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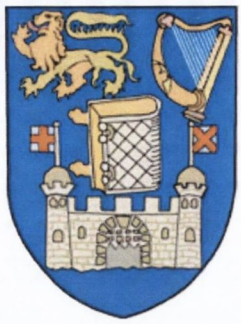
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The University of Dublin, Trinity College

Ollscoil Átha Cliath, Coláiste na Tríonóide

High dose right unilateral versus moderate dose bilateral ECT for major depression: time to re-orientation, physical functioning, quality of life and attitudes

PhD Thesis

2012

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April 2012

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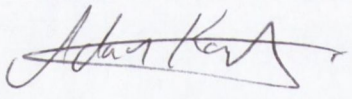
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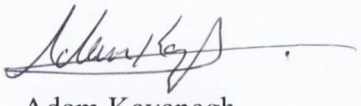
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Declaration

This work has not been submitted as an exercise for a degree at this or any other University. Interim findings for recovery, physical functioning and HRQOL outcomes and attitudes towards ECT for the first 100 participants of the EFFECT-DEP randomised, rater-and-patient-blinded controlled trial (ISRCTN23577151) are reported. I worked on the EFFECT-DEP TRIAL as part of team totalling nine different researchers over a period of four years. As one of the nine researchers working on the EFFECT-DEP TRIAL I collected post ECT recovery data and completed 29% of all assessments carried out. Full details of contribution of work and assessments carried out are available on page 4 and Appendix 8.



Adam Kavanagh

Summary

The objective of this study was to compare the effects of 1.5 × seizure threshold (ST) bitemporal ECT with high dose (6 × ST) right unilateral (RUL) ECT with respect to immediate recovery from treatment, change in physical functioning and health related quality of life (HRQOL) and the attitudes of service users towards these different treatments with 6 months follow-up.

100 participants were randomly allocated to receive 1.5 × ST bitemporal ECT or high dose (6 × ST) RUL ECT, N = 50 per group. ECT was administered twice weekly. Participants were administered a battery of clinical and neurocognitive assessments prior to treatment, at the end of treatment course, 3 months and 6 months after the end of treatment. This study provides a unique opportunity to obtain prospective data on high-dose RUL ECT and compare this to the standard version. Recovery data were used to compare time to reorientation and the incidence of physical side effects immediately following treatment between groups. The Physical Self Maintenance Scale and Instrumental Activities of Daily living Scale were used to compare the different forms of ECT regarding their effect on physical functioning in severe depression. The Medical Outcomes Study Short Form 36 Item Health Survey was used to compare the effects of the different forms of ECT on HRQOL over time. Attitudes of service users towards the different forms of ECT were explored for the first time using a combination of two published ECT attitudes questionnaires.

Using a Cox Mixed Effects survival model high dose RUL ECT was associated with quicker reorientation after treatment of approximately 65% for the first treatment session and 44% for subsequent treatment sessions. There was no difference between the treatment groups in the number of participants that experienced prolonged disorientation.

Using a Generalized Estimating Equations (GEE) approach it was found that there was no difference in the number of people complaining of headache, nausea or myalgia between the treatment groups. High dose RUL ECT was associated with a greater initial increase in blood pressure. Hypertension and tachycardia that required intervention were very rare but more common after RUL ECT.

There was no difference between the treatment groups in recovery of ability to perform basic ADL. Controlling for the effect of executive function there was no difference between the treatment groups in performance of IADL.

Change score ANCOVA was used to compare subjective Health Related Quality of Life (HRQOL). HRQOL improved significantly in both treatment groups 6 months after treatment. After adjusting for pre-intervention scores, there was no significant difference between the two treatment groups 6 months after ECT.

In general participants had positive attitudes towards ECT except for the resultant impact on memory. Factor analysis of the attitudes questionnaire revealed seven latent variables that were used to compare attitudes between groups. RUL participants were neutral while bitemporal participants were negative towards the memory effects of ECT. Attitudes did not change over time.

Remission at the end of the treatment was the only explanatory variable that predicted superior functioning, HRQOL and positive and negative attitudes towards ECT 6 months after treatment.

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I would like to thank my father Des, whose dedication to work in his own personal and professional life has been a continuous inspiration to me. I would like to thank my mother Marie, who has made her children her life's work and without her support and dedication this PhD would not have been possible.

This PhD would not have been possible without the contribution, love and support of my wife Shauna. Her understanding and effort throughout the last four years has been immeasurable. I would also like to thank Shauna for our son and daughter, Rían and Callie,

both of whom were born during this journey and have added so much love and happiness to our family.

I would like to thank my mother in law Margaret for all the child-minding that allowed me to work on this thesis and my father in law John, who sadly passed away on Friday 6th May 2011. His style, knowledge and opinion will always be missed.

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	List of Abbreviations
ANOVA	Analysis of Variance
ANCOVA	Analysis of Covariance
ACE-R	Addenbrooke's Cognitive Examination – revised
ADL	Activities of daily living
BP	Blood Pressure
BDI	Beck Depression Inventory
CBT	Cognitive Behavioural Therapy
CI	Confidence Interval
CSSES	The Columbia ECT Subjective Side Effect Schedule
DMEC	Data Monitoring and Ethics Committee
DSM	Diagnostic and Statistical Manual
ECG	Electrocardiography
ECTAS	Electroconvulsive Therapy Accreditation Service
ECT	Electroconvulsive therapy
EEG	Electroencephalography
EFFECT-DEP	Enhancing the eFFectiveness of ElectroConvulsive Therapy in severe Depression
EOT	End of treatment
FET	Fisher's exact test
GEE	Generalized Estimating Equations
GLM	Generalized Linear Model
HDRS	Hamilton depression rating scale
HDRUL	High dose right unilateral
HR	Heart-rate
HRQOL	Health related quality of life
HSE	Health Service Executive
IADL	Instrumental activities of daily living
IPT	Interpersonal Psychotherapy
ISRCTN	Current Controlled Trials Ltd registration number
IOP	Institute of Psychiatry
LME	Linear mixed effects
MAP	Mean arterial blood pressure
mC	Millicoulombs (unit of electrical charge)
MDD	Major depressive disorder
MDE	Major depressive episode
mEq/L	Serum Lithium Level
MHC	Mental Health Commission

mmHg	millimeter of mercury
MOS	Medical Outcomes Study
N	Number
NART	National Adult Reading Test
NHS	National Health Service (United Kingdom)
NICE	National Institute of Health and Clinical Excellence
OHLS	Oxford Healthy Lifestyle Survey
OR	Odds Ratio
O^2 Sat	Oxygen saturation level
PSMS	Physical self-maintenance scale
QOL	Quality of life
R	R is a free software environment for statistical computing and graphics
r^2	Coefficient of determination
RCT	Randomized controlled trial
RUL	Right unilateral
SEAN	Scottish Electroconvulsive Therapy Accreditation Service
SCID	Structured clinical interview for DSM-IV Axis 1 disorders
sd	Standard deviation
SF-36	Medical outcomes study short form 36 item health questionnaire
SPSS	Statistical Package for the Social Sciences
ST	Seizure threshold
TMT	Trail Making Test
UBP	Ultra brief pulse
WHO	World Health Organisation
χ^2	Chi square

1 Chapter 1

Chapter 1 presents a comprehensive review of the effects of depression on society and on the individual followed by an introduction of treatment options available to mental health professionals. Part 2 of this chapter provides a thorough examination of electroconvulsive therapy with respect to: its development as a treatment; indications for its use; contemporary practice; the evidence base supporting its use; different types of ECT and aspects of the procedure integral to its effectiveness. This review is not a systematic review or meta-analysis but online databases were searched for relevant studies: Pubmed, Cochrane library, CINAHL, EMBASE, MEDLINE, PsycLIT. Literature was only included if it was based on empirical evidence (e.g. meta-analysis, randomized controlled trial, observational study, systematic review). Some textbooks were included in the review if they made reference to statistics based on empirical evidence. Also, some opinion pieces without reference to evidence were included as a means of posing questions that were subsequently answered with empirical evidence.

1.1 Depression

Mental illness is routinely classified by the Diagnostic and Statistical Manual of Mental Disorder or DSM-IV-TR (American Psychiatric Association 2000) and the International Classification of Diseases or ICD 10 (World Health Organization 1994) which is an international standard diagnostic classification tool published by the World Health Organisation (WHO) since 1948.

Symptoms are used to construct a diagnosis of depression and are common between DSM-IV-TR and ICD-10. They include low mood and/ or anhedonia and the presence of five of the following symptoms: weight loss or gain, insomnia or hypersomnia, fatigue/ anergia, poor concentration, suicidal ideation or intent, guilt or worthlessness, psychomotor

retardation or agitation. Symptoms result in clinically significant impairment in social, occupational or other functioning, are not due to effects of substance abuse and are not better accounted for by bereavement. These symptoms have been present during the same two week period during the last month. In DSM-IV-TR these criteria are used to diagnose a major depressive episode (MDE) which, without the history of a manic or mixed episode, constitutes a diagnosis of major depressive disorder (MDD). ICD-10 uses these symptoms to specify a diagnosis of depression as mild, moderate or severe.

1.1.1 Epidemiology

Rates of depression vary considerably, and much more than rates for bipolar disorder (Tsuang & Tohen 2002). Based on general population surveys conducted in many countries the World Health Organisation estimates that depression has a lifetime risk of 7% - 12% for men and 20% - 25% for women (World Health Organization 2004). Women are at greater risk for new onset of major depression with a ratio of approximately 2:1 (Weissman & Klerman 1977; Henderson *et al.* 1979; Bebbington *et al.* 1981; Hodiamont *et al.* 1987). There is no difference in length of illness or recurrence of depression between the sexes (Eaton *et al.* 1997). With advancing age episodes of MDE decline but specific symptoms of depression increase (Gallo & Lebowitz 1999). Unemployment is a risk factor for depression (Weissman *et al.* 1988) but the exact nature of this relationship is unclear. Low level of education and low socio-economic status are also associated with greater likelihood of depression (Weissman & Myers 1978; Kessler *et al.* 1994). There is persistently conflicting evidence regarding the rates of depression in rural versus urban settings (Weissman *et al.* 1988; Kessler *et al.* 1994) suggesting complex contributing factors that are potentially not subject to generalization (Tsuang & Tohen 2002). Compared to normal controls first degree relatives of probands with MDD are at least

twice as likely as controls to develop MDD (Winokur & Morrison 1973; McGuffin *et al.* 2003) and twin studies further demonstrate a genetic influence (McGuffin *et al.* 2003).

While epidemiological evidence highlights rates of occurrence and risk of disease in certain populations, it does not fully explain why some people exposed to the same biopsychosocial development and lifestyle get depressed and others do not.

1.1.2 Aetiology

The aetiology of depression is not clearly established because the pathophysiology of mood disorders is not well understood (Belmaker & Agam 2008). The heterogeneity of presentation, trajectory of course and inconsistent response to treatment prevent a clear understanding of the pathophysiology of depression (Belmaker & Agam 2008). Theories of aetiology include: a genetic influence revealed, for example, by twin studies (McGuffin *et al.* 2003); biochemical influences (Leonard & Myint 2009); structural influences (Elkis *et al.* 1995); cognitive models (Beck 1989); early developmental influences (Kendler *et al.* 2000); and organic causes of depression. The actual cause of any individual's depression can be one or a combination of these factors and aetiology in depression is best thought of from a biopsychosocial perspective.

1.1.3 Impact of depression

Depression has a profound impact on society in terms of its direct and indirect costs. The cost of health care and loss of productivity in the workplace are examples respectively. There is also a considerable effect to the individual such impaired ability to function across a spectrum of domains.

1.1.3.1 Economic impact

Depression causes the greatest burden of non-fatal illness worldwide and by 2020 the World Health Organisation estimate that depression will represent the second largest contributor to the global burden of disease (Murray & Lopez 1997a). The cost of depression in Europe was about 118 billion euro in 2004, approximately 1% of the total economy (Sobocki *et al.* 2006). Evidence suggests that depression causes 6% of the burden of all diseases in Europe in terms of disability adjusted life years (DALYs) and unipolar depression accounts for more DALY's in Ireland than the three most prevalent forms of cancer combined (World Health Organization 2009). 30% of all admissions to the psychiatric services in Ireland in 2008 were for the treatment of depressive illness, approximately 7000 admissions (Daly & Walsh 2009). Depression is often refractory to treatment with anti-depressant drugs with or without psychotherapy (Rush *et al.* 2006) and this resistance increases treatment costs by at least 40% (Gibson *et al.* 2010).

Depression negatively influences labour force participation in terms of absenteeism and total hours worked (Broadhead *et al.* 1990; Conti & Burton 1994). Persons diagnosed with MDD take significantly more sick days per year than persons diagnosed with medical ailments (10 versus 5.4-7.5 days respectively (Druss *et al.* 2000)). Presenteeism, when an employee is able to attend work but is not functioning at an optimum level, is also common among those suffering depression (Katon 2009). Persons diagnosed with MDD are less productive than those with common medical conditions (arthritis, back pain and hypertension) and demonstrate more pronounced decrements in task focus (Wang *et al.* 2004).

1.1.3.2 Physical functioning

There is substantial evidence that depression has a profound impact on overall functional ability that increases the total burden of disease, limits functioning more than common medical conditions and increases years of life lost to premature mortality (Wells *et al.* 1992; Hays *et al.* 1995; Murray & Lopez 1997c). Substandard physical functioning is a feature (McCall *et al.* 2002a) and recovery of optimal physical ability lags behind remission (McCall *et al.* 2001; Rhebergen *et al.* 2010), the extent of which is predictive of earlier relapse (Conradi *et al.* 2008). Recovery of optimum physical functioning lags behind recovery of social functioning that recovers in synchrony with recovery of depressive symptoms to a greater extent (Simon *et al.* 2005; Rhebergen *et al.* 2010). Little research has focused directly on the impact of depression on the ability of medically healthy, non-elderly people to perform basic and instrumental activities of daily living (McKnight & Kashdan 2009). Depression affects cognitive functioning such as executive control (Bell-McGinty *et al.* 2002) that affects performance of instrumental activities of daily living and in turn one's ability to live and function independently. This is probably more pronounced in the elderly (Kiosses *et al.* 2000).

1.1.3.3 Social functioning

The impact of depression on social functioning is well established (Weissman *et al.* 1974; Paykel *et al.* 1978; Hays *et al.* 1995; Leader & Klein 1996; Tse & Bond 2004). Social adaptation is one's ability to adapt behaviour appropriately to different social situations (Briley & Moret 2010): an inability to engage appropriately in diverse social situations may negatively impact an individual's social support network (Briley & Moret 2010). The resultant shortfall in social support from family, extended family and friends is a well-established risk factor for depression and relapse following symptomatic recovery (Stefos *et al.* 1996). There is evidence that impaired social functioning can persist up to

four years (Bothwell & Weissman 1977), negatively impacting marital and interpersonal relationships (Moos *et al.* 1998).

1.1.3.4 Cognitive functioning

Cognitive functions essential to independent normal life performance such as executive function, episodic memory, attention, concentration and processing speed (Christensen & Duncan 1995; Bearden *et al.* 2006; Pardo *et al.* 2006; Rose & Ebmeier 2006) are also affected (McDermott & Ebmeier 2009). Severity of depression influences the extent of impact (McDermott & Ebmeier 2009) and even though improvements are evident with remission (Butters *et al.* 2004a), impairments often persist and possibly more so in the elderly (Tielkes *et al.* 2008).

1.1.3.5 Physical health

The physical health consequences of depression range from dysregulation of neuro-chemicals associated with mood (Myint & Kim 2003) to hypercortisolemia that can be a risk factor for a host of medical conditions (Leonard & Myint 2009). This impact on physical health is further compounded by the unhealthy lifestyle led by depressed persons in general (Chuang *et al.* 2008; Leonard & Myint 2009); e.g. the prevalence of obesity in psychiatric populations ranges from 2 to 5 times that of the general population (Gopalaswany & Morgan 1985) and depression in associated with significantly higher rates of nicotine dependence and increased rates of daily smoking (Fergusson *et al.* 2003). The long term effects of depression on physical health are evidenced by increased risk of type 2 diabetes mellitus (odds ratio) 1.96), coronary artery disease (OR 2.30), stroke (OR 3.15) and hypertension (OR 2.0) (Edge 2007). Chronic depression may even increase risk of developing dementia by two to four fold (Geerlings *et al.* 2008).

1.1.3.6 Quality of life

Quality of life (QOL) is more than the absence of disease or infirmity and health itself is just one aspect of QOL. Health Related Quality of Life (HRQOL) is a subjective expression of the impact of illness and treatment for illness on health and wellbeing (Wenger & Furberg 1990). People suffering depression perceive their health and QOL worse than those suffering chronic medical conditions (Wells *et al.* 1989; Ormel *et al.* 1993a; Hays *et al.* 1995). In fact, people suffering depression co-morbidly with a medical illness perceive their health worse than those with chronic medical conditions or depression alone (Ormel *et al.* 1993b).

1.1.4 Prognosis

The prognosis or long term trajectory of depression is alarming. In a prospectively observed sample of 431 people diagnosed with depression only 50% recovered within the first 6 months and approximately 12% did not recover over a five year period (Keller *et al.* 1992). Another prospective, naturalistic long term follow-up study found that up to 25% of remitters will suffer a recurrence within 12 months, 42% within 2 years and 60% within 5 years (Solomon *et al.* 2000). With each successive recurrence of MDD the risk of a subsequent recurrence increases by approximately 16% (Solomon *et al.* 2000). There is considerable variation in time to recurrence between remitters so it is almost impossible to predict who will relapse (Solomon *et al.* 2000). Early intervention is crucial as increasing duration of depression reduces the probability of recovery (Keller *et al.* 1992; Solomon *et al.* 2000). It is positive, however, that as the duration of time in recovery increases the risk of recurrence decreases (Keller *et al.* 1983; Lavori *et al.* 1984; Frank *et al.* 1990; Solomon *et al.* 2000). Therefore, appropriate treatment and relapse prevention are fundamental to the treatment of depression.

1.1.5 Treatment

Remission from depression will result in improved daily functioning, superior quality of life and a better prognosis (Judd *et al.* 1997; Miller *et al.* 1998; Van Londen *et al.* 1998). Treatment options include pharmacotherapy, psychotherapy and physical therapies (Aronson & Ayres 2000; Taylor *et al.* 2009).

1.1.5.1 Pharmacotherapy

In the acute phase pharmacotherapy will successfully treat up to 70% of persons with major depression (Rush *et al.* 2006). However, time to remission increases and remission rates decrease as the number of failed adequate anti-depressant drug treatment courses increase (Rush *et al.* 2006). Increased treatment resistance is indicative of a poorer prognosis and approximately 30% of depressed persons do not, or only partially, respond to pharmacotherapy (Rush *et al.* 2006).

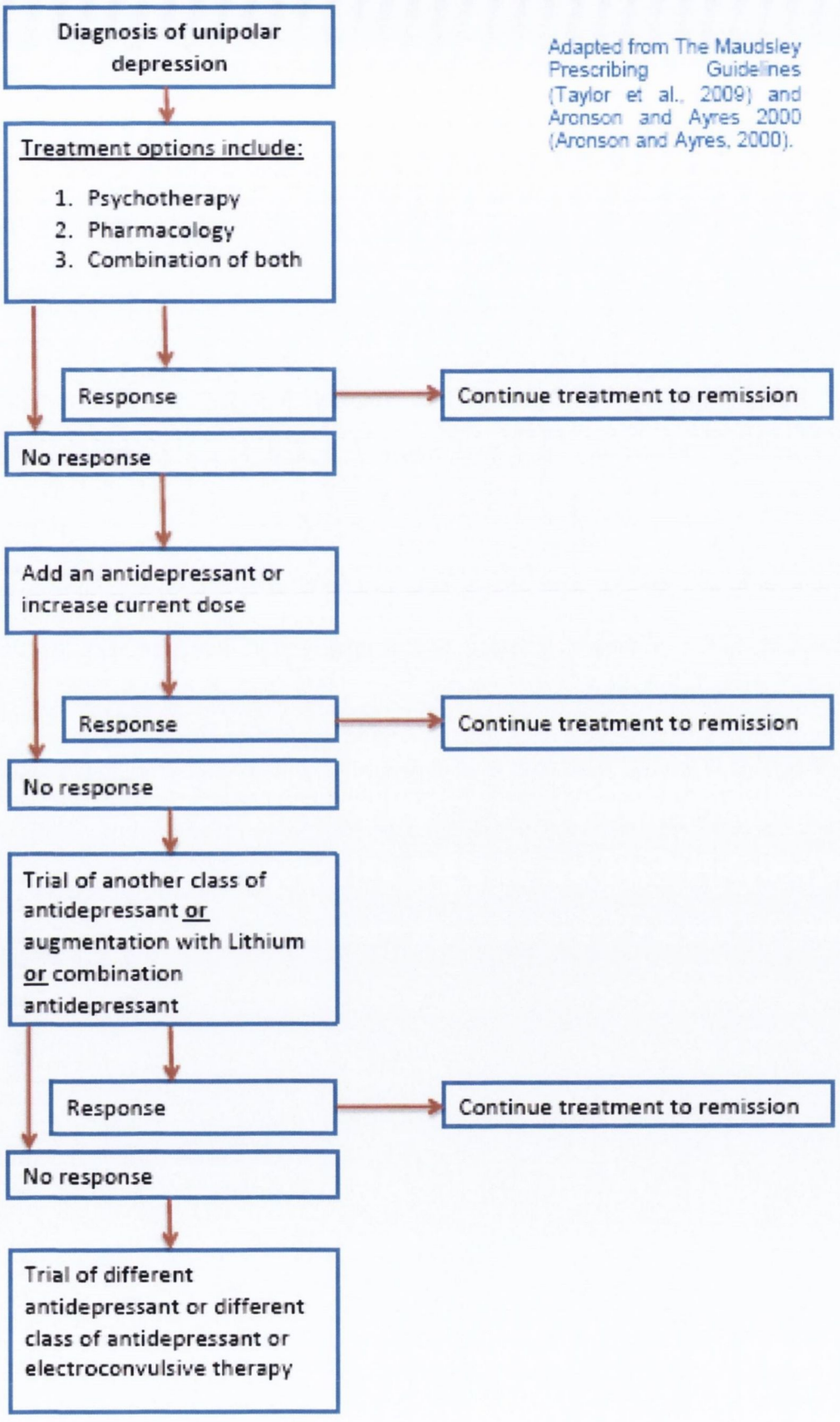
1.1.5.2 Psychotherapy

Psychotherapy is preferred as a first line treatment for mild to moderate depression (Seligman 1995) and demonstrates good effectiveness in outpatient samples and mild to moderate depression (National Institute for Health and Clinical Excellence 2009). However, NICE (2009) updated clinical evidence review indicated that "CBT alone may be more costly yet less clinically effective" than antidepressant drug treatment. Given the superiority of ECT compared with antidepressant drug treatment (section 1.2.4) ECT may also be considered more effective in terms of antidepressant effect, although no trial has directly compared the effects of ECT with CBT.

1.1.5.3 Electroconvulsive therapy (ECT)

Remission rates with ECT range from 50% to 80%, depending upon treatment population and method of ECT employed (Eranti *et al.* 2007; Lisanby 2007a; Kavanagh & McLoughlin 2009). Psychopharmacology and psychotherapy are first line treatments for depression and ECT is normally considered a third or fourth line treatment once a second course of chemical antidepressant therapy and augmentation with lithium or other chemical antidepressant with or without psychotherapy has failed or if a rapid response (due to acute suicidality or significant physical deterioration) is required (Aronson & Ayres 2000; Taylor *et al.* 2009) (Figure 1.1).

Figure 1. 1 Treatment algorithm for unipolar depression



1.2 Electroconvulsive therapy

1.2.1 History

Medically induced seizures have been recognised as having therapeutic potential for the treatment of mental ill health since the early 20th century. At this time there was no effective treatments available for the severely mentally unwell and interventions were mainly limited to custodial care and sedation (Endler 1988). A Hungarian neurologist, Ladislas Joseph Von Meduna (1896–1964), in 1934 observed that schizophrenia did not occur as frequently among people with epilepsy and proposed that schizophrenia and epilepsy were mutually incompatible. This hypothesis proved to be incorrect but the practice of convulsive therapy gained support because of the dramatic clinical improvements observed in patients treated, especially those suffering depressive symptoms (Berrios 1997). Initially, seizures were induced with chemicals such as camphor but patients often suffered distressing and prolonged pre-ictal effects. Physicians explored new methods of administering seizures that would maintain the observed therapeutic results (Stein *et al.* 2005). In 1938 in Rome two physicians, Cerletti and Bini, successfully induced seizures using electricity while maintaining the therapeutic effect (Stein *et al.* 2005). ECT, as it came to be known, became one of the first effective treatments for severe mental illness and because of its success was quickly taken up worldwide.

Unfortunately, there were no other effective treatments for mental ill health at this time and ECT was used almost indiscriminately for a period during the mid-twentieth century (Glass 2001). This period has contributed greatly to the fear and stigma that currently surrounds ECT, much of which overshadows the evidence base demonstrating the effectiveness of ECT. Such fear may be inhibiting the potential of an effective treatment for those suffering severe mental ill-health in terms of treating teams' likelihood of prescribing ECT and patients' willingness to accept it (Kavanagh & McLoughlin 2009).

It has been suggested that an effective method of overcoming this stigma is for health care professionals and the general public to be aware of the facts of contemporary ECT, including: indications, effectiveness and adverse effects (Glass 2001; Besani *et al.* 2011).

1.2.2 Indications

Although initially used for the treatment of schizophrenia, it became obvious that the primary indication for ECT was the treatment of affective disorders (Kavanagh & McLoughlin 2009). In its first review of ECT, the National Institute for Health and Clinical Excellence (NICE) in the UK recommended that ECT be used only for the treatment of severe depressive illness, a prolonged or severe episode of mania, or catatonia (National Institute for Health and Clinical Excellence 2003). NICE did not recommend ECT for the treatment of schizophrenia, apart from catatonic schizophrenia, as there was insufficient evidence to either support or refute its benefit. This guidance was updated in 2009 as part of the NICE guidance on depression (National Institute for Health and Clinical Excellence 2009). Considering the stronger evidence base, the use of maintenance ECT is supported for those that not maintaining remission with pharmacological or psychological interventions following successful ECT, that ECT be used for less severe, but usually resistant, forms of depression and more emphasis on patient choice is highlighted (National Institute for Health and Clinical Excellence 2009). There are some differences with other national guidelines. For example, the American Psychiatric Association is consistent with NICE guidelines but also makes provision for treating some forms of schizophrenia such that ECT is indicated following unsuccessful treatment with antipsychotic medication and for the treatment of patients with schizoaffective or schizophreniform disorder (American Psychiatric Association 2001). In Ireland the Mental Health Commission has a Code of

Practice governing the use of ECT but does not specify indications for its use (Mental Health Commission 2006a).

1.2.3 Effectiveness of electroconvulsive therapy

ECT was originally proposed as a treatment for schizophrenia but superior clinical improvements were quickly observed in patients with mood disorders (Royal College of Psychiatrists 2005). Open trials in the 1940s and 1950s reported response rates as high as 80% to 90% (Kalinowsky & Hoch 1946; Sargent & Slater 1954). Concrete empirical evidence demonstrating the effectiveness of ECT as an antidepressant treatment was established through sham controlled trials, summarized in Appendix 1. These trials randomly allocated participants to receive real ECT or simulated ECT: all aspects of the treatment were performed including the additional nursing care, preparation for treatment and anesthesia but no stimulus was administration and there was no seizure. These early randomized controlled trials did not use remission criteria and so did not compare numbers that remitted in one group with another but instead reported significant improvements on objective, and in some cases subjective, depression rating scales, and compared these between groups. In all of these trials participants treating clinical teams were independent of the research trial and decided when the participant should stop receiving ECT and all trials adopted a double blind system where participants and treating teams were blind to treatment allocation. One limitation of these trials is that normal treatment commenced as soon as the treatment course ended. Therefore, as participants may have been treated with further ECT or new courses of antidepressant drugs it is not possible to evaluate the effectiveness of ECT in the real ECT groups compared to the simulated ECT groups beyond the acute phase of treatment. It is also not possible to comment on the relapse rate after this period.

Freeman et al (1978) administered real ECT to one group and simulated ECT on the first two treatments to the other group. There was no difference between the groups in severity of depression prior to treatment; the simulated ECT group required statistically significantly more ECT treatments than the real ECT group to achieve the same level of improvement; and after six treatments both groups had improved significantly from pre-treatment and the simulated ECT group were no longer significantly more depressed than the real ECT group (Freeman 1978).

Lambourn and Gill (1978) reported that their ECT group made no statistically significantly superior response compared to the sham ECT group and hypothesized that the beneficial effects of ECT reported in other trials were in fact due to placebo, characterized by the procedure itself and additional care from Nurses prior to and after treatment (Lambourn & Gill 1978). One significant limitation to this trial is that right unilateral electrode placement was used which we now know to be ineffective as an antidepressant unless administered at high doses (Sackeim *et al.* 1993) which it was not in this trial.

Johnstone et al (1980) reported the Northwick Park Electroconvulsive Therapy Trial. At the end of the treatment course the real ECT group had made statistically significant mean improvements in severity of depression compared to the simulated ECT group (Johnstone *et al.* 1980). In another trial West (1981) reported that after six treatments, statistically significant improvements were rated by a psychiatrist, a nurse and the patients themselves in the real ECT group while all three rating groups reported little clinical change in the simulated ECT group (West 1981). Brandon et al (1984) reported that at the end of the treatment course (8 treatments) on an objectively rated 7 point scale of change in participants' condition, participants in the real ECT group made a significantly greater improvement (mean rank 45.98) compared with participants in the

sham ECT group (mean rank 25.34); Mann-Whitney U Test = 300.0, P = 0.00005 (Brandon *et al.* 1984).

Gregory et al (1985) compared the response of 69 participants randomly allocated to bilateral, right unilateral and simulated ECT groups and administered 6 sessions. They reported that at the end of treatment all three groups made a statistically significant improvement in depression severity but the two electricity groups improved statistically significantly more than the simulated ECT group but there was no significant difference between the two real ECT groups. They also report that the bilateral group received significantly fewer ECTs after the trial ended than the RUL group who received significantly less ECTs than the SHAM ECT group (Gregory *et al.* 1985).

The UK ECT Review Group (2003) conducted a meta-analysis of these data, combining the results of six trials comprising a total of 256 patients (Wilson *et al.* 1963; Freeman 1978; Lambourn & Gill 1978; Johnstone *et al.* 1980; West 1981; Gregory *et al.* 1985). Real ECT was found to be significantly more effective than simulated ECT: the mean difference in reduction in Hamilton Depression Rating Scale score (HDRS) was 9·7 (95% CI 5·7 to 13·5) points for real ECT compared with simulated ECT (UK ECT Review Group 2003).

Following the development of antidepressant drugs such as Monoamine Oxidase Inhibitors (MAOI) and Tricyclic antidepressants there were a number of randomly allocated trials where ECT was used as the gold standard treatment against which the effectiveness of these new treatments was measured. These data were meta-analyzed by Janicak et al (1985) and ECT was found to be more effective than TCA by 20% and more effective than MAOIs by 45% (Janicak *et al.* 1985a). To date only one study has compared ECT with an SSRI in a double blind randomized controlled trial. Folkerts et al (1997) found ECT significantly more effective than Paroxetine: ECT was associated with a

reduction in the HDRS score of 59% while paroxetine was associated with a 29% reduction (Folkerts *et al.* 1997).

Despite the evidence base supporting the use of ECT for the acute treatment of severe depression there is opposition to the use of ECT.

The primary concern with ECT is adverse cognitive effects; especially memory impairment (Rose *et al.* 2003). People may experience anterograde amnesia, i.e. difficulty forming new memories. This may be present throughout the course of treatment but in the majority of cases resolves within three days of the ECT course ending and in many cases cognitive functioning is superior to pre-treatment functioning within two weeks of course end (Lisanby 2007a; Semkovska & McLoughlin 2010). Retrograde amnesia may also occur; this is loss of ability to retrieve memories formed before the onset of treatment. Autobiographical memories (memory of events and issues related to oneself) may be less affected than impersonal memories (Lisanby *et al.* 2000). Retrograde amnesia also improves as time from the end of treatment increases but some people complain of persistent retrograde memory impairment. One study of a large community sample found that approximately 12% of participants experienced persistent retrograde amnesia (Sackeim *et al.* 2007). However, this study used a non-standardized instrument to assess retrograde amnesia with no control group or normative data for comparison. A systematic review of studies that specifically asked participants about retrograde amnesia reported a rate of at least 30% (Rose *et al.* 2003). These areas continue to be the subject of research interest. One aspect of the adverse cognitive effect profile of ECT that has not been adequately examined is post ictal disorientation. There are a number of treatment parameters that modify the effects of ECT on memory and these are discussed in the following sections. Research in recent years has identified a number of areas that have reduced the impact on memory.

Corry (2008) asserts that ECT can be associated with a loss of intellectual function (Corry 2008). To date there are no controlled trials in this area (Robertson & Pryor 2006) but there are a number of case reports and service user surveys: Philpott et al (2004) asked participants if they had experienced a loss of intelligence soon after treatment and 40% stated that they had (Philpot 2004). However, participants were not asked if the effects persisted and we now know that many aspects of cognitive functioning that are effected by ECT show significant deficits in the first three days after the course of treatment but the majority of these areas show improvements to at least pre-treatment levels and in some areas improve beyond pre-treatment levels within weeks of the end of treatment (Semkovska & McLoughlin 2010).

Corry (2008) also asserts that ECT results in docile behaviour. There is no evidence to support this claim. The predominant indication for ECT is severe depression or depression that is refractory to other forms of treatment such as psychotherapy or antidepressant drugs. The primary manifestations of severe depression are: inertia, loss of interest, loss of concentration, loss of motivation, loss of concentration, and often in real terms, docile behaviour.

Breggin (1998) asserts that ECT is associated with structural brain damage (Breggin 1998). Dwork et al (2004) administered ECT to primates daily for 6 weeks and compared the effects on brain structures with that of primates administered anaesthesia alone. They found no pathological findings in the primates administered ECT compared with controls (Dwork *et al.* 2004). Cardoso et al (2008) found no evidence that neurons located in the hippocampus were particularly vulnerable to repeated seizures that were properly administered with appropriate intervals between administrations (Cardoso *et al.* 2008). There have been few well designed brain imaging studies conducted in humans (Devanand *et al.* 1994). Recent evidence of the structural abnormalities associated with

major depression further confound this area; e.g. in depression the hippocampus, a region of the brain that is involved in mood and memory, is significantly smaller and has a reduced concentration of neurons, increased apoptosis and decreased neurogenesis (Coffey *et al.* 1993; Sheline 1996; Malberg *et al.* 2000a; Sheline *et al.* 2003). Kolbeinsson et al (1986) reported a study of 22 patients previously treated with ECT that were compared to age and sex matched controls that never received ECT, but were diagnosed with depression, and a second control group of healthy volunteers. All participants received a computed tomography scan (CT scan). Both patient groups had similar structural changes that were not present in healthy controls. These changes were most likely associated with their illnesses as discussed previously (Coffey *et al.* 1993) but there were no differences between patients treated with ECT and those not treated with ECT (Kolbeinsson *et al.* 1986). Bergsholm et al (1989) conducted the only available prospective computed tomography scan study comparing the structural brain of 40 patients administered ECT before and after their course of treatment (Bergsholm *et al.* 1989). No CT changes occurred following ECT, even though there were a number of participants that experienced prolonged seizures.

It is alleged that ECT is associated with an increased risk of mortality (Breggin 1998; Corry 2008) and that deaths associated with ECT are not reported (Breggin 1998). Since 1993 Texas requires the reporting of all ECT administered in the state and details of any death that occurs within 14 days of ECT. Shiwach et al (2001) analysed the first 5 years of these data. 8,148 patients received a total of 49,048 ECT treatments (Shiwach *et al.* 2001). No deaths occurred during ECT over the five year period, 30 patients died within 14 days of receiving ECT, 1 of those patients died the same day as the treatment from laryngospasm, 7 died within 48 hours of the treatment (2 cardiac related deaths, 3 sepsis related deaths, 1 suicide and 1 death for which the cause was unknown). A conservative estimate of 2 to 10 deaths per 100,000 treatments in a 5 year period compares favourably

with 3.3 to 3.7 deaths per 100,000 treatments reported for general anaesthesia (Roy & Overdyk 1997). Danish citizens are assigned a personal registration number since 1968. Munk-Olsen et al (2007) conducted a Register-based cohort study of all in-patients admitted to a large regional psychiatric hospital in Aarhus, Denmark from 1976 to 2000 to assess the risk of mortality from natural and unnatural causes among patients treated with ECT compared with other psychiatric in-patients over a 25-year period (Munk-Olsen *et al.* 2007). A total of 783 patients treated with ECT died during the study period: 593 (76%) from natural causes and 190 (24%) from unnatural causes. The relative risk (RR) of mortality compared with psychiatric in-patients not treated with ECT was 0.86 (95% CI 0.79–0.94) (RR < 1 = statistically significantly less likely than other group).

It has been alleged that ECT is used as a means of control (Breggin 1998), that it is administered frequently against peoples will (Breggin 1998; Corry 2008) and that if Psychiatrists were to stop administering ECT it would lead to a loss of power (Corry 2008). While ECT may have been administered in the past to patients that were aggressive or 'uncontrollable', especially when ECT was first developed and there were no other effective forms of treatment apart from sedation and custodial care (Endler 1988), contemporary Psychiatry and contemporary ECT practice is quite different. As already stated, the major indication for ECT is severe depression and there seems no plausible motivation for a collective struggle for control on the part of modern mental health professionals over sufferers of severe depression. ECT is not administered without consent frequently: In Ireland approximately 10% of all patients treated with ECT annually are treated in the absence of consent (Mental Health Commission 2012). There were 19,619 admissions to approved centres in Ireland in 2010. 347 programmes of ECT were administered to 260 individuals in 2010 which is comparable to Scotland (Network 2009) and Canada (Rapoport *et al.* 2006). Therefore, ECT was administered to less than 0.02% of patients admitted to approved centres in Ireland in 2010. As such ECT is a relatively

unemployed treatment in modern-day Psychiatric treatment. If ECT were to be abandoned, while it may deprive people with severe or treatment resistant depression the opportunity of recovery, it would not appear so influential that it would lead to a loss of power from mental health professionals.

Perhaps the most appropriate debate to have about the use of ECT is not actually about ECT but is the foundation to most arguments against its use: What is the cause of depression? There are those who believe that depression is a biological disorder and as such a biological intervention such a pharmacotherapy or ECT is the most likely treatment to be successful. However, others believe depression is the manifestation of psychospiritual crisis and liken the use of a biological treatment as an intervention to the use of a defibrillator to interrupt the cardiac electrical rhythm in the hope of easing the pain of a broken heart (Corry 2008). The real truth here is as disconcerting as either of the above positions believes the other to be. Despite the many theories of depression (section 1.1.2), knowledge of the many factors that can contribute to cause depression, knowledge of the many factors that make depression more likely and knowledge of the many factors that can maintain depression, we do not know the cause of depression and we cannot predict who will experience depression, nor can we predict who will respond to certain treatments, psychological or biological. Working in such a vacuum it appears sensible to follow theories as a means of pursing research as we attempt to fill the gaps in our knowledge but it appears more appropriate to rely on the evidence we do have to base treatment decisions upon. As such, ECT practice is based on a considerable evidence base demonstrating anti-depressant effect. However, there are potentially severe adverse cognitive effects that prospective patients need to be made aware of and the decision to accept treatment or not should be made by the fully informed patient (provided they have capacity to do so) based on a judgement of potential risk and potential benefit.

1.2.4 Contemporary modified electroconvulsive therapy

Contemporary ECT is a controlled medical procedure modified with general anaesthesia and muscle relaxant medication (Tess & Smetana 2009). In the United States treatment three times a week is common while in Europe twice weekly treatment is standard practice (Lerer *et al.* 1995).

