	20 mg
Chloprothixene(Taractan)	50 mg	100 mg	200 mg
Butyrophenone			
Haloperidol(Haldol)	2 mg	4 mg	8 mg
Haloperidol decanoate		0.25cc/mo	0.5cc/mo
Dibenzoxazepine			
Loxapine(Loxitane)	15 mg	30 mg	60 mg
Amoxapine(Ascendin)	125 mg	250 mg	500 mg
Dibenzazepine			
Clozapine(Clozaril)	60 mg	120 mg	240 mg
Dihydroindolone			
Molindone(Moban)	10 mg	20 mg	40 mg
Diphenylbutylpiperidine			
Pimozide(Orap)	2 mg	4 mg	8 mg
Risperidone(Risperdal)	1.5 mg	3 mg	6 mg
Paliperidone (Invega)	(S/A)		
Iloperidone (Fanapt)	2	4	6
Generic name (Trade names)	Equivalent Doses		
Sulpiride	300 mg	600 mg	1200 mg
Olanzepine (Zyprexa)	5 mg	10 mg	20 mg

Quetiapine (Seroquel)	100mg	200mg	400mg
Ziprasidone (Geodon)	40 mg	80 mg	160 mg
Aripiprazole (Abilify)	7.5 mg	15 mg	30 mg
Asenapine (Saphris)		5	10
Lurasidone (Latuda)		40	80

Appendix 2: Maudsley Staging Method criteria for adequacy of antidepressant medication trial dosing and duration

British Brand Name	Generic Name	Dose	Duration (In weeks or specified)	Comments & Side effects		Drug taken for at least:		Minimum Dose* (mg/day)		Maximum Dose* (mg/day)		Augmentation
				Beneficial	Adverse	6 weeks	10 weeks		Equal or greater		Equal or greater	
Monoamine Oxidase Inhibitors (MAOIs) / (RIMA) / (MAOI-B)												
	Isocarboxazid							30		60		
Nardil	Phenelzine							45		90		
Parnate	Tranylcypromine							20		60		
Manerix	Moclobemide							300		1200		
Azilect	Rasagiline							-		-		
Eldepryl/Zelapar	Selegeline							-		-		
Tricyclic Antidepressants												
Tryptizol	Amitriptyline							125		200		
	Amoxapine							125		250		
Anafranil	Clomipramine							125		250		
	Desipramine							125		250		
Prothiaden	Dosulepin / Dothiepin							125		225		
Sinepin	Doxepin							125		300		
Tofranil	Imipramine							125		300		
Gamanil	Lofepramine							140		210		
Allegron	Nortriptyline							75		150		
	Maprotyline							125		250		
	Protriptyline							30		60		
Surmontil	Trimipramine							125		300		
Selective Serotonin Reuptake Inhibitors (SSRIs)												
Cipramil	Citalopram							20		60		
Cipralex	Escitalopram							10		20		
Prozac	Fluoxetine							20		60		
Faverin	Fluvoxamine							50		300		
Seroxat	Paroxetine							20		50		
Lustral	Sertraline							50		200		

British Brand Name	Generic Name	Dose	Duration (In weeks or specified)	Comments & Side effects		Drug taken for at least:		Minimum Dose (mg/day) *	Equal or greater	Maximum Dose (mg/day) *	Equal or greater	Augmentation
				Beneficial	Adverse	6 weeks	10 weeks					
Noradrenergic and Selective Serotonergic Antidepressants (NaSSA) & Related												
Zispin	Mirtazepine							30		45		
Mianserin	Mianserin							30		90		
Molipaxin	Trazodone							150		600		
Serotonin-Noradrenaline Reuptake Inhibitors (SNRI)												
Cymbalta	Duloxetine							60		120		
Efexor	Venlafaxine							75		375		
Noradrenaline Reuptake Inhibitors (NRI)												
Edronax	Reboxetine							8		12		
Noradrenaline Dopamine Reuptake Inhibitor (NDRI)												
Zyban	Bupropion							300		450		
5HT1A Partial Agonist												
Buspar	Buspirone							15		45		
Mood Stabilisers												
Camcolit / Liskonum / Priadel	Lithium							0.4mmol/l		1mmol/l		
Tegretol	Carbamazepine							600		-		
Epilim	Sodium Valproate							-		-		
Depakote / Convulex	Semisodium Valproate							-		-		
Lamictal	Lamotrigine							50		200		
Lyrica	Pregabilin							300		600		
Neurontin	Gabapentin							-		-		
Topamax	Topiramate							-		-		

British Brand Name	Generic Name	Dose	Duration (In weeks or specified)	Comments & Side effects		Drug taken for at least:		Minimum Dose (mg/day)*	Equal or greater	Maximum Dose (mg/day)*	Equal or greater	Augmentation
				Beneficial	Adverse	6 weeks	10 weeks					
Atypical Antipsychotics												
Solian	Amisulpiride											
Abilify	Aripiprazole							2.5		15		
Clozaril	Clozapine							-		-		
Zyprexa	Olanzapine							10		-		
Invega	Paliperidone							-		-		
Seroquel	Quetiapine							300		-		
Risperdal	Risperidone							0.5		-		
Serdolect	Sertindole							-		-		
Zoleptil	Zotepine							-		-		
Geodon/Zeldox	Ziprasidone*							-		160		
Typical Antipsychotics												
Largactil	Chlorpromazine							-		-		
Fluanxol	Flupentixol							-		-		
Modecate	Fluphenazine							-		-		
Haldol	Haloperidol							-		-		
Nozinan	Levomepromazine							-		-		
Neulactil	Pericyazine							-		-		
Fentazine	Perphenazine							-		-		
Orap	Pimozide							-		-		
Prochlorperazine	Prochlorperazine							-		-		
Promazine	Promazine							-		-		
Sulpor/dolmatil	Sulpiride							-		-		
Melleril	Thioridazine							-		-		
Stelazine	Trifluoperazine							-		-		
Clopixol	Zuclopenthixol							-		-		

British Brand Name	Generic Name	Dose	Duration (In weeks or specified)	Comments & Side effects		Drug taken for at least:		Minimum Dose (mg/day)*	Equal or greater	Maximum Dose (mg/day)*	Equal or greater	Augmentation
				Beneficial	Adverse	6 weeks	10 weeks					
T3/T4												
Tertroxin	Liothyronine							20		50		
Eltroxine	Thyroxine							-		-		
Beta Blockers												
Visken	Pindolol							7.5		15		
Inderal	Propranolol							-		-		
Dopamine Receptor Agonists & Stimulants												
Symmetrel	Amantadine							-		300		
Strattera	Atomoxetine							-		-		
Dexedrine	Dexamphetamine							20		-		
Ritalin	Methylphenidate							20		40		
Provigil	Modafinil							100		400		
Mirapexin	Pramipexole							0.125		5		
Miscellaneous												
Dexamethasone	Dexamethasone							3		4		
Metopirone	Metyrapone							1000		-		
Mifegyne	Mifepristone							-		-		
Nizoral	Ketoconazole							400		800		
Optimax	Tryptophan							6000		9000		
	Yohimbine							-		30		
Others												

Publications

Conference abstracts

Jelovac, A., Kolshus, E., & McLoughlin, D. M. (2012). Relapse rates following a successful course of electroconvulsive therapy for depression: A systematic review and meta-analysis. *International Society for Affective Disorders Congress 2012*, 18th-20th April 2012, London, United Kingdom.

Peer-reviewed journals

Jelovac, A., Kolshus, E., & McLoughlin, D. M. (2013). Relapse following successful electroconvulsive therapy for major depression: a meta-analysis. *Neuropsychopharmacology*, 38(12), 2467-2474.

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Semkovska, M., Landau, S., Dunne, R., Kolshus, E., Kavanagh, A., Jelovac, A., Noone, M., Carton, M., Lambe, S., McHugh, C., & McLoughlin, D. M. (2015). Bitemporal versus high-dose unilateral twice-weekly electroconvulsive therapy for depression (EFFECT-Dep): a pragmatic, randomised, non-inferiority trial. *American Journal of Psychiatry*, in press.

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Relapse Following Successful Electroconvulsive Therapy for Major Depression: A Meta-Analysis

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High rates of early relapse following electroconvulsive therapy (ECT) are typically reported in the literature. Current treatment guidelines offer little information to clinicians on the optimal nature of maintenance therapy following ECT. The aim of this study was to provide a systematic overview of the existing evidence regarding post-ECT relapse. A keyword search of electronic databases was performed for studies appearing in the peer-reviewed literature before January 2013 reporting on relapse rates in responders to an acute course of ECT administered for a major depressive episode. Meta-analyses were performed where appropriate. Thirty-two studies with up to 2 years' duration of follow-up were included. In modern era studies of continuation pharmacotherapy, 51.1% (95% CI = 44.7–57.4%) of patients relapsed by 12 months following successful initial treatment with ECT, with the majority (37.7%, 95% CI = 30.7–45.2%) relapsing within the first 6 months. The 6-month relapse rate was similar in patients treated with continuation ECT (37.2%, 95% CI = 23.4–53.5%). In randomized controlled trials, antidepressant medication halved the risk of relapse compared with placebo in the first 6 months (risk ratio = 0.49, 95% CI = 0.39–0.62, $p < 0.0001$, number needed to treat = 3.3). Despite continuation therapy, the risk of relapse within the first year following ECT is substantial, with the period of greatest risk being the first 6 months. The largest evidence base for efficacy in post-ECT relapse prevention exists for tricyclic antidepressants. Published evidence is limited or non-existent for commonly used newer antidepressants or popular augmentation strategies. Maintenance of well-being following successful ECT needs to be improved.
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Keywords: depression; relapse; electroconvulsive therapy; meta-analysis

INTRODUCTION

Electroconvulsive therapy (ECT) is a highly effective acute treatment for major depression (Eranti *et al*, 2007; Kellner *et al*, 2010; The UK ECT Review Group, 2003). Although remission rates exceed those seen with other somatic treatments, high rates of relapse, especially early relapse, are observed and acknowledged as a major clinical problem (Kellner *et al*, 2006; Sackeim *et al*, 2001). Consolidating and prolonging remission is a key clinical challenge surrounding ECT use (Kellner 2013).

Following introduction of the first effective antidepressants, continuation antidepressant monotherapy following ECT appeared to minimize the likelihood of relapse. Early research from the United Kingdom demonstrated the efficacy of antidepressants over placebo with 6-month relapse rates in tricyclic antidepressant (TCA)- or monoamine oxidase inhibitor (MAOI)-treated patients of about 20% compared with 40–70% in untreated or benzodiazepine-only-treated patients (Imlah *et al*, 1965; Kay *et al*, 1970; Seager and Bird, 1962). However, more recent studies are less favorable, with relapse rates typically about 40–50% at 6 months despite vigorous continuation therapy, such as antidepressant–lithium combination or continuation ECT (C-ECT; Kellner *et al*, 2006; Prudic *et al*, 2013; Sackeim *et al*, 2001). Of note, in a more recent trial where patients were randomized to TCA monotherapy, TCA–lithium combination, or placebo, TCA monotherapy was not significantly more effective than placebo in preventing relapse (Sackeim *et al*, 2001).

Higher rates of relapse in recent decades may be due to historical changes in ECT patient populations (Sackeim, 1994). ECT is a unique treatment in psychiatry that predates modern psychopharmacology. Once used as first-line treatment for severe depression in often medication-naive patients, its use nowadays is reserved for a minority of patients with severe, chronic, difficult-to-treat depression where several treatment steps have usually been unsuccessful. Such treatment-resistant patients are generally less likely to achieve full remission and, when they do, are prone to relapse (Fekadu *et al*, 2009).

The negative impact of medication resistance on ECT outcomes had been noted decades ago (Bruce *et al*, 1960; Hamilton, 1974) and was subsequently demonstrated by studies showing that patients with established medication resistance have worse acute (Prudic *et al*, 1996; Prudic *et al*, 1990) and longer-term (Sackeim *et al*, 1990) outcomes.

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A recent meta-analysis confirmed that acute remission rates with ECT are lower in treatment-resistant patients (48%) compared with those in whom medication resistance had not been established (65%) (Heijnen *et al*, 2010).

Currently, there is no agreement on what constitutes optimal post-ECT relapse prevention treatment. The American Psychiatric Association guidelines on ECT, now over a decade old, recommend continuation therapy with either pharmacotherapy or C-ECT for virtually all patients (American Psychiatric Association, 2001). However, no specific guidelines on choice of agent or duration of treatment exist. Most experimental work over the past 3 decades has focused primarily on optimizing ECT treatment parameters (eg, electrode placement, stimulus dose, and pulse width) to produce the best possible balance between clinical and neuropsychological outcomes. These studies unequivocally show that ECT is a powerful treatment option capable of producing full remission where other treatments have failed (Dunne and McLoughlin, 2012; Eranti *et al*, 2007; Kellner *et al*, 2010; Loo *et al*, 2012; Sackeim *et al*, 2009). However, given that relapse following ECT is a key clinical problem, we carried out a systematic review of all existing evidence, randomized and observational, to provide an overview of current knowledge on this important question.

MATERIALS AND METHODS

Search Strategy

An electronic literature search of PubMed, Embase, CINAHL, PsycINFO, and Cochrane Library databases was performed up to January 2013 with no time, language or other restrictions. Keywords used were (ECT OR electroconvulsive therapy OR convulsive therapy) AND (depression OR depressive OR mood disorder OR bipolar disorder OR affective disorder OR melancholi*) AND (long term OR follow up OR relapse OR prognosis OR mortality OR maintenance OR continuation). Hand-searches of reference sections of previous reviews and included studies were carried out.

Following exclusion of database duplicates and clearly ineligible reports, judging by title and abstract screening, two reviewers (AJ, EK) independently evaluated for eligibility all studies retained for full-text screening. Where studies met inclusion criteria (described below), the reviewers independently extracted data from reports. Information regarding study design, ECT treatment parameters, sample characteristics, type of continuation therapy, type of outcome measure, definition of relapse, valid sample size at each follow-up, cumulative number of relapses at each time point, and cumulative number of dropouts at each time point was extracted. Discrepancies were resolved by joint re-evaluation of reports.

When extracting relapse proportions from reports, preference was given to information in the body of texts and tables. Where the study explicitly reported relapse rates only for the study endpoint but where patients were assessed at multiple intermediate time points, survival curves were examined; where it was deemed that the number of relapses could be extracted from graphs, this was done jointly by the reviewers. Where studies met inclusion criteria but data were reported in a non-extractable format, we contacted the authors. Given the literature age span, this was not always possible as authors were sometimes untraceable or deceased.

Study Eligibility Criteria

The following inclusion criteria were applied:

(1) prospective study reported in a peer-reviewed publication;
(2) participant age $\geqslant$18 years;
(3) an acute course of ECT was administered for treating a major depressive episode (unipolar or bipolar) diagnosed by clinical judgement or formal diagnostic criteria (eg, DSM-IV);
(4) those deemed to be ECT responders or remitters were prospectively followed-up and monitored for relapse;
(5) relapse was operationally defined by the original investigators and reported in a categorical fashion (ie, as the percentage of the initial responder or remitter sample who relapsed);
(6) relapse was ascertained on the basis of clinical judgement or by using formal diagnostic criteria and/or pre-specified cutoff scores on clinician-rated depression severity rating scales (eg, Hamilton Depression Rating Scale); and
(7) clinical outcome assessment was carried out $\geqslant$3 months following the last ECT session.

Exclusion criteria:

(1) case studies or series with N$<$10;
(2) retrospective studies;
(3) prospective studies where relapse was not established directly via patient interview but instead on the basis of proxy measures (eg, rehospitalization rates), mailed self-report questionnaires, or information obtained from third-parties (eg, patients' relatives or treating physicians);
(4) presence of non-affective psychosis, dementia, neurological disease, or unstable medical conditions in the sample; and
(5) unmodified ECT.