The anaesthetist administers a short acting anaesthetic; methohexital, propofol, etomidate and sodium thiopentone are commonly used (Freeman 1999; Eranti *et al.* 2009). Once the patient is asleep, a short acting muscle relaxant (succinylcholine) is administered to reduce the physical extent of the motor seizure. ECG, pulse oximetry, blood pressure, and expired carbon dioxide are continuously monitored throughout treatment while the cerebral seizure itself is monitored by dual channel electroencephalography (EEG). Oxygen is administered until the treatment ends, the anaesthesia wears off and the patient resumes breathing independently. Electrodes are placed on the anaesthetised patient's scalp and a brief electrical charge is passed through the brain. The patient is anesthetised and muscles relaxed to prevent injuries and minimize discomfort; the toes may twitch or become rigid, their jaw may clench (the anaesthetist will have inserted a disposable mouth guard to protect the patient's tongue and teeth), heart rate may initially drop followed by a subsequent increase in blood pressure and heart rate. The latter changes are due to autonomic sympathetic discharge during the seizure and because of this management of all cardiac conditions are optimised before treatment (Tess & Smetana 2009). Seizures last about 30 seconds and once the anaesthetist is satisfied with the patient's condition (s)he is transferred to a recovery area. Observations are monitored until the patient regains orientation and the team are satisfied with the patient's physical and cognitive state. He/she is then transferred back to their originating ward for further observation. ECT Research in recent years has focused on optimising ECT by focusing on treatment parameters such as stimulus dosing and electrode placement.

1.2.5 Stimulus dosing

Seizure threshold (ST) is the minimum electrical charge that induces an adequate seizure. The aim of a stimulus dosing protocol is to establish the patient's ST and titrate to an appropriate treatment dose to induce an adequate seizure; thereafter the patient is treated with a suprathreshold dose. A supra-threshold treatment dose is used because it is more effective for relieving depression than administering a ST dose (Sackeim *et al.* 1993). However, excessive stimulation increases the potential for adverse cognitive effects.

An adequate seizure is defined as generalised tonic-clonic motor activity lasting more than 15 seconds or an EEG recording of seizure activity lasting more than 25 seconds and featuring 3 Hz spike and wave activity (Sackeim *et al.* 1987b; Shapira *et al.* 1998; Sackeim *et al.* 2000). Duration of seizure activity indicates the presence of an adequate seizure but is not correlated with effectiveness. The electrical stimulus dose appears to directly influence the effectiveness of ECT (Sackeim *et al.* 1993). A supra-threshold treatment dose is more effective than administering a stimulus dose just at ST and it is in fact possible to induce seizures that have little therapeutic benefit, especially with unilateral ECT (Sackeim *et al.* 1993).

Treatment is thus tailored for the individual patient and the most effective dose with the least potential to cause adverse cognitive effects is determined. The same intensity used for bitemporal treatment is much less effective for unilateral treatment (Sackeim *et al.* 1993; Sackeim *et al.* 2000). Once the ST is established the standard treatment dose is 1.5 times ST for bitemporal ECT while the optimal treatment dose for unilateral ECT may be six times ST and is currently the subject of on-going research (McCall *et al.* 2000; Sackeim *et al.* 2000).

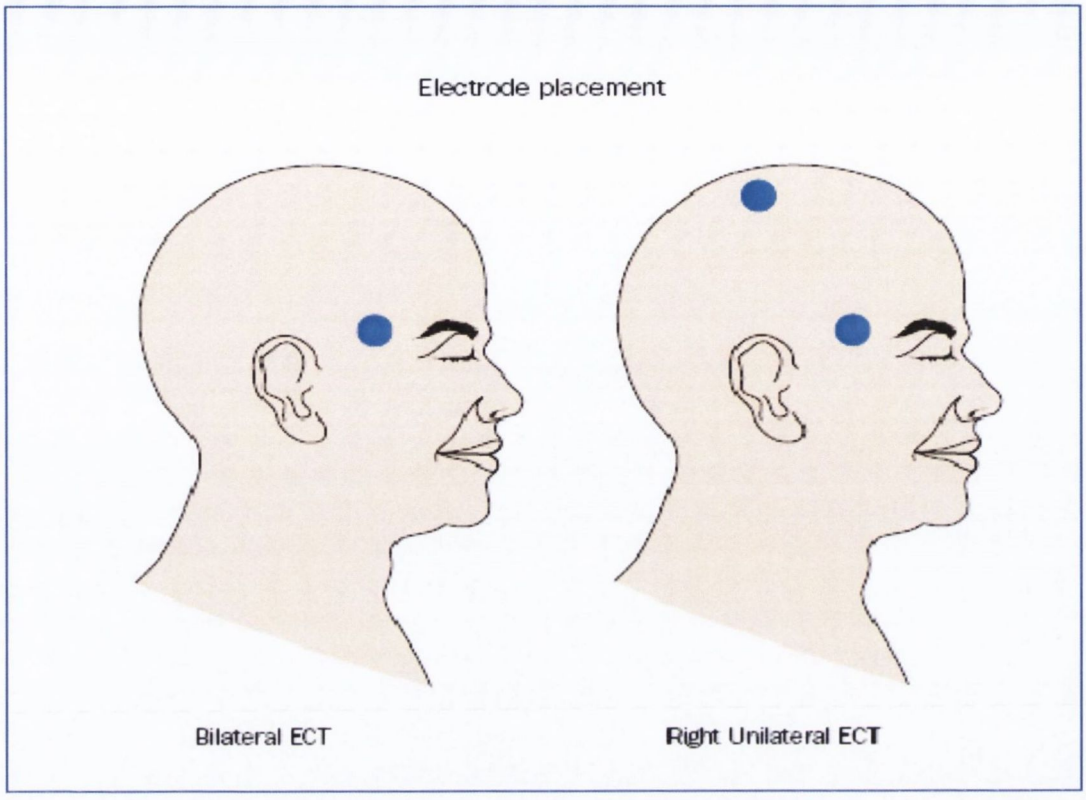
1.2.6 Electrode positioning

The comparative effectiveness of different positions of electrode placement has attracted considerable interest in recent years (Figure 1.2). Bitemporal ECT entails the application of one electrode to each temple (about 4 cm superior to the point midway between the outer angle of the eye and the auditory canal) and is currently the standard positioning of electrodes for ECT (Lisanby 2007a).

Unilateral ECT is an adapted version of the treatment used in an attempt to reduce potential adverse cognitive effects while maintaining the established effectiveness of bitemporal treatment. It is theorised that the electrical current does not pass through the language centre located in the left hemisphere when the right unilateral position is used and consequently reduces adverse cognitive effects (Kellner *et al.* 2010). One electrode is positioned on the temple of the non-dominant hemisphere (usually the right) in the same arrangement as in bitemporal ECT and the other is placed onto the vertex region just lateral to the midline on the same side of the head.

Data regarding the number of bitemporal and unilateral courses of ECT administered per annum are not collected in most countries. However, Scotland does collect such data: In 2010, 94% of ECT courses involved bitemporal and 13% were unilateral. There was a change in treatment modality (unilateral to bilateral) in 9% of ECT courses (NHS National Services Scotland 2011).

Figure 1. 2 Bitemporal and unilateral electrode placement (Kavanagh & McLoughlin 2009)



A recent meta-analysis found that bitemporal ECT is a more powerful antidepressant than unilateral ECT but it is associated with more cognitive side-effects (UK ECT Review Group 2003). However, the majority of unilateral studies analysed used less than adequate stimulus dosing. We now know that high-dose RUL ECT can be as effective as standard bitemporal ECT in terms of antidepressant effect: McCall and colleagues (2002) and Kellner and colleagues (2010) found no difference in remission rates between groups randomly allocated to receive high dose RUL or 1.5 × ST bitemporal ECT (McCall *et al.* 2002b; Kellner *et al.* 2010). However, we do not yet know if high dose RUL ECT will result in less adverse cognitive side-effects compared with 1.5 × ST bitemporal ECT. The majority of prescribing teams currently choose the established bitemporal placement with brief pulse stimulation because of the large evidence base demonstrating its effectiveness (Kavanagh & McLoughlin 2009).

1.2.7 Mechanism of action

There is not a clear understanding of the pathophysiology of mood disorders (Belmaker & Agam 2008). However, understanding the mechanism of action of effective treatments, like antidepressant drugs and ECT, is likely to be informative also about the neurobiology of depression (Krishnan & Nestler 2008). There is evidence from animal models of ECT that repeated administration of ECT is needed to entrain a series of molecular and structural changes within the brain that are thought to be relevant to its antidepressant effect (Malberg *et al.* 2000b). Important changes include upregulation of neuronal growth factors, such as brain derived neurotrophic factor (BDNF), that enhance neuronal survival and plasticity or the way that neurones can adapt to strengthen the way they connect with one another. Another important finding is that ECT increases neurogenesis (i.e. new nerve cells formation) in the adult hippocampus, a region of the brain that is involved in mood regulation and memory. Antidepressant drugs have similar effects but to a lesser extent than ECT (Hanson *et al.* 2011).

1.2.8 ECT in Ireland

The Mental Health Commission (MHC) provides a Code of Practice for ECT (Mental Health Commission 2009a) as well as Rules (Mental Health Commission 2009c) for when ECT is used for persons detained in hospital under the provisions of the Mental Health Act 2001. The MHC also gathers and reports ECT related information for Ireland (Mental Health Commission 2006b). ECT was used by 24 out of 66 approved centres and 2 out of 8 independent centres in Ireland in 2009. There were 373 programmes of ECT administered to inpatients in approved centres; comprised of 2,672 treatments administered to 362 people (some people had multiple programmes). This represents a rate of 8.8 programmes per 100,000 of the population (Mental Health Commission 2009b). 89% of

these programmes were administered on a voluntary basis. The most common diagnosis of patients referred for ECT was Depression (78%) (Mental Health Commission 2009b). See Figure 1.3 for the distribution of diagnoses referred for ECT in Ireland 2009.

The most common indications for ECT were: refractory to medication (47%), rapid response required (20.1%), a combination of two or more of the following indications - acute suicidality, maintenance ECT, physical deterioration and/ or rapid response required (20.4%) (Mental Health Commission 2006b) (Figure 1.4). Following a programme of ECT outcome was assessed objectively by the patients treating clinical team and recorded according to mental health commission guidelines. Improvement was the main reason for terminating ECT in nearly 85% of cases (Figure 1.5).

Figure 1. 3 Number of programmes of ECT per diagnosis 2009 (Mental Health Commission 2011)

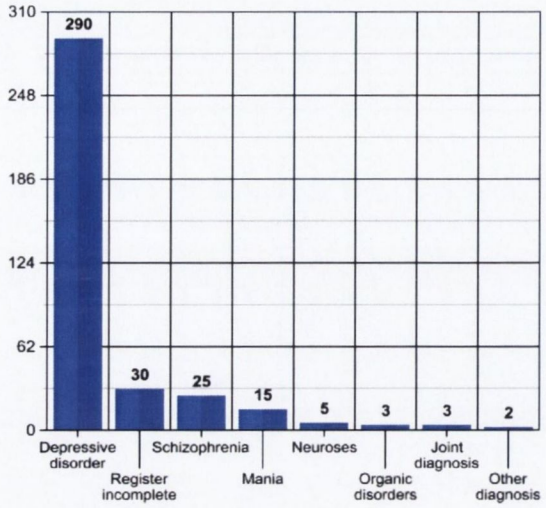


Figure 1. 4 Number of programmes of ECT per indication 2009 (Mental Health Commission 2011)

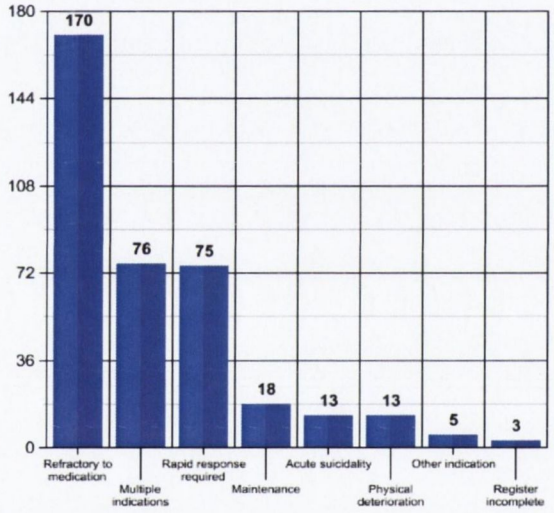
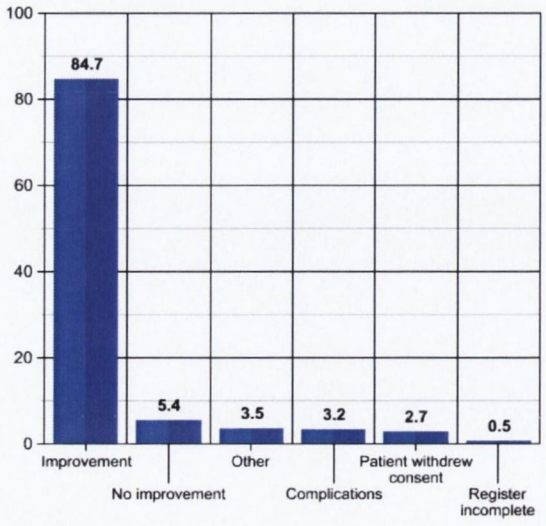


Figure 1. 5 Outcome at end of ECT as a percentage of programmes in 2009 (Mental Health Commission 2011)



1.2.9 Ethics of electroconvulsive therapy

Electroconvulsive therapy is a stigmatized medical intervention. Some believe it unethical to administer ECT in the belief that it is not an effective treatment and results in significant adverse effects (Barker 2011). Others view ECT as a safe, evidence based treatment, and that denial of its use for perceived unscientific reasons is unethical (Otto Ottosson & Fink 2004). An ethical framework is useful for evaluating these conflicting perspectives.

Beneficence states that clinicians should only ever act in the best interest of the patient (Gillon 1994). Actions and interventions should be based solely on evidence based research and not influenced by prejudice, superstition or tradition. Any discussion about the effectiveness of ECT should be grounded in evidence that reflects contemporary practice. Recent high quality evidence in the form of systematic review and meta-analysis demonstrates the antidepressant effectiveness of ECT in comparison to sham ECT and multiple classes of antidepressant pharmacological treatments (UK ECT Review Group 2003). The effectiveness of ECT for the acute treatment of severely depressed patients has a substantial evidence base that is difficult to counter (Section 1.2.4).

Non-maleficence or, do no harm, is also a core principal of medical ethics (Gillon 1994). The clinician must evaluate interventions to ensure that they are not only effective but also do no harm. In reality, treatments often carry the risk of some harm in some form. Chemotherapy for cancer treatment is an example. Thus, non-maleficence often means to reduce the risk of harm as much as possible. In this case beneficence can outweigh non-maleficence but again evidence based decisions are essential to adequately evaluate this cost-benefit analysis. The physical risks of ECT have been eliminated to such an extent that systemically ill, the pregnant and the elderly can be safely treated (Otto Ottosson & Fink 2004). It is more appropriate to consider non-maleficence in the context of cognitive

impairment which may well be a feature (Semkovska & McLoughlin 2010). There are three types: post-ictal disorientation is transient lasting less than 40 minutes in the majority of cases with no longer lasting effects (Sobin *et al.* 1995). In over 95% of cases anterograde memory impairment and a wide spectrum of other cognitive variables improve to at least pre-treatment levels within two weeks of treatment course end, and many aspects of cognitive functioning improve beyond pre-treatment levels (Semkovska & McLoughlin 2010). Retrograde amnesia is reported (Rose *et al.* 2003) but poorly measured because of a lack of standardized measures, studies with control groups and normative data (Semkovska & McLoughlin 2010). Moreover, as yet it has not been possible to measure the extent of retrograde amnesia because of an inability to separate the confounding effects of depression on memory that is correlated with symptom intensity (Fraser *et al.* 2008). In all cases ECT is indicated because the potential benefits outweigh any potential for harm.

Autonomy indicates a respect for an individual's choice (Gibson 1993). Less than 11% of patients treated with ECT in Ireland in 2009 were treated under mental health legislation (Mental Health Commission 2011). ECT practitioners have called for clear capacity legislation to further protect the autonomy of the patient (Dunne *et al.* 2009). When ECT is prescribed the Mental Health Commission Code of practice (Mental Health Commission 2009a) states that the prospective patient be told about the nature of ECT, description of the process, purpose of treatment, intended benefit, possible consequence of not having ECT and treatment alternatives. Information is provided on the likely adverse effects of ECT, including the risk of cognitive impairment and the risk of amnesia and other potential side effects (Mental Health Commission 2006b). Clear and simple information is provided in both oral and written forms. The patient referred for ECT consents to not only the course of ECT but also provides written consent for each individual treatment.

Justice requires that equal opportunity for medical care be available to all (Gibson 1993). Access to health care should be available irrespective of environmental, personal, social or professional qualities or concerns. Access to treatments with an established high quality evidence base should be available to all persons.

1.3 Side effects of electroconvulsive therapy

There is a considerable evidence base in the scientific literature examining the potential adverse effects associated with electroconvulsive therapy. These can be divided into adverse physical effects and adverse cognitive effects.

1.3.1 Physical effects of electroconvulsive therapy

ECT is a medically low-risk procedure (Tess & Smetana 2009). ECT is ten times safer than childbirth (Abrams 1997). Abrams (1997) argues that the mortality rate associated with ECT is ten times safer than childbirth because he compares the mortality rate associated with childbirth with that of ECT. In the United States, the maternal death rate was 21 maternal deaths per 100,000 live births in 2010 (Central Intelligence Agency 2012). The mortality rate associated with ECT is less than two deaths per 100,000 treatments (Shiwach *et al.* 2001). In terms of patients treated rather than the number of treatments; Scarano et al (2000) found the two-week mortality rate per patient treated was 10 deaths/10,000 patients treated (Scarano *et al.* 2000). Apart from raised intracranial pressure, there are no absolute contraindications for ECT (Datto 2000) and it may be tolerated better than pharmacotherapy, and perhaps more so in the elderly (Manly *et al.* 2000). However, ECT is rarely administered within 3 months of a myocardial infarct or cerebrovascular accident. There are certain risk factors that need to be taken into account (Datto 2000) and it is essential that pre-existing cardiovascular risk factors are identified

and treated before, during and after ECT (Zielinski *et al.* 1993; Rice *et al.* 1994). There are two types of potential adverse physical effects: intra-treatment effects such as any cardiac or respiratory event that may potentially occur during treatment and post treatment adverse effects such headache, nausea or muscle aches.

1.3.1.1 Intra treatment adverse effects

ECT-induced generalised tonic-clonic seizures are hypermetabolic states that have a dramatic effect on blood pressure and heart rate (Sackeim *et al.* 1986a; Tess & Smetana 2009). The administration of the electrical pulse stimulates the vagus nerve which produces a parasympathetic response that is characterised by increased vagal tone that reduces heart rate (Tess & Smetana 2009). A rebound sympathetic response is evident in surges of catecholamines during and after the seizure (Tess & Smetana 2009). These reactions result in dramatic effects on heart rate such as bradycardia or even a brief period of aystole when electrically stimulating the brain results in vagus nerve stimulation prior to the seizure and hypertension or tachycardia during and after the seizure (Tess & Smetana 2009). If they occur, cardiac arrhythmias, tachycardia and hypertension normally resolve unaided but occasionally require intervention such as a β-blocker (Tess & Smetana 2009), e.g. metoprolol.

There is some evidence that vagal response may be sensitive to dose and electrode placement. Nagler et al (2010) found a significantly greater proportion of patients treated with unilateral ECT developed asystole compared to patients treated with bifrontal placement. This study demonstrates that different electrode placements can produce different cardiac response. This is probably due to the longer distance of the electrode to the vagus nerve during stimulation. There is therefore potential that electrode placement or stimulus intensity will influence the physical response to ECT and the rate and type of

adverse physical effects such as cardiac arrhythmias, tachycardia or hypertension that require medical intervention in this study.

1.3.1.2 Post treatment adverse effects

The most common post ECT side effects are headache, nausea or muscle aches (Royal College of Psychiatrists 2005). Little evidence is available regarding the influence of electrode placement and stimulus intensity on the incidence of these potential side effects (Fleminger *et al.* 1970; Gomez 1975; Sackeim *et al.* 1987c). In one randomized trial comparing electrode placements, headaches, nausea and muscle aches were reported in 36%, 29% and 15% of the total sample respectively when assessed later the same day as treatment (Sackeim *et al.* 1987c). Headaches and nausea occurred more frequently in patients treated with RUL ECT compared with bitemporal placement (Sackeim *et al.* 1987c). Conversely, another randomized trial comparing electrode placements found that bitemporal placement reported greater rates of headaches, nausea and longer time to reorientation (Fleminger *et al.* 1970). Assessment in this study was conducted prior to second and fourth treatment.

These studies used doses just above ST (Sackeim *et al.* 1987c) and at predetermined fixed doses (Fleminger *et al.* 1970) so do not reflect current ECT practice. However, this evidence establishes the type of physical side effects that can occur in the post ECT period and that different electrode placements may produce different rates of these side effects. There may be no difference in the effectiveness of ECT in terms of antidepressant effect using bitemporal or right unilateral placement administered at optimum stimulus intensities. However, Fleminger et al (1970) found the degree of physical side effects and/ or time to reorientation influenced patients' acceptance of further

ECT and so choice of which placement to use may therefore depend on other factors such as physical side effects for example.

1.3.2 Adverse cognitive effects of electroconvulsive therapy

As discussed previously the primary concern with ECT is adverse cognitive effects; especially memory impairment (Rose *et al.* 2003). People may experience anterograde amnesia (difficulty forming new memories). This normally resolves within three days of the ECT course ending and in many cases cognitive functioning is superior to pre-treatment functioning within two weeks of treatment course end (Lisanby 2007a; Semkovska & McLoughlin 2010). Retrograde amnesia may also occur (this is loss of ability to retrieve memories formed before the onset of treatment). Retrograde amnesia also improves as time from the end of treatment increases but some people complain of persistent retrograde memory impairment. These areas continue to be the subject of research interest but one aspect of the adverse cognitive effect profile of ECT that has not been adequately examined is post ictal disorientation.

1.3.2.1 Time to recovery of orientation

As with an epileptic seizure, where there is amnesia for the ictal event and post-ictal disorientation (Engel 1996), there is a well-documented but usually brief period of post-ictal disorientation following ECT (Calev *et al.* 1991a). This feature is the most striking adverse effect of ECT and prolonged disorientation (defined as disorientation lasting more than 90 minutes (Sobin *et al.* 1995; Sackeim *et al.* 2000; Sackeim *et al.* 2008) is considered a significant adverse cognitive effect (Royal College of Psychiatrists 2005). Prolonged disorientation can occur in approximately 2% of patients treated with high dose right unilateral ECT (6×ST) and 13% of patients treated with high dose (2.5×ST) bitemporal ECT (Sackeim *et al.* 2000). Prolonged acute disorientation immediately following treatment may be associated with persistent amnestic side effects (Sobin *et al.* 1995). While it is unlikely that prolonged disorientation following ECT is responsible for persistent amnestic side effects, the same factors producing one may be involved in producing the other (Sobin *et al.* 1995). Therefore, reduced time to reorientation is not only a desirable objective in its own right (Loo *et al.* 2008) but may contribute to reductions in persistent amnestic side effects (Sobin *et al.* 1995).

There is considerable variation in time to recovery of orientation following ECT and this is dependent upon treatment parameters (Sackeim *et al.* 1986b; Sackeim *et al.* 1993; Sackeim *et al.* 2000; Sackeim *et al.* 2007; Sackeim *et al.* 2008) and patient factors (Fraser & Glass 1978; Sobin *et al.* 1995; Sackeim *et al.* 2007).

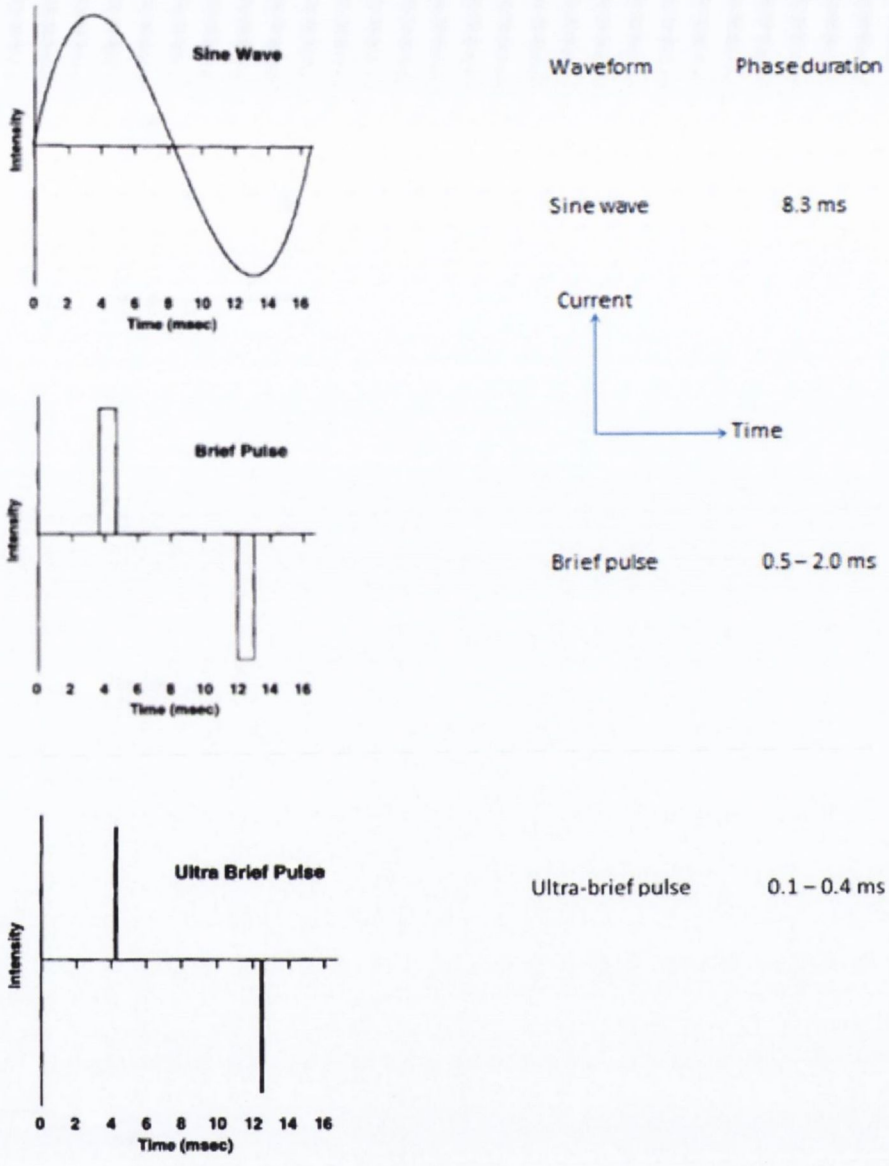
1.3.2.1.1 Treatment parameters

There are multiple ECT treatment parameters that influence time to recovery of orientation independently and potentially in combination with each other.

1.3.2.1.2 Stimulus waveform

Three types of electrical stimulus waveform have been used in ECT: sine wave, brief pulse (BP) and ultra-brief pulse (UBP) (Sackeim *et al.* 1994) (Figure 1.6). Outmoded sine wave is slow to reach peak stimulation and has an unnecessarily long duration, approximately 8.3 milliseconds, while it is suggested that optimal current duration is 0.1 to 0.2ms (Sackeim *et al.* 1994). Sine wave is too slow inducing the seizure and much of the stimulation is administered after the point of usefulness (Stein *et al.* 2005). Brief pulse reaches peak intensity almost immediately and delivers within 2 milliseconds. BP is as effective as sine wave in terms of antidepressant effect (Valentine *et al.* 1968; Carney 1976; Andrade *et al.* 1988; Scott *et al.* 1992) but has significantly reduced the extent of adverse cognitive effects (Valentine *et al.* 1968; Carney 1976; Weiner & Coffey 1986). UBP is a pulse with shorter width (0.1 to 0.4 milliseconds) than standard BP (0.5 to 2ms). It is theorized that UBP is more efficient still than BP and will further reduce adverse cognitive effects (Loo *et al.* 2007; Loo *et al.* 2008) but this is the subject of further investigation (Loo 2011).

Figure 1. 6 Examples of stimulus waveforms (American Psychiatric Association 2001)



Graphics adapted from: The Practice of Electroconvulsive Therapy: Recommendations for Treatment, Training, and Privileging 2001:140.

1.3.2.1.3 Laterality

It has been consistently demonstrated that time to reorientation is longer for bitemporal than RUL ECT at predetermined fixed doses and doses administered at seizure threshold (Fraser & Glass 1978; Sackeim *et al.* 1986a; Shapira *et al.* 1987). This is also true when laterality is alternated on consecutive treatments (Fraser & Glass 1978). One trial reported that patients treated with high dose bitemporal ECT (2.5 × ST) recovered orientation in approximately 45 minutes while patients treated with high dose right unilateral ECT (6 × ST) recovered orientation in approximately 30 minutes (Sackeim *et al.* 2000). One randomised trial has compared time to recovery of orientation for bitemporal ECT administered at 1.5 times ST with high dose right unilateral ECT administered at 6 times ST administered thrice weekly (Kellner *et al.* 2010). No significant difference was found between groups. These data need further examination since this trial had a significant rate of attrition (total N = 237, total attrition = 26%), especially for the high dose RUL group (attrition rate = 37.5%). This trial also adopted an unusual method of assessing reorientation relative to the majority of previous work in this area: this trial scored the number of questions answered correctly at 20 minutes (rather than asking participants to answer a set of reorientation questions throughout the recovery period and defining reorientation as the ability to answer 4 out of 5 questions correctly) and defined reorientation as the time the person was able to get up and walk (Kellner *et al.* 2010). No trial has yet examined recovery of orientation when ECT is administered twice weekly which is the norm in Ireland and Europe.

1.3.2.1.4 Stimulus intensity

Seizure threshold is higher in RUL ECT compared with bitemporal ECT (Sackeim *et al.* 1993). In 1982, Robin & De Tissera concluded that the minimum amount of electricity needed for optimum therapeutic effect was greater than the patient's established ST (Robin & De Tissera 1982). The percentage above ST that ECT is most therapeutically effective is also different for different electrode placements. In this regard, greater stimulus intensity for respective placements may produce longer time to recovery of orientation but this has not been conclusively demonstrated (Carney 1976; Calev *et al.* 1991a).

1.3.2.1.5 Total number of treatments

Total number of treatments is significantly related to adverse cognitive effects at course end and this effect may persist beyond six months for patients treated with bitemporal placement but not for right unilateral placement (Sackeim *et al.* 2007). However, there is no evidence of the effect of additional treatments on recovery of orientation. Current guidelines suggest that patients should be assessed after each treatment to establish the necessity for further treatments (Royal College of Psychiatrists 2005).

1.3.2.1.6 Frequency or interval between treatments

In the United States, treatment three times a week is common, while in Europe twice weekly treatment is standard practice (Lerer *et al.* 1995). ECT twice or three times a week produces the same level of antidepressant effect by course end (Shapira *et al.* 1998). However, while ECT three times a week may produce a more rapid initial response, it will contribute to more significant cognitive side-effects by course end (Lerer *et al.* 1995; Shapira *et al.* 1998). Treatment three times per week is used in America as it is theorized

that the increased treatment schedule is associated with quicker symptomatic recovery (American Psychiatric Association 2001).

1.3.2.1.7 Seizure duration

The effect of seizure duration on time to reorientation has not been well studied. However, Calev et al (1991) found seizure duration correlated with time to recovery of orientation that was independent of stimulus intensity and patient characteristics (Calev *et al.* 1991a).

1.3.2.1.8 Patient characteristics and cognitive side-effects

There is also considerable variability is patient factors that may increase vulnerability to adverse cognitive effects and produce significant differences in recovery times (Sobin *et al.* 1995). Research has been unable to determine patient characteristics that might predispose people to longer periods of post-ictal disorientation or delirium (Devanand *et al.* 1989). There is some evidence that older patients are more at risk but this has not been conclusively demonstrated (Fraser & Glass 1978). Poor pre-treatment global cognitive function (Sobin *et al.* 1995), lower pre-morbid intellectual function (Sackeim *et al.* 2007), lower baseline (as opposed to pre-morbid) intelligence, and the presence of psychotic symptoms (Calev *et al.* 1991a), have all been implicated with longer time to reorientation following ECT. It is possible that a greater severity or number of these features combined indicates poorer cognitive functioning that may contribute to produce longer times to reorientation.

Sackeim et al (1987) found a difference in time to reorientation associated with gender (Sackeim *et al.* 1987a) but others did not (Calev *et al.* 1991a). If a difference does exist, it is possibly related to the lower ST in women but this has not been confirmed (Sackeim *et al.* 1987a). Female gender has also been found to be associated with greater cognitive deficits in other areas such as persistent retrograde amnesia following ECT which may support a potential relationship between sex and time to reorientation (Sackeim *et al.* 2007). However, a non-standardized measure of retrograde amnesia was used to reach this finding and further evidence is required to substantiate it (Sackeim *et al.* 2007). Calev et al (1991) found baseline level of depression did not correlate with change in post-ictal disorientation time. However, Hamilton Depression Rating Scale change score correlated with time to recovery of orientation, i.e. the longer the time to reorientation the greater the improvement in depression (Calev *et al.* 1991b). The finding that there may be a relationship between time spent disorientated following ECT and extent of recovery from depression requires further scrutiny.

Due to the heterogeneity of patient and treatment factors that interact to contribute to adverse cognitive effects there is inadequate knowledge to predict which patients are most vulnerable to prolonged disorientation following ECT (Royal College of Psychiatrists 2005). The Royal College of Psychiatrists advise prescribing teams that they must do all that is possible to reduce the acute adverse effects of ECT that influence the patients experience of ECT and the presence of severe or persistent adverse cognitive effects (Royal College of Psychiatrists 2005).

In summary, ECT is a very effective and medically safe procedure. There are however some adverse physical effects that can occur during and after treatment and there is a lack of knowledge about the factors that contribute to produce these. Although potential adverse physical effects related to ECT are not fatal, they may influence the

overall adverse effect profile of ECT, the choice of laterality to prescribe (assuming both placements are equally effective), the patient's experience of ECT and the likelihood of patients accepting further treatment when indicated. The primary concern with ECT is actually adverse cognitive effects. Post ictal disorientation is one type of adverse cognitive effect that is little studied. The evidence presented clearly describes the treatment factors that influence time to recovery of orientation. Equally, the lack of understanding of the patient characteristics that increase vulnerability to adverse cognitive effects is highlighted. There is little evidence comparing time to recovery of orientation following ECT administered at contemporary treatment doses and twice weekly frequency.

1.4 Physical functioning and depression

There is substantial evidence demonstrating the impact of depression, as an illness in its own right, on physical (Wells *et al.* 1989; Wells *et al.* 1992; Hays *et al.* 1995), social (Leader & Klein 1996; Rhebergen *et al.* 2010), and occupational functioning (Broadhead *et al.* 1990; Johnson *et al.* 1992; Conti & Burton 1994; Kessler & Frank 1997) and cognitive functioning (Butters *et al.* 2004b; McDermott & Ebmeier 2009). In general, recurrent major depression is not associated with more disability in functional ability than a single episode of major depression (Kruijshaar *et al.* 2003). There is a considerable evidence base demonstrating the impact depression can have on ability to perform basic and instrumental activities of daily living (ADL) in the medically unhealthy, the elderly and those recovering from illness (Chemerinski *et al.* 2001; Graf 2008a; Schram *et al.* 2009). However, little research has focused on the impact of depression on ability to perform basic and instrumental ADL in otherwise medically healthy, non-infirm people.

Basic activities of daily living are those skills needed in typical daily self-care, e.g. bathing, dressing, feeding and toileting (McCall *et al.* 2002a). Instrumental activities of daily living are life skills beyond basic self-care and refer to activities that require independence, volition and organization (Katz 1983; Lawton 1988). Instrumental ADLs include domestic tasks such as driving, cleaning, cooking and shopping, etc. (McCall *et al.* 2002a). These areas are of specific interest because: (1) depressed persons referred for ECT have worse functioning in basic and instrumental ADLs than those not referred for ECT (McCall *et al.* 1999b) and (2) basic and instrumental ADL are essential to independent living such that less than optimal recovery from depression in these aspects of functioning are predictive of relapse (Conradi *et al.* 2008).

1.4.1 Performance of basic and instrumental activities of daily living

Deficits in basic and instrumental ADL increase risk of depression (Conradi *et al.* 2008), reduce a person's ability to live independently, limit recovery from depression and increase the risk of relapse in those recovering from depression (Conradi *et al.* 2008). Depression normally produces significantly more impairment in ability to perform IADL than basic ADL (McCall *et al.* 1999b; McCall *et al.* 2001; McCall *et al.* 2002c; McCall & Dunn 2003). The cognitive effort hypothesis may explain this - depression interferes more with effortful tasks requiring additional cognitive capacities than with automatic processes, that are less cognitively demanding (Hammar *et al.* 2010). The finding by McCall and Dunn (2003) that performance of ADL was related to severity of depression while performance of IADL was associated with cognitive status but not the depressed mood state would seem to support this hypothesis (McCall & Dunn 2003). As such, treatments that produce symptomatic recovery will counter the effects of depression on ability to perform basic ADL but ability to perform IADL is dependent upon cognitive function. As

such, the impact of depression or related treatments on cognitive function may have considerable implications for performance of IADL. Treatments that preserve or enhance global cognition while relieving symptoms of depression would lead to the best functional outcomes (McCall & Dunn 2003). While McCall and Dunn (2003) found that ability to perform IADL was associated with global cognitive function (McCall & Dunn 2003), Bell-McGinty et al (2002) found executive function the specific aspect of cognitive function most accurate in predicting deficits in ability to perform IADL in older adults (Bell-McGinty *et al.* 2002).

1.4.2 Impact of ECT on performance of basic and instrumental activities of daily living

Remission from depression produces improved functioning and better prognosis (Rush *et al.* 2006). It has been proposed that while ECT may produce symptomatic remission, functional recovery may be limited by adverse cognitive effects (McCall *et al.* 2004). However, some observational evidence has demonstrated a positive effect on recovery of ability to perform basic and instrumental ADL (McCall *et al.* 2001; McCall *et al.* 2002c; McCall & Dunn 2003) and in some cases ECT treated patients show at least the same level of recovery in these areas than non-ECT treated patients (McCall *et al.* 2001).

It is also not yet known if different types of ECT result in different degrees of recovery of functioning. Recent investigation has found that high dose RUL ECT can be as effective as 1.5 × ST bitemporal ECT in terms of anti-depressant effect (Kellner *et al.* 2010) but there is still no consensus regarding the adverse cognitive effect profile of the comparative placements. There is potential that high dose RUL ECT may result in less of an impact on executive function and therefore superior performance of basic and

instrumental functioning. This may have a significant impact on recovery of functioning, sustained remission and recovery.

The majority of evidence is based on results from trials from the USA where right unilateral ECT has been administered at less than optimum stimulus doses and invariably bitemporal ECT was administered at supra-maximal stimulation and three times weekly (McCall *et al.* 1999a; McCall *et al.* 2001; McCall *et al.* 2002a; McCall *et al.* 2004). There is thus a need for evidence regarding the impact of both electrode placements, administered at optimal stimulus intensities, and administered twice weekly, on recovery of ability to perform basic and instrumental functioning.

1.5 Health related quality of life, depression and ECT

Health is just one aspect of QOL (Cummins 1997). HRQOL is a multidimensional concept that is subjective and people can report a varying state of HRQOL depending upon their perception of ill-health and intervention. As such, HRQOL is well defined as; "those attributes valued by patients, including their resultant comfort or sense of wellbeing; the extent to which they were able to maintain reasonable physical, emotional, and intellectual function; and the degree to which they retain their ability to participate in valued activities within the family, in the workplace, and in the community" (Wenger & Furberg 1990).

1.5.1 The impact of depression on HRQOL

Depression is associated with significant impairment in HRQOL compared to a healthy population and the effects are more pronounced than the negative impact of many medical conditions (Hays *et al.* 1995; Murray & Lopez 1997a, 1997b). Major depression directly impacts HRQOL across multiple domains (Trivedi *et al.* 2006; Reed *et al.* 2009)

and severity of depression correlates with all domains of HRQOL independently of what outcome measure is used (Trivedi *et al.* 2006). While this is so, factors other than severity of depression also play a significant role in deficits in HRQOL and subsequent improvement: HRQOL can improve independently of remission from depression (Hirschfeld *et al.* 2002) while it has also been found that remission from depressive symptoms does not always produce a concomitant improvement in HRQOL (Simon *et al.* 1998). Factors such as age, sex, culture, age at onset of illness, marital status, education and life experience affect one's perception of the impact of illness (Trivedi *et al.* 2006).

1.5.2 Electroconvulsive therapy and HRQOL

The Health Technology Assessment that informed the National Institute for Health and Clinical Excellence (NICE) 2003 guidelines on ECT found that no trial had explored the impact of ECT on quality of life. NICE also reported that no research had "adequately captured either users' views or quality of life" evidence (National Institute for Health and Clinical Excellence 2003; Greenhalgh *et al.* 2005). NICE published further guidelines on the treatment of depression in 2009 that deal specifically with ECT and its lack of any mention of new QOL evidence since the original 2003 guidance highlights the continuing need for HRQOL evidence to inform future guidance (National Institute for Health and Clinical Excellence 2009).

Since the original NICE report there has been an effort to address this gap in our knowledge. However, many of the reports are characterised by small sample sizes (n = 45 for example) (Lapid *et al.* 2010), use of poor outcome measures to assess QOL (McCall *et al.* 2004), assessment conducted at time-points in the follow-up period that have not allowed participants to engage with activities related to HRQOL (e.g. 24 hours after end of treatment course) (Antunes & Fleck 2009), heterogenic methods of ECT administration

and a lack of a definition of the concept of interest: HRQOL (McCall *et al.* 2004; Antunes & Fleck 2009; Lapid *et al.* 2010).

Current evidence suggests that the initial restricted guidelines from NICE on the use of ECT may have been excessive and indeed they have reduced slightly in the 2009 guidelines (National Institute for Health and Clinical Excellence 2009) because of new data to inform the use of maintenance ECT (Kellner *et al.* 2006). ECT has the potential to produce transient adverse cognitive effects that in the vast majority of cases return at least to baseline level within two weeks of finishing treatment (Semkovska *et al.* 2010; Semkovska & McLoughlin 2010). These adverse cognitive effects can occur independently of antidepressant effect (Sackeim *et al.* 1993) and it has been suggested that they could limit recovery of HRQOL (McCall *et al.* 2004). However, there is not only evidence that failure to remit with ECT is not associated with any deterioration in HRQOL relative to pre-treatment (Kellner *et al.* 2006; McCall *et al.* 2006), but it has been repeatedly demonstrated that ECT produces net improvements in HRQOL that are sustained over time (McCall *et al.* 2001; Fisher *et al.* 2004; McCall *et al.* 2006; Antunes & Fleck 2009; Lapid *et al.* 2010). In fact, some observational evidence of ECT treated patients report greater recovery of HRQOL compared with non-ECT groups (McCall *et al.* 2001; Fisher *et al.* 2004).

The future role of ECT in an evidence-based hierarchy of treatment alternatives is dependent upon empirical evidence (Rosenquist *et al.* 2006). There is potential that high dose RUL ECT may produce less adverse cognitive effects than 1.5 × ST bitemporal ECT and in turn lead to a superior outcome in HRQOL. Evidence such as this may not only optimise ECT treatment further but also contribute to a more positive perception of ECT from patients' and others (Besani *et al.* 2011).

1.6 Attitudes towards electroconvulsive therapy

Despite over 70 years of continued use and a substantial anthology of evidence demonstrating antidepressant effect, ECT continues to be one of the most provocative treatments in medicine (Fink 2001a, 2001b; Dowman *et al.* 2005). The overuse of ECT as a treatment when there were few effective alternatives, sensationalized negative media portrayals of ECT in representations such as *One Flew Over The Cuckoo's Nest,* the lack of a definitive understanding of the mechanism of action of depression and ECT and fears about the nature of electricity have contributed to the stigma that surrounds ECT (Kavanagh & McLoughlin 2009; Chakrabarti *et al.* 2010). This stigma undermines public acceptance of ECT (Chakrabarti *et al.* 2010) and fear and lack of contemporary knowledge may be inhibiting the uptake of ECT for those suffering major depressive disorder or treatment-resistant depression in terms of the likelihood of its prescription and likelihood of acceptance when prescribed (Kavanagh & McLoughlin 2009; Chakrabarti *et al.* 2010).

ECT attitudes research is concerned with more than just the level of positive or negative opinion ECT-treated patients have towards ECT. The subjective experience of ECT, patient's knowledge about ECT, the level of information given to prospective ECT patients, their capacity to consent, perceived coercion, informed consent and experience of adverse effects are all subjects of interest in ECT attitudes research.

1.6.1 Knowledge about electroconvulsive therapy

There is no disagreement that the attitudes of service users must inform ECT administration and standards of care (ECTAS 2005-2007). Knowledge of a subject is a key influencing factor of one's attitude towards it. For example, level of knowledge about ECT among healthcare professionals is positively related to their attitude towards ECT (Janicak *et al.* 1985b; Gass 1998). The same relationship is true among lay people (Besani

et al. 2011). It is reasonable to assume the same relationship among ECT patients and some research has focused on this (Freeman & Kendell 1980; Hughes *et al.* 1981; Baxter *et al.* 1986; Benbow 1988; Malcolm 1989; Riordan 1993; Walter *et al.* 1999; Taieb *et al.* 2001; Tang *et al.* 2002; Bustin *et al.* 2008). There is a trend that patients know about the major aspects of ECT such as the induction of a seizure, the use of anaesthesia and the use of electricity but patients are much less likely to know about the indications for ECT, potential adverse effects or mechanism of action for example (Rose *et al.* 2003; Chakrabarti *et al.* 2010).

1.6.2 Information prior to treatment

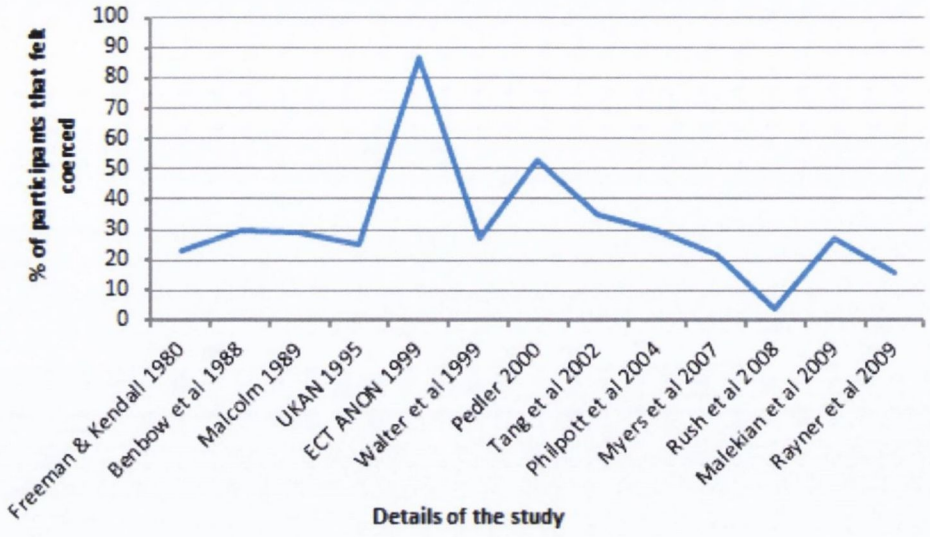
Consent to medical treatment can only be considered valid once the prospective patient has been given adequate information to make an informed voluntary decision (Appelbaum 2007). A number of studies asked participants if they felt they were given adequate information prior to commencing treatment (Freeman & Kendell 1980; Hughes *et al.* 1981; Baxter *et al.* 1986; Malcolm 1989; Szuba *et al.* 1991; Jenaway 1993; MIND 1995; Sestoft *et al.* 1995; UKAN 1995; Walter *et al.* 1999; Wheeldon *et al.* 1999; Taieb *et al.* 2001; Philpot *et al.* 2004; Sienaert *et al.* 2005; Myers 2007; Virit *et al.* 2007; Rush *et al.* 2008; Malekian *et al.* 2009; Rayner *et al.* 2009). Although there are some exceptions (Jenaway 1993; Rush *et al.* 2008), the majority of studies found patients dissatisfied. In 11 out of 20 available studies involving more than 1108 participants, greater than 50% of participants felt they were not given adequate information prior to commencing ECT (Freeman & Kendell 1980; Baxter *et al.* 1986; Szuba *et al.* 1991; MIND 1995; Sestoft *et al.* 1995; UKAN 1995; Wheeldon *et al.* 1999; Sienaert *et al.* 2005; Myers 2007; Virit *et al.* 2007; Malekian *et al.* 2009). The studies with the greatest satisfaction with information are those that used written information leaflets and were accredited with the Royal College of

Psychiatrists' ECT Accreditation Service (ECTAS) (Jenaway 1993; Rush *et al.* 2008; Rayner *et al.* 2009).

1.6.3 Perceived coercion

In Ireland and many other countries there is a defined consent process for ECT that requires the prescribing team to explain sufficiently the treatment process and obtain written informed consent from patients with capacity to do so (Dunne *et al.* 2009). A number of studies have asked if participants felt pressurised or forced to have ECT (Freeman & Kendell 1980; Benbow 1988; Malcolm 1989; UKAN 1995; ECT Anonymous 1999; Walter *et al.* 1999; Pedler 2000; Tang *et al.* 2002; Philpot *et al.* 2004; Myers 2007; Rush *et al.* 2008; Malekian *et al.* 2009; Rayner *et al.* 2009). Of these studies, Rush et al (2008) and ECT ANON (1999) found exceptionally low (4%) and high (87%) rates of perceived coercion respectively (ECT Anonymous 1999; Rush *et al.* 2008). Most studies however, found rates of perceived coercion of approximately 20-30%. A previous systematic review found similar rates of perceived coercion but Rose et al (2003) found a trend towards an increasing rate of perceived coercion over recent years (Rose *et al.* 2005). Current evidence that includes more recent studies suggests a decline in rates of perceived coercion in recent years (Figure 1.7).

Figure 1. 7 Percentage of participants that felt coerced to have ECT across multiple studies



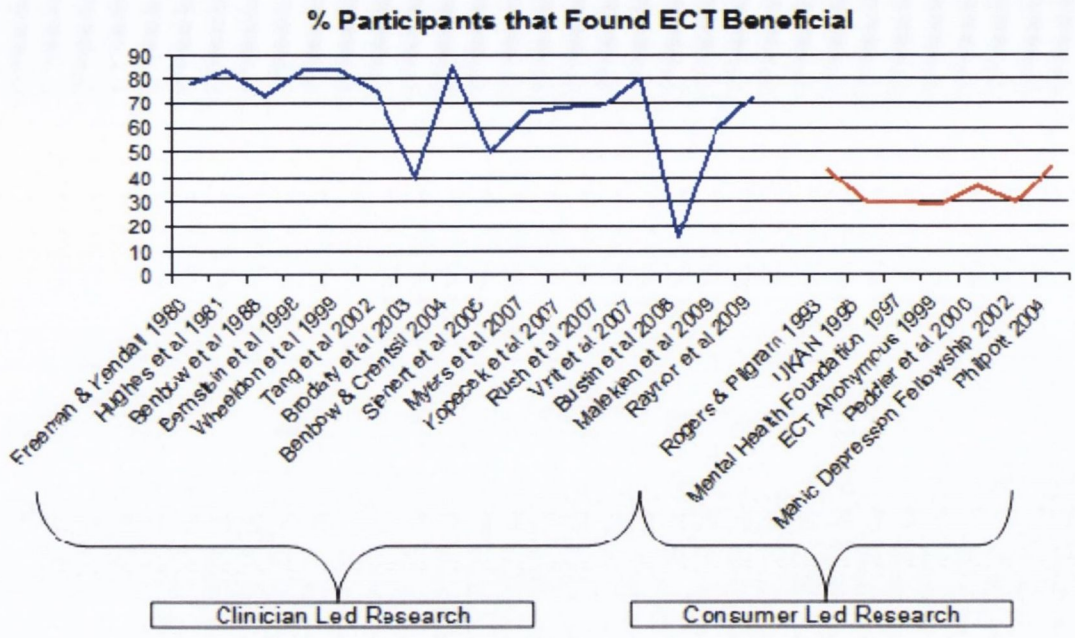
1.6.4 Perceptions of benefit

Although the effectiveness of ECT as an antidepressant treatment has been repeatedly demonstrated in clinical trials (UK ECT Review Group 2003), patients' perceptions of benefit are based on more than symptomatic relief (Chakrabarti *et al.* 2010). Attitudes towards ECT are likely to be based upon a complex cost-benefit analysis of the treatment, its effect and resultant adverse effects (Chakrabarti *et al.* 2010). As an indicator of general attitude towards ECT, studies ask participants if they feel they have benefited from treatment (Chakrabarti *et al.* 2010). Interestingly, responses appear to be polarised in relation to who is asking the question (Figure 8) (Rose *et al.* 2003). Clinician led research finds more favourable attitudes towards ECT than consumer led research (Rose *et al.* 2003; Myers 2007; Chakrabarti *et al.* 2010) (Figure 1.8). However, consumer led studies have been criticised as being open to selection bias in favour of selecting patients who are

antagonistic towards ECT (Rose *et al.* 2003; Chakrabarti *et al.* 2010). This criticism is based on the fact that these studies have not typically used rigorous research designs where all participants during a specified period of time had an equal opportunity of entering the study and answering the questions posed. The only prospective consumer led study conducted by a consumer group (at the Maudsley Hospital, London) reported a higher rate of patient satisfaction with ECT (Philpot *et al.* 2004) but it was still lower than reports from clinician led studies (Rose *et al.* 2003). Systematic analysis has found that other factors have a significant influence on the positivity of attitude of patients towards ECT (Rose *et al.* 2003). Assessments conducted in hospital, interviews conducted by the treating doctor or member of the treating team and studies that used an assessment of low complexity or conducted soon after the end of treatment are associated with more positive attitudes towards ECT (Rose *et al.* 2003).

Clinician-led studies also ask participants about their likelihood of having ECT again in the future. Consumer led studies tend not to ask this question with two exceptions (UKAN 1995; Philpot *et al.* 2004). There is a notable difference between the two consumer led studies: 20% of the UKAN sample and 60% of the Communicate participants would have ECT again if needed. Participants in clinician led studies were more willing to have ECT again in the future if needed with rates of 36-98%.

Figure 1. 8 Percentage of participants that found ECT beneficial across multiple studies



1.6.5 Attitudes towards adverse effects

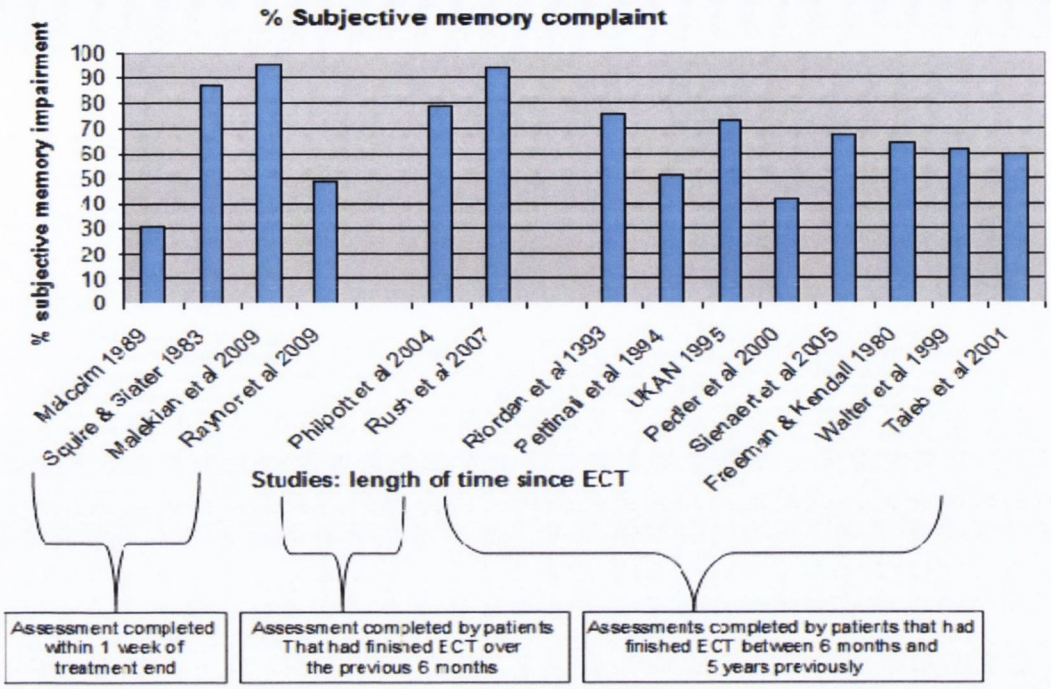
Few studies have examined the experience of adverse physical effects. When asked about "side effects" in the follow-up period after their course of ECT, patients have spontaneously reported: headaches (21%), no side effects (10%), tiredness (10%), stiffness and aches (5%) and nausea (3.6%) (Rayner *et al.* 2009). These adverse physical effects may be reported to a greater extent if questions are asked later same day as treatment: Sackeim et al (1987) found 36% of patients reported headaches, 44% reported tiredness, 29% nausea, 16% muscle pain and 16% reported other pain (Sackeim *et al.* 1987c).

Many studies have examined the subjective experience of adverse cognitive effects following ECT (Freeman & Kendell 1980; Malcolm 1989; Riordan 1993; Pettinati *et al.* 1994; UKAN 1995; Walter *et al.* 1999; Pedler 2000; Taieb *et al.* 2001; Philpot *et al.* 2004; Sienaert *et al.* 2005; Rush *et al.* 2007; Malekian *et al.* 2009; Rayner *et al.* 2009). There is

considerable variation in the question asked and the time between ending treatment and the assessment taking place. In general, participants are more likely to complain of memory impairment if the assessment is conducted in the week following treatment and in the majority of studies, more than 50% of participants complain of memory impairment. It also appears that as the time from the end of treatment increases, people are less likely to complain of memory impairment (Figure 1.9).

Attitude studies are needed because they examine the intervention and the outcome of treatment from multiple perspectives that are valued by patients. Attitude studies consistently convey that clinicians need to do more to inform prospective patients about ECT, especially about potential adverse effects. Through accreditation and best practice ECT clinics can increase rates of knowledge, information sharing and decrease rates of perceived coercion (Jenaway 1993; Rush *et al.* 2008; Rayner *et al.* 2009). More objective evidence of the perceived benefit of service users towards ECT over time is needed and more emphasis is needed on the subjective experience of adverse effects following ECT, in particular subjectively perceived memory impairment.

Figure 1. 9 Percentage of participants complaining of memory impairment following ECT



1.7 Objective

The objective of this study is to compare the effects of 1.5 × ST bitemporal ECT with high dose (6 × ST) RUL ECT on immediate recovery from treatment, longer term functional outcomes and quality of life, and attitudes of patients towards ECT.

This work is being conducted as part of the EFFECT-DEP Trial, a randomized controlled trial comparing the effects of 1.5 × ST bitemporal ECT with 6 × ST RUL ECT primarily on retrograde memory function, autobiographical memory and semantic memory.

1.7.1 Aims

I. To compare time to recovery of orientation immediately following treatment with bitemporal (1.5 x ST) and high dose (6 x ST) RUL ECT and to identify modifying factors.

II. To compare the incidence of adverse physical effects immediately following treatment with 1.5 x ST bitemporal ECT and high dose RUL ECT and to identify contributory factors.

III. To compare the impact of 1.5 x ST bitemporal ECT with high dose RUL ECT on performance of activities of daily living and to identify factors that influence functional recovery.

IV. To compare the long term effects of 1.5 x ST bitemporal ECT with high dose RUL ECT on health related quality of life (HRQOL) and to examine factors contributing to persisting deficits in HRQOL.

V. To compare patients' attitudes towards high dose RUL ECT with 1.5 x ST bitemporal ECT for major depression and identify factors contributing to positive and negative attitudes.

1.7.2 Hypotheses

The hypotheses that will be tested to achieve these aims are:

I. Time to recovery of orientation will be shorter with high dose RUL ECT (6 × ST) compared with standard (1.5 × ST) bitemporal ECT.

II. High dose RUL ECT will be associated with fewer complaints of physical side-effects immediately after ECT and there will be less of an impact on the physical effects immediately following treatment compared with bitemporal ECT.

III. High dose RUL ECT will be associated with superior performance of activities of daily living compared with 1.5 × ST bitemporal ECT.

IV. High dose RUL ECT six months after treatment will be associated with superior health related quality of life (HRQOL) compared with bitemporal ECT.

V. Patients' treated with high dose RUL ECT will have a more positive attitude towards ECT compared with those treated with bitemporal ECT.

2 Chapter 2 Materials and Methods

2.1 Materials

2.1.1 Demographic details

Demographic information was collected using a participant information sheet (Appendix 2). Information regarding age, education, weight, height and alcohol were used to present demographic details of the sample and for further statistical analysis.

2.1.2 ECT administration

ECT was administered with a Spectrum 5000m ECT device. Seizure duration was measured manually by recording duration of visible motor seizure activity in seconds and also by electroencephalography (EEG) recording.

2.1.3 Diagnostic assessment

2.1.3.1 The Structured Clinical Interview for DSM-IV (SCID-I)

The Structured Clinical Interview for DSM-IV Axis 1 Disorders (SCID-I) (First *et al.* 2005b) is a semi-structured interview developed to enable psychiatric diagnosis according to DSM-IV-TR criteria. The researcher version (SCID-I) includes additional information regarding specifiers and subtypes of illness (Biometrics Research Department 2012). It comprises nine diagnostic modules but it is appropriate to focus on those of relevance (First *et al.* 2005a). In this study the mood disorder component was used to confirm the diagnosis of depression and establish inclusion criteria were satisfied. Questions are asked that reflect DSM-IV criteria for specific disorders and are scored 1 = absent, 2 = subthreshold and 3 = present. Rather than accumulating a score the number of

responses coded 3 or 'present' are used to guide the interviewer towards a diagnosis. The SCID-I has demonstrated good test-retest reliability for diagnosing major depression (Lobbestael *et al.* 2011).

2.1.4 Treatment resistance

Participants were recorded as treatment resistant or not based on success or failure of pharmacotherapy or psychotherapy since the beginning of the current index episode of major depression. The criterion for treatment resistance was failure to achieve remission with psychotherapy and an adequate trial of a chemical antidepressant or two adequate trials of a chemical antidepressant for the current episode of depression. An adequate trial in terms of dose for individual antidepressant medications and duration of use before termination in order to be considered a failed trial followed published guidelines (Sackeim 2001).

2.1.5 Depression outcome

2.1.5.1 The Hamilton Depression Rating Scale

The Hamilton Depression Rating Scale (HDRS) (Guy 1976) was designed to measure the severity of depressive symptoms once a diagnosis has been made (Hamilton 1960). It is the most commonly used observer rated depression rating scale and is used to estimate symptom severity before treatment, to determine the effect of treatment and to identify relapse (McDowell 2006). Initially developed with 21 items, Hamilton recommended scoring only the first 17 because the remaining items occurred infrequently or were designed to be descriptors of depression rather than an indication of severity (e.g. depersonalisation and diurnal variation) (Williams 2001). The HDRS 24-item is the most

frequently used version in ECT research. It was designed for use by those with experience with psychiatric patients but can also be used by others trained in its use (McDowell 2006). The 24 item HDRS takes approximately 15-20 min to complete and consists of 24 questions with a score range of 0-77: higher scores indicate greater severity.

The HDRS 24-item demonstrates good concurrent validity with other observer rated instruments such as the Montgomery-Asperg Depression Rating Scale (MADRS) (Kearns *et al.* 1982). The HDRS 24-item is equally reliable when conducted in person or over phone (Potts *et al.* 1990). The HDRS 24-item demonstrates very good reliability when a structured interview is used: internal consistency scores measured with Cronbach's alpha are as high as ≥ 0.8 and inter-rater reliability scores on Cohen's kappa > 0.9 (Potts *et al.* 1990).

The HDRS has been criticised because it has been modified on multiple occasions where questions have been added without psychometric evaluation and because of an over-emphasis on somatic symptoms so those with co-morbid illness may score higher. However, the HDRS is sensitive to change and has been used extensively in ECT studies (Sackeim *et al.* 1987a; Sackeim *et al.* 1993; McCall *et al.* 2000; Sackeim *et al.* 2000; Sackeim *et al.* 2001; Kellner *et al.* 2006; Sackeim *et al.* 2007; Sackeim *et al.* 2008; Kellner *et al.* 2010).

2.1.5.2 The Beck Depression Inventory, second version

The Beck Depression Inventory (BDI) (Beck *et al.* 1961) was originally developed to identify depression and describe its severity (McDowell 2006). The BDI comprises a list of statements, created from the author's experience of psychotherapy with depressed people and the most common symptoms that arose, and a number of responses that indicate severity (Beck *et al.* 1961). Version two is a modified version that reflects DSM-IV criteria

for depression and extends the time-frame of concern to two weeks (Beck *et al.* 1996). It is a self-report questionnaire comprising twenty one questions and respondents are asked to select the response that best describes how they feel for that category and greater scores reflect greater severity of depression.

Internal consistency reliability has been repeatedly demonstrated and produces Cronbach's alpha scores > 0.80 (Beck *et al.* 1996). The BDI-II demonstrates good concurrent validity with the BDI I and clinical assessments such as the HDRS (McDowell 2006). The BDI is sensitive to change over time and is used regularly for research purposes.

2.1.6 Cognition

2.1.6.1 The National Adult Reading Test (NART)

The National Adult Reading Test (NART) (Nelson 1982) is commonly used in clinical settings for estimating premorbid intelligence. The NART is widely used in research settings and has been used in previous ECT research (Sackeim *et al.* 1993; Sackeim *et al.* 2000; Sackeim *et al.* 2007; Sackeim *et al.* 2008). Research has demonstrated that the correlation between NART scores and age 11 IQ is moderately high with a correlation coefficient of 0.60 (McGurn B. *et al.* 2004) supporting the use of the NART as a proxy for premorbid intelligence. The NART was completed in this study prior to each participant's first treatment.

2.1.6.2 The Addenbrooke's Cognitive Examination - revised edition (ACE-R)

The Addenbrooke's Cognitive Examination (ACE) was developed to be a brief assessment of cognition that could be completed without specialised equipment and to be administrable at the bedside (Mathuranath *et al.* 2000). The ACE incorporated the Mini Mental State Exam (Folstein *et al.* 1975) but expanded the assessment of memory, language, visuo-spatial components and added tests of verbal fluency to measure executive function (Mathuranath *et al.* 2000). The original ACE was a significant development for cognitive screening in dementia assessment: not only did it demonstrate very good sensitivity and specificity for detecting dementia with cut off values that show high positive predictive values, further analysis of the subgroups can differentiate between different types of dementia (orientation, attention, and memory are worse in Alzheimer's disease and letter fluency, language and naming are worse in fronto-temporal dementia).

The ACE was revised to make subgroup scoring formal, less emphasis was placed on memory to balance scoring across all domains and a maximum score of 100 is now calculated from attention/orientation (18 points), memory (26 points), fluency (14 points), language (26 points) and visuo-spatial (16 points). In addition, three versions are now available to reduce the potential of practice effect; a ceiling effect observed in the naming section of the ACE was addressed by changing all pictures; visuo-spatial tasks were made more difficult; and scoring of the clock drawing test was expanded to reflect greater range of ability (Mioshi *et al.* 2006). Reliability using Cronbach's alpha coefficient is 0.80 and based upon standard criteria for evaluating cognitive decline the ACE-R demonstrates very good concurrent validity (Mioshi *et al.* 2006). Prior randomized trials examining the cognitive effects of ECT (Sackeim *et al.* 2000; Sackeim *et al.* 2008) have used the Mini-Mental State Exam (Folstein *et al.* 1975) or the Modified Mini-Mental State Exam (Stern *et al.* 1987) as an assessment of global cognitive performance. The ACE-R will be used

here because it is a more comprehensive assessment of global cognition (Mathuranath *et al.* 2000).

2.1.7 Trail Making Test

The Trail Making Test (TMT) (Army Individual Test Battery 1994) is an efficient and sensitive instrument that reliably distinguishes individuals with and without brain impairment (Arbuthnott & Frank 2000). TMT requires the participant in part A to join a set of numbers from 1 - 25 in ascending order and part B requires them to join numbers and letters alternating between them in ascending and progressive order (i.e. 1-A-2-B-3-C). Time to completion including time needed for the examiner to recognise and point out the mistake is the most accepted measure of outcome (Bowie & Harvey 2006).

Part A is a measure of attention and visuo-motor tracking (Bowie & Harvey 2006). This is relevant because problems attributed to memory impairment can often be problems of attention, that is, the ability to perform many everyday activities is influenced by ability to maintain attention, to divide attention when necessary and to sustain attention until a task is complete (Lezak *et al.* 1995).

Part B is recognised as a valid measure of executive function not only because one must inhibit the inclination just to join a set of numbers as in part A but they must switch to part B and alternate between numbers and letters (Arbuthnott & Frank 2000; Bell-McGinty *et al.* 2002).

Executive functions are higher-order cognitive processes that control planning, initiation, sequencing and monitoring of complex goal directed behaviour (Stuss & Alexander 2000; Royall *et al.* 2002). Instrumental activities of daily living can be defined as complex, real-world adaptive human behaviours that require independence, volition,

organizational ability and judgment (Katz 1983). Executive function therefore is essential to independent living and performance of IADL (Bell-McGinty *et al.* 2002). Bell-McGinty et al (2002) found the Trail Making Test Part B the best predictor of executive function among many routine neuropsychological tests of executive function (Bell-McGinty *et al.* 2002).

2.1.8 Adverse effects

2.1.8.1 The Columbia ECT Subjective Side Effect Schedule

The Columbia ECT Subjective Side Effect Schedule (CSSES) (Sackeim *et al.* 1987c) is a 53 item checklist of adverse effects that lists potential adverse reactions to treatment. Originally, this assessment was conducted the same day as treatment with the intention of eliciting the type and severity of adverse effects experienced in the acute phase following treatment (Sackeim *et al.* 1987c). There are three a-priori categories: physical, cognitive and mood categories. The cognitive category only was used to record participant's subjective experience of adverse cognitive side-effects. Six questions were embedded among the 53 questions to comprise this cognitive category: were you confused/ disorientated since treatment? Are you confused/ disorientated now? Have you had memory problems since treatment? Do you have memory problems now? Since treatment have you had trouble concentrating? Do you have trouble concentrating now? Responses to these questions are highly structured (No, Mild, Moderate, Severe) and so not open to interpretation by raters. Higher scores indicate greater subjectively perceived ECT related adverse effects and the minimum to maximum score range is 0 – 18.

2.1.9 Clinical recovery data

2.1.9.1 Adverse physical effects

Any medical illness or significant medical history was recorded in the participant's ECT treatment booklet as well as prescribed medications and doses. Prior to treatment each patient had an electrocardiogram (ECG) and, if indicated, a chest X-ray. Data regarding intra-treatment and post treatment adverse effects are routinely collected and recorded in the participant's ECT treatment booklet. An administration record was completed by the treating doctor recording dose, laterality, electroencephalogram (EEG) and motor seizure duration and any other details of note (Figure 2.1). There was no a priori definition of cardiac response that would require intervention and individual cases were examined and treated on a case by case basis at the discretion of the treating Anaesthetist. Medical intervention for respiratory complication, cardiac arrhythmia, hypertension, bradycardia or tachycardia was recorded by the Consultant Anaesthetist at individual treatments.

Blood pressure, heart rate and oxygen saturation were recorded using a Philips C3CO2 vital signs monitor in the treatment room and a Philips Suresigns VM4 vital signs monitor throughout the recovery period. Pre-treatment blood pressure, heart rate and oxygen saturation were recorded at each treatment session. Patient's blood pressure, heart rate and oxygen saturation were recorded at fixed time-points throughout the treatment and recovery period (Figure 2.2): specifically, upon resumption of spontaneous breathing a stopwatch was started and a set of observations were recorded from this point forward. Potential post treatment adverse physical effects included: headache, nausea and muscle aches. Once the patient was deemed reoriented they were asked for the presence of these symptoms and these data were also recorded in the ECT record (Figure 2.3). Participants that failed to meet criteria for reorientation were also asked for the presence of these potential side-effects before they left the ECT department.

Figure 2. 1 St. Patrick's University Hospital ECT administration record

ADMINISTRATION RECORD **TREATMENT NO 1**

TO BE COMPLETED BY ADMINISTERING DOCTOR IMMEDIATELY AFTER ADMINISTRATION OF E.C.T.

	Dose (mC)	Unilateral/ Bilateral	Seizure Length (s)		Comments	Signed
			Clinical	EEG		
1.						
2.						
3.						

Figure 2. 2 St. Patrick's University Hospital post ECT record of observations

Interval	Time	Pulse	BP	O2 Sat	Diabetic- Post ECT BSL:
Initial ob's		bpm	/		
5 min		bpm	/		
10 min		bpm	/		
15 min		bpm	/		
25 min		bpm	/		
40 min		bpm	/		
60min		bpm	/		
4 hours		bpm	/		

Figure 2. 3 St. Patrick's University Hospital post ECT record of adverse physical effects

Please Answer **Yes** or **No**

Do you have a headache?	
Do you feel Nauseated?	
Do your muscles feel sore?	

2.1.9.2 Time to recovery of orientation

To gather the relevant data, a set of orientation questions were asked at predetermined time-points (Figure 2.4): What is your name? Where are you now? What age are you? What is your date of birth? What day is it today? These questions are the standard questions used to establish reorientation following ECT in the majority of studies since the 1980's (Daniel & Crovitz 1982; Sobin *et al.* 1995; Sackeim *et al.* 2000; Sackeim *et al.* 2007; Sackeim *et al.* 2008). Once the patient resumed spontaneous breathing following treatment the Anaesthetist's Assistant started a stopwatch. This was the first time that level of post ECT reorientation was checked. This initial point was the starting point for all participants from which level of reorientation was checked again at predetermined fixed time-points. Patients were be deemed to be reoriented when they successfully answered four of five questions asked and patients that did not meet this criterion by the 50 minute time-point were recorded as having suffered a prolonged disorientation.

Figure 2. 4 St. Patrick's University Hospital post ECT re-orientation checklist

Please Tick or Cross

	Initial	5 min	10 min	15 min	20 min	30 min	40min	50min
What is your Name?								
Where are you now?								
What age are you?								
What is your D.O.B?								
What Day is it?								

2.1.10 Physical functioning

2.1.10.1 The Physical Self Maintenance Scale

The Lawton and Brody Physical Self Maintenance Scale (PSMS) (Lawton & Brody 1969) assesses ones level of ability in performing the most basic activities of daily living (ADL). The underlying theory proposed by the creators of this scale and others like it, such as Katz's Index of ADL (Katz 1983), is that human behaviour can be ordered in a hierarchy of complexity (Lawton & Brody 1969; Lawton 1988). It is proposed that the hierarchy begins with physical health, through to self-maintaining ADL, through more complex instrumental ADL, to time spent on work and hobbies and finally to social interaction (McDowell 2006). Within each category there are activities with their own hierarchy of basic to complex activities (McDowell 2006).

The PSMS consists of six items measuring competence on a spectrum of ability from dependence to independence in basic activities of living (ADL): using the toilet, feeding oneself, dressing, grooming, ambulating and bathing (Lawton & Brody 1969). The questions are arranged in a Guttman scale (McDowell 2006). As such, each question has five possible responses and these responses are arranged in an order so that an individual who agrees with a particular response also agrees with items of lower rank-order. Higher scores demonstrate greater independence. The PSMS is criticised for being insensitive to change but this criticism is common to all brief assessments of basic ADL unless used in populations that are the most severely physically debilitated (McDowell 2006). The PSMS correlates quite strongly ($r = 0.62$) with physician rating of functional decline (Lawton & Brody 1969) and high inter-rater reliability has been reported using Cohen's Kappa of 0.91. The PSMS has been used previously in ECT research (McCall *et al.* 2002a).

2.1.10.2 *The Instrumental Activities of Daily Living Scale*

The Instrumental Activities of Daily Living Scale (IADL) (Lawton & Brody 1969) consists of eight items measuring competence in more complex activities of daily living (ADL): shopping, cooking, using the telephone, housekeeping and doing laundry, transportation, managing finances and medications. Higher scores indicate greater independence in ability to perform instrumental ADL. The IADL scale takes approximately 10-15 minutes to complete and can be done with the patient or their relative or carer. All domains require some degree of both physical and cognitive function (Graf 2008b). Originally, Lawton and Brody suggested that men not be scored on all eight items, (omitting food preparation, housekeeping and laundry) but contemporary practice is to include all eight domains for both sexes (Graf 2008b).

The IADL scale is more sensitive than the PSMS in detecting earlier, less severe dysfunction (Graf 2008b). Limitations of the instrument include the self-report or proxy report method of administration rather than an objective assessment and rating. Also, the instrument may not be sensitive to very small, incremental changes in function. However, inter-rater reliability has been measured with Cohen's Kappa to be > .85 (Graf 2008a). Concurrent validity has been established comparing the IADL with other similar instruments such as The Behaviour and Adjustment Rating Scale an achieving significant correlations between both (Graf 2008a). This assessment has been successfully used in depression and ECT research previously including a comparison of ECT with psychopharmacology and was used in this research to compare the recovery of ability to perform IADL between treatment groups (McCall *et al.* 2001; McCall *et al.* 2002c; McCall & Dunn 2003; McCall *et al.* 2004).

2.1.11 Health related quality of life

The Medical Outcomes Study (MOS) took place in the United States in the late 1980's. The purpose of this research was to (1) determine if variations in patient outcomes could be explained by variations in systems of care and/ or clinician specialities and abilities and (2) to develop self-administered questionnaires and generic scales to assess outcomes (Tarlov *et al.* 1989). The Medical Outcomes Study led to the development of the MOS Short Form 36-item Health Questionnaire (SF-36): a subjective and generic multidimensional health assessment that produces an eight scale profile of functional health and well-being scores: physical functioning (10 items), role limitation due to physical limitation (4 items), role limitation due to emotional problems (3 items), social functioning (2 items), mental health (5 items), energy/ vitality (4 items), pain (2 items), general health perception (5 items). The SF-36 also provides a subjective expression of perceived change in health and psychometrically-based physical and mental health summary measures. There is no Irish version or Irish normative data available but the UK version of the SF-36 has been used for this study with six questions modified from the standard US version to make it more acceptable for British use (Jenkinson *et al.* 1996). Normative data is available for a UK sample for comparison. The SF-36 is sensitive to change and is widely considered to be the leading generic health outcome measure and takes approximately five to ten minutes to complete (Jenkinson et al 1996).

The construct validity of the SF-36 is demonstrated through comparison of results with standard findings: men, higher social class, younger age groups, those without chronic illness and those that had not been to their G.P in the recent two weeks proved to have better health across all domains (Jenkinson *et al.* 1996). The SF-36 is capable of discriminating between patient groups suffering medical and psychiatric conditions. The subscales have been compared for criterion validity against their full versions from the Medical Outcomes Study and all compare favourably. The SF-36 also proves to have

excellent internal reliability within dimensions: reliability coefficients measured with Cronbach's alpha range from 0.65 for the general health perception scale to 0.94 for the physical functioning scale (Ware *et al.* 2007).