Outcomes

Relapse rate was defined as the proportion of the original ECT responder or remitter sample that subsequently experienced a return of depressive symptoms deemed to be significant enough to merit the designation of relapse by the original investigators. Specific criteria for relapse varied between the studies; original investigators' definitions were retained. Studies using inadequate measures of relapse likely to underestimate its true prevalence (eg, rehospitalization rates only) were excluded.

The primary outcome was cumulative relapse proportion at the 6-month follow-up after last ECT for which we expected most data would be available. In all primary analyses, only samples treated with antidepressant pharmacotherapy were included, because virtually all ECT patients today receive long-term prophylactic therapy most commonly administered in the form of medication. We also carried out secondary analyses of relapse rates on C-ECT,

which is used less frequently than medication. C-ECT is a form of relapse prevention where the patient continues to receive ECT after the acute course at a reduced schedule. It is indicated in patients with a past history of good ECT response where antidepressant continuation therapy was either ineffective or could not be tolerated at therapeutic doses (American Psychiatric Association, 2001). Other secondary analyses investigated relapse rates on placebo or no maintenance treatment.

Additional secondary outcomes were relapse rates at 3, 12, and 24 months after last ECT, again in patients receiving antidepressant medication. Finally, to investigate the relative efficacy of different relapse prevention strategies, we aimed to calculate relative risks (RRs) of relapse in randomized controlled trials (RCTs) of different continuation therapies at 3, 6, and 12 months where at least two studies comparing the same strategy were available.

Statistical Analyses

All analyses were based on study completers. Attrition rates for each study were recorded. Mean relapse proportions with 95% confidence intervals (CIs) were calculated by pooling samples using a random-effects model (DerSimonian and Laird, 1986), as we expected substantial differences in study designs and patient populations. Heterogeneity was assessed using the I^2 statistic (Higgins *et al*, 2003). Where substantial heterogeneity was observed and where sufficient data were available, random-effects meta-regression analyses with unrestricted maximum likelihood estimation were carried out to explore possible sources of heterogeneity. Pre-specified covariates investigated were mean age, proportion of psychotic patients, and proportion of medication-resistant patients. Planned subgroup analyses compared study designs (trial *vs* observational), relapse criteria (standardized symptom rating scale *vs* clinical judgement), and whether concomitant pharmacotherapy was allowed during the index ECT course. To investigate the possibility of changes in relapse rates over time, a cumulative meta-analysis was carried out for the primary endpoint (6 months).

For head-to-head comparisons of different continuation therapies, RRs with 95% CIs and numbers needed to treat (NNT) were calculated.

Publication bias was assessed by visual inspection of funnel plots where >10 studies were available. All statistical analyses were carried out using Comprehensive Meta Analysis Version 2.2 software (Borenstein *et al*, 2011).

Results

Search Results

The computerized search retrieved 4198 results (Figure 1). Hand-searches identified four additional eligible studies. Following exclusion of database duplicates and initial exclusion of ineligible studies, 194 titles were retained for full-text screening. Of these, 32 studies met inclusion criteria and provided extractable data either from published reports or contact with original authors (Supplementary Table 1).

Relapse Rate at 6 Months

By 6 months following ECT, 34.0% (95% CI = 27.2–41.5%, $I^2 = 76\%$) of patients ($N = 844$) treated with continuation pharmacotherapy had relapsed. Because long-term outcomes are believed to have worsened over the many decades of ECT use, we performed a cumulative meta-analysis with each study added to the previous ones in chronological order (Figure 2a). Beginning with the first controlled studies of continuation pharmacotherapy in the 1960s, relapse rates held at around 20%. As modern studies of more treatment-resistant patients and clearer reporting of methodology began to be conducted, relapse rates rose towards present-day levels. It should be noted that following the publication of three important early trials (Imlah *et al*, 1965; Kay *et al*, 1970; Seager and Bird, 1962), with the exception of one small trial in 1984 (Krog-Meyer *et al*, 1984), no other prospective long-term follow-up studies of continuation pharmacotherapy meeting inclusion criteria were found between 1970 and the early 1990s, perhaps coinciding with diminishing use of ECT. Given this gap in evidence, it is unclear when precisely the shift in relapse rates might have occurred.

Due to the historical trend observed in the data, we carried out a sensitivity analysis where only modern post-DSM-III studies of pharmacologically treated patients ($N = 710$) were included in the meta-analysis. Relapse rate across these studies was 37.7% (95% CI = 30.7–45.2%, $I^2 = 70\%$) (Figure 2b). Visual inspection of the funnel plot showed no evidence of publication bias (data not shown).

Due to remaining high heterogeneity, we performed random-effects meta-regressions to investigate the possible contribution of study characteristics on outcome. As only a small number of studies reported relevant moderators, multivariate analyses could not be conducted; hence, each moderator was modelled separately. In modern studies, there was no effect of baseline medication resistance on likelihood of relapse ($p = 0.429$). However, there was a suggestion of lower relapse rates in samples with a greater percentage of psychotic patients ($p = 0.004$) and a higher mean age ($p = 0.038$).

Methodological factors appeared to influence outcome. In subgroup analyses, studies using clinical judgement to determine relapse reported lower rates (28.3%, 95% CI = 17.1–43.1%) than studies using cutoff scores on depression rating scales (41.7%, 95% CI = 34.8–48.9%). Studies where concomitant pharmacotherapy was permitted during the ECT course had lower relapse rates (29.2%, 95% CI = 18.0–43.6%) than those where maintenance pharmacotherapy was begun after the course (41.6%, 95% CI = 35.0–48.6%). Naturalistic studies (39.1%, 95% CI = 29.2–50.0%) and controlled trials (36.1%, 95% CI = 26.9–46.4%) of continuation pharmacotherapy did not differ in relapse rates.

Relapse Rates at 3, 12 and 24 Months

By 3 months following ECT, 27.1% of patients ($N = 350$) on continuation pharmacotherapy had relapsed (95% CI = 20.5–34.8%, $I^2 = 48\%$) (Figure 3a), and by 1 year ($N = 348$) 51.1% (95% CI = 44.7–57.4%, $I^2 = 27\%$) had relapsed (Figure 3b). Only three prospective studies with a

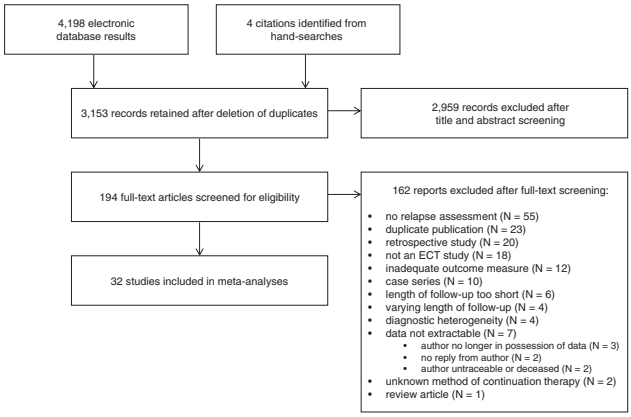

Figure 1 Study flow diagram.

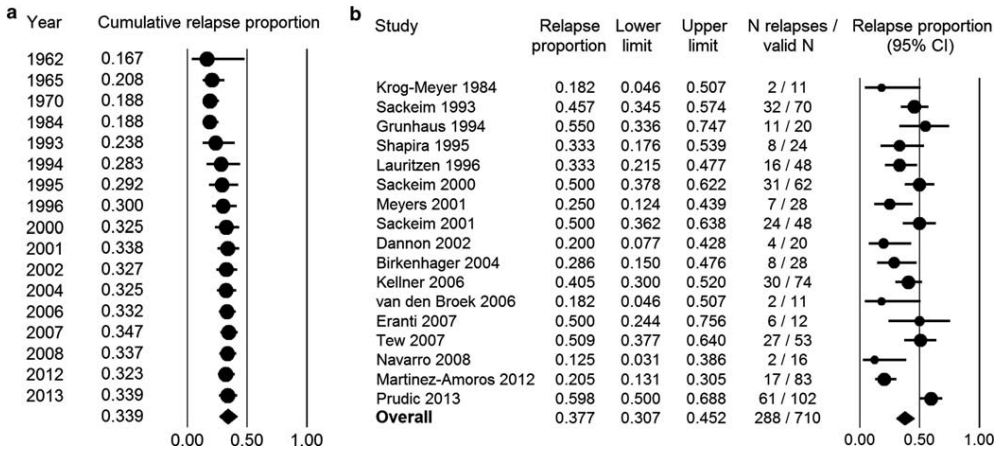

Figure 2 Outcomes at 6 months following ECT. Panel (a) shows a cumulative meta-analysis of relapse rates at 6 months following ECT across all eligible studies from 1962 onwards. Panel (b) shows relapse rate at 6 months following ECT in modern-era studies.