2.1.12 Attitudes towards electroconvulsive therapy

Attitudes data was gathered using a summated rating scale that has four characteristics: there are multiple items that will be combined or summed; each individual item measures something that has an underlying quantitative measurement continuum (e.g. an attitude can vary from unfavourable to favourable); each item has no correct answer and so a summated rating scale cannot test knowledge or ability; and each item is a statement and respondents rate their level of agreement with each statement (Spector 1992).

A summated rating scale (one type of which is called a Likert type scale (Kerlinger & Lee 2000)) is a multi-item questionnaire devised to elicit the positivity/ negativity of participants towards a latent object (Desselle 2005). The purpose of the summated rating scale is to place an individual somewhere on a continuum of agreement with the attitude in question (Kerlinger & Lee 2000). We assume that every question is of equal attitude value, thus weighting of questions is not necessary (Kerlinger & Lee 2000; Desselle 2005). The summated rating scale comprises Likert type questions that contain a mid-point separating unfavourable and favourable attitudes (Spector 1992). Participants respond with degrees of agreement or disagreement (intensity) (Desselle 2005). Responses are summed and averaged to yield an individual's attitude score (Kerlinger & Lee 2000). Multiple questions are asked because single questions are unreliable, imprecise and the scope of a single question is too narrow to encompass attitudes. The objective is to rate a person's positivity towards the phenomenon of interest in total and locate the position of this attitude upon a

scale or continuum, ranging from unfavourable through a midpoint of neutral towards a position of positive attitude (Spector 1992).

There are many advantages to using a summated rating scale: they are easy to construct, administer and complete. It is a very reliable and valid method of establishing attitude (Spector 1992). A summated rating scale facilitates precision in that intensity of attitude can be placed on a continuum where neutral is a valid answer with its own meaning. Chance error will even out over multiple questions and multiple response choices will increase precision of answers; those who feel strongly, one way or another can be distinguished from those with moderate feelings. A summated rating scale allows individuals to express intensity of their attitude rather than having to make an all or nothing decision (Spector 1992; Kerlinger & Lee 2000; Babbie 2008).

Some disadvantages of using a summated rating scale include: respondents need a reasonable level of literacy; ambivalent respondents may answer erratically and response sets are possible, i.e. neutral responses, agree responses, disagree responses and extreme responses, where respondents choose to select agree or disagree responses for every question (Spector 1992; Kerlinger & Lee 2000; Babbie 2008).

For the purposes of this study two established questionnaires were combined to form a very comprehensive summated rated scale (Appendix 3). The Freeman and Kendall (1980) questionnaire was the first ECT attitudes questionnaire, developed by clinicians and is very comprehensive. The Philpot et al (2004) questionnaire is one developed by Communicate, the service user group at the Maudsley Hospital, London. These questionnaires were combined because; they were both used in research studies in the past; one was developed by clinicians and the other by service users and it was hoped that this marriage would overcome criticisms of questionnaires developed only by one group; and

when combined, these questionnaires examined an expansive range of aspects related to ECT and provided an abundance of information that could be factor analysed.

2.2 Methods

2.2.1 Methodology

In order to conduct any piece of research one needs a research question. A research question is formulated by thoroughly reviewing the relevant literature and identifying concepts that may be appropriate for study (Noll Hoskins & Mariano 2004). These concepts provide a conceptual framework that begins to guide the potential methodology. A conceptual framework is described as a number of concepts, identified by thoroughly reviewing the relevant areas of interest, that are suitable for investigation (Noll Hoskins & Mariano 2004). The methodology is decided upon once research aims have been determined and theoretical perspectives considered.

Theoretical perspectives refer to how one views the world and makes sense of it (Crotty, 1998). Consideration of theoretical perspectives informs an appropriate research strategy for answering the specific research question. There are two main opposing theoretical perspectives; a deductive approach where hypotheses are tested and an inductive approach where data are examined for themes that emerge and theories are developed (Gray 2009). If an inductive approach is chosen theories are not developed until after data collection and analysis. An inductive or qualitative perspective comprises a collection of approaches that believe that phenomena can be understood by examining the meaning people attach to them and the context in which they occur. Some inductive approaches may include grounded theory or phenomenology.

A deductive approach to answering research questions evolved from a positivist perspective where the researcher believes they can deduce laws to explain and predict behaviour (reductionism). This approach is objective and regards empiricism, i.e. only that which is observable by the human senses, to be fact. Cause and effect (determinism) is used to explain and predict behaviour (Noll Hoskins & Mariano 2004). This approach works less well is the social sciences than the natural sciences and because of its obvious limitations in this area evolved into a postpositivist paradigm at the beginning of the 21st Century. This view is less strict, accepting that there may be more than just one true way to examine reality and that researchers can never be completely objective when their social and cultural views are considered (Noll Hoskins & Mariano 2004). A postpositivist perspective accepts that rules or laws cannot always predict social phenomena as in the natural sciences and instead attempts to predict the probability of events occurring given certain circumstances or conditions (Noll Hoskins & Mariano 2004). Cause and effect is sought but correlations are acceptable and the intention is that results will be generalizable. A postpositivist perspective recognises that more than just human senses can be used to address research questions and valid and reliable self-report tools can be also be used (Noll Hoskins & Mariano 2004).

This deductive approach was deemed more suitable to achieve the research aims of this study. In a deductive approach a conceptual framework is used to generate a theoretical framework where theories are defined and proposed. A theoretical framework is a set of theories developed from the conceptual framework that guide the research from that point forward. These theories are used to identify hypotheses suitable for testing that will achieve the research aims (Noll Hoskins & Mariano 2004). Once theories are proposed from the theoretical framework, hypotheses are generated with the intention of testing these hypotheses to prove or disprove the proposed theories. This quantitative approach is

a formal, objective and systematic attempt to use numerical data and statistical tests to address the research question.

2.2.2 Trial name and location

The work presented here is part of an on-going randomized controlled trial. The EFFECT-DEP Trial (Enhancing the eFFectiveness of ElectroConvulsive Therapy in severe Depression) is being conducted in St. Patrick's University Hospital and Trinity College Institute of Neuroscience, Trinity College Dublin. The trial is registered with Current Controlled Trials Ltd: ISRCTN 23577151 and recruitment began in May 2008.

2.2.3 Design

The EFFECT-DEP TRIAL is a pragmatic two-group randomised, participant- and rater-blinded, non-inferiority trial with a one year follow-up. The trial is designed to reflect routine clinical practice and no other aspect of patient care was altered. The hypothesis is that high dose right unilateral ECT will be at least, but no more effective, than 1.5 × ST bitemporal ECT. Both participants and raters are blind to treatment allocation for the duration of the one year follow-up period. Participants have been randomized to separate groups. This ensures an equal distribution of demographic characteristics and facilitates the control of variables that may otherwise affect outcome (for e.g. source of referral, age, sex, previous experience of ECT). The primary aim of the EFFECT-DEP TRIAL is to compare the effects of 6 × ST RUL ECT with 1.5 × ST bitemporal ECT on different types of memory and cognitive functioning. This study was conducted within the context of the EFFECT-DEP TRIAL but aims to achieve independent objectives and is not itself a randomized controlled trial.

2.2.4 Method

Three groups of participants were recruited to this study:

(1) Patients referred for ECT were randomised to receive a course of either 1.5 x ST bitemporal ECT or high-dose (6 x ST) right unilateral ECT. Ideally, patients continued to receive ECT until they met remission criteria, i.e. Hamilton Depression Rating Scale-24 item score had declined by 60% or more from baseline and is 10 points or less on two consecutive weekly assessments or they had received a maximum of 12 treatments (Mental Health Commission 2006a).

(2) Participants designated next of kin (NOK) that lives with the participant so as to have knowledge of their ability to perform basic and instrumental ADL during the 2 weeks prior to the assessment. If the participant was in hospital for the 2 weeks prior to the assessment then;

(3) A Registered Nurse that was regularly involved in their care and had sufficient knowledge of the participants ability to perform basic and instrumental ADL during the 2 weeks prior to the assessment.

2.2.5 Inclusion and exclusion criteria

Data were collected from primary participants and minor participants: primary participants were patients referred for ECT from whom all data but data for one outcome measure were collected. Minor participants in this study were the primary participants designated next of kin (NOK) or in the event that the participant had been in hospital for the 2 weeks prior to the assessment (as the particular assessment requires information about functioning over the previous 2 weeks) a Registered Nurse that was regularly

involved in their care. In this thesis participant refers to primary participants that were randomly allocated to a treatment group and received ECT unless otherwise stated.

2.2.5.1 Inclusion criteria

Primary participants: patients ≥ 18 years old with major depressive disorder as confirmed by the Diagnostic and Statistical Manual of Mental Disorders, fourth edition [DSM-IV-TR] (American Psychiatric Association 2000) and referred for ECT. All primary participants had a HDRS 24-item score ≥ 21.

Minor participants: the primary participants designated NOK that lives with the primary participant so as to have knowledge of their ability to perform basic and instrumental ADL during the 2 weeks prior to the assessment. A Registered Nurse that was regularly involved in their care and had sufficient knowledge of their ability to perform basic and instrumental ADL while in hospital during the 2 weeks prior to the assessment.

2.2.5.2 Exclusion criteria

Primary participants: exclusion criteria include being younger than 18 years old, any condition rendering patients medically unfit for general anaesthesia or ECT, treatment with ECT in the previous six months, dementia or other axis 1 diagnosis, alcohol/other substance abuse in previous six months or an inability/refusal to consent.

Minor participants: A designated NOK that did no live with the primary participant. Any Nurse that was not regularly involved in the patients care while they were in hospital over the 2 weeks prior to the assessment being due.

2.2.6 Administration of ECT

At each participants first treatment session their individual seizure threshold (ST) was established using a stimulus dosing protocol. At subsequent treatment sessions participants randomized to receive bitemporal ECT were administered 1.5 × ST doses and those randomized to receive high dose RUL ECT were administered 6 × ST doses. Trial participants clinical ECT details such as group allocation, stimulus intensity administered, seizure duration and other relevant clinical details were recorded in a separate administration record and stored in a locked cabinet in a locked room in the ECT department.

2.2.7 Termination of treatment

Each participants independent treating clinical team made the decision to end the ECT treatment course without consultation or influence from the EFFECT-DEP TRIAL team. The decision to terminate the treatment course was based on clinical judgement and assessment of the clinical response and/ or experience of adverse effects.

2.2.8 Power

The primary outcome measure for the EFFECT-DEP TRIAL is the HDRS 24-item. It is estimated that 69 patients per treatment group are needed to have 80% power to demonstrate that mean reduction in HDRS score for high dose RUL ECT is no more than 4 points less than that achieved using standard bitemporal ECT. This calculation was informed by previous research (Petrides *et al.* 2001a). This study is not powered in this way but maintains many of the advantages of the randomized design.

2.2.9 Study site and population

St Patrick's University Hospital (SPUH) is an independent mental health service provider with 288 inpatient beds between the main hospital campus (238) and its sister hospital, St. Edmundsbury Hospital, Lucan, Co. Dublin (50). St Patrick's University Hospital provides a nationwide mental health service and is the largest single provider of mental health services in the country. St Patrick's University Hospital is a tertiary referral centre that provides a range of specialist therapies for depression including assessment, pharmacological therapy, psychological therapy and ECT.

St Patrick's University Hospital receives many referrals for patients from the Health Service Executive (HSE). The ECT clinic is accredited with excellence by the Royal College of Psychiatrists' ECT Accreditation Service (ECTAS).

St Patrick's University Hospital provided 124 (30%) of ECT programmes in Ireland in 2008. Due to data collection methods used by the Mental Health Commission it was not possible to construct epidemiological data on regional use of ECT in Ireland. Over a 3 year period from 2007-2009 St Patrick's University Hospital provided ECT at a frequency that approximately matched the distribution of the general population relevant to each HSE administrative region in Ireland (McLoughlin & Dunne 2010).

Patients referred for ECT in St Patrick's University Hospital are in the most part typical of patients referred for ECT elsewhere: depression is the primary indication, greater numbers of women than men are referred for treatment, the mean age is approximately fifty five years and patients are normally treatment resistant. Although St Patrick's University Hospital is an independent hospital, approximately 50% of the Irish population has health insurance (The Health Insurance Authority 2010) and a significant number of referrals from the HSE are treated annually. Results should therefore be generalizable to other similar settings.

2.2.10 Sample size

The EFFECT-DEP Trial is recruiting 138 participants in total and participants are randomly allocated to two distinct intervention groups. The current work presents results from the first 100 participants that have completed six month follow-up assessments. This study is not powered for any specific outcome measure but retains all the advantages of the trial design and in particular the randomization procedure. With 100 primary participants between the two groups the work presented in this thesis; will represent a large sample compared to previous work in these areas; and will present original results regarding recovery of orientation, physical functioning, HRQOL and attitudes of service users that will add significantly to current knowledge.

2.2.11 Study procedures

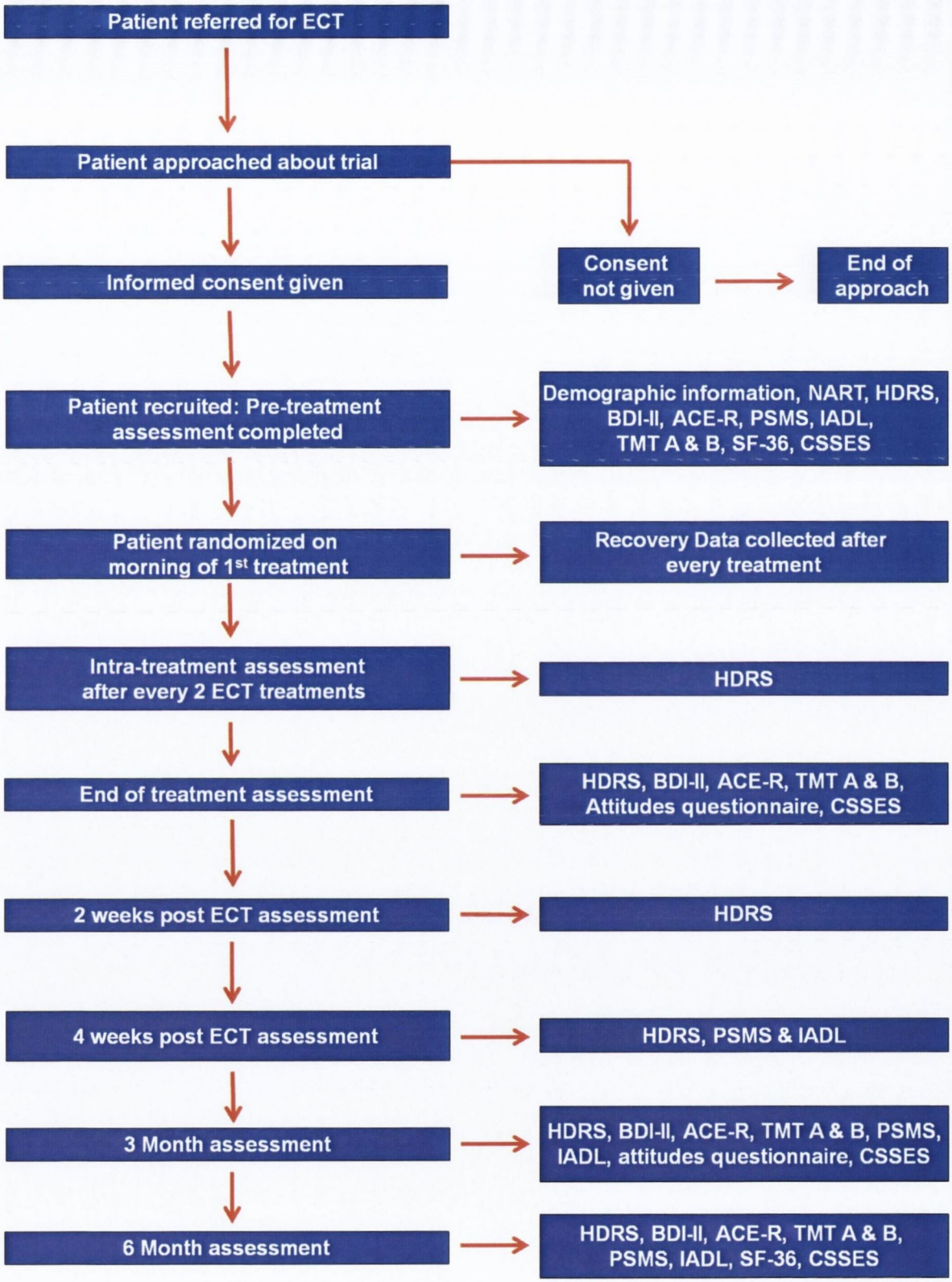
Standardized delivery of intervention and assessment of outcomes are imperative elements to reducing potential sources of bias in randomized control trials. The assessors underwent rigorous training for the primary outcome measure and standard training for the remaining measures. Inter-rater reliability was established for the primary outcome measure at six monthly intervals. This was achieved by raters watching pre-recorded assessments and independently scoring the HDRS 24-item. Cohen's kappa was then calculated to determine inter-rater reliability which was always > 0.85. Assessors were blinded to the intervention and assessments were conducted as close to predetermined time-points as was practicable.

Data were collected at multiple time-points. Each independent treating clinical team had given written consent for the research team to approach their patients about the EFFECT-DEP TRIAL once a referral for ECT was made. Once a patient was referred for ECT by their treating clinical team the ECT department made the research team aware of

the referral. A member of the research team and the trial primary investigator then approached the prospective participant to make them aware of the trial, give them sufficient information in oral and written forms to allow them make an informed decision whether to participate in the trial or not and to gain informed consent from the participant if they agreed to take part. If patients did not consent to take part in the trial they continued to have ECT as per normal procedures. If patients consented to take part in the trial a research registrar obtained written informed consent from the participant; consent to contact their designated NOK to obtain functional data; contacted the participants NOK and obtained expressed verbal consent to provide such data; conducted a battery of clinical, neurocognitive and functional assessments prior to the participants first treatment session. On the morning of the first treatment session the participant was randomly allocated to one treatment group using the computer randomization service provided by the Institute of Psychiatry, London. Once randomized each participant was allocated to a rater that was responsible for completing all other assessments after the first treatment session. After every two treatments the responsible rater conducted a HDRS assessment with the participant. At the end of the treatment course, which was decided by the independent treating clinical team in conjunction with the participant and based on the participant's clinical presentation, the responsible rater conducted the full battery of clinical, neurocognitive and functional assessments again. Two weeks after the treatment course ended the rater conducted a HDRS assessment again. Four weeks after the end of treatment the rater conducted the HDRS and functional (PSMS and IADL) assessment: the HDRS was conducted with the service user and the functional assessment was conducted with the service users named next of kin or if the participant had been in hospital for the 2 weeks prior to the assessment, with a Registered Nurse that was involved with the participants care regularly over the 2 weeks prior to the assessment. At three months and six months

follow-up after the end of treatment the responsible rater conducted the full battery of clinical, neurocognitive and functional assessments again (Figure 2.5 and Appendix 4).

Figure 2. 5 Study flow chart of assessments



HDRS	Hamilton Depression Rating Scale
BDI-II	Beck Depression Inventory version two
ACE-R	Addenbrookes Cognitive Exam – revised edition
PSMS	Physical Self Maintenance Scale
IADL	Instrumental Activities of Daily Living Scale
SF-36	Medical Outcomes Study, Short Form 36-item Health Questionnaire
Attitudes	ECT Attitudes Questionnaire
CSSES	Columbia ECT Subjective Side-Effects Schedule

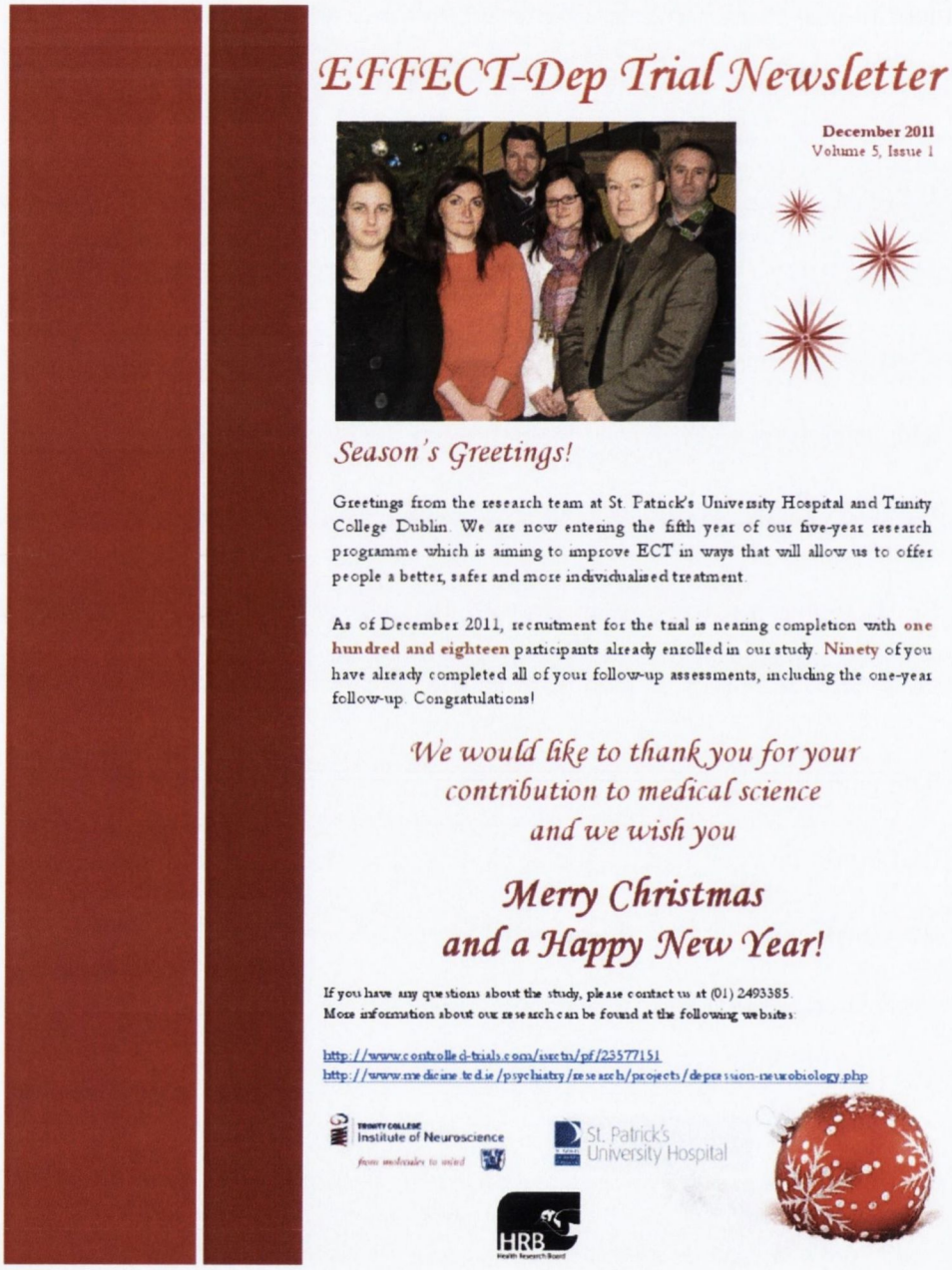
2.2.12 Optimising recruitment

Recruiting participants to randomized trials presents a challenge and it is common for trials to recruit less than targeted sample participants or for trials to extend the recruitment period to achieve their target (Watson & Torgerson 2006). Poor or slow recruitment to trials may result in a reduction in the statistical power, an increased risk of a Type II error, prolonging the trial period and/ or increased costs.

Recruitment rates were evaluated and assessed on an ongoing basis throughout the trial. In an effort to obtain optimum recruitment rates in the EFFECT-DEP Trial a number of strategies were employed that focused mainly on education and information:

- The trial was highlighted to referring teams and updates on trial progress were regularly given at clinical meetings.
- Staff including Consultant Psychiatrists, Registrars and Nursing Staff were educated about ECT at clinical meetings and in the ECT Department.
- The trial information leaflet was designed to be very informative and in a language that could be easily understood. This not only facilitated informed consent but was designed with the awareness that increased knowledge about the facts of ECT is associated with better acceptance of its use (Janicak *et al.* 1985b; Besani *et al.* 2011).
- Participants were sent a quarterly newsletter with updates on the progress of the trial and a message of continued appreciation for their continued support of the research (Figure 2.6).

Figure 2. 6 Example of the participant newsletter sent quarterly



EFFECT-Dep Trial Newsletter

December 2011
Volume 5, Issue 1

Season's Greetings!

Greetings from the research team at St. Patrick's University Hospital and Trinity College Dublin. We are now entering the fifth year of our five-year research programme which is aiming to improve ECT in ways that will allow us to offer people a better, safer and more individualised treatment.

As of December 2011, recruitment for the trial is nearing completion with **one hundred and eighteen** participants already enrolled in our study. **Ninety** of you have already completed all of your follow-up assessments, including the one-year follow-up. Congratulations!

We would like to thank you for your contribution to medical science and we wish you

Merry Christmas and a Happy New Year!

If you have any questions about the study, please contact us at (01) 2493385.
More information about our research can be found at the following websites:

http://www.controlled-trials.com/isrctn/pf/23577151
http://www.medicine.tcd.ie/psychiatry/research/projects/depression-neurobiology.php

Trinity College Institute of Neuroscience
from molecules to mind

St. Patrick's University Hospital

HRB Health Research Board

2.2.13 Intention to treat analysis

The EFFECT-DEP TRIAL followed an intention to treat principle; once randomized the participants data is analyzed as part of the group they were randomized to even if they never receive treatment or discontinue the trial (Glasziou *et al.* 2007). Trial participants who improve clinically are more likely to co-operate with trial procedures such as multiple follow-ups over an extended period of time for example. Conversely, participants who do not improve are more likely to drop out or to complete less of the assessments (Glasziou *et al.* 2007). Therefore, without an intention to treat principle, researchers may only have access to positively biased data (Montori & Guyatt 2001). If the course of ECT was unsuccessful or if participants reached 12 treatments which is the maximum administered in one course, they were offered a course of standard ECT as per routine procedures. In this case only trial data were analyzed for recovery evidence and follow-up assessments were conducted as normal.

2.2.14 Randomization and allocation concealment

The findings presented in this work are based on this randomized controlled design and maintain many of the benefits of this design. Randomization is the major keystone of a randomized controlled trial and comprises two elements: the generation of a random sequence to allocate participants and concealing this sequence from the researchers (Schulz & Grimes 2002a). Allocation concealment is concerned with the implementation of the random sequence and not the method used to generate it (Schulz & Grimes 2002a). Patients are randomised after baseline data collection. The clinician researcher responsible for conducting the baseline assessment also randomized the participant. Random allocation is done independently by the Clinical Trials Unit at the Institute of Psychiatry (London) to ensure allocation concealment. Randomisation is minimized according to:

1: History of treatment with ECT

2: Source of the referral:

1) St. Patrick's University Hospital

2) St. James's Hospital

3) Health Service Executive (HSE), other than St. James's Hospital.

2.2.15 Blinding

Blinding, in which the participant, assessor or both do not know which group of participants is receiving which intervention, is used in an attempt to reduce bias (Schulz & Grimes 2002b). Just as a patient may perceive benefit from commencing treatment, assessors can also believe participants are improving or are more likely to improve depending on which treatment they are receiving (Babbie 2008). To account for this patients, their clinicians and raters have no way to find out to which treatment participants have been allocated and clinicians administering ECT are not involved in assessments conducted after randomization. Also, gel is applied to the scalp of the anaesthetised patient before application of the electrodes. Every participant is applied gel in both the bitemporal and RUL positions to conceal the true electrode positioning. Success of blinding for patients and raters is assessed after the second and final treatments.

2.2.16 Training of raters

Standard training was undertaken by all raters involved in data collection for the primary outcome measure, the HDRS. All raters made videos of themselves conducting a HDRS assessment with a number of patients in St. Patricks University Hospital that were not approached for the EFFECT-DEP TRIAL. This procedure was also approved by the St. Patrick's University Hospital Research Ethics Committee. All participants were given written information on the purpose of these assessments and assured that anonymity would be guaranteed. These videos were stored in a locked cabinet, in a locked room in a locked research centre on the grounds St. Patrick's University Hospital and only accessible by members of the research team. These videos were watched and scored by all raters and the level of inter-rater agreement was established using Cohen's kappa, which was always above 0.85. All raters received standard training in the administration of all other instruments.

2.2.17 Data collection

Data were collected in a standardized way that all assessors were trained in. Assessments were conducted in St. Patrick's University Hospital and in the community where it was more convenient for the participant. Once assessments were completed they were scored and stored in a locked press in a locked room in the research building, St. Patrick's University Hospital. Assessment scores were recorded on individual score sheets also stored with the original assessments.

2.2.18 Quality control

There are several researchers involved in data collection and a quality control system is used for organising data. This process has five levels of data checking for each completed assessment. These checks identify any errors in the calculation and entering of the data. These levels are:

1- Each team member corrects the assessments they have carried out.

2- Each team member is paired with another team member. Once a fortnight this pair cross check each other's first level ratings for errors. All errors that were identified were discussed between the pair of raters and corrected. The number of errors found was not recorded.

3- Every two weeks the team leader ensures all checks are complete and correct and every four weeks a team review is conducted.

4- Monthly data computation in SPSS Data Entry Builder.

5- Every six months statistical analyses are carried out to discover any input errors.

6- When the researcher was unblinded the data were examined more thoroughly for input errors. Data entry was be re-checked and corrected where necessary.

2.2.19 Ethical considerations

1. Privacy

Assessments were conducted with participants in quite, comfortable and private areas within the hospital setting (either in the ward environment or in a meeting room in the research center on the hospital grounds) or in the participants own home. At no time were assessments conducted in the company of others or within earshot or sight of others. All

participant information was coded using an identification number to protect anonymity and all data were stored in a locked cabinet in a locked room in the research building located on the grounds of St. Patrick's University Hospital.

2. Misrepresentation

Prospective participants were given both oral and written information about ECT and the proposed research study. Information about ECT was primarily given by the prescribing team in both written and oral manner as is hospital policy. Prior to consenting to the research study prospective participants were also given as much time as they felt necessary to discuss ECT, evidence on effectiveness and potential adverse effects with the team member recruiting that participant. Prospective participants were also provided with written and oral information about the proposed research study by the team member recruiting that participant. This information contained an invitation to take part in a research study, the purpose of the study, why they had been approached, did they have to take part in the study, what would happen if they agreed to take part in the study, possible benefits of taking part in the study as well as possible disadvantages of taking part, the confidential handling of information, what would happen to the results of the study and where to get further information.

3. Bias

All participants were given the empirical facts about ECT in general and more specifically about bitemporal ECT, right unilateral ECT and potential adverse effects associated with ECT. No information was given to patients that was not evidence based or bias.

4. *Participant burden*

Data were collected from three sources: all data were collected directly from participants except for two outcome measures (the PSMS and the IADL) where data were collected from the participants expressed next of kin (based on the fact that the designated person was in a position to provide the required information) or from a Nurse caring for the participant if they had been in hospital for two weeks prior to the assessment taking place. The participant gave written informed consent to participant in the study. Participants gave verbal consent for their NOK to be contacted and the NOK gave verbal consent to provide such information. Also, the participant gave verbal consent for this information to be collected from a Nurse if they had been in hospital more than 2 weeks prior to the assessment taking place. The Nurse from whom these data were collected also gave verbal consent to provide this information for the purposes of research. Consent to contact the participants NOK or Nurse was sought from the participant prior to contact with the NOK or Nurse at each assessment time-point and contact with the NOK or Nurse was never made prior to any assessment without such expression of continued consent from the participant. If at any time any of these groups refused to give written or verbal consent to provide information then the required data were not collected and were recorded as missing data.

5. *Invisibility (Researchers should never put their subjects in a compromising position where there is a potential for danger)*

Participants were only approached after their treating clinical team had made a referral for them to receive ECT. Once a referral was received the ECT department and/ or the

treating team notified the research team. Once notified the research team member allocated to recruiting prospective participants approached the prospective participant. Although participants were randomly allocated to receive high dose RUL ECT or 1.5 × ST bitemporal ECT no other aspect of their care or treatment was influenced or altered by the research protocol. The decision to prescribe, adjust or terminate medications and the decision to continue with treatment or end the course of ECT was made by the treating clinical team independent of research protocol. These aspects of the research design not only facilitated the collection of real world data but also meant that participants were not exposed to any additional risk of danger as a result of participating in the research study.

Participants' anonymity was protected as all participant information was stored in a locked cabinet in a locked room in a locked building on the grounds of St. Patrick's University Hospital and only accessible by the research team. On treatment days no aspect of normal pre-treatment preparation or aftercare was altered as a result of participation in the research study. As a result only those with direct input into the patients care knew they were involved in the research study.

6. Participant group

Moore and Miller (1999) describe a vulnerable person as an individual who is diagnosed with an illness and due to that illness lacks the ability to maintain autonomy, personal independence and self-determination (Moore & Miller 1999). Participants in this trial may be considered vulnerable. Participants in this study were referred for ECT. They were given adequate information about ECT, expected outcomes, all potential risks and alternatives that was in plain simple English in a manner they could understand and they were able to reason with this information (this was assessed informally prior to consent being obtained) and provide written informed consent. Patients referred for ECT in St.

Patrick's University Hospital would normally have received 1.5 × ST bitemporal ECT but in this study were randomly allocated to receive that treatment or 6 × ST RUL ECT. There is no evidence that 6 × ST RUL ECT is associated with an increased risk of mortality, adverse physical effects or adverse cognitive effects.

7. *Number of participants required*

This study recruited 100 participants in total; 50 participants in each treatment group. The EFFECT-DEP TRIAL is estimated to have 80% power to detect a 4 point difference between the treatment groups on the primary outcome measure: the HDRS. While this study is not powered in this way, it does maintain many of the advantages of the randomized design.

8. *Design/ methodology used*

Data for this study were collected as part of the EFFECT-DEP non-inferiority, rater-and-participant blinded, randomized controlled trial. While this study is not itself a randomized controlled trial it does maintain many of the advantages of the randomized design.

9. *Reliability and validity*

The primary outcome measure for the EFFCET-DEP TRIAL is the 24 item HDRS. All raters were trained in the use of this measure and conducted 6 monthly inter-rater reliability testing. Cohen's kappa was used to measure inter-rater reliability and was always

above 0.85. All raters received standard training on the administration and scoring of all other secondary outcome measures by a Senior Research Psychologist.

10. Location that participants were tested or interviewed

Participants were assessed in St. Patrick's University Hospital in a quiet and private room in the hospital ward setting, in a private room in the research center on the grounds of St. Patrick's University Hospital or in the comfort of their own home if they were unable to attend St. Patrick's University Hospital for assessment.

11. Duration of assessments

Duration of assessments varied. The longest and most involved assessments were conducted prior to randomization, after the treatment course had ended, 3 months, 6 months and 12 months after the treatment course had ended. At these time-points participants were requested to complete the entire battery of clinical, neuropsychological and functional assessments, or as much as they felt able to complete. Completion of the entire battery of assessments takes between 2 and 3 hours to complete. Shorter assessments were conducted after every two ECT treatments, 4 weeks after the treatment course ended and 9 months after the treatment course ended. These assessments comprised of the HDRS only and takes only 10 to 15 minutes to complete.

12. Randomization and blinding

Participants were randomly allocated to each treatment group and blinded to group allocation. Randomization was conducted using a computer randomisation service provided by the Institute of Psychiatry, London. Blinding or allocation concealment strengthens the credibility of randomized controlled trials by minimizing bias (Miller & Stewart 2011). Participants were informed of this aspect of the study protocol prior to giving consent. Equipoise is the point where there is no preference between treatments, i.e. it is thought equally likely that treatment A or B will turn out to be superior (Lilford & Jackson 1995). In plain English, clinical equipoise exists when there is a standard treatment available and the trial treatment is truly believed to be at least as effective as that treatment. This study was conducted within a non-inferiority trial i.e. The EFFECT-DEP TRIAL intended to show that the effect of a new treatment (high dose RUL ECT) is not worse than that of an active control (1.5 × ST bitemporal ECT) by more than a specified margin (Snapinn 2000). Evidence informs us that high dose RUL ECT is as effective as 1.5 × ST bitemporal ECT in terms of antidepressant effect and there is no evidence that high dose RUL ECT is associated with greater risk or severity of adverse effects. However, there is a chance that RUL ECT will be associated with less adverse cognitive effects. A Data Monitoring Ethics Committee (DMEC), an independent group of experts who monitor patient safety and treatment efficacy data while a clinical trial is ongoing (Food and Drug Administration 2006), was given the trial raw data annually. Their role was to examine these data and suggest changes to trial protocol and to advise termination of the trial if it became clear that one treatment group was significantly outperforming the other. To date the DMEC has not advised changes.

13. Physical risk to the participants

The first tenant of research ethics frameworks often adopted, beneficence, states that one should do no harm. There is no additional risk to participants involved in this study. All participants enrolled in this study were referred to receive ECT and there is no evidence that either form of ECT is associated with any greater physical risk than the other.

14. *Psychological risk to participants*

There is no additional risk to participants involved in this study. All participants in this study were referred to receive ECT and there is no evidence that either form of ECT is associated with any greater psychological risk than the other. All participants were involved in inpatient treatment with a multidisciplinary team that gave consent for their patients to be approached to part-take in the research study. Being treated as inpatients by a comprehensive multidisciplinary team also ensures that participants' psychological response to treatment was monitored and treated as necessary.

15. Sensitive information

Participants that gave informed consent to part-take in the research study were required to give information that may be considered sensitive. This information was treated with the greatest of respect and maintained in a locked cabinet in a locked room in a locked building on the grounds of St. Patrick's University Hospital. No-one outside of the trial research team had access to these data.

16. Assurance of confidentiality

All information was anonymised with code numbers allocated to each trial participant and this information was stored in a locked cabinet in a locked room in a locked building on the grounds of St. Patrick's University Hospital. No-one outside of the trial research team had access to these data. All assessments were conducted in a private room either on the ward setting, in the research center located on the grounds of St. Patrick's University Hospital or in the participants own home.

17. Withdrawal from the study

Prior to giving informed consent all participants were informed that they were free to withdraw from the study at any stage. Once participants expressed a wish to withdraw from the study they were offered the opportunity to complete only the primary outcome measure if that was acceptable to them. If they continued to with to terminate their involvement with the study this was done without issue.

2.2.1 Statistical Analysis

Data were analysed using SPSS version 16.0 (SPSS Released 2007) and R studio version 0.94.92 (R Development Core Team 2011). Data were presented as mean (standard deviation) when possible and number per group (percentage of group) when mean (sd) was not appropriate. Models were constructed based on evidence from the literature. Treatment parameters such as electrode placement, treatment number, total stimulus intensity administered, total seizure duration and whether the participant was re-stimulated or not were included as each variable has been implicated as having an effect on time to recovery of orientation or other areas of cognitive impairment. As stated previously there is no

direct evidence linking patient characteristics with recovery of orientation so participant age, sex, weight, height, smoker or smoking status and pre-treatment cognitive status were included in initial model building in an attempt to identify such evidence. Physical response to ECT in terms of heart rate and blood pressure has not previously been included in analysis of time to recovery of orientation but is included here as different heart rate and blood pressure responses may, on face value, influence one's ability to wake up and regain reorientation following anaesthesia and treatment. Mean arterial blood pressure (MAP) is a term used to describe average blood pressure and provides a useful method of including blood pressure in the analysis without using systolic and diastolic measures that are correlated. MAP = (diastolic BP × 2) + (systolic BP) ÷ 3 (Klabunde 2010). Lithium has been implicated as increasing time to recovery and potentially increasing the risk of prolonged disorientation and was included in data analysis (Thirthalli *et al.* 2010). Other common medications were also included in the analysis to explore possible additional modifying factors (benzodiazepines, antipsychotics, antidepressants, antihypertensive medication and statin medications).

2.2.1.1 Recovery of orientation data analysis

Recovery of orientation data were analysed using survival analysis: a commonly used method in epidemiological and medical research where the phenomenon of interest is survival time or time to event (Kleinbaum & Klein 2010). In most cases the event of interest is time to death or failure, such as time to disease incidence, but survival analysis is just as appropriate for identifying time to a positive event such as time to return to work following medical intervention or in this case time to recovery of orientation following ECT (Kleinbaum & Klein 2010). Cox Proportional Hazards model is the most commonly used method of survival analysis. However, data were derived from repeated measures at

repeated treatments from the same patients and so are correlated, violating the statistical assumptions underpinning this method of analysis. Therneau et al (2003) provide a statistically sound method of performing a survival analysis on repeated measures data called the Cox Mixed Effects model (Therneau *et al.* 2003). This model is a method of regression analysis that accommodates both fixed and random effects. In this analysis the random effect is the participant's trial identification record number because this identifies each participant as an individual from whom multiple measurements that are correlated were taken and it is expected that there will be random variation that cannot be controlled for between individuals. The fixed effects in this case are treatment parameters, patient's characteristics, medications at time of treatment course and cardiac effects of ECT.

2.2.1.2 Prolonged disorientation data analysis

Prolonged disorientation was a dichotomous outcome variable originating from correlated data. Inferential statistical analysis was conducted using a Generalized Estimating Equation (GEE) approach to carry out logistic regression for correlated dichotomous responses (Zeger *et al.* 1988). Responses are correlated within the same cluster but are independent between different clusters (i.e. treatments within a treatment course for one patient are correlated but the treatment courses of all patients are independent). This correlated analysis accounts for the variation of the outcome from both within and between clusters. The outcome for this model is a dependant variable with a dichotomized score: 0 = no prolonged disorientation, 1 = prolonged disorientation. It is important to note that the outcome for individual treatments can change over the course of treatments and the independent variables can also change values from treatment to treatment. Other variables do not change from treatment to treatment such as sex and laterality. As such, time-dependant variables can vary in value over the course of

treatments, time independent variables do not vary and the outcome variable can vary from treatment to treatment.

2.2.1.3 Subjective side-effects data analysis

Data from the first and subsequent treatment sessions were analysed separately. The response variable (headache, nausea or muscle pain) was binomial and therefore standard linear regression was not possible. The Generalized Linear Model (GLM) is an extension of the General Linear Model to include response variables that follow any probability distribution in the exponential family of distributions such as the binomial distribution used in this case (Nelder & Wedderburn 1972). Hypothesis tests applied to GLM do not require normality of the response variable and do not require homogeneity of variances. Therefore, GLM can be used when response variables follow distributions other than the normal distribution, and when variances are not constant (Nelder & Wedderburn 1972).

Data for treatments other than the first treatment were not independent as they were derived from the same participant on multiple occasions throughout their treatment course. These data were therefore correlated and clustered within treatments. Inferential statistical analysis was conducted using a Generalized Estimating Equation (GEE) approach to carry out logistic regression for correlated dichotomous responses (Zeger *et al.* 1988). Observations were grouped into clusters that are in this case clustered according to treatment number. The assumption for correlated analyses that is satisfied in this case is that the responses are correlated within the same cluster but are independent between different clusters (i.e the treatments within a treatment course for one patient are correlated but the treatment courses of all patients are independent). The outcome for this model is a dependant variable with a dichotomized score: for example, 0 = no headache, 1 =

headache. It is important to note that the outcome for individual treatments can change over the course of treatments and the independent variables can also change values from treatment to treatment (time-dependant variables). Other variables do not change from treatment to treatment such as sex and laterality (time-independent variables). As such, time dependant variables can vary in value over the course of treatments, time independent variables do not vary and the outcome variable can vary from treatment to treatment. The GEE model produces an odds ratio and Wald P value as in standard logistic regression (The GEE method of analysis does not automatically produce a standard P value and so a Wald P value is produced that is comparable to a standard P value (Gelman & Hill 2006)).

2.2.1.4 Cardiac effects of ECT data analysis

Data from heart rate and blood pressure recordings were interval data and were normally distributed. However, these data violate the assumptions necessary to perform standard parametric analysis because they were generated from repeated measures at repeated time-points from the same participants and are therefore correlated. Linear Mixed Effects (LME) modelling facilitates both fixed and random effects and so provides a statistically rigorous method of analysis for this type of data (Lindstrom & Bates 1988). The random effect that represents the correlated aspect of the data is partitioned into a recognised but separate part of the model so it does not influence the fixed effects. In this case the random effects were the participant's trial number (because this identifies each participant as an individual from which multiple measurements that are correlated were taken and it is expected that there will be random variation that cannot be controlled for between individuals) and the respective treatment number (because the number of treatments prescribed for each participant varied). The fixed effects were patient characteristics, medications at time of treatment course and treatment parameters.

Descriptive statistics are presented for the occurrence of cardiac adverse effects. This count data was non-parametric and was analysed using chi squares to compare the treatments groups for difference.

2.2.1.5 Physical Self Maintenance data analysis

In measurement terms a ceiling effect occurs when there is a certain level in the scale above which the scale does not discriminate (Austin & Brunner 2003). When plotted on a histogram data are negatively skewed and show an overabundance of scores on the right hand side of the histogram. In this case there is very little variability in the data and standard methods of analysis, e.g. regression and ANOVA, are not possible (Pallant 2005). In such data, alternative approaches are required. The PSMS data were transformed from scale data to a binomial variable where scores of 29 and 30 were chosen to represent full functioning and scores of less than or equal to 28 were chosen to represent suboptimal functioning. These data also violated the assumptions necessary to perform standard parametric analysis because they were generated from repeated measures from the same participants and were therefore correlated. Linear Mixed Effects (LME) modelling facilitates both fixed and random effects and so provides a statistically rigorous method of analysis for these types of data (Lindstrom & Bates 1988). In this type of model the repeated assessments are specified as the random effects and unequal sample sizes are accommodated. In this case the random effects were the participant's trial number (because this identified each participant as an individual from which multiple measurements were taken). The fixed effects were the treatment group and the assessment time-point (to identify change over time): pre-treatment, 4 weeks post treatment, 3 months and 6 months post treatment.

2.2.1.6 Instrumental Activities of Daily Living data analysis

Repeated measures ANOVA is a common approach in longitudinal research that was used to analyse the IADL data. As with an ordinary ANOVA repeated measures ANOVA compares the equality of means but in repeated measures ANOVA all members of the sample are measured under repeated conditions or at repeated time-points (Pallant 2005). Standard ANOVA does not take account of the correlation associated with the same participants being measured repeatedly. Repeated measures ANOVA provides a statistically accurate way to compare multiple groups over time. There are four basic assumptions of standard ANOVA: (i) independence, (ii) the expected values of the errors are zero, (iii) they are normally distributed and (iv) the variances of all errors are equal to each other. In repeated measures ANOVA most of the same assumptions apply. The main difference is that, instead of the variance between groups needing to be homogeneous, repeated-measures ANOVA assumes sphericity, i.e. the variance of population difference scores for any two groups should be the same as the variance of the population difference scores for any other two groups (Field 2005). Sphericity requires that the variances for each set of difference scores are equal. Results from repeated measures ANOVA that violate this assumption may not be reliable (Field 2005). Analysis of covariance (ANCOVA) is similar to ANOVA except a specific variable is specified to account for pre-treatment differences between groups. The model controls for these differences and compares the effects between groups with this specific variable removed.

2.2.1.7 Health Related Quality of Life data analysis

The SF-36 produces four types of scores:

- Raw scores for each of the eight health and well-being domains
- 0 - 100 scale scores for these domains
- norm based scores to facilitate comparison with a healthy population
- Two summary scores: the physical component summary score and the mental component summary score.

Six steps were followed to score this instrument (Jenkinson *et al.* 1996; Ware *et al.* 2008) and these procedures facilitate comparison of results with normative data from the Oxford Healthy Lifestyles Survey (OHLS) (Wright *et al.* 1992).

Step 1: Once participants had completed the paper version of the UK SF-36 their responses were used to calculate raw scores using the algorithm in Table 2.1.

Table 2. 1 SF-36 scoring algorithm to calculate raw scores and to convert raw scores 0-100 scale

Scale	Sum of final response values	Lowest and highest possible total raw scores	Possible total raw scores range
Physical functioning	3a+3b+3c+3d+3e+3f+3g +3h+3i+3j	10,30	20
Role-physical	4a+4b+4c+4d	0,4	4
Bodily pain	7+8	2,11	9
General health	1+10a+10b+10c+10d	5,25	20
Vitality	9a+9e+9g+9i	4,24	20
Social functioning	6+9j	2,11	9
Role-emotional	5a+5b+5c	0,3	3
Mental health	9b+9c+9d+9f+9h	5,30	25

Step 2: Transforming raw scores to the 0-100 scale for each domain involved subtracting the lowest possible raw score from the actual raw score, dividing by the possible raw score range and multiplying by 100.

Step 3: Calculation of Norm Based Scores for the eight health domain scales involved standardizing each SF-36 health domain score using a *z*-score (Table 2.2). In statistics, a standard score or z-score is the conversion of a set of scores by subtracting the mean from each score and then dividing by the standard deviation, thus giving a mean of 0 and a SD of 1 (Jenkinson *et al.* 1996). Z-scores indicate how many standard deviations an observation is above or below the mean of the population under study. To compare this study population to another sample (comparison with norm based scores), the mean of the comparative sample was subtracted from this study population mean and the result was

divided by the comparative population's standard deviation (Jenkinson *et al.* 1996). In this case:

Z = (domain score – OHLS mean for that domain) / OHLS SD for that domain

Table 2. 2 OHLS mean and standard deviation scores needed to transform SF-36 0-100 scores to z-scores

Health Domain Scale	Mean	Standard Deviation
PF	88.40	17.98
RP	85.52	29.93
BP	82.93	31.76
GH	88.01	19.58
VT	73.77	17.24
SF	61.13	19.67
RE	81.49	21.69
MH	73.52	19.90

RF = Physical functioning, RP = role-physical, BP = bodily pain, GH = general health, V = vitality, SF = social functioning, RE = role-emotional, MH = mental health

Step 4: Transformation of z-scores to norm-based scores involved a T-score transformation (Mean = 50, SD = 10) (Jenkinson *et al.* 1996). This simply means that rather than having a mean of 0 and a SD of 1 (as with z-scores), the data is assigned a new mean and SD. Instead of reading results on the basis of how many SD above or below the mean of that population an observation is, results are presented with a mean of 50 and SD of 10. This facilitates an easier interpretation of the data. A T-score transformation is

accomplished by multiplying each z-score by 10 and adding 50 to the resulting product (Jenkinson *et al.* 1996).

Step 5: The Physical (PCS) and Mental Component Summary (MCS) score are calculated by:

1. Multiplying each UK SF-36 health domain scale z-score by its respective factor score coefficient from the OHLS sample (Table 2.3) and then summing the eight products.
2. Secondly, aggregate PCS and MCS scores were standardized using a linear *T*-score transformation with a mean of 50 and a standard deviation of 10 as described in step 4.

Table 2. 3 Factor score coefficients from OHLS UK general population data needed to calculate norm based scores

Health Domain Scale	PCS	MCS
PF	0.418	-0.213
RP	0.334	-0.087
BP	0.366	-0.125
GH	0.222	0.036
VT	-0.017	0.286
SF	0.083	0.201
RE	-0.179	0.394
MH	-0.200	0.444

PCS = Physical component summary score, MCS = mental component summary score, RF = Physical functioning, RP = role-physical, BP = bodily pain, GH = general health, V = vitality, SF = social functioning, RE = role-emotional, MH = mental health

Once the SF-36 raw scores were converted to 0 – 100 scales and the norm based scores were calculated data were analysed in a number of ways. Firstly, pre-treatment SF-36 scores were compared between the two treatment groups using individual samples T-Test. Secondly, SF-36 scores were compared within each group over time (from pre-treatment to 6 month follow-up) using paired T-Test with the appropriate Bonferroni correction (i.e. the resultant P value × 16). A statistically significant result means that the result was unlikely to have been found by chance. In tests of significance one accepts a degree of risk, normally set at 5% or $\alpha = 0.05$. This means that if the test was repeated 100 times the same result would be found 95% of the time. If one performs multiple tests, the risk of type 1 error (accepting the null hypothesis when it should have been rejected) increases proportionate to the number of tests performed. To account for this a correction is required and Bonferroni correction is one of the most popular (Field 2005). It means that instead of setting the significance level at $\alpha = 0.05$, it is set at α/n, where n is the number of tests to be performed.

Thirdly, treatment groups were compared for effectiveness using analysis of covariance (ANCOVA). ANCOVA combines ANOVA with linear regression. The purpose of ANCOVA is to compare the effect of groups (e.g. treatment group with a placebo group) while statistically controlling for an additional variable, the covariate. The covariate is measured prior to the intervention so that scores on the covariate are not affected by the intervention. Regression procedures remove the variation in the dependent variable caused by the covariate. Then the ANOVA is conducted on the adjusted scores. Accounting for the effect of a covariate increases the sensitivity of the F-test, which indicates the significance of the result. ANCOVA is often used to control for pre-intervention scores in pre-test post-test studies comparing multiple groups and pre-test scores are used to control any pre-existing differences between the groups (Pallant 2005). It can occur, especially with very large samples that one can find a statistically significant

result but the actual difference in the mean scores between the groups is very small and clinically insignificant. Partial Eta Squared is a guide to interpret the actual effect size of statistically significant results (Pallant 2005). Partial Eta Squared is a common effect size statistic that represents the proportion of variance of the dependent variable that is explained by the independent variable. Values for Eta Squared can range from 0 to 1 and standard interpretations are that values around 0.01 represent a small effect, 0.06 represents a moderate effect and greater than 0.14 represents a large effect (Cohen 1988).

Finally, a multiple linear regression model was constructed to identify factors that predict better subjective HRQOL 6 months after ECT. Two separate multiple linear regression models were constructed using the physical and mental component summary scores as dependant variables. The end of treatment variables included in the model were; an a priori definition of remission status (HDRS score of $\leq$ 10); a measure of global cognitive functioning (ACE-R); a specific measure of executive function (Trail Making Test Part B); subjectively perceived cognitive side-effects (CSSES); treatment resistance; age; gender and laterality.

2.2.1.8 Attitudes Data analysis

2.2.1.8.1 Factor analysis

The majority of trials and studies of the attitudes of patients treated with ECT since the first study of this type in 1980 have used a descriptive approach to data analysis. Numbers and percentages of patients that responded positively or negatively to specific questions has been the most frequent method of reporting results. Initially, results will be presented in this way but in order to compare treatment groups a more advanced statistical approach was needed. The 53 attitude questions were factor analysed to uncover the concepts that influenced patient's attitude towards ECT. The aim of factor analysis is to

simplify a matrix of correlations so that they can be explained in terms of a reduced number of latent variables (Kline 1994). The questions administered cover an expansive range of the phenomenon of interest. However, using this quantity of questions prohibits rigorous statistical analysis through multiple comparisons and factor analysis was used to uncover the unobservable latent variables that emerge from the data. Unlike most statistical tests, factor analysis is not a method of comparing groups for difference or hypothesis testing but is a data reduction technique (Pallant 2005). The few latent variables that are uncovered emerge from inter-correlations from the original data (Kline 1994). They represent major themes of a considerably reduced number compared to the original questionnaire and facilitate more rigorous statistical analysis. The steps in factor analysis are:

1. Administer the survey or questionnaire and collect the responses.
2. Generate a correlation matrix which is a set of correlation coefficients between all of the variables (Kline 1994).
3. Determine the factorability of the data (Pallant 2005). Kaiser-Meyer-Olkin (KMO) is an index for comparing the observed correlation coefficients to partial correlation coefficients and large values indicate that the data are suitable for factor analysis (Pallant 2005). Bartlett's Test of Sphericity tests the null hypothesis that the variables in the correlation matrix are uncorrelated (Kline 1994). A significant value ($P < 0.05$) indicates that the strength of the relationship among the variables is strong so factor analysis is recommended.
4. Select the number of factors to be determined. It is important that the model accounts for as much of the variance in the data with as few factors as possible (Kline 1994). Two methods were used to determine the number of factors to establish from the data. A parallel analysis in which eigenvalues (the proportion of variance explained by each factor (Kline 1994)) obtained from a randomly

generated data set of the same size were compared to the study dataset (Hayton *et al.* 2004). Only those eigenvalues that exceeded the corresponding values from the random data set were retained. This approach to identifying the correct number of factors to retain has been shown to be the most accurate (Pallant 2005). SPSS does not have a procedure to run a parallel analysis but it is possible to run a parallel analysis using a recognised and validated syntax procedure (O'Connor 2000). A Scree plot was also used as it visually represented the number of factors to determine and facilitated understanding (Catell 1966).

5. Extract the factors. A factor is a linear combination of variables (Kline 1994). Factor analysis generates factors so that the combination of variables accounts for the most variance in the correlations from the correlation matrix (Kline 1994). Factor loadings define the factors and are correlations of the variables with the factor or the weighted combination of variables that best explains the variance in the factor (Kline 1994). Factor loadings represent the amount of variance a variable in each factor accounts for. The squared factor loading of a variable indicates the percentage of variance of that variable that is explained by the factor. In turn, the average of all the squared loadings of each factor indicates the percentage of variance in the correlation matrix explained by each factor (Kline 1994). This is a complicated mathematical process and as with all statistical procedures contemporary statistical software packages facilitate the procedure. In small samples or in questionnaires with few questions it is possible that one factor would account for all of the variance. However, in larger samples or more complicated questionnaires the factor analysis process calculates the first factor which accounts for a certain amount of variance in the correlation matrix. Then the process partials out the explained variance and the process calculates a second factor from the residual matrix and so on until all of the meaningful variance in the correlation

matrix is accounted for (Kline 1994). In this way the first factor is uncorrelated with the second and remaining factors. In this process a set of uncorrelated factors is derived from a single correlation matrix. There are a number of different extraction methods, including maximum likelihood and principal component analysis. The best method is generally maximum likelihood (DeCoster 1998).

6. Rotation of the factors to a final solution. Again, statistical software packages facilitate this procedure but, in brief, factors are rotated to find a factor solution (combination of variables and factor loadings) that has the simplest interpretation. The aim of rotating the factors is to achieve a "simple structure" where variables load highly on one factor only and low on all others, which greatly increases ease of interpretation of factors (Thurstone 1947). One must chose the type of rotation from a choice: orthogonal (uncorrelated and included only on the basis of the variance they account for) or oblique (factors can be correlated, which is most often the case in the social sciences) (Kline 1994).
7. Interpret the factor structure. Each of the variables (questions on the original questionnaire) will be linearly related to each of the factors. The strength of this relationship is contained in the respective factor loading, produced by the rotation. Interpretation of the factors is a subjective process. Some questions may need to be excluded if they do not fit with the remaining questions to form the factor. Interpretation of the factors (domains) from the following factor analysis is described in detail later.
8. Construct factor scores (composite scores) for further analysis. The score for a given factor is a linear combination of all of the measures, weighted by the corresponding factor loading. These factor scores can then be used in analyses just like any other variable (DeCoster 1998). In this case the factors were labelled once

they were interpreted (step 7) and used as scales representing intensity of attitude regarding their respective domains.

2.2.1.8.2 Interpretation of composite scores

Each question in the questionnaire was framed as a statement to identify a participant's intensity of agreement or disagreement with that statement. Some questions were framed so that agreement was recorded as positive (a high score of 4 or 5) while others were framed so that disagreement was positive (again, a high score of 4 or 5). Responses that were negative about ECT were recorded as low scores, such as a 1 or 2. Neutrality always scored a 3. With this in mind it is reasonable to accept that composite factor scores are structured the same way. Values around the midpoint of each factor represent a neutral attitude towards that factor whereas low scores represent a negative attitude and high scores represent a positive attitude. Although it is not possible to compare mean scores with the respective midpoint value to identify if participants in each group were statistically significantly positive or negative, these data are presented visually and levels of positivity or negativity in each factor relative to a neutral attitude can be seen. Group comparisons and changes over time were performed with more advanced statistical methods.

2.2.1.8.3 Group comparisons

Once domain scores were created a mixed between-within subjects analysis of variance (ANOVA) (Tabachnick & Fidell 2001), sometimes referred to as a split plot ANOVA (Pallant 2005) was performed for each individual factor to compare attitudes between the two treatment groups over time. While a between-groups analysis compares two or more different groups (two types of ECT for example) and a within-groups analysis compares

one group of subjects exposed to two or more conditions (1 group with 2 different assessment time-points for example), a mixed between-within subjects ANOVA combines both in one model (Pallant 2005). In this case there are two independent variables: one is a between-subjects variable (treatment group) and the other is the within-subjects variable (time: end of treatment assessment and 3 month follow-up). This type of analysis reveals; (1) if there is a change in participants' level of positivity towards ECT across the two time periods (after the intervention and 3 months later) (main effect for time); (2) It will compare the two interventions in terms of their effect on positivity of attitudes (main effect of group); and (3) finally, it will reveal if the change in attitudes over time was different between the two groups (interaction effect).

2.2.1.8.4 Prediction of positive and negative attitudes

Multiple linear regression is specified using a continuous dependent variable but none of the factors that emerged from the factor analysis was suitable to represent positive or negative attitude towards ECT as a variable in its own right. Also, responses to the individual questions in the questionnaire were not suitable to use as a continuous dependent variable as individually they were ordered Likert type responses. Therefore, logistic regression was used to identify the factors that influence attitudes towards ECT. Logistic regression facilitates the use of a categorical dependent variables and facilitates the use of predictor variables that are categorical or continuous, or a combination of both in one model (Pallant 2005). Responses to the question "I think ECT helped me" at end of treatment were used as the dependent variable to predict a positive attitude towards ECT. Responses to the question "I would never have ECT again" at end of treatment were used as the dependent variable to predict a negative attitude towards ECT. Responses to the 5 point Likert type statement, "I think ECT helped me" (strongly disagree, disagree, don't

know, agree and strongly agree) were dichotomized: agree and strongly agree responses were recoded as positive responses and strongly disagree and disagree responses were recoded to negative responses. Also, responses to the 5 point Likert type statement, "I would never have ECT again" (strongly disagree, disagree, don't know, agree and strongly agree) were dichotomized: agree and strongly agree responses were recoded as negative responses and strongly disagree and disagree responses were recoded to positive responses. Don't know responses were excluded from these analyses. Remission status at end of treatment, cognitive status at end of treatment, laterality, gender and treatment resistance were included as explanatory variables in these models.

2.2.1.8.5 Analysis of the knowledge questions

The five knowledge questions were excluded from the factor analysis because the answers to these questions were either right or wrong and could not be measured as intensity of attitude. Responses to these questions were dichotomized to correct or incorrect responses (i.e. definitely or probably answers were coded as correct and probably not or definitely not were coded as incorrect). These data were then compared between groups using Chi Squared Tests or Fishers Exact Test where the number of responses was too small to use Chi Squares.

2.2.1.8.6 Qualitative data analysis

The attitudes questionnaire also requested participants to complete a free-text section where they were encouraged to write down anything they would like to say about their experience of ECT.

Template analysis was used as a means to analyse these qualitative data. Template analysis (TA) refers to a particular way of thematically analysing qualitative data (School of Human & Health Sciences 2007). Generally, interview transcripts are analysed but any kind of textual data such as responses to open-ended questions on a questionnaire can also be analysed using this method. In TA a coding template is developed that encapsulates themes identified by the researcher as important in a data. This template organises these themes in a meaningful and useful structure with which to analyse the data. The a priori codes that are defined are expected to be relevant to the analysis. These codes can be modified or deleted if they are found not to be useful. Once a priori themes are defined, the researcher reads through the data thoroughly, coding passages that relate to and inform the research question. If these passages relate to a priori themes they are coded so and if not new themes are created that inform the continuing analysis (School of Human & Health Sciences 2007). When analysing multiple detailed transcripts the researcher may develop an initial template by creating codes or themes from the initial number of manuscripts and apply this template to the remaining transcripts, continually modifying and adding to the template whenever additional data informs the research question. However, in this study an initial template was devised from the composite scores that were derived from the factor analysis of the attitudes questionnaire. This initial template was applied to the textual responses and modified when new themes emerged. These themes were used to provide structure and a means to interpret the responses of participants. This qualitative analysis was also compared for consistency with the quantitative analysis that preceded it.

3 Results

3.1 Recovery of orientation

From May 2008 to March 2011 there were 324 patients referred for ECT. 308 of these patients were referred acutely for the treatment of depression and 165 of these were eligible to take part in the trial. 100 patients gave informed consent to take part in the trial and were randomized to receive either standard 1.5 × ST bitemporal ECT or 6 × ST right unilateral ECT (Appendix 5). The 100 participants were white, Irish and 60% of the sample were female. There were fifty participants randomly allocated to each treatment group. Demographic and clinical details are presented in Table 3.1. There were no statistically significant differences in demographic or clinical details between the treatment groups prior to treatment.

Table 3. 1 Pre-treatment clinical & demographic details	High-dose RUL Mean (SD)	Bitemporal Mean (SD)	t-test (d.f.)	χ^2-test (d.f.)	P
Demographic details					
Age	56.7 (15.0)	59.1 (13.8)	-1.173 (98)		P = 0.244
Female	29 (58%)	31 (62%)		0.167 (1)	P = 0.683
Smoker	19 (38%)	16 (32%)		1.165 (1)	P = 0.280
Alcohol consumer	19 (28%)	18 (36%)		0.581 (1)	P = 0.446
Clinical details					
Baseline HDRS	30.3 (6.8)	29.3 (7.0)	0.720 (98)		P = 0.473
Baseline BDI II	32.1 (11.9)	37.2 (13.6)	-1.515 (56)		P = 0.135
Benzodiazepine medication	28 (56%)	36 (72%)		2.127 (1)	P = 0.145
Antihypertensive medication	10 (20%)	6 (12%)		0.670 (1)	P = 0.413
Statin medication	10 (20%)	12 (24%)		0.058 (1)	P = 0.809
Antipsychotic medication	37 (74%)	38 (76%)		2.127 (1)	P = 0.145
Antidepressant medication	42 (84%)	47 (94%)		1.634 (1)	P = 0.201
Lithium	17 (34%)	13 (26%)		0.762 (1)	P = 0.383
Psychotic	8 (16%)	6 (12%)		0.500 (1)	P = 0.479
Treatment resistant	25 (50%)	30 (60%)		0.646 (1)	P = 0.421
Precious ECT	22 (44%)	20 (40%)		0.041 (1)	P = 0.839
Days in hospital before treatment	33.0 (29.5)	23.7 (28.1)	1.601 (97)		P = 0.113
Total days in hospital	88.4 (69.7)	69.3 (56.8)	1.495 (97)		P = 0.138

According to NICE (2009) ECT is indicated for the treatment of severe depressive illness, catatonia or prolonged or severe mania and these indications were recorded in patient's treatment record. Severe depressive illness was the primary diagnosis in both groups: n = 50 (100%) participants in the bitemporal group and n = 48 (96%) of participants in the high-dose RUL group. Other indications for ECT were also recorded from a choice of: rapid response required, acute suicidality, physical deterioration, refractory to medication, maintenance ECT or other indication and referring teams could select more than one option (Table 3.2). It is worth noting that treatment resistant in Table 3.1 refers to criteria used in this study as outlined in chapter 2. Table 3.2 documents reasons for referral for ECT recorded by the referring team in the participants ECT booklet as required by the Mental Health Commission: Refractory to medication is one of 5 options referring teams have to choose from as they select the indications for a course of ECT.

Table 3. 2 Indications for ECT for each treatment group recorded by prescibing Consultant Psychiatrist

	High-dose RUL N (%)	Bitemporal N (%)
Refractory to medication	28 (56%)	34 (68%)
Rapid response required	10 (20%)	6 (12%)
Acute suicidality	2 (4%)	2 (4%)
Physical deterioration	0	0
Other indication	0	0

There were 374 treatments administered in the high-dose RUL group (mean = 7.5) compared with 392 treatments administered in the bitemporal group (mean = 7.8). The first ECT treatment session was used to establish participant's seizure threshold (ST). The vast majority of participants' ST were established at the first treatment session and in almost all cases by the second treatment session (Table 3.3 - Table 3.6). There were 15 more second

stimulations and 19 more third stimulations required in the bitemporal group compared to the high-dose RUL group but this may be accounted for by the fact that ST is higher for bitemporal electrode placement, and not as readily achievable.

Table 3. 3 Total number of second stimulations for each treatment group

2nd Stimulation	Not re-stimulated	Re-stimulated	Total
High-dose RUL group (N)	324 (87%)	50 (13%)	374
Bitemporal group (N)	327 (83%)	65 (17%)	392
Total	651 (85%)	115 (15%)	766

Table 3. 4 Number of participants that required a second stimulation in proportion to the number of participants that had ECT at each treatment session

Treatment session number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
High-dose RUL group (N) (%)	37 (74)	8 (16)	1 (2)	1 (2)	3 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Bitemporal group (N) (%)	40 (80)	17 (34)	2 (4)	0 (0)	2 (4)	1 (2)	0 (0)	1 (4)	1 (6)	1 (8)	0 (0)	0 (0)

Table 3. 5 Total number of third stimulations for each treatment group

3rd Stimulation	Not re-stimulated	Re-stimulated	Total
High-dose RUL group (N)	357 (95%)	17 (5%)	374
Bitemporal group (N)	356 (91%)	36 (9%)	392
Total	713 (93%)	53 (7%)	766

Table 3. 6 Number of participants that required a third stimulation in proportion to the number of participants that had ECT at each treatment session

Treatment session number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
High-dose RUL group (N) (%)	16 (32)	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Bitemporal group (N) (%)	32 (64)	3 (6)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

There was no statistically significant difference between the treatment groups in the number of participants that required a second stimulation, $\chi^2(1) = 1.307$, $P = 0.253$. However, participants in the bitemporal group required twice as many third stimulations as the RUL ECT group which was a statistically significant difference between the treatment groups, $\chi^2(1) = 5.693$, $P = 0.017$.

ECT treatment details are summarised in table 3.7. As expected, seizure threshold was lower in the RUL group while stimulus intensity was significantly higher for this group compared with the bitemporal group. There was no difference in seizure duration between the treatment groups.

Table 3. 7 ECT details in each treatment group

	High-dose RUL		Bitemporal		
	Mean	SD	Mean	SD	t
Seizure threshold (mC)[1]	125.3	56.5	292.0	192.6	$P < 0.001$
Stimulus intensity (mC)[2]	670	391.3	443.9	316.0	$P < 0.001$
Seizure duration[3]	39.6	20.8	40.2	19.1	$P = 0.691$
Number of treatments[4]	7.5		7.8		

1 – Mean seizure threshold

2 – Cumulative stimulus intensity from 1st, 2nd and 3rd stimulation, if applicable, at each treatment session

3 - Cumulative seizure duration in seconds from 1st, 2nd and 3rd stimulation, if applicable, at each treatment session

4 – Mean number of treatments administered for each treatment group

3.1.1 Time to recovery of orientation

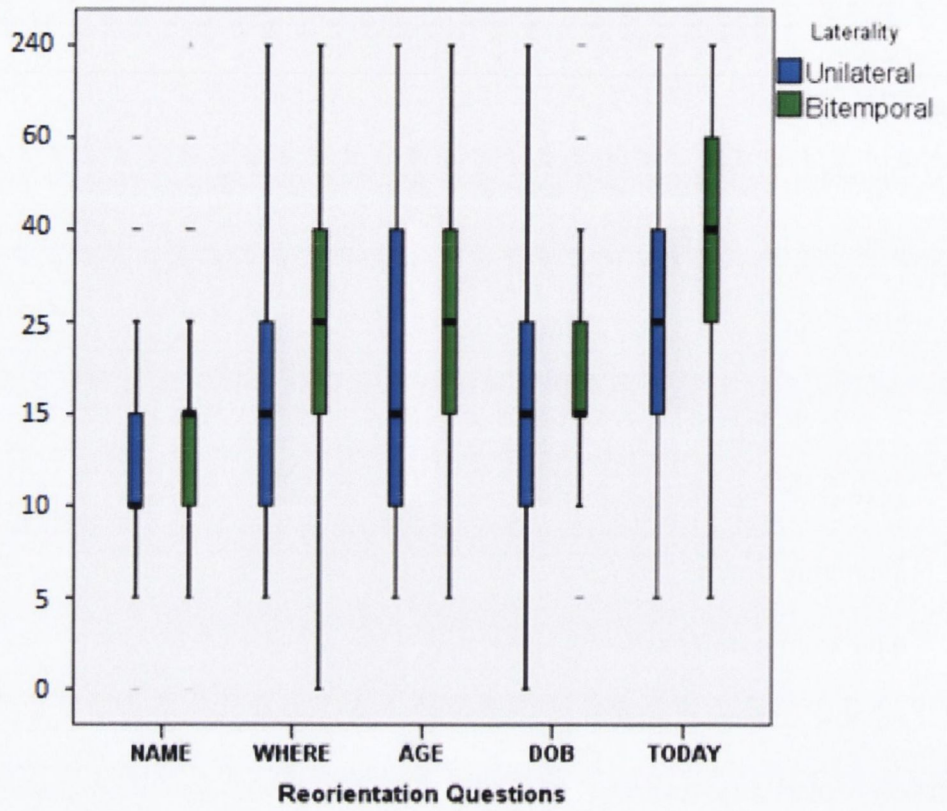
Mean times to respond to individual questions are presented in Table 3.8 and visually in Figure 3.3. Response times to individual questions was faster in the high-dose RUL than in the bitemporal group and the order in which questions were answered was the same for both groups and is consistent with previous findings (Daniel & Crovitz 1982; Calev *et al.* 1991a). Name was the first question correctly answered followed by date of birth, where one is, age and day of the week.

It has been standard practice to calculate recovery times by averaging time to answer 4 out of 5 questions for each individual at each treatment session and then averaging time to reorientation for all individuals in each treatment group. However, these data are not independently generated and are therefore correlated. Such averaging is not a reliable statistical method of analysis for these data and fails to make use of a wide range of explanatory information. It was therefore not appropriate to compare these results further with direct comparisons. The differences in time to reorientation were analysed using survival analysis as described in 2.2.1.1.

Table 3. 8 Mean time in minutes to answer each question for the bitemporal and high-dose RUL groups

	Name Mean (sd)	Where Mean (sd)	Age Mean (sd)	DOB Mean (sd)	Today Mean (sd)
High-dose RUL ECT group	13.02 (6.2)	16.36 (9.9)	20.24 (11.6)	15.11 (7.8)	21.61 (11.9)
Bitemporal ECT group	15.03 (5.8)	23.13 (11.4)	23.67 (11.4)	17.67 (7.6)	27.44 (12.1)

Figure 3. 1 Time to answer reorientation questions per treatment group

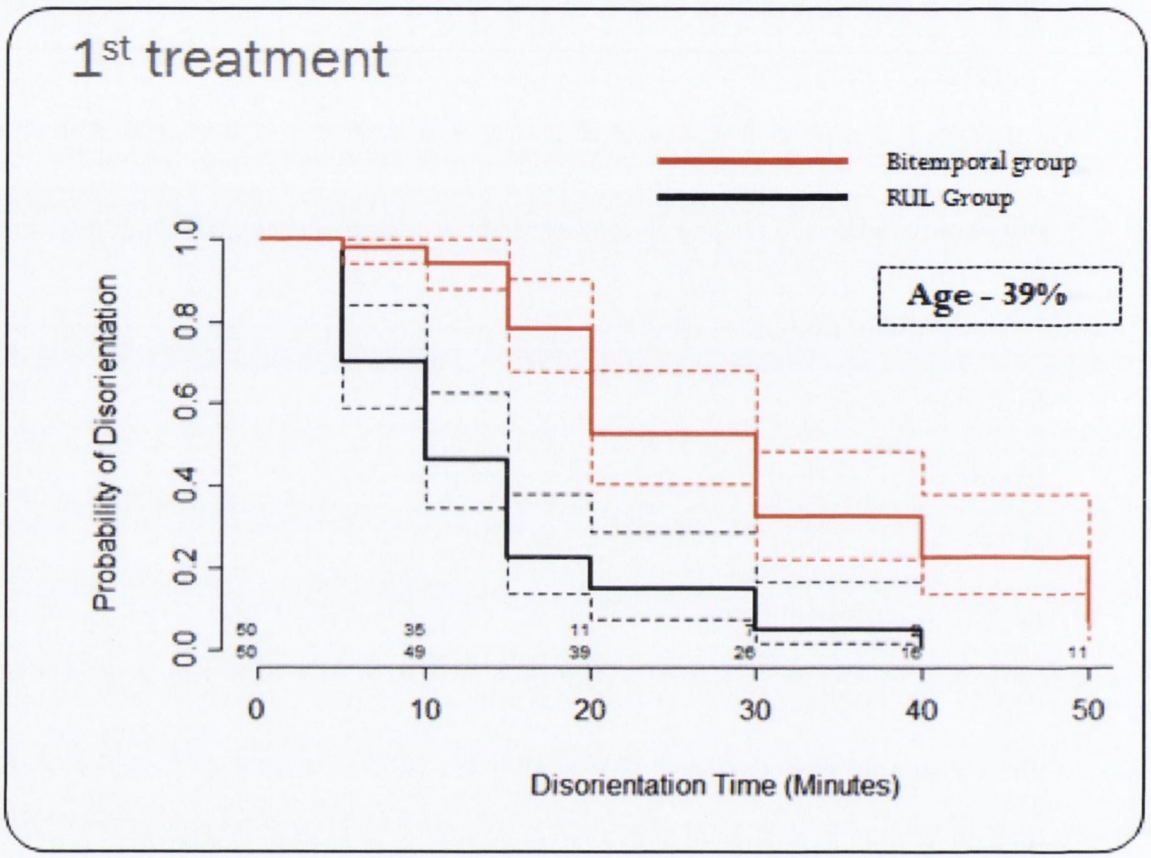


The X-Axis represents each of the five reorientation questions asked during the recovery period. The Y-axis represents time from resumption of spontaneous breathing at which the reorientation questions were asked. The blue box represents the high dose RUL group. The green box represents the bitemporal group. The black line within each box is the median value. The upper end of each box above the median represents the upper quartile or 25% of data greater than the median. The lower end of each box below the median represents the lower quartile or 25% of data less than the median. Whiskers extending above and below the box represent the maximum and minimum values excluding outliers. Dots above and below the whiskers represent scores that were considerably lower than normal for these data.

The first treatment session was used to establish the patient's seizure threshold (ST) and as such, ECT may not have been administered at a therapeutic dose or in the bitemporal group may have been closer to a therapeutic dose than the high-dose RUL group. Also, there may have been multiple stimulations administered at the first treatment session as the participant's ST was established. For these reasons time to recovery of orientation data were analysed separately for first and subsequent treatments.

At the first treatment session, there was a significant difference between the treatment groups; bitemporal electrode placement was associated with an 65% reduced likelihood of reorientation compared with high-dose RUL ECT at each of the time-points at which orientation was measured throughout recovery (P = 0.012) (Figure 3.2). Increasing decades of age were also associated with a 39% reduced likelihood of reorientation throughout the recovery period at the first treatment (P = 0.033). Conversely, the consumption of alcohol was associated with a protective effect on reorientation: increasing units of alcohol consumed per week was associated with a 13% increased likelihood of reorientation throughout the recovery period (P = 0.013). Alcohol consumption was measured in standard units consumed per week as reported by participants themselves. However, participants would not have consumed alcohol during their inpatient treatment. Participants were in hospital 33.0 (29.5) and 23.7 (28.1) days prior to treatment (Table 3.1) in the RUL group and the bilateral group respectively so this effect on reorientation time is difficult to explain.