2-year follow-up were found: two investigating outcomes in psychotic elderly patients ($N=28$) treated with nortriptyline monotherapy (Flint and Rifat, 1998; Navarro *et al*, 2008) and one in a general adult sample ($N=83$) maintained on treatment-as-usual pharmacotherapy (Martinez-Amoros *et al*, 2012). Relapse rate at 2 years was 50.4% (95% CI = 41.2–59.6%, $I^2=0$) (Figure 3c).

Relapse Rates With C-ECT

At 6-month follow-up, relapse rate across the four eligible C-ECT samples ($N=146$) was 37.2% (95% CI = 23.4–53.5%, $I^2=57\%$), a virtually identical relapse rate to the figure for modern-era pharmacologically treated patients presented above (37.7%). Given the similarity in 6-month relapse rates in medication and C-ECT samples, we also carried out a meta-analysis of all eligible modern-era studies where patients were treated with any form of recognized continuation therapy, pharmacological or C-ECT. Across 19 eligible studies ($N=1001$), 39.5% of patients had relapsed (95% CI = 31.9–47.7%, $I^2=81\%$).

When the two studies (Kellner *et al*, 2006; Wijkstra *et al*, 2000) where patients ($N=86$) were treated with C-ECT only and where no concomitant medication was permitted were analyzed separately, relapse rate at 6 months rose to 45.4% and heterogeneity was eliminated (95% CI = 35.2–55.9%, $I^2=0$). For 1 and 2-year follow-ups, only two studies at each time point met inclusion criteria. Patients in these studies were treated with C-ECT and pharmacotherapy combination therapy. Relapse rate at 12 months ($N=33$) was 20.5%

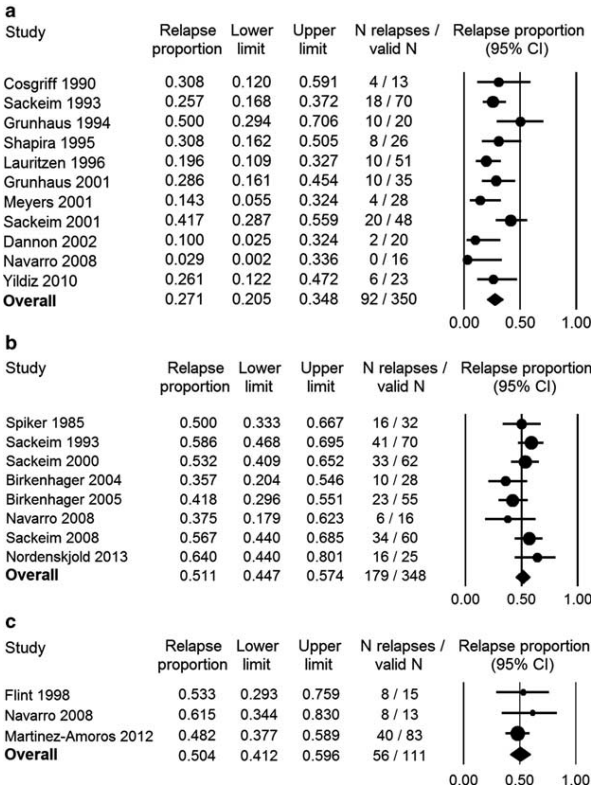

Figure 3 Outcomes at 3, 12, and 24 months following ECT. Panels a, b, and c show relapse rates at 3, 12, and 24 months following ECT, respectively.

(95% CI = 3.0–68.1%, $I^2 = 73\%$), and at 24 months ($N = 56$) it was 30.3% (95% CI = 2.9–86.4%, $I^2 = 85\%$). High levels of heterogeneity were present in the analyses.

Relapse Rates in Untreated Samples

To examine the long-term efficacy of a course of ECT in the absence of continuation treatment, studies reporting outcomes in unmedicated patients were meta-analyzed. Two studies published in 1973, both with a 3-month follow-up, reported relapse in ECT responders not permitted to take antidepressant medication during follow-up (Arfwidsson *et al*, 1973; Barton *et al*, 1973). By 3 months after ECT, 47.9% had relapsed (95% CI = 38.1–57.9%, $I^2 = 0$). No modern studies featuring entirely untreated (including no placebo) samples were found.

Next we analyzed relapse rates in placebo-treated samples where some non-specific benefit can be expected. Three RCTs (Lauritzen *et al*, 1996; Sackeim *et al*, 2001; Yildiz *et al*, 2010) provided extractable data at 3 months and seven (Imlah *et al*, 1965; Kay *et al*, 1970; Krog-Meyer *et al*, 1984; Lauritzen *et al*, 1996; Sackeim *et al*, 2001; Seager and Bird, 1962; van den Broek *et al*, 2006) at 6 months. Relapse rates were 62.7% (95% CI = 47.6–75.8%, $I^2 = 0$) at 3 months and 65.5% (95% CI = 49.7–78.5%, $I^2 = 72\%$) at 6 months. As with active continuation therapy, relapse rates were substantially lower in earlier placebo samples. When only modern day RCTs (Krog-Meyer *et al*, 1984; Lauritzen *et al*, 1996; Sackeim *et al*, 2001; van den Broek *et al*, 2006) are considered ($N = 65$), relapse rate on placebo reached 78.0% (95% CI = 66.1–86.5%, $I^2 = 0$) at 6 months.

RR of Relapse on Continuation Antidepressant Pharmacotherapy *vs* Placebo

RRs of relapse in RCTs of active relapse prevention strategies *vs* placebo were investigated at 3 and 6 months after ECT (Figure 4a and b).

For the 3-month follow-up, three placebo-controlled RCTs ($N = 128$) provided extractable data: two (Lauritzen *et al*, 1996; Yildiz *et al*, 2010) evaluating selective serotonin reuptake inhibitor (SSRI) monotherapy *vs* placebo and the other (Sackeim *et al*, 2001) comparing TCA monotherapy and TCA–lithium combination to placebo. The first

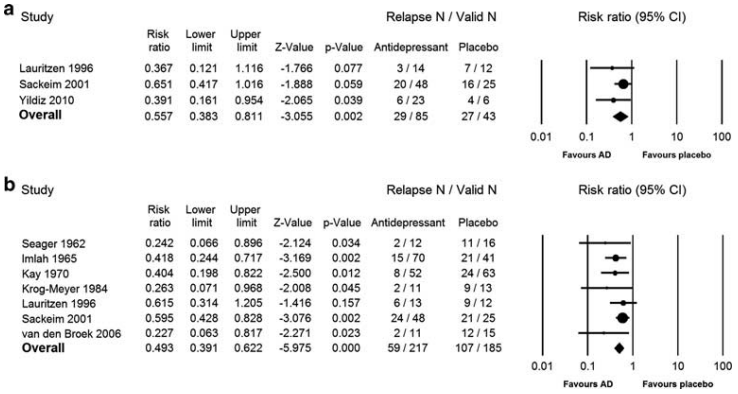

Figure 4 Relative risk (RR) of relapse in patients treated with pharmacotherapy *vs* placebo at 3 and 6 months following ECT. Panels a and b, respectively, show the RR of relapse in patients maintained on active antidepressant pharmacotherapy *vs* placebo at 3 and 6 months following ECT.

meta-analysis measured RR of relapse in patients treated with any antidepressant pharmacotherapy *vs* placebo. RR of relapse on medication was 0.56 (95% CI = 0.38–0.81, $p = 0.002$, NNT = 3.5, $I^2 = 0$). Next, the two studies ($N = 55$) comparing SSRI monotherapy *vs* placebo were separately analyzed. Pooled analysis showed SSRI monotherapy to be significantly more effective than placebo in preventing relapse at 3 months (RR = 0.38, 95% CI = 0.19–0.77, $p = 0.007$, NNT = 2.7, $I^2 = 0$).

At 6 months, two meta-analyses could be carried out: one featuring any antidepressant pharmacotherapy *vs* placebo; another featuring TCA monotherapy *vs* placebo. No meta-analyses of other medication classes or combination strategies *vs* placebo could be carried out for the 6-month time point as only one study evaluated efficacy of an MAOI *vs* placebo (Imlah *et al*, 1965), one study compared an SSRI with placebo (Lauritzen *et al*, 1996), while one study featured a TCA–lithium combination treatment group *vs* placebo (Sackeim *et al*, 2001). Across the seven included studies (Imlah *et al*, 1965; Kay *et al*, 1970; Krog-Meyer *et al*, 1984; Lauritzen *et al*, 1996; Sackeim *et al*, 2001; Seager and Bird, 1962; van den Broek *et al*, 2006; $N = 402$), continuation pharmacotherapy halved the risk of relapse compared with placebo at 6 months (RR = 0.49, 95% CI = 0.39–0.62, $p < 0.0001$, NNT = 3.3, $I^2 = 0$). Patients in these studies were predominantly treated with TCAs. When TCA monotherapy samples are considered separately, this strategy was found to reduce the RR of relapse slightly further (RR = 0.44, 95% CI = 0.29–0.66, $p < 0.0001$, NNT = 3.2, $I^2 = 36\%$). In all included studies where TCAs were used, with the exception of one trial that compared nortriptyline with placebo (Sackeim *et al*, 2001), TCA monotherapy was significantly more effective than placebo. Other included studies used either imipramine (Imlah *et al*, 1965; Seager and Bird, 1962; van den Broek *et al*, 2006) or amitriptyline (Kay *et al*, 1970; Krog-Meyer *et al*, 1984) monotherapy.

No placebo-controlled RCTs of continuation pharmacotherapy with a 1-year (or longer) follow-up were identified. No meta-analyses of head-to-head comparisons of different active relapse prevention strategies could be carried out as only one study contained the same comparison.

DISCUSSION

Relapse rates following ECT are disappointingly high and appear to have increased over time. In patients treated with continuation pharmacotherapy, the main focus of our investigation, relapse was highest in the first 6 months, plateauing afterwards. In present day clinical practice, nearly 40% of ECT responders can be expected to relapse in the first 6 months and roughly 50% by the end of first year.

A course of ECT, in the absence of active continuation therapy, does not appear to have much lasting effect. In early trials where no continuation therapy was permitted, half of all patients who responded to ECT relapsed within 3 months (Arfwidsson *et al*, 1973; Barton *et al*, 1973). This suggests that the natural course of depressive illness severe enough to warrant ECT is a prompt return to depression in the absence of long-term treatment. When modern placebo samples were analyzed, relapse rates were even higher, approaching 80% at 6 months. In the current ECT practice, therefore, we recommend that initial gains are consolidated with vigorous maintenance therapy.

Nonetheless, these findings need to be interpreted in the context of superior acute remission rates with ECT compared with other existing treatments for treatment-resistant depression. A meta-analysis investigating acute outcomes found ECT to be more effective than pharmacotherapy (The UK ECT Review Group, 2003). Although our systematic review did not identify any long-term studies directly comparing outcomes in ECT *vs* medication-treated patients, when our results are compared with the existing literature on short- and longer-term antidepressant effectiveness in refractory MDD, similar outcomes are observed. In the STAR*D study (Rush *et al*, 2006), relapse rates were predictably higher in patients entering follow-up after more previous failed treatment steps. During the 1-year follow-up, remitters from the third and fourth successive treatment steps relapsed at rates of 43 and 50%, respectively. These

long-term outcomes in medication-treated patients with similar degree of treatment resistance to modern ECT samples are very similar to our findings of a 51% relapse rate 1 year following ECT. Acute remission rates for every treatment step in STAR*D, however, were much lower compared with those typically observed in ECT trials, hence more patients overall can be expected to benefit from ECT.

Our systematic review cannot offer clear guidance on what type of continuation therapy works best and for which patients. Many ECT patients routinely receive continuation therapy with the same medication(s) that failed to elicit a clinical response before ECT, a counterintuitive strategy (Sackeim, 1994). To our knowledge, no evidence is available to suggest this practice might be effective, although no particular evidence to the contrary exists either. Our meta-analysis suggests that continuation pharmacotherapy is significantly more effective than placebo at both 3- and 6-month follow-ups. Most available evidence consists of trials of older antidepressants, such as imipramine and amitriptyline. Our search of the published literature could not identify any placebo-controlled trials of some of the most commonly used newer-generation antidepressants, such as serotonin-norepinephrine reuptake inhibitors, mirtazepine, or popular augmentation strategies with mood stabilizers (other than lithium) or atypical antipsychotics. Even for SSRIs, published evidence is relatively sparse. ECT research has favored the use of TCAs; however, as TCAs produce many undesirable side-effects, carry an overdose risk, and cannot be tolerated at adequate doses by many patients, efficacy of newer antidepressants with more favorable side-effect profiles merits further investigation. Also requiring future study is the optimization of treatment schedules for C-ECT, which has thus far tended to be used with fixed dosing schedules in prospective studies. This may have underestimated its true efficacy when using more flexible, symptom-titrated dosing schedules currently under investigation (Lisanby *et al*, 2008).

When interpreting results of this meta-analysis, certain limitations should be borne in mind. Much of the available evidence comes from small, underpowered, predominantly observational studies. There was substantial variability between the included studies in design, quality, and patient selection criteria that appeared to influence outcomes. Very few RCTs of continuation therapies with long-term follow-up exist, with evidence particularly lacking for outcomes beyond 6 months. Data from prospective controlled studies are particularly lacking for certain important clinical outcomes such as suicide and indeed all-cause mortality in this severely ill and treatment-resistant patient population.

In summary, our review found that up to half of all patients who respond to ECT relapse within the first year, the period of highest risk being the first 6 months. Continuation pharmacotherapy or C-ECT significantly reduces the risk of relapse. However, many questions remain unanswered. Future studies should clarify which patient characteristics might predict relapse and what the optimal post-ECT continuation treatment or combination thereof entails. More focus is required on treatments other than TCAs, including psychotherapy and indeed optimization of treatment schedules for C-ECT, preferably in conjunction with concomitant pharmacotherapy. Such research is required to keep ECT patients in remission for as long as possible and with the fewest side-effects.

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The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the Neuropsychopharmacology website (http://www.nature.com/npp)

Autobiographical Memory Specificity in Major Depression Treated With Electroconvulsive Therapy

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Objective: Autobiographical memory in major depression is characterized by reduced specificity, which reflects the tendency to summarize categories of events rather than recall specific instances of events situated in a time and place. This widely studied cognitive marker for depression has not been extensively examined in patients treated with electroconvulsive therapy (ECT).

Methods: We conducted a retrospective chart review of a naturalistic cohort of patients receiving a course of brief-pulse predominantly bitemporal ECT for a major depressive episode. Patients completed the recent life section of the Kopelman Autobiographical Memory Interview (AMI) at pre-ECT baseline, end of treatment course, and 3-month follow-up as part of routine clinical practice. Mood was assessed using the 24-item Hamilton Rating Scale for Depression.

Results: We identified 48 patients (mean age, 61.6; female, 62.5%) meeting inclusion criteria. A total of 77.1% of patients responded to the ECT course, 29.7% subsequently relapsed. There were no significant changes over time on either AMI total score or semantic and episodic subscales. However, patients were markedly impaired on episodic autobiographical memory compared with the normative sample at all 3 assessment points, whereas personal semantic memory recall was normal. Specificity of episodic autobiographical memory at baseline did not predict response to ECT or likelihood of relapse.

Conclusions: We found reduced specificity of episodic autobiographical memory in depressed patients before ECT, which persisted at long-term follow-up despite significant improvement in mood. The finding of no detectable retrograde amnesia likely reflects lack of sensitivity of the recent life section of the AMI to detect ECT-induced changes.