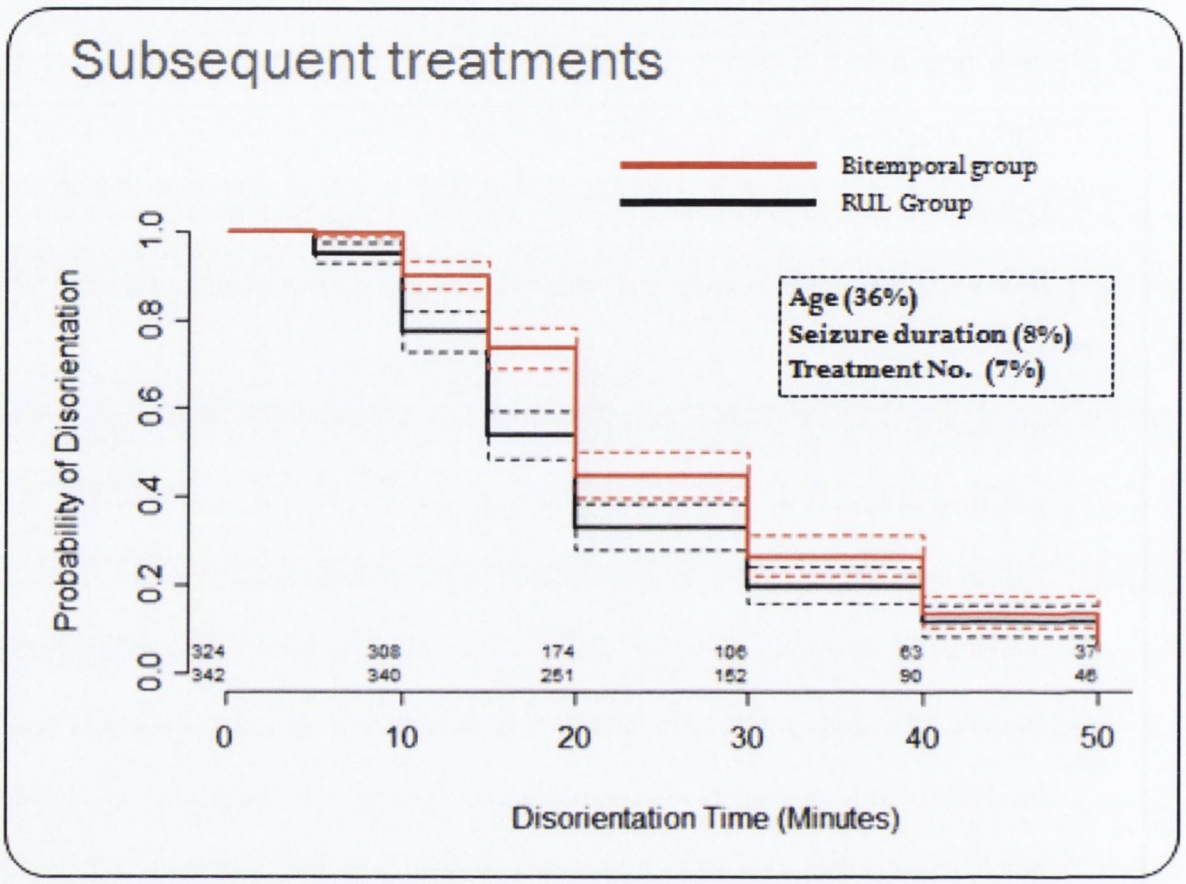
Figure 3. 2 Kaplan-Meier survival curves for time to reorientation for the first ECT treatment session only



- Solid red line represents probability of disorientation for respective time-points for the 1.5 × ST bilateral ECT group
- Dashed red lines represent confidence intervals for probability of disorientation for respective time-points for the 1.5 × ST bilateral ECT group
- Solid black line represents probability of disorientation for respective time-points for the 6 × ST RUL ECT group
- Dashed black lines represent confidence intervals for probability of disorientation for respective time-points for the 6 × ST RUL ECT group
- Y-axis represents the probability of disorientation
- X-axis represents the time-points in minutes following resumption of spontaneous breathing at which assessments of reorientation were performed
- Numbers above the X-axis represent the number of treatment sessions at which reorientation was yet to be achieved by the respective time-point:
    - Upper numbers represent the high-dose RUL ECT group
    - Lower numbers represent the 1.5 × ST bilateral ECT group

For treatments other than the first, bitemporal ECT was associated with a reduced likelihood of reorientation of approximately 44% compared with high-dose RUL ECT at each time-point at which orientation was assessed throughout the recovery period ($P = 0.013$) (Figure 3.3). Increasing decades of age were associated with a reduced likelihood of reorientation of approximately 36% ($P < 0.001$) i.e. being ten years older increases ones time to reorientation by approximately 36% compared to another patient ten years younger. For every ten seconds of seizure activity (measured by EEG) there was an associated reduced likelihood of reorientation of 8%, $P = 0.012$. Increasing numbers of treatment sessions were also associated with a reduced likelihood of reorientation of approximately 7% for each additional treatment session, $P = 0.006$. Somewhat counter intuitively, 100mC increases in the total dose of millicoulombs administered at treatment sessions were associated with an increased likelihood of reorientation of approximately 29%. However, the fact that the high-dose RUL group received higher stimulus intensities and recovered much more quickly than the bitemporal group most likely accounts for this. Also, unit (beats per minute) increases in heart rate measured upon resumption of spontaneous breathing were associated with a protective effect: five point increases in post ECT heart rate were associated with an increased likelihood of reorientation of 5% ($P = 0.033$). Similarly, a 5 point higher pre-treatment mean arterial blood pressure was associated with a 7% increased likelihood of reorientation, $P = 0.023$.

Figure 3. 3 Kaplan-Meier survival curves for time to reorientation for subsequent ECT treatment sessions



- Solid red line represents probability of disorientation for respective time-points for the 1.5 × ST bilateral ECT group
- Dashed red lines represent confidence intervals for probability of disorientation for respective time-points for the 1.5 × ST bilateral ECT group
- Solid black line represents probability of disorientation for respective time-points for the 6 × ST RUL ECT group
- Dashed black lines represent confidence intervals for probability of disorientation for respective time-points for the 6 × ST RUL ECT group
- Y-axis represents the probability of disorientation
- X-axis represents the time-points in minutes following resumption of spontaneous breathing at which assessments of reorientation were performed
- Numbers above the X-axis represent the number of treatment sessions at which reorientation was yet to be achieved by the respective time-point:
    - Upper numbers represent the high-dose RUL ECT group
    - Lower numbers represent the 1.5 × ST bilateral ECT group

3.1.2 Prolonged disorientation

Reorientation was defined a priori as having answered four of the five questions that were asked within 50 minutes of resumption of spontaneous breathing. Participants who failed to achieve this criterion after 50 minutes were considered to have experienced an episode of prolonged disorientation. Twenty four individuals (24%) experienced fifty-two episodes of prolonged disorientation (7% of all treatments) (Table 3.9).

Table 3. 9 Prolonged disorientation following bitemporal and high-dose RUL ECT treatment sessions

	Re-orientated	Prolonged disorientation	Total
High-dose RUL ECT	351 (94%)	23 (6%)	374
Bitemporal ECT	363 (93%)	29 (7%)	392
Total	714 (93%)	52 (7%)	766

In the bitemporal group there were 13 individuals that experienced prolonged disorientation representing 26% of bitemporal participants. These 13 participants experienced 29 episodes of prolonged disorientation (56% of all episodes of prolonged disorientation, 7.4% of all bitemporal treatments). Of these 13 individuals there were three males and ten females.

In the high-dose RUL group there were 11 cases of prolonged disorientation representing 22% of high-dose RUL participants. These 11 participants experienced 23 episodes of prolonged disorientation (44% of all episodes of prolonged disorientation, 6%

of all high-dose RUL treatments). Of these 11 individuals there were four males and seven females.

There was no significant difference between the treatment groups in the number of individuals that experienced prolonged disorientation, χ^2 (1) = 0.055, P = 0.815.

In total between both groups there were 17 females (28% of women) and 7 men (17.5% of men) that experienced prolonged disorientation. There was no significant difference between the sexes in likelihood of prolonged disorientation, χ^2 (1) = 1.007, P = 0.316.

The mean age of the twenty four participants that experienced prolonged disorientation was 65 (±13.1) years. The mean age of the group that did not experience prolonged disorientation (N = 76) was 56 (±13.5) years. The group that suffered prolonged disorientation was statistically significantly older than those that did not, t(41) = -3.03, P = 0.004.

It has been reported in the past that patients with high serum Lithium levels are more susceptible to prolonged disorientation (Thirthalli *et al.* 2010). In this sample 29% (N=22) of the group that did not suffer prolonged disorientation were taking regular Lithium with a mean Lithium level of 0.52 (0.23) mEq/L. 33% (N=8) of the group that did experience prolonged disorientation were prescribed regular Lithium and this group had a mean Lithium level of 0.74 (0.33) mEq/L. There was a trend for the group that experienced prolonged disorientation to have higher serum Lithium levels but there was no statistically significant difference in average Lithium level between the group that suffered prolonged disorientation and that group that did not, t(26) = -1.970, P = 0.060.

To elucidate the factors that contribute to cause prolonged disorientation a GEE model was constructed comprising relevant treatment parameters, patient characteristics, physical observations, anaesthetic medications and the previously described medication groups.

There was no statistically significant difference between the treatment groups in the likelihood of prolonged disorientation, $P = 0.781$. Older age was the most significant factor associated with prolonged disorientation: Increasing decades of age were associated with an 80% increased likelihood of prolonged disorientation ($P < 0.001$). A five point increase in the difference between pre-treatment heart rate and heart rate taken immediately post treatment was associated with a 10% decreased likelihood of prolonged disorientation ($P = 0.025$). This finding is significant as the average difference in heart rate was 6.6 beats per minute (bpm) for the high-dose RUL group and 7.5 bpm for the bitemporal group. Consistent with this, a ten point increase in mean arterial blood pressure from pre-treatment to immediately post treatment was associated with a 28% decreased likelihood of prolonged disorientation ($P = 0.046$). None of the medication groups, including Lithium, had an effect on the likelihood of experiencing prolonged disorientation.

3.2 Subjective physical side-effects of electroconvulsive therapy

3.2.1 Headaches

Upon reorientation participants were asked for the presence of headache. Those who did not achieve reorientation during the recovery period were also asked for the presence of headache. All those who complained of headaches were included in the analysis. 25 participants in the high-dose RUL treatment group (50%) and 24 participants from the bitemporal group (48%) complained of headaches ($\chi^2(1) = 0.040$, $P = 0.841$). There were 108 episodes of headache in total from 766 treatments (14% of all treatments): 65 (17%) from the bitemporal group and 43 (11%) from the high-dose RUL group. Headaches occurred most frequently at the first treatment session and were less likely to occur as the treatment course progressed. Headaches did occur more frequently in the bitemporal group than in the high-dose RUL group on subsequent treatments: 13 participants in each group experienced only one headache throughout their treatment course. 7 participants in the RUL group and 3 in the bitemporal group complained of headaches on two occasions. 4 people in the RUL group experienced a headache on three occasions. Only 1 participant in the RUL group and two in the bitemporal group experienced a headache after four separate treatments. No-one in the RUL group complained of more than 4 headaches while 1, 2, and 4 participants complained of five, six and seven headaches respectively in the bitemporal group (Table 3.10).

Table 3. 10 Number (%) of trial participants reporting headaches per group per treatment session

Treatment session number[1]	N bitemporal[2]	N (%) headaches[3]	N RUL[4]	N (%) headaches[5]
1	50	12 (24)	50	12 (24)
2	50	8 (16)	50	5 (10)
3	50	9 (18)	50	7 (14)
4	48	6 (13)	48	4 (8)
5	47	6 (13)	46	3 (7)
6	45	7 (16)	42	3 (7)
7	34	5 (15)	30	3 (10)
8	25	3 (12)	22	1 (5)
9	17	1 (06)	17	3 (18)
10	13	4 (31)	9	1 (11)
11	8	2 (25)	6	1 (17)
12	5	2 (40)	4	0 (0)
Total	392	65 (17)	374	43 (11)

1 – Treatment session number. A course of ECT consists of up to 12 treatments.

2 – Number of bitemporal participants treated at each treatment session

3 – Number of bitemporal participants that complained of headache after each treatment and as a percentage of all participants treated with bitemporal ECT at each treatment session

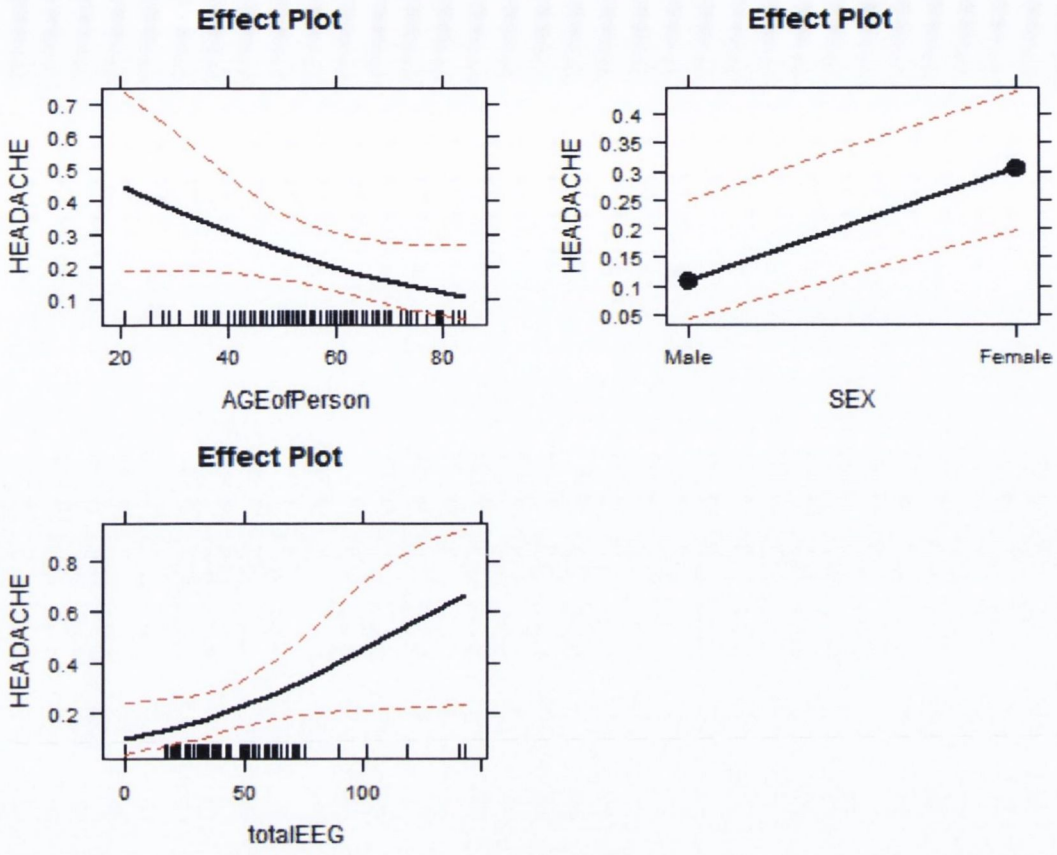
4 – Number of high-dose RUL participants treated at each treatment session

5 - Number of RUL participants that complained of headache after each treatment and as a percentage of all RUL participants that had ECT at each treatment session

There was no statistically significant difference between the treatment groups in the likelihood of complaining of headache after the first treatment session (P = 0.958). Women were approximately 29% more likely than men to complain of headaches at the first treatment session (P = 0.027). Ten second increases in seizure duration, compared to a seizure lasting ten seconds less, increased the likelihood of headache by 23%, P = 0.039. Age had a trend-worthy effect being associated with a mean decrease in headaches of approximately 35% for each increasing decade of age (P = 0.078) (Figure 3.4).

Using the generalized estimated equations (GEE) model potential predictors of headache were examined for the remaining treatments. There was no difference between the treatment groups in the likelihood of headache throughout the treatment course, P = 0.119. Females were twice as likely as men to complain of headache after treatment which is consistent with the analysis of the first treatment (P = 0.041). Total seizure duration, as measured by EEG, had a highly significant effect that was consistent with the previous analysis; ten second increases in seizure duration increased the likelihood of headache by 26%, P < 0.001. Being on a statin medication was also associated with being 90% more likely to develop a headache after ECT, P = 0.033.

Figure 3. 4 Individual effect plots for variables included in generalized linear model analysis of headaches at the first treatment session only



- Effect plots are for the total sample combined as there was no statistically significant difference between the treatment groups.
- Each effect plot represents a variable that affected the likelihood of headache
- Y-axis of each effect plot is a probability scale (Gulevich *et al.* 1961). Increases or decreases in the X-axis are associated with relative changes in the proportion of people who experience headaches.
- Short vertical dashes on bottom of each effect plot are individual raw scores
- Solid black lines represent the relationship of each variable and the likelihood of headache
- Red dashed lines represent confidence intervals

3.2.2 Nausea

Ten people in the unilateral group (20%) complained of 24 episodes of nausea (6% of unilateral treatments), which represents 61% of all complaints of nausea. There were 5 participants that complained of one episode of nausea only, 1 who experienced nausea twice, 1 that complained of nausea three times, 2 that experienced nausea four times and 1 participant that complained of nausea six times (Table 3.11).

Nine people in the bitemporal group (18%) complained of 15 episodes of nausea (4% of all bitemporal treatments), which represents 39% of all complaints of nausea. 7 participants complained of nausea on one occasion and 2 participants experienced nausea four times.

There was no difference between the groups in the number of individuals that complained of nausea: χ^2 (1) = 0.065, P = 0.799. Of the 19 participants that complained of nausea 14 were women and 5 were men: χ^2 (1) = 4.159, P = 0.041.

Table 3. 11 Number (%) of trial participants reporting episodes of nausea per treatment group per treatment session

Treatment session number[1]	N bitemporal[2]	N (%) nausea[3]	N RUL[4]	N (%) nausea[5]
1	50	5 (10)	50	5 (10)
2	50	3 (6)	50	5 (10)
3	50	2 (4)	50	3 (6)
4	48	3 (6)	48	4 (8)
5	47	0 (0)	46	2 (4)
6	45	1 (2)	42	3 (7)
7	34	0 (0)	30	0 (0)
8	25	0 (0)	22	2 (9)
9	17	0 (0)	17	0 (0)
10	13	0 (0)	9	0 (0)
11	8	1 (12.5)	6	0 (0)
12	5	0 (0)	4	0 (0)
Total	392	15 (4)	374	24 (6)

1 – Treatment session number. A course of ECT consists of up to 12 treatments.

2 – Number of bitemporal participants treated at each treatment session

3 – Number of bitemporal participants that complained of nausea after each treatment and as a percentage of all participants treated with bitemporal ECT at each treatment session

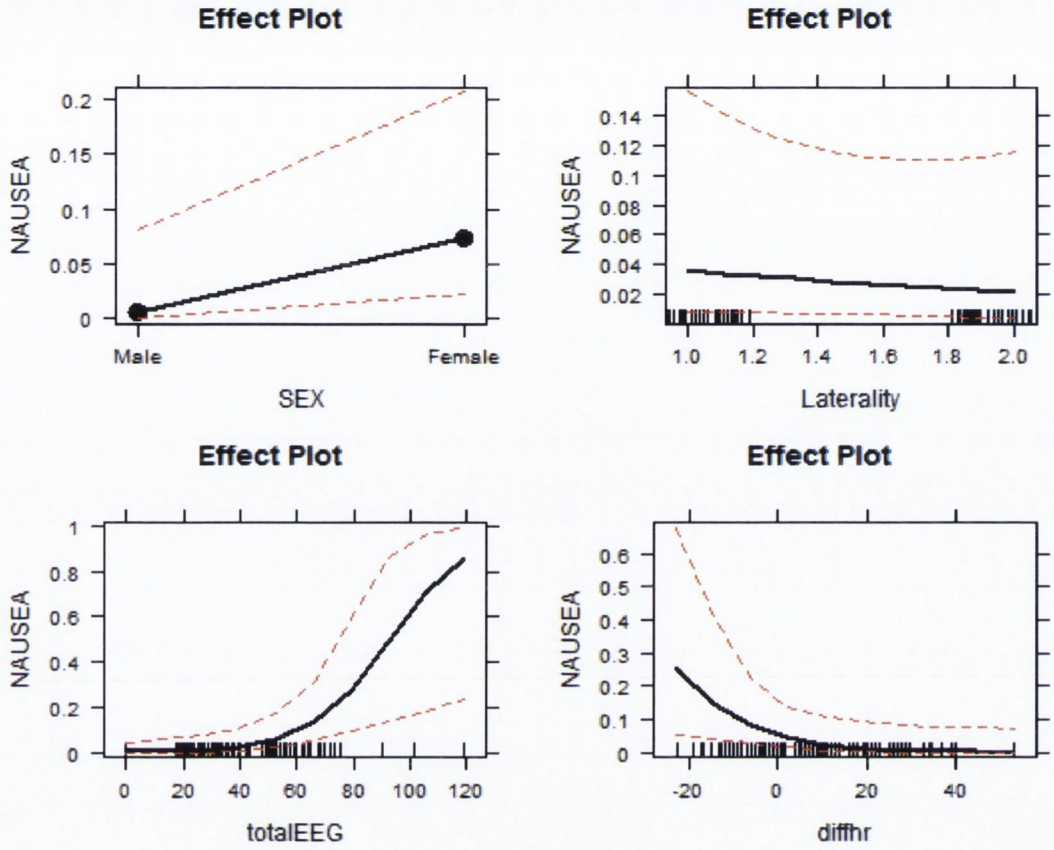
4 – Number of high-dose RUL participants treated at each treatment session

5 - Number of RUL participants that complained of nausea after each treatment and as a percentage of all RUL participants that had ECT at each treatment session

It was intended to elucidate the factors that contribute to cause Nausea. Data were analysed for the first treatment separately to data for subsequent treatment sessions. Nausea was expected to occur more frequently at the first treatment session and less thereafter because patients who complained of nausea were pre-treated with antiemetic medication prior to subsequent treatments. Ondansetron was administered to 13 participants on 67 occasions: 9 participants from the high-dose RUL group on 42 occasions and 4 participants from the bilateral ECT group on 25 occasions. Six participants did not receive ondansetron having previously complained of nausea because they refused the drug having discussed it with the anaesthetist prior to the ECT treatment. There was no statistically significant difference between the groups in the number of participants that received Ondansetron: $\chi^2(1) = 1.415$, $P = 0.234$.

There was no difference between the treatment groups in the likelihood of nausea following the first ECT session, $P = 0.524$. Being female was associated with an average increased likelihood of 56% of feeling nauseated after treatment, $P = 0.038$. Total seizure duration, as measured by EEG, was associated with an average increased likelihood of nausea of 41% for every five seconds of seizure duration, $P = 0.006$. The difference between pre and post treatment heart rate was also significantly associated with nausea after the first treatment, $P = 0.042$ but mean arterial blood pressure was not. A one point increase in the difference between pre-treatment and post treatment HR was associated with on average, an 8% reduction in the likelihood of nausea following treatment (Figure 3.5).

Figure 3. 5 Individual effect plots for variables included in generalized linear model analysis of nausea at the first treatment session only



- Effect plots are for the total sample combined as there was no statistically significant difference between the treatment groups.
- Each effect plot represents a variable that affected the likelihood of nausea
- The Y-axis of each effect plot is a probability scale (Gulevich *et al.* 1961). Increases or decreases in the X-axis are associated with relative changes in the proportion of people who experienced nausea.
- The short vertical dashes on bottom of each effect plot are individual raw scores
- Solid black lines represent the relationship of each variable and the likelihood of nausea
- Red dashed lines represent confidence intervals

The GEE model was used to examine the effect of patient characteristics, cardiac effects of ECT and treatment parameters on nausea for treatments other than the first treatment. On subsequent treatments there was no difference between the treatment groups in the likelihood of feeling nauseated, $P = 0.202$. Consistent with the previous analysis total EEG seizure duration was significantly associated with nausea, $P < 0.001$. Ten second increases in seizure duration were associated with an increased likelihood of nausea of approximately 34%. Participants on Lithium were approximately 20% less likely to complain of nausea after treatment, which was also significant, $P = 0.024$.

3.2.3 Muscle discomfort

ECT is modified with a muscle relaxant medication called Suxamethonium that is used to minimize the extent of the motor seizure and reduce the risk of pain or injury associated with muscle contraction during the seizure. Muscle relaxation is often preceded by brief irregular muscle contractions called fasciculations that can themselves result in muscle discomfort following treatment. First reported in 1952, muscle discomfort associated with Suxamethonium has been reported to occur in varying frequencies but estimates range from 15% to 35% of people following its use (Bourne *et al.* 1952; Leatherdale *et al.* 1959). Upon reorientation participants were asked if they felt muscle discomfort. There were six participants in the RUL group and five participants in the bitemporal group that complained of muscle discomfort: $\chi^2 (1) = 0.102$, $P = 0.749$. There were seven episodes of muscle discomfort in the high-dose RUL group (2% of all high-dose RUL treatments) and five episodes in the bitemporal group (1% of all bitemporal treatments). Five of these cases in the high-dose RUL group and two in the bitemporal group occurred after the first treatment and only one participant complained of muscle pain on two occasions, a male from the high-dose RUL group. Given the rare occurrence of

muscle discomfort following ECT, probably due to the extremely short acting duration of muscle relaxation, it was not possible to perform further inferential analysis on this data. It is possible to conclude that muscle discomfort following contemporary ECT is a rare event regardless of laterality, Table 3.12.

Table 3. 12 Number of participants that complained of muscle aches upon reorientation in each treatment group by gender

	Males			Females		
	n	(number that got muscle pain)	%	n	(number that got muscle pain)	%
High-dose RUL	21	(4)	20%	29	(2)	7%
Bitemporal	19	(0)	0%	31	(5)	16%

3.3 Cardiac effects of electroconvulsive therapy

3.3.1 Mean arterial blood pressure

Prior to each individual's first treatment mean arterial blood pressure (MAP) for the high-dose right unilateral group was 90.23 ± (10.39). Mean MAP for the bitemporal group was 93.73 ± (11.95): $t(98) = -1.56$, $P = 0.121$. Table 3.13, is the mean systolic, mean diastolic and mean arterial blood pressure for both treatment groups prior to treatment, immediately upon resumption of spontaneous breathing after ECT and change scores for each treatment group. These data are correlated within clusters and so it was not possible to subject them to further inferential analysis, i.e. for example post treatment systolic blood pressure is the mean post treatment systolic blood pressure for each participant and each participant had multiple post treatment systolic blood pressure readings, one for each treatment they were administered. Therefore, these data violate the assumption of independence necessary to perform tests of the general linear model such as t-test, analysis of variance (ANOVA) or standard regression for example.

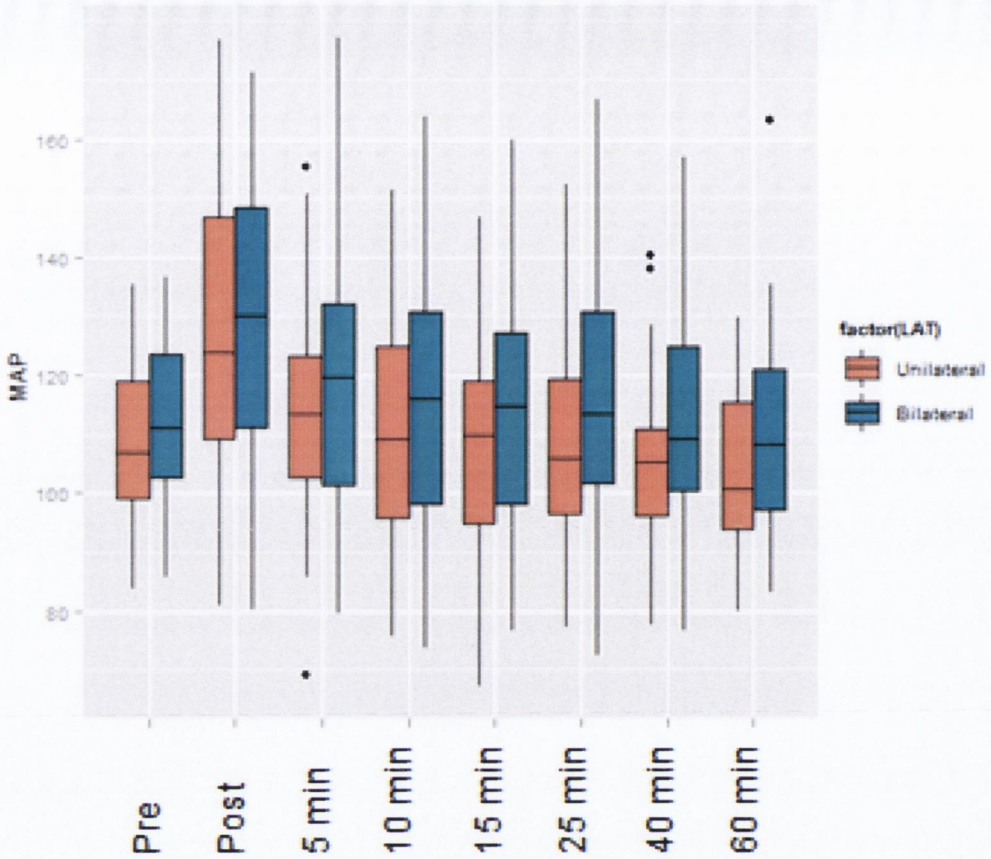
Table 3. 13 Mean systolic, mean diastolic and mean arterial blood pressure (MAP) for both treatment groups prior to treatment, immediately upon resumption of spontaneous breathing after ECT and change scores

	Pre-treatment mean (sd)	Post treatment mean (sd)
Systolic BP		
High-dose RUL	126.72 (18.29)	169.73 (27.47)
Bitemporal	130.36 (17.54)	158.13 (26.29)
Diastolic BP		
High-dose RUL	72.55 (12.41)	98.41 (15.79)
Bitemporal	74.34 (10.94)	92.49 (14.76)
MAP		
High-dose RUL	90.23 (10.39)	122.24 (18.20)
Bitemporal	93.73 (11.95)	114.42 (16.60)

From Table 3.13 there appears to be a greater change in systolic, diastolic and mean arterial blood pressure from pre-treatment to post treatment in the high-dose RUL ECT group compared to the bitemporal group. It was originally hypothesised that although ECT would have a dramatic effect on mean arterial blood pressure (MAP) there would be no difference in effect between the groups. A linear mixed effects model (LME) was constructed to test this hypothesis and to identify modifying factors.

Data for the first treatment session were analysed separately. MAP was measured at eight time-points: immediately prior to treatment, immediately after treatment upon resumption of spontaneous breathing, 5, 10, 15, 25, 40 and 60 minutes after resumption of spontaneous breathing (Figure 3.6).

Figure 3. 6 Box and whisker plot of mean arterial blood pressure (MAP) for both treatment groups for the first treatment only

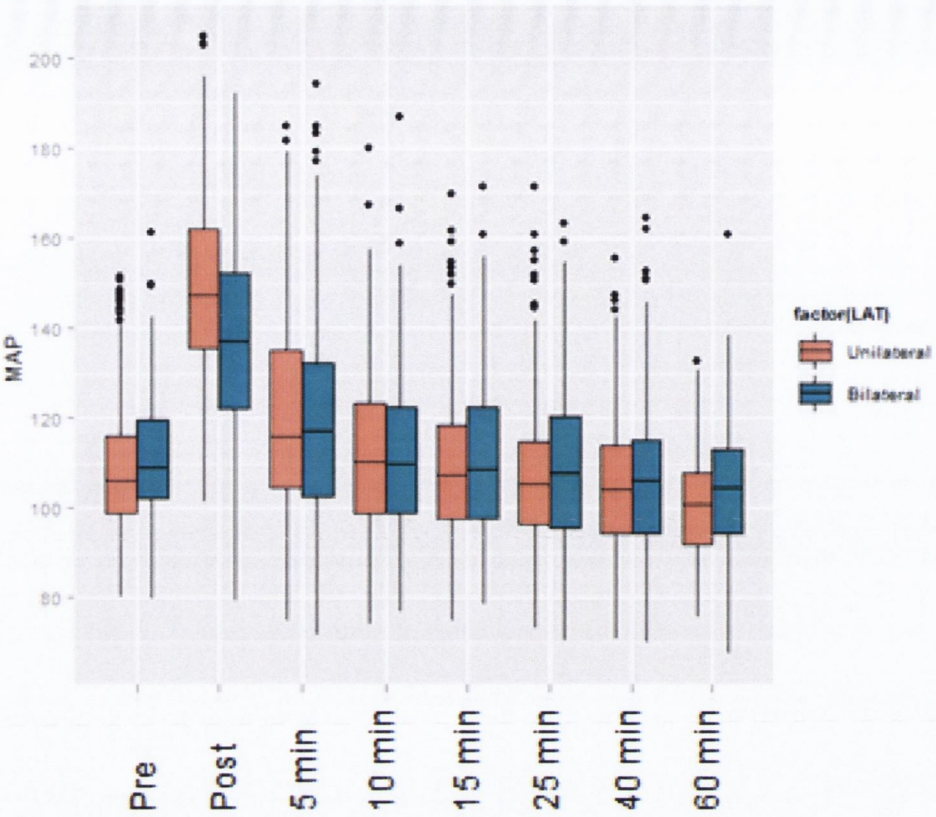


- Pre – MAP for both treatment groups immediately prior to treatment
- Post – MAP for both treatment groups upon resumption of spontaneous breathing
- 5 min - MAP for both treatment groups 5 minutes after resumption of spontaneous breathing
- Each box represents the 25th percentile at the bottom, the 75th percentile at the top and the median marked by the line within each box.
- Lines extending from the top and bottom of each box represent the range of values
- Black dots represent outliers (an observation that deviates distinctly from other members of the sample from which it occurs (Gravetter & Wallnau 2004)) in the data

There was no difference in MAP between the treatment groups prior to treatment but MAP significantly increased from pre-treatment across a number of time-points following stimulation, $P < 0.001$. This is not surprising given the dramatic effect ECT was expected to have on MAP. MAP rose in unison in both groups upon resumption of spontaneous breathing, but MAP in the high-dose RUL group reduced towards pre-treatment levels quickly while MAP in the bitemporal group remained higher for longer, on average MAP was 5.65 (2.99) mm/Hg higher in the bitemporal group (Figure 4.7). While this difference was not statistically significant it was trend-worthy, $P = 0.062$. The point of greatest change in MAP occurred upon resumption of spontaneous breathing. MAP increased by 18.3 (2.07) mm/Hg in the high dose RUL group ($P = 0.000$) and by 19.2 (2.10) mm/Hg in the bitemporal group ($P = 0.000$). However, there was no difference between the groups at this point, $P = 0.316$.

Data for the remaining treatments in the course were examined next, Figure 3.7. There was no difference in MAP between the treatment groups prior to treatment but there was a significant increase in MAP from pre-treatment to resumption of spontaneous breathing after treatment, $P < 0.001$. Accordingly, MAP was significantly different across multiple time-points at which it was measured, $P < 0.001$. There was also a significant interaction between laterality and time-point confirming this analysis, $P < 0.001$. Post hoc pairwise comparison using Bonferroni correction confirmed that immediately after treatment was the only point at which there was a significant difference between the treatment groups, $P = 0.006$. High-dose RUL ECT resulted in an increase in MAP from pre-treatment of approximately 36.3 (0.86) mm/HG ($P < 0.001$) while bitemporal ECT resulted in an increase in MAP from pre-treatment of approximately 29.2 (0.84) mm/HG ($P < 0.001$). On average, for the remainder of the treatment course excluding the first treatment session, high-dose RUL ECT produced an increase in MAP that was 7 mm/Hg higher than the increase associated with bitemporal ECT, $P = 0.032$.

Figure 3. 7 Box and whisker plot of mean arterial blood pressure (MAP) for both treatment groups for treatments other than the first



- Pre – MAP for both treatment groups immediately prior to treatment
- Post – MAP for both treatment groups upon resumption of spontaneous breathing
- 5 min - MAP for both treatment groups 5 minutes after resumption of spontaneous breathing
- Each box represents the 25th percentile at the bottom, the 75th percentile at the top and the median marked by the line within each box.
- Lines extending from the top and bottom of each box represent the range of values
- Black dots represent outliers (an observation that deviates distinctly from other members of the sample from which it occurs (Gravetter & Wallnau 2004)) in the data

3.3.2 Heart rate

Prior to each individual's first treatment mean heart rate (HR) for the high-dose RUL group was 82.4 (15.25). Mean heart rate for the bitemporal group was 86.7 (14.31). There was no significant difference between the treatment groups in HR prior to the first treatment session: $t(98) = -1.45$, $P = 0.149$. Table 3.14 shows mean HR for each treatment group prior to treatment, immediately after treatment upon resumption of spontaneous breathing and the respective change scores. These data are correlated within clusters and so it was not possible to subject them to further inferential analysis, i.e. pre-treatment HR is the mean pre-treatment HR for each participant and each participant had multiple pre-treatment HR readings (one for each treatment they were administered). Therefore, these data violate the assumption of independence necessary to perform tests of the general linear model.

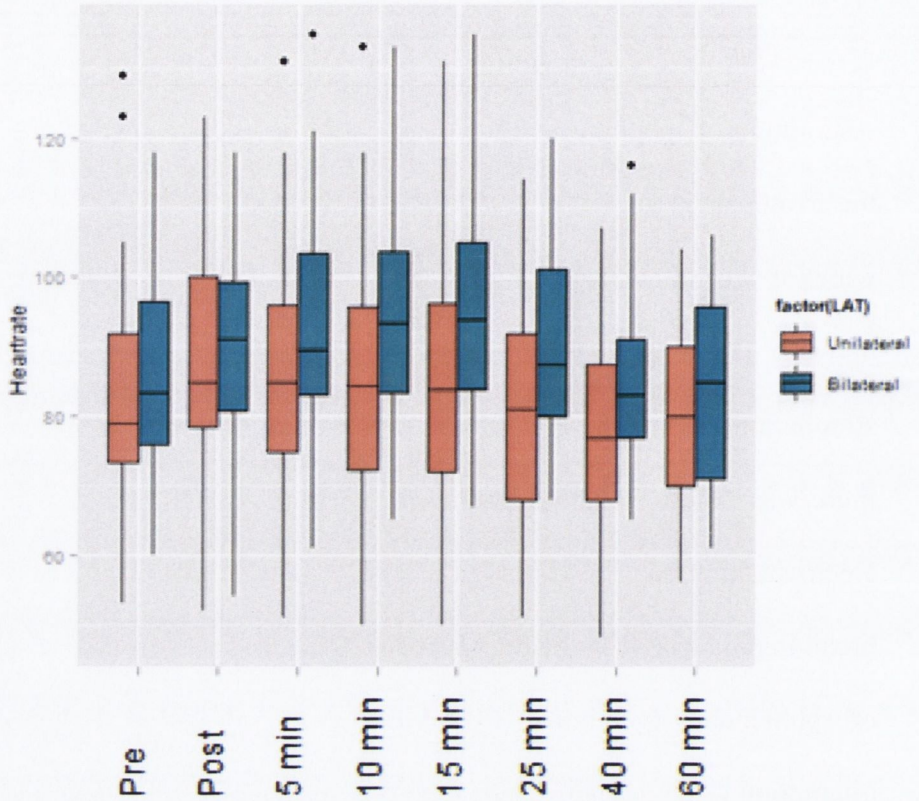
Table 3. 14 Mean heart-rate prior to treatment and after treatment upon resumption of spontaneous breathing for both treatment groups

Heart-rate	Pre-treatment Mean (SD)	Post treatment Mean (SD)
High-dose RUL	82.36 (15.25)	88.60 (16.16)
Bitemporal	86.66 (14.31)	90.15 (14.34)

The aim of this analysis was to compare the effects of bitemporal ECT with high-dose RUL ECT on HR and to identify modifying factors.

For the first treatment session HR increased on average by 2.5 bpm upon resumption of spontaneous breathing but there was no overall average difference between the treatment groups, $P = 0.457$. A significant difference in HR across the time-points at which it was measured during the recovery period ($P < 0.001$) and a significant interaction between laterality and time-point ($P = 0.002$) confirms that HR was altered by the stimulation (Figure 3.8). Post hoc tests of laterality across the time-points revealed that there was no statistically significant difference in HR prior to the administration of the electrical stimulus. HR increased in both groups in unison upon resumption of spontaneous breathing but as HR in the high-dose RUL group declined by five minutes after resumption of spontaneous breathing, HR in the bitemporal group remained elevated. HR in the bitemporal group remained statistically significantly higher than the RUL group from 15 to 60 minutes after the resumption of spontaneous breathing (HR at 15 minutes, $P = 0.007$, HR at 25 minutes, $P = 0.002$, HR at 40 minutes , $P = 0.005$, HR at 60 minutes, $P = 0.062$). Being on benzodiazepines produced an average reduction in heart rate of approximately 3 bpm that was statistically significant ($P = 0.014$). Being on antihypertensive medication also had a significant effect, $P = 0.037$, increasing heart rate by approximately 3 bpm.

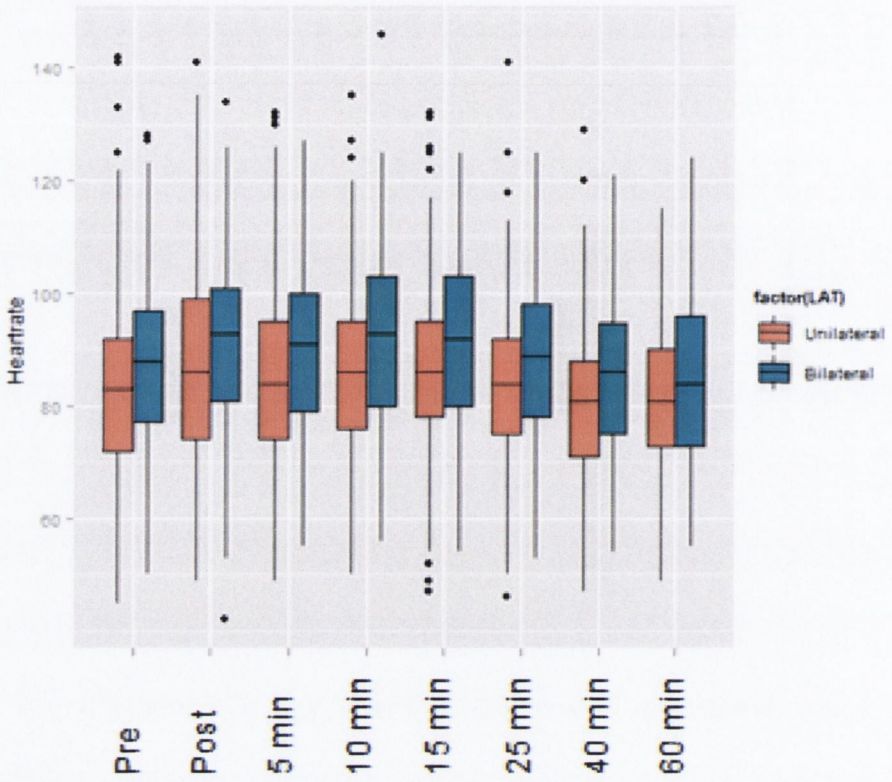
Figure 3. 8 Box and whisker plot for heart rate (HR) for both treatment groups for the first treatment only



- Pre – MAP for both treatment groups immediately prior to treatment
- Post – MAP for both treatment groups upon resumption of spontaneous breathing
- 5 min - MAP for both treatment groups 5 minutes after resumption of spontaneous breathing
- Each box represents the 25th percentile at the bottom, the 75th percentile at the top and the median marked by the line within each box.
- Lines extending from the top and bottom of each box represent the range of values
- Black dots represent outliers (an observation that deviates distinctly from other members of the sample from which it occurs (Gravetter & Wallnau 2004)) in the data

HR data for treatments other than the first are now examined, Figure 3.9. HR was significantly different across the time-points at which it was measured, $P < 0.001$. Bitemporal ECT was associated with a mean increase in HR that was on average 4.4 bpm higher than the mean increase associated with high-dose RUL ECT, $P = 0.046$. Being female was also associated with a greater mean increase in HR of approximately 4.4 bpm, $P = 0.054$,which although not statistically significant is certainly trendworthy. None of the medication groups had an effect on HR.

Figure 3. 9 Box and whisker plot of heart rate (HR) for both treatment groups for treatments other than the first treatment



- Pre – MAP for both treatment groups immediately prior to treatment
- Post – MAP for both treatment groups upon resumption of spontaneous breathing
- 5 min - MAP for both treatment groups 5 minutes after resumption of spontaneous breathing
- Each box represents the 25th percentile at the bottom, the 75th percentile at the top and the median marked by the line within each box.
- Lines extending from the top and bottom of each box represent the range of values
- Black dots represent outliers (an observation that deviates distinctly from other members of the sample from which it occurs (Gravetter & Wallnau 2004)) in the data

3.3.3 Adverse cardiac effects of electroconvulsive therapy

The passage of an electric current across the brain stimulates the vagus nerve that produces a parasympathetic and sympathetic response described in section 1.3.1.1 (Tess & Smetana 2009).

There was no a priori definition of cardiac response that would require intervention and individual cases were examined and treated on a case by case basis at the discretion of the treating Anaesthetist. Medical intervention for respiratory complication, cardiac arrhythmia, hypertension, bradycardia or tachycardia was recorded by the Consultant Anaesthetist at individual treatments.

Atropine was administered only twice in 766 treatments: once for the treatment of sustained bradycardia and once for the treatment of bigeminy (a premature heart beat during a normal sinus rhythm). There was one episode of bronchospasm that required medical intervention and one episode of laryngospasm that resolved unaided.

Transient hypertension is common immediately following administration of the electrical stimulus; this normally resolves unaided but on occasion medical intervention is required because of associated factors such as history of cardiac event or sustained effect. There were nineteen episodes of hypertension from five different patients that required further consideration (5% of the sample). Eighteen of these episodes required intervention with Metoprolol and one resolved unaided. Interestingly, these five patients were treated with high-dose right unilateral ECT. This is not a statistically significant difference between the groups but is certainly trend-worthy, Fisher's Exact Text, $P = 0.056$.

There were sixteen incidents of tachycardia (2% of all treatments) from ten patients (10% of the sample). Seven of these patients received right unilateral treatment but this difference was not statistically significant, Fisher's Exact Test, $P = 0.318$. Three were treated with Metoprolol on thirteen occasions and all of these were treated with right

unilateral ECT which again was not statistically significantly different between groups, Fishers Exact Test P = 0.242.

3.4 Basic and instrumental functioning

There were 50 participants in the high-dose RUL group and 50 participants in the bitemporal group. Complete sample demographic and treatment details are described in section 3.4. Unfortunately there was an amount of missing data in this study with regard to the PSMS (Table 3.15). PSMS assessments were completed by 86% of participants in the RUL group and 80% of participants in the bitemporal group prior to treatment. Table 3.15 contains details of participants that completed PSMS assessments at pre-treatment and each respective follow-up assessment. While retention rates were very good up to 4 weeks after treatment, PSMS completion rates dropped considerably by the 3 month assessment and further at the 6 month follow-up assessment.

Table 3. 15 Number (%) of PSMS assessments completed at pre-treatment, 4 weeks, 3 months and 6 months after treatment for both treatment groups. Participants' 4 weeks, 3 months and 6 months post treatment assessments were only included if the participant had completed a pre-treatment assessment.

	Laterality	N (%)
PSMS pre-treatment assessment	**Unilateral group**	**43 (86)**
	Bitemporal group	**40 (80)**
PSMS 4 weeks assessment	**Unilateral group**	**35 (81)**
	Bitemporal group	**33 (83)**
PSMS 3 months assessment	**Unilateral group**	**26 (61)**
	Bitemporal group	**25 (63)**
PSMS 6 months assessment	**Unilateral group**	**23 (54)**
	Bitemporal group	**20 (50)**

PSMS = Physical Self Maintenance Scale, N = at pre-treatment N represents the number of participants that completed assessments: at follow-up N represents the number of participants that completed the baseline assessment and the assessment at the respective time-point, % = Proportion of participants in each group that completed the PSMS assessment prior to treatment and at the respective assessment time-points.

There was no difference between the treatment groups in the number of participants that completed PSMS assessments prior to treatment (χ^2 (1, N=100) = 0.283, P = 0.594), at 4 weeks after the treatment course (χ^2 (1, N=83) = 0.017, P = 0.896), 3 months after the treatment course (χ^2 (1, N=83) = 0.036, P = 0.849) and six months after the treatment course (χ^2 (1, N=83) = 0.101, P = 0.751).

Table 3.16 compares depression severity, cognitive function, subjective side effects, gender and numbers that were treatment resistant between those that completed PSMS assessments and those that did not prior to treatment, at 4 weeks, 3months and 6 months after treatment. Only those who completed a pre-treatment PSMS assessment were included in these analyses.

The only difference between those that completed the PSMS assessment and those that did not occurred 3 months and 6 months after the treatment course: those that had previously had ECT were more likely to not complete an assessment (Table 3.16). However, given that the participant's next of kin or carer completed the PSMS this was unlikely to be a contributing factor for non-completion.

Table 3. 16 Analysis of outcomes for those that completed the PSMS and those that did not complete the PSMS at all assessment time-points

	Completers [N] Mean (sd)	Non-completers [N] Mean (sd)	t (d.f.)	χ^2 (d.f.)	P
Pre-treatment	**N = 83**	**N = 17**			
HDRS	29.9 (6.91)	29.5 (7.21)	0.202 (98)		0.840
ACE-R	80.21 (11.91)	83.86 (5.60)	- 1.114 (83)		0.268
CSSES	4.64 (3.97)	5.28 (3.18)	- 1.543 (70)		0.127
Age	58.04 (14.24)	56.53 (15.29)	0.393 (98)		0.695
Gender (Female)	47 (57%)	13 (77%)		2.32 (1)	0.128
Previous ECT (Yes)	32 (40%)	10 (59%)		2.14 (1)	0.143
Resistance (Yes)	48 (58%)	7 (44%)		1.08 (1)	0.299
4 week assessment	**N = 68**	**N = 15**			
HDRS 4 weeks post	12.50 (9.33)	11.71 (9.10)	- 0.043 (70)		0.966
ACE-R EOT	78.37 (12.67)	78.33 (11.89)	- 0.009 (75)		0.993
CSSES EOT	5.13 (4.61)	6.00 (4.81)	- 0.612 (72)		0.542
Age	58.44 (13.91)	56.20 (15.8)	0.549 (81)		0.584
Gender (Female)	38 (56%)	9 (60%)		0.085 (1)	0.771
Previous ECT (Yes)	26 (39%)	6 (40%)		0.002 (1)	0.965
Resistance (Yes)	38 (56%)	10 (67%)		0.586 (1)	0.444

	Completers [N] Mean (sd)	Non-completers [N] Mean (sd)	t (d.f.)	χ^2 (d.f.)	P
3 month assessment N = 51		**N = 32**			
HDRS	13.86 (10.39)	14.95 (8.66)	- 0.405 (68)		0.687
ACE-R	81.98 (9.76)	88.50 (8.62)	-1.758 (47)		0.085
CSSES	3.66 (3.20)	5.25 (6.67)	-1.068 (50)		0.291
Age	58.84 (13.87)	56.75 (14.94)	0.650 (81)		0.518
Gender (Female)	28 (55%)	19 (59%)		0.160 (1)	0.689
Previous ECT (Yes)	15 (30%)	17 (57%)		4.940 (1)	0.026
Resistance (Yes)	29 (57%)	19 (59%)		0.051 (1)	0.822
6 month assessment N = 43		**N = 40**			
HDRS	13.93 (10.11)	14.47 (9.77)	-0.225 (68)		0.823
ACE-R	83.69 (8.24)	81.82 (12.23)	0.629 (47)		0.532
CSSES	3.63 (3.11)	4.47 (5.99)	- 0.730 (50)		0.469
Age	56.95 (14.16)	59.20 (14.41)	- 0.716 (81)		0.476
Gender (Female)	25 (58%)	22 (55%)		0.083 (1)	0.827
Previous ECT (Yes)	12 (29%)	20 (51%)		4.364 (1)	0.043
Resistance (Yes)	23 (54%)	25 (63%)		0.690 (1)	0.406

- HDRS – Hamilton Depression Rating Scale
- ACE-R – Addenbrokes Cognitive Exam – Revised
- CSSES – Columbia ECT Subjective Side Effect Schedule
- Previous ECT (Yes) – N (%) of participants that had a course of ECT prior commencing this course of ECT.
- Resistance (Yes) – N (%) of participants presenting as treatment resistant as per criteria in section 2.1.4.

3.4.1 Basic activities of daily living

As measured by the PSMS there was no difference in pre-treatment level of basic ADL functioning between the treatment groups, $t(81) = 0.718$, $P = 0.475$. Table 3.17 presents mean (SD) PSMS scores at pre-treatment, 4 weeks after treatment, 3 months and 6 months after the treatment course for both treatment groups. Change scores (95% confidence intervals) are presented comparing each follow-up assessment with scores prior to treatment. Change scores indicate that there was an improvement in PSMS functioning 4 weeks after treatment and this improvement was maintained at 3 months and 6 months after the treatment course. Differences between treatment group means (95% CI) are also presented that indicate that the bitemporal group improved 0.9 points, 1.2 points and 0.9 points more than the RUL group at 4 weeks, 3 months and 6 months after treatment respectively. These differences were subjected to a between groups comparison to identify statistically significant differences. Due to the extent of missing data at 3 months and 6 months after the treatment course the following analysis focused on ability to perform basic ADL up to 4 weeks after treatment. A subgroup analysis of the reduced sample size up to 6 months after treatment was also conducted.

Table 3. 17 Physical Self Maintenance Scale mean scores with confidence intervals for both treatment groups at all assessment time-points and respective change scores. Only participants that completed a pre-treatment PSMS were included in these analyses.

Physical Self Maintenance Scale scores and change scores			
	RUL group (SD/CI) N	Bitemporal group (SD/CI) N	Difference between means (CI)
Pre-treatment	26.4 (4.16) N=43	25.7 (4.66) N=40	0.695 (-1.23 – 2.62)
4 week F/U	29.1 (2.01) N=35	29.2 (1.33) N=33	0.152 (-0.95 – 0.65)
3 month F/U	29.3 (1.42) N=26	29.0 (1.86) N=25	0.276 (-0.59 – 1.15)
6 month F/U	29.2 (1.26) N=23	29.0 (2.09) N=20	0.154 (-0.82 – 1.12)
Change 1	2.8 (1.11 – 4.50) N=35	3.7 (1.96 – 5.44) N=33	0.897 (-3.28 – 1.49)
Change 2	2.7 (0.89 – 4.58) N=26	3.9 (1.52 – 6.24) N=25	1.149 (-4.06 – 1.76)
Change 3	3.2 (1.25 – 5.10) N=23	4.1 (1.75 – 6.45) N=20	0.926 (-3.84 – 1.99)

Change 1 – Change in PSMS from baseline to 4 weeks follow-up in each treatment group. Change 2 – Change in PSMS from baseline to 3 months follow-up in each treatment group. Change 3 – Change in PSMS from baseline to 6 months follow-up in each treatment group. F/U – Follow-up. SD/CI – standards deviations are presented to demonstrate the variation in a mean score. Confidence intervals are presented to indicate the reliability of an estimate.

PSMS scores were negatively skewed (the majority of participants scored at the upper limit of the scale) at baseline for both groups and severely negatively skewed in both groups on all three follow-up assessments. Transformations of any kind had no effect on these data as there were too many scores of the same value. Thus, once transformed, the majority of new values were also of the same value. Data of this type lack variability and it was therefore impossible to compare the groups for difference across the time-points using standard general linear model means such as ANOVA. PSMS scores were therefore converted to a binomial outcome: 0 = suboptimal functioning, 1 = fully functioning. First the number of fully functioning participants in each treatment group was compared using Chi Square analysis to establish if there was a difference between the groups at any time-point. Three Chi Square analyses were performed comparing the number of fully functioning participants in each treatment group with each respective follow-up assessment. Only participants that completed a pre-treatment and respective post treatment PSMS assessment were included in each analysis. Then, a linear mixed effects model was used to compare the dependent variable (fully functioning or suboptimal functioning) between the groups over time.

35 (70%) RUL and 33 (66%) bitemporal participants completed the PSMS prior to treatment and 4 weeks after treatment. While there were 14 (33%) RUL participants and 11 (40%) bitemporal participants fully functioning prior to treatment ($\chi^2(1, N = 68) = 0.325$, $P = 0.569$), 4 weeks after treatment there were 29 (83%) RUL and 25 (76%) bitemporal participants fully functioning ($\chi^2(1, N = 68) = 0.524$, $P = 0.469$) (Figure 5.1).

26 (52%) RUL and 25 (50%) bitemporal participants completed the PSMS prior to treatment and 3 months after treatment. While there were 12 (46%) RUL participants and 8 (32%) bitemporal participants fully functioning prior to treatment ($\chi^2(1, N = 51) = 1.071$, $P = 0.301$), 3 months after treatment there were 22 (85%) RUL and 19 (76%) bitemporal participants fully functioning ($\chi^2(1, N = 51) = 0.600$, $P = 0.439$).

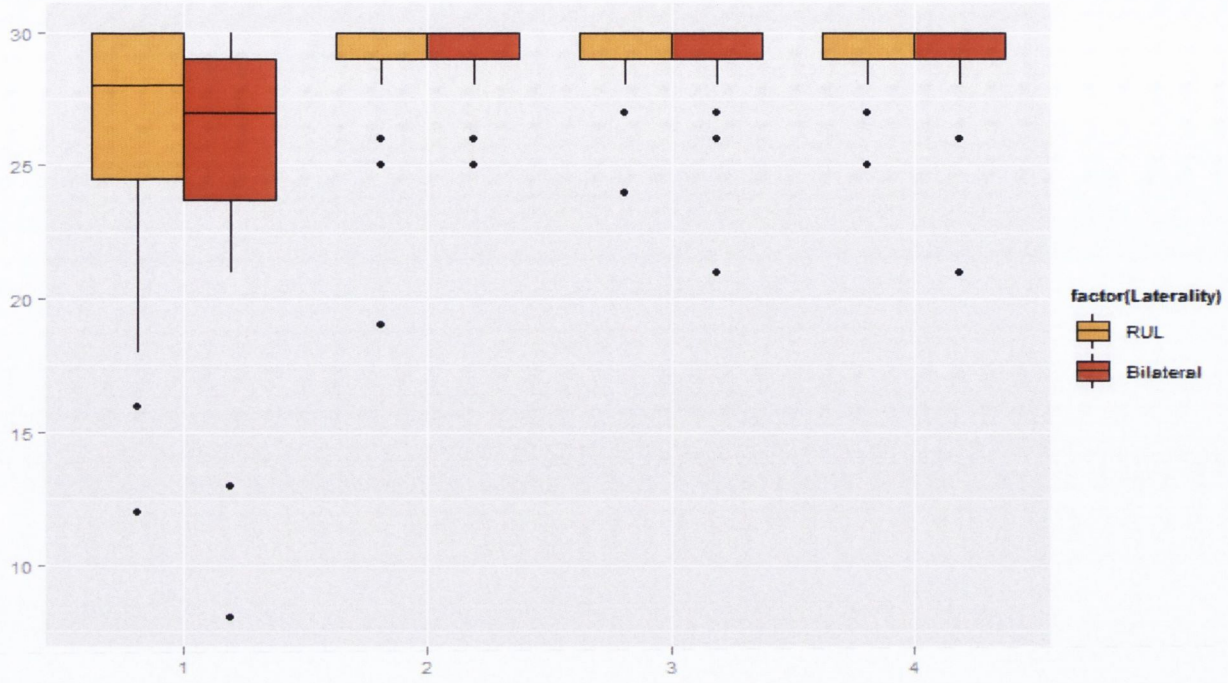
23 (46%) RUL and 20 (40%) bitemporal participants completed the PSMS prior to treatment and 6 months after treatment. While there were 10 (44%) RUL participants and 8 (40%) bitemporal participants fully functioning prior to treatment ($\chi^2(1, N = 43) = 0.053$, $P = 0.818$), 6 months after treatment there were 20 (87%) RUL and 16 (80%) bitemporal participants fully functioning ($\chi^2(1, N = 43) = 0.380$, $P = 0.538$).

The full sample that completed a pre-treatment PSMS assessment was included in a linear mixed effects model. 43 (86%) participants in the RUL group and 40 (80%) participants in the bitemporal group completed the PSMS prior to treatment. 17 (40%) RUL participants and 13 (33%) bitemporal participants were fully functioning prior to treatment ($\chi^2(15, N = 83) = 13.301$, $P = 0.579$). 4 weeks ($P < 0.001$), 3 months ($P < 0.001$) and 6 months ($P < 0.001$) after treatment there was a statistically significant increase in the number of fully functioning participants from pre-treatment and laterality had no effect on PSMS functioning, $P = 0.461$ (Figure 3.10).

A logistic regression model was constructed to identify the main predictors of recovery of ability to perform basic ADL 4 weeks after treatment. The model included the predictor variables laterality, age, gender, remission status at end of treatment and treatment resistance. None of the independent variables were a significant predictor of basic functioning 4 weeks after treatment

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Figure 3. 10 Boxplot of PSMS raw scores for both treatment groups at baseline, 4 weeks, 3 months and 6 months after treatment. Only participants that completed a pre-treatment Physical Self Maintenance Scale assessment were included in these analyses.



Each box represents the 25th percentile at the bottom, the 75th percentile at the top and the median marked by the line within each box. Lines extending from the top and bottom of each box represent the range of values. Black dots represent outliers (an observation that deviates distinctly from other members of the sample from which it occurs (Gravetter & Wallnau 2004). The Y-Axis represents PSMS raw scores. The X-Axis represents: 1 = Pre-treatment; 2 = 4 weeks post treatment; 3 = 3 months post treatment; and 4 = 6 months post treatment.

3.4.2 Instrumental activities of daily living

Sample participants' clinical and demographic details for IADL outcomes were identical to the PSMS sample described in section 5.4.1. The nature and extent of missing data were also identical (Table 3.15). There were no differences in depression severity, cognitive function, subjective side effects, gender and numbers that were treatment resistant between those that completed and those that did not complete the IADL assessment at any time-point (Table 3.18). Due to the extent of missing data the following analyses focuses on ability to perform IADL 4 weeks after treatment. A subgroup analysis with a reduced sample size from pre-treatment examines ability to perform IADL at 6 months after treatment.

There was no difference in pre-treatment level of IADL functioning between the treatment groups, $t(81) = 0.485$, $P = 0.629$. There were significant improvements in both treatment groups following the treatment course and these improvements were maintained up to six months following the treatment course (Table 5.4).

Table 5.4 presents mean (SD) IADL functioning scores at pre-treatment, 4 weeks after the treatment course, 3 and 6 months after the treatment course for both treatment groups. Change scores (95% CI) are presented comparing each follow-up assessment with pre-treatment scores. Change scores indicate that there was an improvement in IADL functioning 4 weeks after treatment that was maintained 3 and 6 months after the treatment course. Differences between treatment group means (95% CI) are also presented in Table 5.4 that indicate that there was a slight difference between the treatment groups in the extent of improvement: i.e. the high dose RUL group improved 1.2 points, 1.9 points and 2 points more than the bitemporal group at 4 weeks, 3 months and 6 months after treatment. To examine if these differences between groups were statistically significant a repeated measures analysis of variance was performed.

Table 3. 18 Mean Instrumental Activities of Daily Living Scale scores with confidence intervals for both treatment groups at all assessment time-points and respective change scores

Instrumental Activities of Daily Living Scale scores			
	RUL group mean (SD/CI) N	**N Bitemporal group mean (SD/CI)**	**Difference between means (95% CI)**
Pre-treatment	20.1 (6.78) N=43	19.9 (6.94) N=40	0.730 (-2.27 – 3.73)
4 week F/U	24.3 (6.17) N=39	23.1 (6.46) N=35	1.219 (-1.71 – 4.15)
3 month F/U	25.9 (5.59) N=29	22.3 (7.19) N=29	3.552 (0.16 – 6.94)
6 month F/U	24.3 (7.04) N=27	22.5 (5.63) N=25	1.853 (-1.72 – 5.42)
Change 1	4.63 (2.05 – 7.21) N=35	3.39 (0.33 – 6.46) N=33	1.235 (-2.68 – 5.15)
Change 2	5.58 (2.15 – 9.01) N=26	3.68 (-0.63 – 7.99) N=25	1.897 (-3.45 – 7.24)
Change 3	5.33 (1.28 – 9.39) N=24	3.33 (-1.49 – 8.15) N=21	2.000 (-4.07 – 8.07)

Change 1 – Change in IADL from baseline to 4 weeks follow-up in each treatment group. Change 2 – Change in IADL from baseline to 3 months follow-up in each treatment group. Change 3 – Change in IADL from baseline to 6 months follow-up in each treatment group. F/U – Follow-up. SD/CI – standards deviations are presented to demonstrate the variation in the mean score of a population. Confidence intervals are presented to indicate the reliability of an estimate

A repeated measures design uses only the data from participants that have provided data at all of the time-points specified in the analysis. Therefore, in order to be included in the repeated measures analysis of all four assessment time-points a participant must have provided a complete assessment at pre-treatment, 4 weeks after treatment, and at 3 months and 6 months after treatment. If the repeated measures analysis is confined to pre-treatment and 4 weeks post treatment only this occurred in N = 35 (70%) in the high dose RUL group and N = 33 (66%) in the bitemporal group but falls to N = 17 (34%) in the high dose RUL group and N = 17 (34%) of the bitemporal group if all four assessment time-points are included in the analysis.

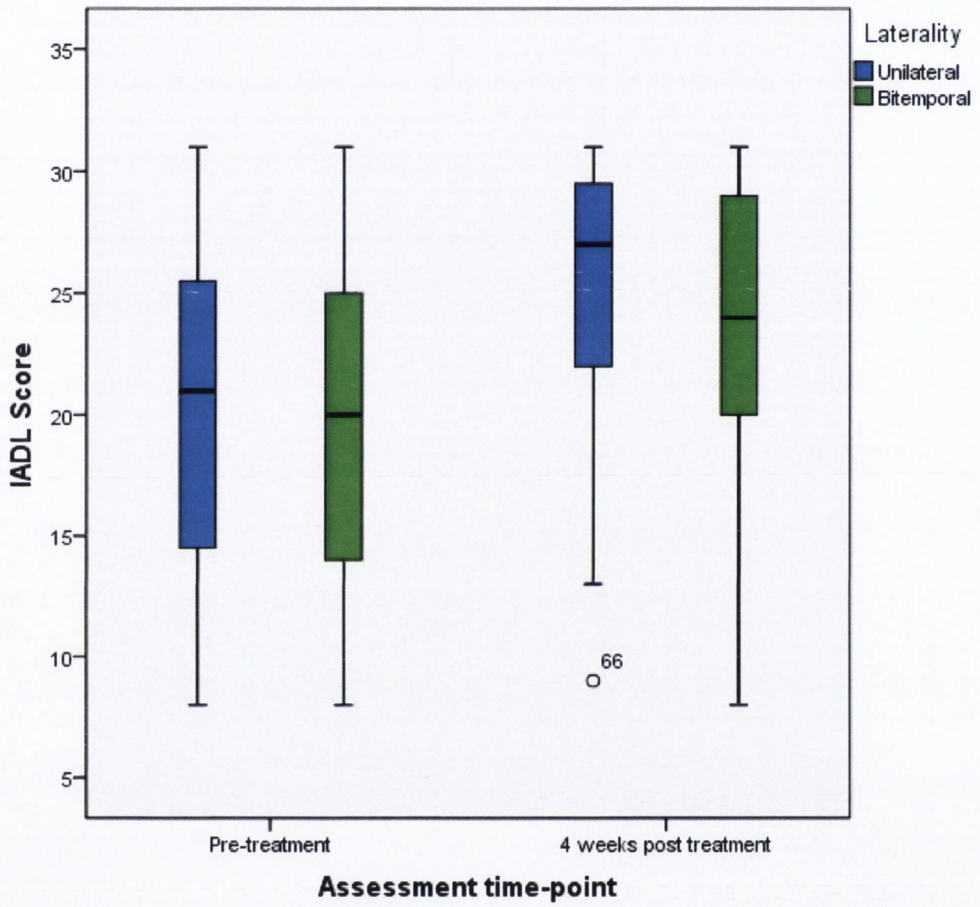
As such, these data were analysed separately. Results are presented for a repeated measures analysis of IADL outcomes up to four weeks following the end of treatment as the primary analysis and a separate subgroup analysis of pre-treatment and 6 months data only as a secondary analysis.

3.4.2.1 Instrumental activities of daily living up to 4 weeks post ECT

To maximize the sample size a repeated measures ANOVA of IADL outcomes up to four weeks after treatment included N = 35 (70%) participants from the high dose RUL group and N = 33 (66%) participants from the bitemporal group. An important assumption is homogeneity of variances and Levene's Test of Equality of Variances showed no significant difference in variance of scores at either time-point in this model (pre-treatment P = 0.998, 4 week follow-up P = 0.807). The repeated measures design compared both treatment groups for difference and over time. There was no statistically significant difference between the treatment groups four weeks after treatment, P = 0.410. While there was no difference between groups there was a significant difference within each group (P < 0.001). The high dose RUL group improved in IADL score from 20.3 (95% CI 18.1 –

22.6) to 25 (95% CI 22.9 – 27.1) while the bitemporal group improved from 20 (95% CI 17.6 – 22.3) to 23.3 (95% CI 21.2 – 25.5) (Figure 3.11).

Figure 3. 11 Boxplot of pre-treatment and 4 weeks post treatment mean Instrumental Activities of Daily Living scores for both treatment groups



The blue box represents the high dose RUL group. The green box represents the bitemporal group. The black line within each box is the median value. The upper end of each box above the median represents the upper quartile or 25% of data greater than the median. The lower end of each box below the median represents the lower quartile or 25% of data less than the median. Whiskers extending above and below the box represent the maximum and minimum values excluding outliers. Dots below the whiskers represent scores that were considerably lower than normal for these data.

It was hypothesized that RUL ECT would be associated with less of an impact on executive function compared with bitemporal ECT and therefore may be associated with greater IADL functioning. To test this hypothesis executive function was included in the repeated measures analysis as a covariate. The Trail Making Test was used as a measure of executive function and time to complete the test (seconds) was the score. Faster scores indicate better executive function. Prior to treatment there was no difference in executive performance between the treatment groups: The high dose RUL group (N=32) mean score was 153.47 (79.75) and the bitemporal group (N=29) mean score was 146.86 (76.76); t(59)=0.329, P=0.743. At end of the treatment course the RUL group (N=26) had improved from 143.04 (70.78) to 108.81 (53.57). A mean improvement of 34.23 (95% CI 7.49 – 60.97) that was significant, t(25)=2.636, P = 0.014. At end of the treatment course the bitemporal group (N=24) had improved from 134.50 (65.59) to 126.63 (75.36). A mean improvement of 7.86 (95% CI –15.71 – 31.46) that was not significant, t(23)= 0.691, P = 0.497. However, there was no statistically significant difference in executive function between the treatment groups at the end of the treatment course, t(71) = - 0.476, P = 0.636.

A repeated measures ANCOVA of IADL outcomes up to four weeks after treatment included N = 27 (54%) participants from the high dose RUL group and N = 26 (52%) participants from the bitemporal group. Both assessment time-point variances showed no significant difference (pre-treatment P = 0.519, 4 week follow-up P = 0.353). Accounting for end of treatment executive function, there was no statistically significant difference between the treatment groups four weeks after treatment, P = 0.549. Executive function itself also had no main effect, P = 0.806. There continued to be a significant improvement within each group (P < 0.001). The high dose RUL group improved in IADL score from 21.2 (95% CI 18.7 – 23.8) to 25.5 (95% CI 23.4 – 27.7) while the bitemporal group improved from 20.1 (95% CI 17.5 – 22.7) to 25.2 (95% CI 23.0 – 27.3).

3.4.2.2 Instrumental activities of daily living up to 6 months post ECT

As a subgroup analysis a repeated measures ANCOVA was performed including only the pre-treatment and 6 month follow up IADL data, while again controlling for executive function at end of treatment. The sample size was relatively small; N = 20 (40%) in the high dose RUL group and N = 16 (32%) in the bitemporal group. Levene's Test of equality of error variances showed that variances between groups of scores were homogenous (pre-treatment P = 0.632 and 6 month follow-up P = 0.682).

Performance of IADL improved significantly in both groups at 6 months from pre-treatment (P = 0.001): The high dose RUL group improved in IADL score from 20.5 (95% CI 17.2 – 23.8) to 25.9 (95% CI 23.3 – 28.5) while the bitemporal group improved from 17.8 (95% CI 14.1 – 21.5) to 23.4 (95% CI 20.5 – 26.3). The mean difference between the treatment groups however was not statistically significant, P = 0.101. Executive function also had no effect in this model, P = 0.415.

3.4.2.3 Predicting recovery of ability to perform IADL

There was a significant recovery of ability to perform IADL after treatment with ECT that was independent of laterality. This was true with the primary analysis of functioning at 4 weeks after treatment and the subgroup analysis of 6 month follow-up functioning. A multiple linear regression model was constructed to identify the main predictors of recovery of ability to perform IADL 4 weeks after treatment. Pre-treatment depression severity, age, gender, remission status at end of treatment (EOT) (N=36 not remitted, 32 remitted), EOT executive function, subjective side effects, global cognitive functioning, laterality, pre-treatment intelligence and treatment resistance were all included in the regression model. Remission status at end of treatment was the only significant predictor of recovery of ability to perform IADL. 4 weeks after treatment being remitted

was associated with an increased IADL score of 4 points (95% CI 1.1 – 6.7) compared to not being remitted, P = 0.007. This model accounted for 10% of the variance (R^2).

A similar multiple linear regression model was constructed to identify predictors of ability to perform IADL 6 months after ECT. Remission status and global functioning at 6 months after treatment were included in this model. Being remitted at EOT was no longer significant (P = 0.683) but being remitted at 6 months after ECT was, P = 0.010. Being remitted 6 months after treatment was associated with an increased IADL score of 5.9 points (95% CI 2.5 – 9.5). Global cognitive function 6 months after treatment was also significant in this model (P = 0.005) but in real terms the effect was relatively small: a 4.5 point increase in ACE-R score was associated with a 1 point increase in IADL function. This model accounted for 34% of the explained variance (R^2).

3.5 Health Related Quality of Life

Prior to treatment there were 36 RUL participants and 32 bitemporal participants that completed the SF-36 ($\chi^2(1, N=100) = 0.735$, P = 0.391). 6 months after the treatment course 26 RUL participants and 28 bitemporal participants that completed the SF-36, ($\chi^2(1, N=100) = 0.161$, P = 0.688). Including only those participants that completed a pre-treatment SF-36, 21 RUL and 22 bitemporal participants completed the SF-36 6 months after the treatment course, ($\chi^2(1, N=68) = 0.791$, P = 0.374).

Participants that did not complete the SF-36 prior to commencing their course of ECT treatment were significantly older (P = 0.001) and had worse global cognitive functioning (P < 0.001) than participants that did complete the SF-36 (Table 3.19). There was no difference in level of depression as measured by the HDRS and gender, having had ECT in the past and treatment resistance were not associated with non-completion of the SF-36 prior to treatment (Table 6.4).

Six months after the treatment course participants that did not complete the SF-36 were slightly older but the difference was only trend-worthy (P = 0.080). Participants that did not complete the SF-36 scored significantly lower on the measure of global cognitive function (ACE-R) than those that completed the SF-36 six months after their course of ECT (P = 0.001) (Table 3.20). However, this result must be taken with caution as in this case only 3 participants did not complete the SF-36 but completed the ACE-R 6 months after the treatment course.

Table 3. 19 Demographic and clinical details for participants that completed and did not complete the SF-36 prior to commencing their course of ECT. N presented in Table 6.4 is the maximum N and may not be as high in all cases

	Completers at EOT N = 68 Mean (sd)	Non-completers at EOT N = 32 Mean (sd)	t-test (d.f.)	χ^2 – test (d.f.)	P
Age	54.66 (14.70)	64.41 (11.14)	3.324 (98)		0.001
Gender (Female)	42 (62%)	18 (56%)		0.276 (1)	0.600
Previous ECT (Yes)	26 (39%)	16 (52%)		1.419 (1)	0.233
Resistance (Yes)	38 (56%)	17 (55%)		0.009 (1)	0.923
HDRS pre-treatment	29.49 (6.23)	30.59 (8.28)	0.745 (98)		0.458
ACE-R pre-treatment	83.65 (9.012)	70.95 (12.67)	- 4.919 (83)		< 0.001

Table 3. 20 Demographic and clinical details for participants that completed and did not complete the SF-36 6 months after their course of ECT. N presented in Table 6.5 is the maximum N and may not be as high in all cases

	Completers at 6 months N = 54 Mean (sd)	Non-completers at 6 months N = 46 Mean (sd)	t-test (d.f.)	χ^2 – test (d.f.)	P
Age	55.46 (15.46)	60.5 (12.56)	1.768 (98)		0.080
Gender (Female)	31 (57%)	29 (63%)		0.329 (1)	0.566
Previous ECT (Yes)	20 (38%)	22 (49%)		1.263 (1)	0.266
Resistance (Yes)	29 (54%)	26 (58%)		0.165 (1)	0.685
HDRS pre-treatment	30.20 (7.16)	29.41 (6.69)	- 0.567 (98)		0.572
HDRS EOT	11.80 (8.79)	12.40 (9.18)	0.334 (97)		0.739
HDRS 6 months	13.81 (9.65)	11.10 (10.95)	- 1.055 (76)		0.295
ACE-R pre-treatment	82.04 (9.63)	79.29 (12.87)	- 1.128 (83)		0.263
ACE-R EOT	79.33 (11.68)	77.15 (12.84)	- 0.847 (89)		0.399
ACE-R 6 months	85.12 (10.71)	63.67 (9.45)	- 3.385 (61)		0.001
CSSES EOT	4.62 (4.27)	5.68 (4.67)	1.128 (88)		0.262
CSSES 6 months	4.63 (4.36)	6.67 (7.58)	0.992 (56)		0.325

3.5.1 Comparison of pre-treatment HRQOL between groups

Participants' in both treatment groups rated their own HRQOL on all eight domains considerably worse than a normal population (Jenkinson *et al.* 1996) (for interpretation guide of high and low scores see Appendix 6). Participants' in both treatment groups also rated their own HRQOL substantially worse compared to a sample of depressed primary care patients' and norms previously established for depressed patients (Wells *et al.* 1989; Duggan 1999). Prior to treatment, there was no statistically significant difference between the treatment groups in any of the SF-36 health and well-being domains or the two norm based summary scores (Table 3.21).