Key Words: electroconvulsive therapy, autobiographical memory, depression

(*J ECT* 2015;00: 00–00)

Electroconvulsive therapy (ECT) is a highly effective treatment for severe depression, but its use is limited by cognitive sequelae. According to patient surveys, retrograde amnesia for autobiographical memories is the side-effect of greatest concern.[1] Routine neuropsychological testing predominantly measures anterograde memory function (ie, the ability to learn new information) and thus fails to adequately capture ECT patients' subjective complaints, which mostly relate to difficulties with retrieving personal memories from past life.[2] Although anterograde memory function tends to return to or indeed improve beyond pre-ECT baseline levels within 2 weeks after a treatment course,[3] retrograde amnesia can persist at long-term follow-up.[4] Despite considerable research,[5] the nature, extent, and duration of autobiographical memory impairment have not yet been fully elucidated.

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For the past 3 decades, there has been an accumulating body of evidence demonstrating autobiographical memory impairment in patients with depression. The phenomenon of so-called overgeneral autobiographical memory (OGM) is a robust finding in the depression literature.[6–8] First observed in a study of survivors of a suicide attempt,[9] OGM refers to the tendency to provide a generic summary of a category of events (eg, "I never enjoy going to parties") rather than a description of a specific event situated in time and place (eg, "the party at my friend's house I went to last Saturday") when asked to recall an event in response to a cue word (eg, "party"). One meta-analysis[6] of 11 studies found a mean effect size (Cohen's d) of 1.12 for severity of OGM in patients with depression compared with healthy controls, whereas another[10] found OGM to predict the longitudinal course of illness with fewer specific and more overgeneral/categorical memories at baseline being associated with greater depressive symptoms at follow-up. Overgeneral autobiographical memory is also present in at-risk individuals,[11,12] suggesting that it may be an underlying cognitive vulnerability factor for the development of depression.

Overgeneral autobiographical memory has not been extensively studied in ECT patients. The preponderance of modern ECT research has focused on the quantification of retrograde amnesia and the extent to which it is influenced by variations in treatment parameters such as dose relative to seizure threshold (ST), electrode placement, and pulse width.[5] These studies, the majority of which have used the short or long form of the Columbia University Autobiographical Memory Interview (AMI),[13] have generally reported significant decreases in consistency of autobiographical memory recall at short- and long-term follow-ups compared with pre-ECT baseline.[4,14–17] These studies focused on overall percentage consistency between answers provided at baseline and follow-ups as an estimate of retrograde amnesia, irrespective of any pre-existing abnormalities in autobiographical memory function such as overgenerality.

One previous study[18] examining OGM in ECT patients, using the cue-word Autobiographical Memory Test[9] discussed previously, found that worse OGM at baseline predicted incipient relapse in the first week after cessation of treatment. Another study[19] using a different instrument, the Autobiographical Interview,[20] showed an impairment in episodic but not semantic autobiographical memory in a sample of 21 patients with depression referred for ECT. The Autobiographical Interview comprises both free recall and a structured interview involving specific probes designed to assess the effect of retrieval support on recall of event, time, place, perceptual, thought, and emotional details of memories, thus reducing the contribution of executive function deficits to observed problems with episodic autobiographical memory retrieval. Both of these studies, however, reported autobiographical memory specificity only at pre-ECT baseline.

The present study aimed to assess autobiographical memory of ECT patients using a standardized neuropsychological instrument, AMI by Kopelman et al,[21] before, immediately after the course, and at long-term follow-up and compare it with published norms. We aimed to study the previously underresearched distinction in the ECT literature between episodic and semantic autobiographical memory and examine the possible differential effect of

ECT on these 2 components of memory. We aimed to also explore the relationship between specificity of episodic autobiographical memory at baseline and the subsequent clinical course of depressive illness after ECT.

MATERIALS AND METHODS

Study Design

The study was conducted at St. Patrick's University Hospital, a nonprofit independent-sector psychiatric facility where Ireland's largest ECT clinic is located. As part of routine clinical practice and in line with current treatment guidelines,[22] cognitive status of patients undergoing a course of ECT was monitored at baseline, end of treatment course, and 3-month follow-up. Here, we report a retrospective chart review of all patients who were successfully followed up during a period of 2.5 years between August 2011 (when routine autobiographical memory testing began) and January 2014. The study was approved by the hospital's research ethics committee.

Participants

Adult inpatients aged 18 years or older with an *International Classification of Diseases*, *10th Revision*, clinical diagnosis of a major depressive episode (in the context of unipolar major depressive disorder or bipolar disorder) referred for a course of ECT were assessed for study eligibility. Exclusion criteria were dementia, another Axis I disorder, and substance abuse in the past year.

Treatment Parameters

Brief-pulse ECT was delivered twice weekly with handheld electrodes using a MECTA 5000M device (MECTA Corporation, Ore) in accordance with the Royal College of Psychiatrists' guidelines.[23] Each patient's ST was established during the first ECT session using an empirical titration method. Subsequent treatments were administered at 1.5× ST for bitemporal ECT or 4× ST for right unilateral (d'Elia placement) ECT. Electrode placement was chosen by the referring psychiatrists in consultation with patients. Methohexital (0.75–1.0 mg/kg) or thiopental (1.5–2.5 mg/kg) were used for anesthesia and succinylcholine (0.5–1.0 mg/kg) for muscle relaxation. Seizure duration was monitored by observation of motor activity and electroencephalogram. Treatment was continued until satisfactory clinical response was achieved as judged by the referring clinician or the patient who received up to 12 treatment sessions, which is the maximum duration of an ECT course set by the Irish Mental Health Commission.

Patients received their regular concomitant pharmacotherapy during the ECT course (Table 1), as is standard clinical practice in Ireland and many other countries. Post-ECT individually tailored continuation treatment with antidepressants and other psychotropic medications was prescribed to all patients by their treating psychiatrist.

TABLE 1. Demographic and Clinical Characteristics

Variable	Total Sample (N = 48)
Age, y	61.6 (12.6)
Female sex, n (%)	30 (62.5)
Education, y	13.6 (2.9)
Bipolar depression, n (%)	8 (16.7)
Psychotic features, n (%)	11 (22.9)
Duration of index episode, median (range), wk	8 (2–104)
History of previous ECT, n (%)*	25 (61.0)
Electrode placement, n (%)	
Bitemporal	44 (91.7)
Right unilateral	4 (8.3)
No. ECT sessions	7.9 (2.2)
Primary clinical indication for ECT, n (%)†	
Medication resistance	37 (77.1)
Rapid response required	7 (14.6)
Acute suicidality	0
Physical deterioration	4 (8.3)
No. of concomitant psychotropic medications	3.8 (1.6)
Concomitant psychotropic medications, n (%)‡	
SSRI	5 (11.4)
SNRI	21 (47.7)
TCA	8 (18.2)
MAOI	1 (2.3)
Mirtazapine	18 (40.9)
Agomelatine	3 (6.8)
Bupropion	1 (2.3)
Pramipexole	1 (2.3)
Lithium	18 (40.9)
T_3	3 (6.8)
Anticonvulsants	15 (34.1)
Antipsychotics	39 (88.6)
Benzodiazepines	14 (31.8)
Z-drug hypnotics	18 (40.9)
HRSD-24 score at baseline	27.9 (9.3)
CGI-S score at baseline	5.4 (0.8)
MMSE score at baseline	27.1 (3.2)

All data are presented as mean (SD), unless otherwise specified.

*Information available for n = 41.

†As indicated by the referring psychiatrist.

‡Information available for n = 44.

CGI-S indicates CGI-Severity scale; MAOI, monoamine oxidase inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; T_3, triiodothyronine; TCA, tricyclic antidepressant.

Measures

Clinical outcomes were evaluated using the 24-item Hamilton Rating Scale for Depression (HRSD-24)[24,25] and the Clinical Global Impression (CGI) scale. Treatment response was defined as a decrease in HRSD-24 score of 60% or greater and an end-of-treatment score of 10 or less. Relapse was defined as an increase in HRSD-24 score of at least 10 points relative to end-of-treatment score and a score of 16 or greater.

Global cognitive status was assessed using the Mini-Mental State Examination (MMSE).[26] Autobiographical memory was measured by the recent life section of the AMI by Kopelman et al.[21] Although initially developed for use in neurological populations,[27] the AMI has previously been found to successfully discriminate between depressed patients and normal controls.[28] Its use in clinical practice is facilitated by published normative data based on 34 controls aged 20 to 78 years,[21] allowing clinicians to compare their patients' performance with that of healthy adults.

The AMI is a semistructured interview consisting of the "personal semantic schedule" measuring memory for facts about one's life and the "autobiographical incidents schedule" measuring recall of specific episodic events from one's past life. The full AMI

covers the following 3 periods: childhood, early adulthood, and recent life. Only the recent life section was administered to maximize compliance. In a previous ECT trial,[29] severely depressed participants found the complete AMI too onerous to complete in full. The aim was also to focus on memories more proximal to the time of treatment because they may be more vulnerable to the effect of ECT than more remote memories.[30,31]

In the present study, specificity of autobiographical memory was operationally defined as the score on the autobiographical incidents schedule of the AMI. Each episodic memory is scored on a 0 to 3 scale depending on the level of descriptive richness and specificity in time and place. Three episodic memories are probed in the recent life section of the AMI, yielding a possible range of performance of 0 to 9 points. Lower scores on this subscale indicate worse specificity of episodic autobiographical memory.

The AMI was administered to patients by a nurse (S.M.) who was trained on the administration of the scale by a clinical neuropsychologist. Two raters (A.J. and S.O.) independently scored verbatim transcripts of interviews with all patients. Interrater reliability was high, with intraclass correlation coefficients exceeding 0.90 for the total score, personal semantic schedule, and the autobiographical incidents schedule. Means of the 2 raters' scores were used in subsequent statistical analyses.

Statistical Analyses

Patients who completed the 3-month follow-up were compared with noncompleters on demographic and clinical characteristics using the χ^2 test or Fisher exact test for categorical variables and independent samples *t* test for continuous variables. Change in mean HRSD-24 score over time was tested with a repeated measures analysis of variance. To test for the effect of time (baseline, after final ECT, and 3-month follow-up) on 3 dependent variables (AMI total score, personal semantic schedule score, and autobiographical incidents schedule score), while controlling for covariates (age, sex, years of education, baseline HRSD-24, and baseline MMSE), a repeated measures analysis of covariance was carried out for each of the 3 measures of autobiographical memory. To measure the effect of baseline autobiographical memory specificity on depression outcomes after ECT, Pearson r correlation coefficients were used to calculate correlations between baseline autobiographical incidents schedule scores and HRSD-24 scores after the final ECT session and at 3-month follow-up. Binary logistic regressions were performed to measure the effect of baseline autobiographical incidents schedule score on the likelihood of response and relapse. Odds ratios (ORs) were calculated for these categorical outcomes. Threshold for statistical significance was set at a P value of <0.05. Statistical analyses were performed in SPSS Version 22.0 (IBM Corp, NY).

RESULTS

Our chart review identified 221 new referrals for a course of ECT during the study period (excluding patients undergoing maintenance ECT and patients hospitalized elsewhere but receiving ECT at our clinic). Of those 221 referrals, 206 were for treatment of a major depressive episode. Of these 206, 129 were excluded from the study because of the following: being unable or unwilling to complete cognitive assessment (74 patients); participating in a concurrent randomized controlled trial in which autobiographical memory was already being assessed (28 patients); repeating a course of ECT being administered to a patient already in this study (18 patients); and having comorbid Axis I disorder or substance abuse (9 patients). Baseline assessments were completed by 77 patients; of which, 29 (37.7%) were lost to 3-month follow-up because of being uncontactable or refusing to complete the assessment. Long-term follow-up was completed by 48 patients whose demographic and clinical characteristics are presented in Table 1.

There were no significant differences between study completers and noncompleters in age ($t_{42} = -0.09$, $P = 0.930$), sex (χ^2 [1, n = 77] = 2.29, $P = 0.130$), polarity (χ^2 [1, n = 76] = 0.78, $P = 0.379$), baseline HRSD-24 ($t_{75} = 0.25$, $P = 0.804$), presence of baseline medication resistance as an indication for ECT (Fisher exact test $P = 0.341$), number of ECT sessions received ($t_{74} = -0.01$, $P = 0.996$), or electrode placement (Fisher exact test $P = 0.704$). Subsequent analyses were carried out on the completer sample (n = 48).

Mean HRSD-24 score (Fig. 1) changed significantly over time ($F_{2,92} = 83.67$, $P < 0.001$, partial $\eta^2 = 0.65$). Post hoc Bonferroni-adjusted paired *t* tests indicated that the mean HRSD-24 end-of-treatment score was significantly lower compared with pre-ECT baseline ($P < 0.0001$); meanwhile, there was a significant increase in mean HRSD-24 score from immediately after final ECT to 3-month follow-up ($P = 0.001$), but the latter score was still significantly lower than the pre-ECT baseline ($P < 0.0001$). Thirty-seven patients (77.1%) were classified as treatment responders immediately after the course of ECT. End-of-treatment mean (SD) CGI-Improvement score was 2.19 (1.28). Of the 37 responders, 11 (29.7%) relapsed during the 3-month follow-up period.

Figure 2 shows patients' uncorrected (raw) mean AMI total, personal semantic schedule, and autobiographical incidents schedule scores with 95% confidence intervals (CIs) at baseline, end of ECT treatment, and 3-month follow-up, as well as the published[21] range of normal performance in healthy controls. On all 3 testing occasions, patients performed within the normal range on semantic personal memory but were in the "definitely abnormal" range (which refers to scores at or below, which none of the controls scored in the normative sample) on episodic autobiographical memory. The patients' reduced total AMI score was therefore entirely accounted for by abnormalities in episodic memory retrieval. In the patient sample, scores on the semantic and episodic subscales showed statistically significant but weak correlations at baseline (r = 0.37, $P = 0.010$) and 3-month follow-up (r = 0.39, $P = 0.006$) and no correlation after final ECT (r = 0.17, $P = 0.241$).

There was no significant effect of time on autobiographical memory performance while controlling for age, sex, years of

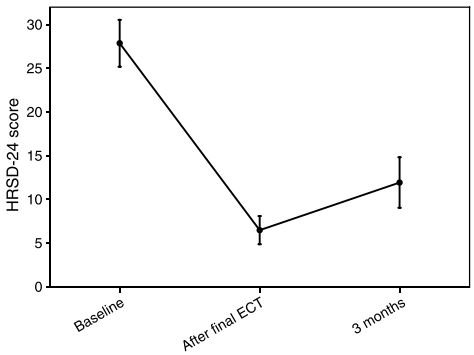

FIGURE 1. Mean depression rating scores with 95% CIs at pre-ECT baseline, end of ECT course, and 3-month follow-up.

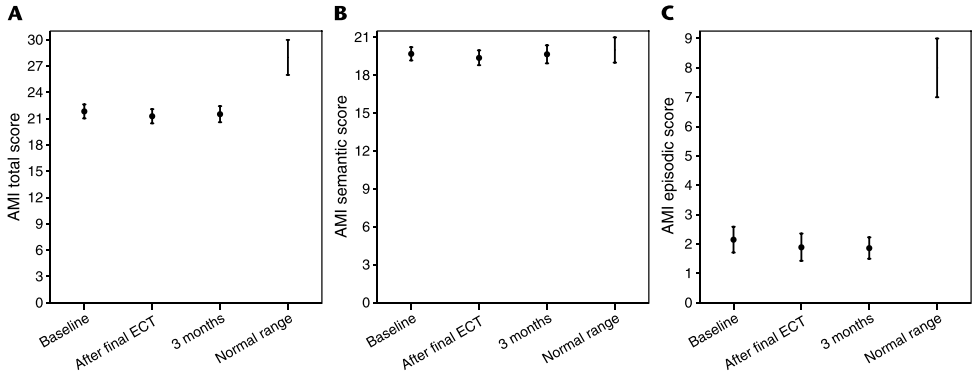

FIGURE 2. Recent life section AMI scores. Total AMI scores (A), AMI personal semantic schedule scores (B), and AMI autobiographical incidents schedule scores (C). Scores are presented as means and 95% CIs at pre-ECT baseline, end of ECT course, and 3-month follow-up, along with the range of normal performance from published norms.[21]

education, baseline HRSD-24, and baseline MMSE, either on the AMI total score ($F_{2,80} = 0.78$, $P = 0.460$) or semantic ($F_{2,80} = 0.71$, $P = 0.494$) and episodic ($F_{2,80} = 0.46$, $P = 0.633$) subscales. These results remained unchanged if the 4 patients who had received right unilateral ECT were excluded from analyses (data not shown). There was no significant correlation between the number of ECT sessions and scores on the AMI after final ECT, either for the total score (r = 0.07, $P = 0.633$) or for the semantic (r = −0.04, $P = 0.781$) and episodic (r = 0.18, $P = 0.235$) subscales. The same lack of correlation was observed between the number of ECT treatments and AMI total (r = −0.16, $P = 0.272$), semantic (r = −0.16, $P = 0.289$) and episodic (r = −0.10, $P = 0.492$) scores at 3-month follow-up.

To address the possibility of reduced baseline performance on the AMI being due to long-term consequences of a previous lifetime ECT course, we evaluated the subsample of those with no previous history of ECT. Information regarding past ECT treatments was available for 41 (85.4%) of 48 study participants. Between-subjects analyses of covariance (controlling for age, sex, years of education, baseline HRSD-24, and baseline MMSE) showed that patients who were now receiving their first ECT course (n = 16) did not differ from those who had previously received 1 or more courses (n = 25) on AMI total ($F_{1,34} = 1.48$, $P = 0.232$), semantic ($F_{1,34} = 2.03$, $P = 0.163$) or episodic ($F_{1,34} = 0.18$, $P = 0.675$) scores at pre-ECT baseline. In patients with no previous history of ECT, there was significant impairment in episodic autobiographical memory already present at pre-ECT baseline and persisting through long-term follow-up, whereas their performance on semantic personal memory was normal at all 3 assessment points (data not shown). In other words, the same pattern of results was observed as for the whole sample.

Next, the effect of current depressive symptoms on autobiographical memory performance was investigated. There was no significant correlation between HRSD-24 score and any of the 3 AMI scores at any of the 3 time points. Correlation coefficients (r) ranged between −0.15 and 0.23 and P values exceeded 0.05 in all instances. Finally, specificity of autobiographical memory at baseline, as measured by the autobiographical incidents schedule score, was examined as a predictor of clinical outcome immediately after the ECT course and at 3-month follow-up. Episodic memory performance at baseline did not significantly correlate with either end-of-treatment HRSD-24 score (r = 0.15, $P = 0.306$) or 3-month follow-up HRSD-24 score (r = 0.23, $P = 0.123$). Likewise, when treatment outcomes after the final ECT treatment were dichotomized into response versus nonresponse, baseline episodic memory score did not predict clinical response (OR, 1.11; 95% CI, 0.68–1.79; $P = 0.685$). In treatment responders, baseline episodic memory specificity did not significantly predict relapse status at 3 months (OR, 1.56; 95% CI, 0.93–2.61; $P = 0.091$).

DISCUSSION

Our results confirm and extend previously published findings[18,19] of reduced episodic autobiographical memory specificity in severely depressed patients referred for ECT. This phenomenon has now been demonstrated in this patient group using 3 instruments (AMI by Kopelman et al,[21] Autobiographical Interview, and Autobiographical Memory Test), which are dissimilar in a number of aspects, suggesting that the finding is robust to variations in assessment technique. The deficit was already present at pre-ECT baseline and could not be attributed to previous lifetime exposure to ECT. On the contrary, retrieval of personal semantic information (eg, names of relatives, neighbors, addresses, locations, dates, etc) was normal, both before and after ECT.

The results showed longitudinal stability of impaired episodic autobiographical memory specificity for a 3-month follow-up despite a significant improvement in mood state. This suggests that autobiographical memory specificity does not necessarily normalize with successful treatment and may thus represent a cognitive trait of depression. Several previous studies,[32–36] although not all,[37] of remitted patients with major depression who were not receiving ECT found that they continued to show reduced episodic autobiographical memory specificity compared with normal controls. In the present study, however, the possibility cannot be ruled out that an underlying improvement in autobiographical memory specificity arising from the resolution of the depressive episode was obscured by a deleterious impact of ECT. A control group of similarly ill depressed patients not treated with ECT assessed at the same time points would have been required to investigate this question.

The finding of no retrograde amnesia at either immediately after ECT or long-term follow-up is surprising given that more than 90% of our patients received brief-pulse bitemporal ECT that

has repeatedly been reported to affect autobiographical memory.[4,13,15,16] Our inability to detect retrograde amnesia in a sample treated with a modality known to induce it likely indicates lack of sensitivity of the recent life section of the AMI by Kopelman et al[21] to detect ECT-induced autobiographical memory dysfunction. In light of this, several recent randomized controlled trials[38–40] that have used this instrument and shown no retrograde amnesia following ultrabrief-pulse high-dose right unilateral ECT need to be interpreted with some caution because this may in part be a methodological artifact.

Notwithstanding its disadvantage in detecting retrograde amnesia in ECT patients (for which the instrument was not originally designed), the AMI allows for in-depth characterization of the 2 theoretical components of autobiographical memory and successfully discriminates between the performance of patients with depression from that of healthy controls. The AMI is also capable of showing a large difference in performance on the episodic versus semantic components of autobiographical memory in major depression, consistent with neuropsychological and functional neuroimaging evidence[41] demonstrating that unique processes, as well as some commonalities, are involved in the storage and retrieval of these 2 types of autobiographical memory.

This study has several important limitations, the most significant of which is its retrospective design. These highly preliminary findings require further replication in prospectively studied samples. However, the sample studied here is representative of patients receiving ECT in clinical practice and taking part in recent ECT trials[14–17] with respect to age, sex, baseline illness severity, acute response to treatment, and relapse rates.[42] We were unable to investigate the effect of electrode placement, a known moderator of autobiographical memory performance, because only 4 patients in our sample received right unilateral ECT. Our findings are therefore applicable mainly to brief-pulse bitemporal ECT, although this is advantageous from the perspective of its still being the most commonly used modality worldwide.[43] We also did not study the effect of other relevant aspects of cognition, particularly executive dysfunction, on autobiographical memory recall. Postictal time to reorientation, a variable previously shown[44] to be a good predictor of retrograde amnesia at short- and longer-term follow-up, was also not measured.

In light of these findings, it would be useful for future (preferably prospective) ECT research to provide separate measurements of semantic and episodic autobiographical memory, not just an overall score, because these 2 memory components seem to be differentially affected by depression and it is possible that a more sensitive measure of retrograde amnesia would be able to show a differential impact of ECT on the two. In addition, our understanding of overgenerality of autobiographical memory as a prominent aspect of cognitive dysfunction in depression needs to be incorporated into design of future instruments measuring retrograde amnesia after ECT. This study highlights the need for an instrument that would address the nature and extent of the problem in a robust way. Normative data for healthy controls, as well as patients with depression not receiving ECT, are required so that the effect of depressive illness on autobiographical memory can be controlled for when attempting to estimate the contribution of ECT to impaired performance. Simply controlling for current mood state is not sufficient because patients with a diagnosis of major depression who are currently in remission often continue to exhibit reduced autobiographical memory specificity. It would also be desirable for ECT studies to incorporate a qualitative assessment alongside objective neuropsychological testing to ascertain whether patients' subjective perception of the nature of their memory impairment also relates mostly to difficulties recalling events rather than personal semantic information.

In conclusion, our retrospective study showed markedly impaired episodic autobiographical memory specificity in depressed patients that is apparent before starting ECT but that does not deteriorate further after ECT, probably due to a lack of sensitivity of the recent life section of the AMI by Kopelman et al[21] in detecting ECT-induced retrograde amnesia. It remains to be seen whether this deficit can be successfully remediated[45,46] and whether its resolution would enhance long-term clinical outcomes by reducing susceptibility to relapse and recurrence of depression.

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