Table 3. 21 Table of independent T-Test results of pre-treatment scores on the eight SF-36 domains between both treatment groups

	RUL Group mean (SD) N=36	Bitemporal mean (SD) N=32	t (d.f.)	P
Physical function	70.83 (21.46)	68.59 (25.82)	0.390 (66)	0.697
Role physical	38.89 (47.60)	29.69 (39.88)	0.858 (66)	0.394
Role mental	2.78 (9.34)	12.12 (27.41)	-1.928 (67)	0.058
Social functioning	21.30 (20.29)	16.50 (22.93)	0.922 (67)	0.360
Mental health	21.22 (12.79)	23.28 (17.57)	-0.558 (67)	0.579
Energy	15.00 (14.64)	11.82 (11.71)	0.991 (67)	0.325
Pain	72.22 (26.09)	71.38 (29.14)	0.127 (67)	0.900
Health perception	43.97 (22.81)	42.88 (20.36)	0.209 (67)	0.835
Norm based PCS	33.76 (10.89)	29.98 (10.10)	1.477 (66)	0.144
Norm Based MCS	13.55 (15.83)	14.86 (8.97)	-0.719 (66)	0.475

T = Two sample T-Test t value, d.f. = degress of freedom, P = P-value, SD = standard deviation, RUL = High dose right unilateral ECT group, Norm based PCS = norm based physical component summary score, Norm based MCS = norm based mental component summary score

3.5.2 HRQOL within treatment groups over time

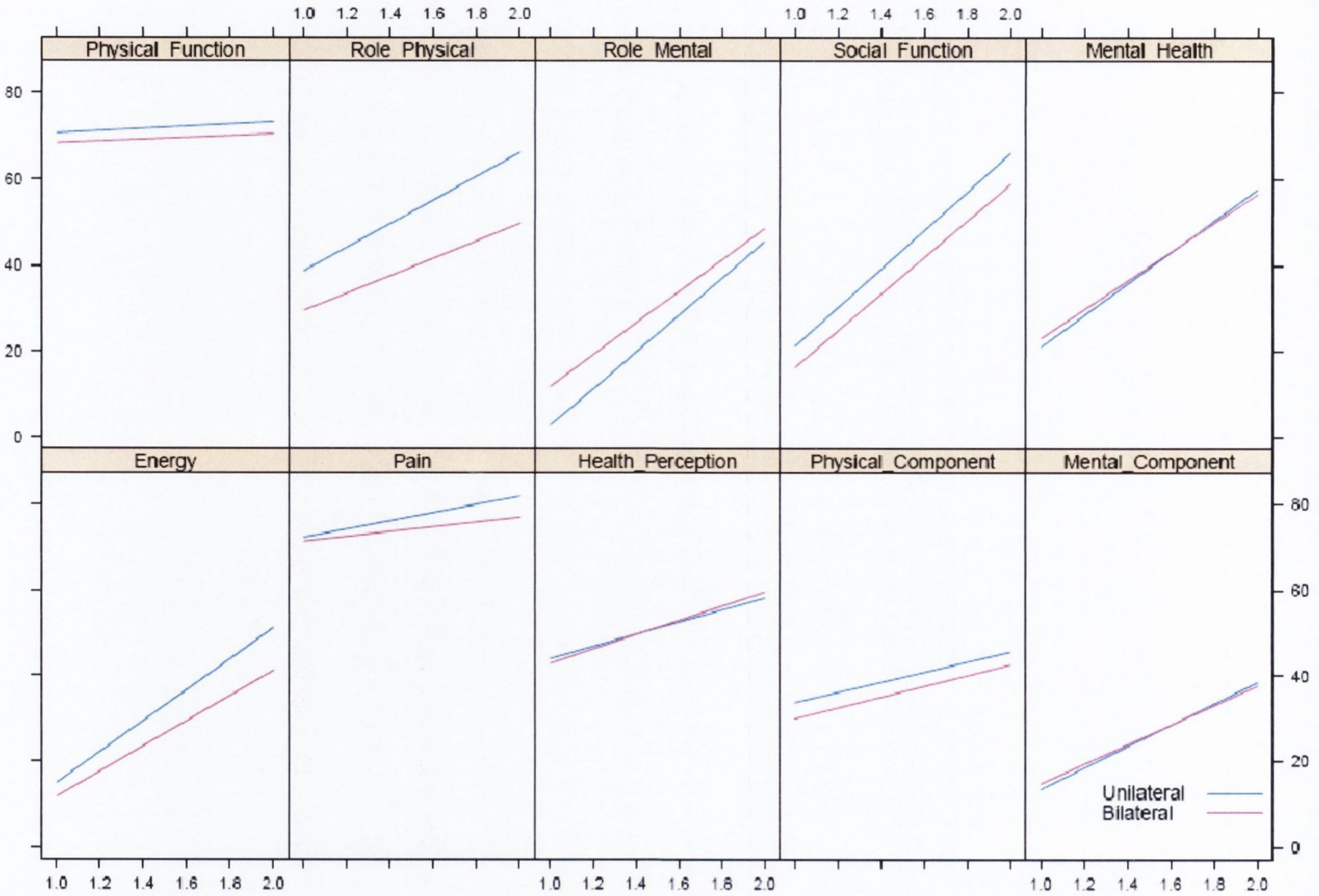
Pre-treatment SF-36 assessments were completed by 36 (72%) of the participants in the high dose RUL group and 32 (64%) of the participants in the bitemporal group. Twenty-seven (54%) participants in the RUL group and 28 (56%) participants in the bitemporal group completed assessments 6 months after completion of the treatment course. Both the pre-treatment and 6 month assessment were completed by N=21 (42%) participants in the high dose RUL group and N=22 (44%) participants in the bitemporal group. As can be seen from Table 6.7 there is less of a deficit in the four physical component domains (physical function, role physical, pain and health perception) and much more of an impact on the mental component domains (role mental, social functioning, mental health and energy). As the four domains that comprise the physical component were less affected by depression there was less recovery in these areas. However, there was still an improvement in these four areas that was not statistically significant. There was a statistically significant improvement in all four mental component domains in both treatment groups (Table 3.22, Figure 3.12). The SF-36 Health Survey comprises eight questions that can be psychometrically grouped into a physical and a mental domain that reflect these changes.

Table 3. 22 Paired sample t-test for pre-treatment and post treatment SF-36 scores in each domain for both treatment groups with Bonferroni correction for multiple tests

	High dose RUL group			Bitemporal group		
	Mean change (95% CI)	t(d.f.)	P	Mean change (95% CI)	t(d.f.)	P
Physical function	- 0.95 (-15.41 – 13.51)	-0.137 (20)	14.27	+ 3.18 (-7.73 – 14.10)	0.606 (21)	8.816
Role physical	+ 9.52 (-16.30 – 35.34)	0.769 (20)	7.22	+ 19.32 (-8.03 – 46.67)	1.469 (21)	2.512
Role mental	+ 40.91 (21.07 – 60.75)	4.287 (21)	P < 0.001	+ 37.68 (17.62 – 57.74)	3.896 (22)	0.016
Social functioning	+ 37.37 (18.60 – 56.15)	4.139 (21)	P < 0.001	+ 43.48 (29.00 – 57.96)	6.227 (22)	P < 0.001
Mental health	+ 31.64 (17.21 – 46.06)	4.560 (21)	P < 0.001	+ 32.17 (18.38 – 45.97)	4.837 (22)	P < 0.001
Energy	+ 30.46 (17.49 – 43.42)	4.886 (21)	P < 0.001	+ 30.87 (17.72 – 44.02)	4.870 (22)	P < 0.001
Pain	+ 11.62 (-0.87 – 24.10)	1.934 (21)	1.07	+ 7.73 (-9.32 – 24.78)	0.940 (22)	5.712
Health perception	+ 11.36 (-3.79 – 26.52)	1.560 (21)	2.14	+ 17.65 (7.388 – 27.92)	3.567 (22)	0.032
Norm based PCS	3.43 (-3.79 – 11.56)	0.885 (18)	0.388	7.37 (1.51 – 13.23)	2.632 (19)	0.016
Norm based MCS	25.62 (15.36 – 35.87)	5.249 (18)	P < 0.000	21.15 (15.60 – 35.40)	5.392 (19)	P < 0.000

RUL = High dose RUL ECT group, mean change = post test score minus pre-test score in each domain, 95% CI = 95% confidence interval for each domain, t = t value, d.f. = degrees of freedom, P = significance level with Bonferroni correction

Figure 3. 12 Line plots showing mean pre-treatment and 6 month F/U scores for both treatment groups on each domain of the SF-36. X-axis represents the assessment time-points: 1 = pre-treatment & 2 = 6 month assessment. Y-axis represents the 0 – 100 scale for each domain.



3.5.3 Change score analysis of covariance (ANCOVA)

A one-way between-groups analysis of covariance (ANCOVA) was conducted for each individual SF-36 domain to compare the effectiveness of the two treatment groups. There were 21 participants (42%) in the high dose RUL group and 22 participants (44%) in the bitemporal group that completed assessments at both time-points and were therefore included in the analysis. The dependent variable was the SF-36 domain change score; the 0 – 100 scale score for each domain at 6 months post treatment minus the 0 – 100 scale pre-treatment score, as is recommended best practice (Ware *et al.* 2008). Participants' scores on the pre-intervention administration of each domain score was used as the covariate in each analysis to control for pre-treatment differences in scores between groups. Preliminary checks were conducted to ensure that there was no violation of the assumptions of normality, linearity, homogeneity of variances, homogeneity of regression slopes and reliable measurement of the covariate (Pallant 2005). After adjusting for pre-intervention scores, there was no significant difference between the two treatment groups on post-intervention change scores on any of the SF-36 Health and Well-being domains (Table 3.23). In fact, laterality explained less than 2% of the variance in the change in the dependant variable in each domain as per the Partial Eta Squared statistic described in section 6.4.4. However, there was a large relationship between the pre-intervention score (covariate) and change scores (dependant variable) on each domain, as indicated by the large Partial Eta Squared statistic.

The SF-36 also facilitates the calculation of summary scores for physical and mental functioning; the physical (PCS) and mental component summary scores (MCS). A one-way between-groups ANCOVA was conducted for the SF-36 PCS and MCS to compare the effectiveness of the two treatment groups. After adjusting for pre-intervention scores, there was no significant difference between the two treatment groups on post-

intervention scores on these summary measures. However, both summary scores also improved from pre-treatment to 6 months after treatment. Mean PCS change score, controlling for baseline scores, in the high dose RUL group was 5.39 (95% CI, -1.07 – 11.85) and in the bitemporal group was 5.50 (95% CI, -0.78 - 11.79) (Table 3.23). There was no significant difference between the treatment groups, P = 0.82. Mean MCS change scores, controlling for baseline scores, improved in the high dose RUL group by 23.94 (95% CI, 15.55 - 32.33) and in the bitemporal group by 27.09 (95% CI, 18.92, 35.27). Although the bitemporal group scored 3.16 (95% CI, -8.621 - 14.932) points higher, this difference between the treatment groups was not statistically significant, P = 0.68. Once again laterality explained very little variance while there was a large relationship between the pre-intervention score and change scores on each summary scale, as indicated by a Partial Eta Squared statistic (Table 3.23).

Table 3. 23 ANCOVA results comparing both treatment groups for the eight SF-36 domains

SF-36 Health Domain Scale	F (d.f.)	P	Partial Eta Squared	
			Group	Covariate
Physical function	0.201 (1, 40)	0.657	0.005	0.136
Role physical	0.287 (1, 40)	0.595	0.007	0.435
Role mental	0.082 (1, 42)	0.776	0.002	0.088
Social functioning	0.002 (1, 42)	0.965	0.000	0.243
Mental health	0.392 (1, 42)	0.535	0.009	0.345
Energy	0.231 (1, 42)	0.633	0.005	0.158
Pain	0.505 (1, 42)	0.481	0.012	0.383
Health perception	0.808 (1, 42)	0.374	0.019	0.310
PCS	0.053 (1, 40)	0.819	0.001	0.250
MCS	0.170 (1, 40)	0.682	0.004	0.241

F = F test result, d.f. = degrees of freedom, P = P value, Partial Eta Squared = measure of effect size, covariate = pre-intervention score for each domain, PCS = Physical component summary score, MCS = Mental component summary score

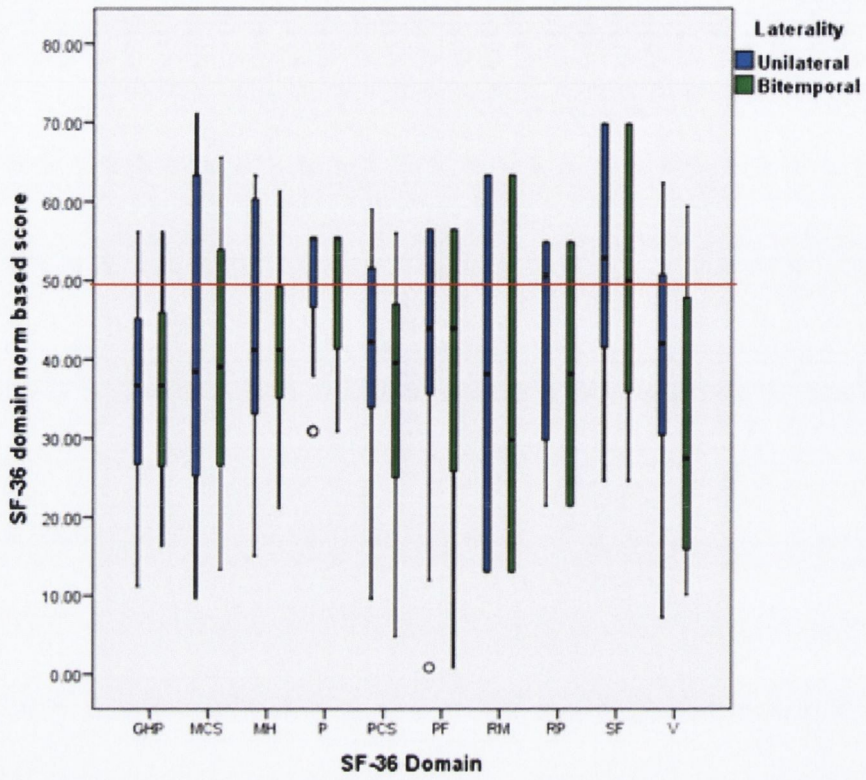
3.5.4 Normative data

It is clear that depression had a significant impact on all domains of health and well-being and normative data was available to put this impact, and the change following treatment, into context. Table 6.9 presents norm based scores for each treatment group. Each score represents the domain score for each group at the respective time-point. These data can be compared to the OHLS normative data that has a mean of 50 and standard deviation of 10 for each domain. There was a clear improvement in health and well-being in all eight domains following treatment with ECT that was independent of treatment group. However, this sample continued to report persistent deficits in health related quality of life 6 months after treatment compared to normative data (Table 3.24, Figure 3.13).

Table 3. 24 SF-36 norm based domain scores for both treatment groups. For each domain the relative normal population has a mean of 50 (10)

	High Dose RUL Group		Bitemporal Group	
	Pre-treatment N=36 Mean (SD)	6 month F/U N=26 Mean (SD)	Pre-treatment N=32 Mean (SD)	6 month F/U N=28 Mean (SD)
Physical Functioning	40.23 (11.94)	41.69 (15.29)	38.98 (14.36)	40.16 (17.37)
Role Physical	34.42 (15.94)	43.59 (13.35)	31.35 (13.32)	38.13 (16.55)
Role Emotional	14.45 (4.70)	33.49 (20.51)	19.15 (13.77)	34.93 (21.52)
Social Functioning	29.75 (10.32)	52.61 (16.17)	27.31 (11.67)	48.98 (17.93)
Mental Health	23.72 (6.43)	42.12 (15.12)	24.75 (8.83)	41.63 (12.20)
Energy	15.91 (8.49)	35.99 (12.90)	14.07 (6.80)	31.45 (12.68)
Pain	46.63 (8.26)	49.67 (8.69)	46.36 (9.17)	48.13 (8.41)
Health Perception	27.51 (11.65)	34.75 (13.62)	26.95 (10.40)	35.50 (12.45)
PCS	33.76 (10.89)	45.60 (12.46)	29.98 (10.11)	42.62 (11.69)
MCS	13.55 (5.83)	38.50 (18.84)	14.86 (8.97)	37.68 (16.28)

Figure 3. 13 Boxplots for the SF-36 norm based scores for each domain and both summary scores at 6 months after treatment compared to normative data scores from the OHLS survey



Blue boxes represent the high dose RUL group; Green boxes represent the bitemporal group. Each box represents the 25th percentile at the bottom, the 75th percentile at the top and the median marked by the line within each box. Lines extending from the top and bottom of each box represent the range of values. Black dots represent outliers (an observation that deviates distinctly from other members of the sample from which it occurs (Gravetter & Wallnau 2004). The Y-Axis represents SF-36 norm based score for each domain. The X-Axis represents each of the 8 SF-36 domains and the 2 summary measures: GHP – Health perception domain, MCS – Mental component summary score, MH – Mental health domain, P – Bodily pain domain, PCS – Physical component summary score, PF – Physical functioning domain, RM – Role emotional domain, RP – Role physical domain, SF – Social functioning domain, V – Energy domain. The red line represents normative data from the OHLS survey for all domains.

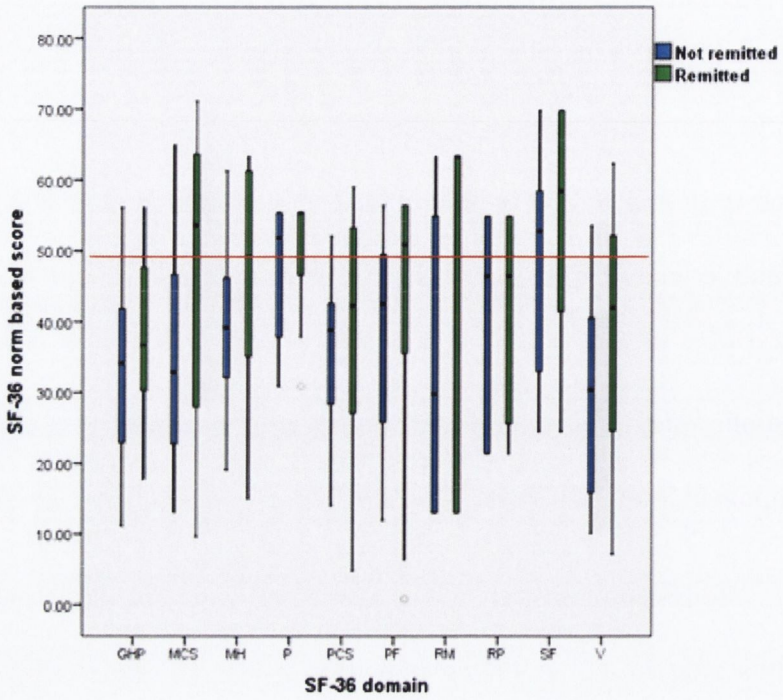
3.5.5 Predicting HRQOL after ECT

It was found that there was no difference in improvement on any of the eight SF-36 health and well-being domains or the two summary scores between the treatment groups 6 months after the treatment course. Although both treatment groups improved on all domains of the SF-36 both groups had persistently low HRQOL compared to OHLS normative data (Jenkinson *et al.* 1996). This raises the question; what predicts HRQOL after ECT? Two multiple linear regression models were constructed to answer this question; one for the Physical Component Summary score and one for the Mental Component Summary score.

Remission status at EOT was the only independent variables that predicted MCS 6 months after ECT. Achieving remission at end of treatment was associated with a 10.4 point (95% CI, 0.253 – 20.49) increase on the mental component norm based summary score, P = 0.045. This model accounted for 8% of the variance ($R^2 = 0.081$). An increase in MCS score of this magnitude would on average have increased MCS scores to the OHLS norm or above. No end of treatment explanatory variables were identified that were associated with higher PCS scores 6 months after ECT. It is clear that achieving remission is associated with better HRQOL than not remitting and this effect is greater for the mental component scores than for the physical component scores. The fact that mental component scores were affected to a greater extent than physical component scores most likely explains this, as there was less improvements to be made on the physical component scale.

To present this visually Figure 3.14 shows boxplots of the SF-36 norm based scores for each domain and the two summary scores for those that were remitted and those that were not remitted at end of treatment.

Figure 3. 14 Boxplots of the SF-36 norm based scores 6 months after the treatment course for remitted and non-remitted participants at end of treatment



Blue boxes represent those that did not remit at 6 months post ECT; Green boxes represent those that remitted 6 months post ECT. Each box represents the 25th percentile at the bottom, the 75th percentile at the top and the median marked by the line within each box. Lines extending from the top and bottom of each box represent the range of values. Black dots represent outliers (an observation that deviates distinctly from other members of the sample from which it occurs (Gravetter & Wallnau 2004). The Y-Axis represents SF-36 norm based score for each domain. The X-Axis represents each of the 8 SF-36 domains and the 2 summary measures: GHP – Health perception domain, MCS – Mental component summary score, MH – Mental health domain, P – Bodily pain domain, PCS – Physical component summary score, PF – Physical functioning domain, RM – Role emotional domain, RP – Role physical domain, SF – Social functioning domain, V – Energy domain. The red line represents normative data from the OHLS survey for all domains.

3.6 Attitudes towards ECT

There were 43 (86%) RUL participants and 39 (78%) bitemporal participants who completed the attitudes questionnaire after the course of ECT, $\chi^2(1) = 1.084$, P = 0.298. 3 months after the course of treatment there were 24 (48%) RUL participants and 25 (50%) bitemporal participants that completed the attitudes questionnaire, $\chi^2(1) = 0.040$, P = 0.841. 24 (48%) participants in each treatment group completed the attitudes questionnaire at both assessment time-points, $\chi^2(1) = 0.000$, P = 1.000. Given the amount of missing data at the 3 month follow-up assessment the primary analysis focused on the attitudes of participants towards ECT at end of treatment. A subgroup analysis with the smaller data set of the 24 participants in each treatment group that completed the questionnaire at both time-points examined the effect of time on attitudes.

Of the 100 participants that completed a course of ECT and had the opportunity to complete the attitudes questionnaire 18 participants did not do so at the end of treatment. There was no difference in severity of depression prior to treatment (P = 0.878) or after treatment (P = 0.877) between those that completed the attitudes questionnaire and those that did not (Table 3.25). There was also no difference in subjective side-effects expressed (P = 0.934). There was a trend for participants that did not complete the questionnaire to be older (P = 0.073), to be female (P = 0.089) and to have had ECT previously (P = 0.083). Those that did not complete an attitudes questionnaire after treatment had significantly worse cognitive functioning prior to treatment (P < 0.001) and after the course of treatment (P = 0.002) as measured by the ACE-R.

Table 3. 25 Comparison of characteristics and clinical details for those that completed the attitudes questionnaire after the treatment course and those that did not

	Completers at EOT N = 82 Mean (sd)	Non-completers at EOT N = 18 Mean (sd)	t-test (d.f.)	χ^2 – test (d.f.)	P
Age	56.57 (14.49)	63.28 (12.64)	1.815 (98)		0.073
Gender (Female) N (%)	46 (56%)	14 (78%)		2.891 (1)	0.089
Previous ECT (Yes) N (%)	31 (39%)	11 (61%)		3.000 (1)	0.083
Resistance (Yes) N (%)	47 (57%)	8 (47%)		0.600 (1)	0.439
HDRS pre-treatment	29.89 (6.93)	29.61 (7.11)	- 0.154 (98)		0.878
HDRS EOT	12.13 (8.88)	11.76 (9.39)	- 0.155 (97)		0.877
ACE-R pre-treatment	82.86 (9.68)	71.27 (13.18)	- 3.936 (83)		< 0.001
ACE-R EOT	79.95 (11.79)	68.92 (10.36)	- 3.170 (89)		0.002
CSSES EOT	5.05 (4.45)	5.17 (4.62)	0.083 (88)		0.934

Including only those participants that completed an end of treatment attitudes questionnaire (43 (86%) RUL participants and 39 (78%) bitemporal participants), there were 24 participants in the high dose RUL group (48%) and 24 participants in the bitemporal group (48%) that completed the assessment 3 months after the course of treatment (1 assessment was excluded as the participant did not complete an attitudes questionnaire at end of treatment course). There were no significant differences between those that did and those that did not complete the assessment 3 months after treatment (Table 3.26).

Table 3. 26 Comparison of characteristics and clinical details for those that completed the attitudes questionnaire 3 months after the treatment course and those that did not

	Completers at 3 months N = 48 Mean (sd)	Non-completers at 3 months N = 34 Mean (sd)	t-test (d.f.)	χ^2 – test (d.f.)	P
Age	56.08 (16.07)	57.26 (12.11)	0.362 (80)		0.719
Gender (Female) N (%)	26 (54%)	20 (59%)		0.175 (1)	0.675
Previous ECT (Yes) N (%)	17 (36%)	14 (42%)		0.319 (1)	0.572
Resistance (Yes) N (%)	26 (54%)	21 (62%)		0.470 (1)	0.493
HDRS EOT	11.35 (8.54)	13.24 (9.36)	- 0.944 (80)		0.348
HDRS 3 month	13.06 (8.08)	14.05 (9.90)	0.440 (68)		0.662
ACE-R EOT	79.98 (11.70)	79.90 (12.13)	- 0.027 (76)		0.978
ACE-R 3 month	85.16 (8.74)	84.00 (12.35)	- 0.337 (52)		0.737
CSSES EOT	4.74 (4.46)	5.50 (4.46)	0.741 (76)		0.461
CSSES 3 month	3.45 (3.17)	5.09 (4.99)	1.355 (53)		0.181

3.6.1 Descriptive analysis

There are a number of aspects of ECT that are quite provocative in the literature. To address these initially, results of nine statements about consent, perception of effectiveness and likelihood of choosing ECT again in the future if needed are presented in Table 3.27.

75% (N = 29) of bitemporal and 84% (N = 36) of RUL participants were happy with the explanation of ECT prior to commencing treatment. 82% (N = 32)of bitemporal and 95% (N = 41) of RUL participants were happy that they had made an informed decision to have ECT. Less than 5% (N = 1 in RUL group and N = 2 in Bitemporal group) in each treatment group felt pressurised or forced to have ECT. 85% (N = 33) of bitemporal and 93% (N = 40) of RUL participants were positive that ECT had help them and 70% (N = 27) of bitemporal and 73% (N = 31) of RUL participants felt that ECT had relieved their depression. However 66% (N = 26) of bitemporal participants and 53% (N = 23) of RUL participants felt ECT had caused problems with their memory and 5% (N = 2) of bitemporal participants rated this effect as very severe and 20% (N = 8) as severe. 12% (N = 5) of RUL participants stated that the memory effects of ECT were very severe and 21% (N = 9) felt it was severe. 77% (N = 30) of bitemporal participants and 84% (N = 36) of RUL participants would readily have the treatment again and 21% (N = 3) of bitemporal participants and 11% (N = 5) of RUL participants stated that they would never have ECT again.

Table 3. 27 Responses to nine statements about ECT from the attitudes questionnaire for both treatment groups

	Strongly agree		Agree		Neutral		Disagree		Strongly disagree	
	RUL N=43 N (%)	BiTem N=39 N (%)	RUL N=43 N (%)	BiTem N=39 N (%)	RUL N=43 N (%)	BiTem N=39 N (%)	RUL N=43 N (%)	BiTem N=39 N (%)	RUL N=43 N (%)	BiTem N=39 N (%)
The explanation of ECT given before treatment was adequate	13 (30)	6 (15)	23 (54)	23 (60)	4 (10)	8 (21)	2 (5)	2 (5)	1 (2)	0 (0)
I think I made a fully informed decision to have ECT	19 (44)	16 (41)	22 (51)	16 (41)	1 (2)	4 (10)	1 (2)	0 (0)	0 (0)	3 (8)
I felt pressurised or forced to have ECT	1 (2)	0 (0)	0 (0)	2 (5)	4 (9)	3 (8)	16 (37)	14 (36)	22 (51)	20 (51)
ECT helped you	25 (58)	21 (54)	15 (35)	12 (31)	1 (2)	3 (8)	2 (5)	1 (3)	0 (0)	2 (5)
ECT relieved your depression	20 (47)	15 (39)	11 (26)	12 (31)	8 (19)	4 (10)	1 (2)	5 (13)	3 (7)	3 (8)
ECT caused problems with your memory (2 participants did not complete this question – both in the bitemporal group)	13 (30)	20 (51)	10 (23)	6 (15)	6 (14)	5 (13)	10 (23)	5 (13)	4 (9)	1 (3)
ECT caused severe memory impairment	5 (12)	2 (5)	9 (21)	8 (20)	8 (19)	12 (31)	11 (26)	9 (23)	10 (23)	8 (21)
If necessary I'd readily have the treatment again	18 (42)	13 (33)	18 (42)	17 (44)	3 (7)	7 (18)	3 (7)	1 (3)	1 (2)	1 (3)
I would never have ECT again	1 (2)	0 (0)	4 (9)	3 (8)	6 (14)	8 (21)	13 (30)	14 (36)	19 (44)	14 (36)

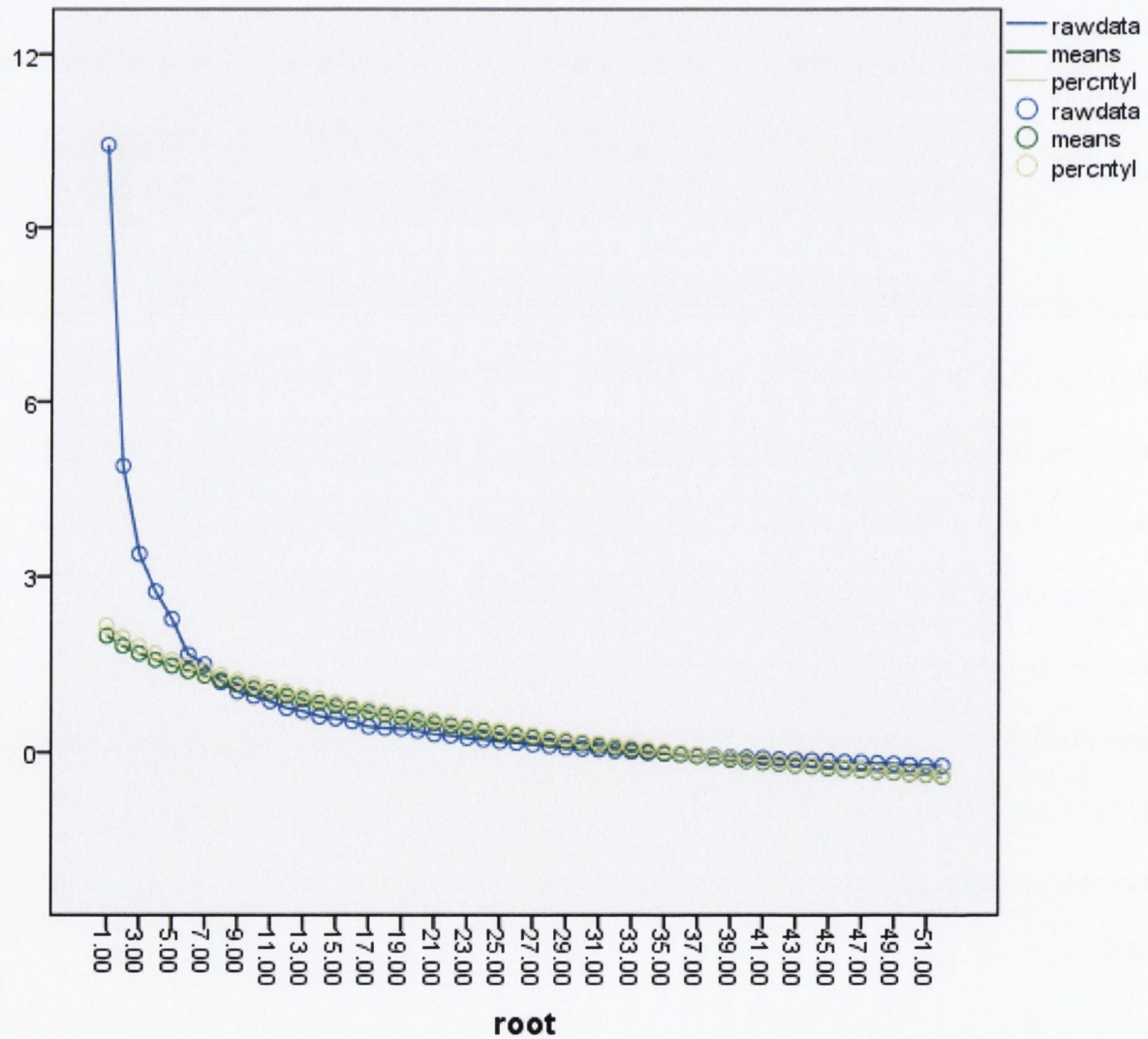
3.6.2 Factor analysis

The 53 items of the attitudes scale were subjected to factor analysis using SPSS Version 16. Prior to performing the factor analysis the suitability of data for factor analysis was assessed. Inspection of the correlation matrix revealed the presence of many coefficients of 0.3 and above which is desirable (Pallant 2005). The Kaiser-Meyer-Oklin (KMO) value was 0.77, exceeding the recommended value of 0.6 (Kaiser 1970, 1974) and the Barlett's Test of Sphericity (Bartlett 1954) reached statistical significance ($P < 0.001$), supporting the factorability of the correlation matrix. A Parallel Analysis revealed the presence of seven factors with eigenvalues exceeding the corresponding criterion values for a randomly generated data matrix of the same size (52 variables × 132 respondents). Table 3.28 shows the result of the parallel analysis. The first 7 factors had eigenvalues greater than their respective 95th percentile equivalent (i.e. if none of the items were sufficiently inter-correlated to combine to form composite groups, none of the eigenvalues would be greater than 1) and were thus determined to be significant factors. Inspection of the screeplot confirms this revealing a clear break after the 7th component (Figure 3.15). It was therefore decided to retain seven components for further investigation. The subsequent factor analysis revealed seven factors with eigenvalues exceeding 1, explaining 18.9%, 9%, 6.2%, 5.3%, 4.3%, 2.8 and 2.8% of the variance respectively or 49.3% of the variance in total. To aid in the interpretation of these seven factors, Direct Oblimin rotation was performed. Rotation of factors changes the order of items in each factor so that the items combine in the most easily interpretable way possible. The rotated solution revealed the presence of simple structure (Thurstone 1947), with all seven factors showing a number of strong loadings and all variables loading substantially on only one factor. The results of this analysis support the use of the seven factors as separate scales.

Table 3. 28 Raw data eigenvalues & mean & 95th percentile random data eigenvalues from parallel analysis of the item responses

Factor	Raw Data	Means (50th Percentile)	95th Percentile
1	10.431110	1.987711	2.161886
2	4.898994	1.818712	1.960202
3	3.387770	1.688032	1.813013
4	2.745811	1.575136	1.684993
5	2.275805	1.477130	1.568723
6	1.668364	1.389733	1.477785
7	1.496521	1.307603	1.389558
8	1.194846	1.229723	1.312796
9	1.035769	1.157403	1.228799
10	0.959250	1.088973	1.160583
11 - 52	Eigenvalue < 0.1		

Figure 3. 15 Scree plot revealing the presence of seven clear factors with eigenvalues above what would be found in a population of the same size



The Y-axis represents the eigenvalue (the proportion of variance explained by each factor). The X-axis represents all of the factors that could be created from the factor analysis. The blue line is the eigenvalues for the raw data. The green line is the mean eigenvalue that would be expected from a standard normal population of the same size and the brown line is the 95th percentile that each eigenvalue should be below if it was from a standard normal population. The number of factors above the point at which the shape of the curve becomes horizontal should be retained as these factors explain most of the variance in the data set (Catell 1966).

Figure 3. 16 Pattern Matrix displaying seven clear factors with individual factor loading scores for each question

	Factor						
	1	2	3	4	5	6	7
Effectiveness of ECT							
Did ECT relieve your depression	.928	-.099	-.081	.110	.074	-.175	.008
ECT made me less depressed	.806	-.087	-.056	.079	-.121	.041	-.067
I think ECT helped me	.790	-.032	-.138	-.017	-.022	-.086	.268
How much did ECT help you	.757	-.003	.086	.082	-.108	-.019	-.016
I would never have ECT again	.701	.017	-.046	-.122	.044	.297	.010
ECT gets you better quicker than drugs	.696	.043	.031	.012	.170	-.115	-.067
ECT is a helpful and useful procedure	.680	.206	-.184	.030	-.044	.083	-.039
ECT made me less anxious	.600	-.064	.059	.099	-.161	.106	.090
If necessary I'd readily have the treatment again	.541	.135	.090	-.023	.161	.460	-.082
ECT made me forget what was bothering me	.377	-.161	.047	.188	-.044	.013	.304
ECT staff were pleasant	.246	.165	.033	-.139	.129	.066	.031
Consent process							
I had enough time to think about ECT and discuss it with my doctor or nurse before agreeing to the treatment	-.007	.923	.039	.040	.028	-.046	.071
I think I made a fully informed decision to have ECT	-.034	.760	.016	.162	.054	-.142	.153
I was offered other treatments before I had ECT (medications/ talking therapy etc)	-.018	.753	.011	-.126	.026	-.067	-.031
I received written information about ECT (e.g. hospital booklet etc) before the treatment	-.040	.624	-.089	.108	-.109	.164	-.020
More explanation should be given to the patients about the treatment	.074	.416	-.185	.157	-.092	.170	-.006
I discussed my decision with others (e.g. family, friends or other patients)	-.038	.395	.019	-.192	.011	.088	.299
I felt pressurised or forced to have ECT	-.014	.339	-.094	-.057	.219	-.016	.331

The explanation of ECT given before treatment was adequate	.116	.238	-.100	.156	.126	.044	.093
Fear of ECT							
Worried about having a fit or turn	.056	-.020	-.920	-.054	-.024	-.016	-.062
Worried about possible brain damage as a result of the treatment	.013	.017	-.758	.009	.056	-.096	.010
Worried that electricity was used in treatment	-.066	-.039	-.731	.069	.073	.197	.019
Worried about losing control of bladder or embarrassing things whilst unconscious	-.019	.008	-.646	-.107	-.064	.042	-.031
Worried about being made unconscious	-.016	.172	-.442	-.107	-.064	.257	.075
Memory Effects of ECT							
Did ECT cause problems with your memory	.033	-.019	.028	.839	.021	.008	-.010
I still have side effects from the ECT treatment	.075	.084	.027	.743	-.069	.118	.112
Did ECT cause side-effects	.065	-.148	-.067	.704	.193	-.008	.192
Did ECT cause problems with your concentration	.146	.049	-.113	.700	.223	-.097	-.168
ECT has no effect on memory at all	-.094	.026	.086	.657	-.031	-.082	-.106
My memory now is better than it has ever been	.005	-.012	.085	.575	-.083	.075	-.065
ECT causes permanent changes to memory	.090	.113	.181	.568	-.046	.201	.052
My memory has never returned to normal after ECT	.041	.058	-.139	.434	-.023	.040	.233
Experience of ECT							
Experience of anaesthetic Injections	-.188	-.092	.196	-.026	.742	.038	.073
Experience of falling asleep	-.148	.024	.146	-.069	.724	.029	.086
Experience of waking up	.023	-.082	.033	.064	.578	-.004	.025
Experience of recovery period	.084	.060	-.201	.114	.531	-.032	-.076
Experience of premedication-Pleasant	.044	.073	-.107	-.024	.481	.057	-.006
Experience of waiting for treatment	-.001	-.047	-.107	-.047	.381	.233	.115
ECT works but the effects are short-lived	.088	.082	-.062	.026	.215	-.009	-.049

Perception of ECT treatment							
ECT is a frightening treatment to have	.068	.061	-.242	-.053	-.091	.666	.021
ECT was more upsetting than going to the dentist	.123	.031	-.110	.010	.118	.486	.115
How frightening or upsetting was ECT compared with what you expected	.107	.026	-.006	.092	.068	.441	-.031
I felt anxious/ frightened before my first ECT treatment	-.081	-.110	-.301	.088	-.012	.438	.176
I was so upset by the treatment I'd be reluctant to have it again	.400	.161	.052	-.038	.155	.430	.074
ECT is helpful but the side effects are severe	-.031	.174	-.063	.349	.117	.418	-.099
I felt pleased the treatment was starting before my first ECT treatment	.293	.052	.050	.078	.150	.325	-.024
I felt that I had no alternative but to have ECT	-.046	-.030	-.005	.033	.032	.266	.030
Perception of care							
Those caring for me took my side-effects seriously	.041	-.078	.073	-.001	.018	.090	.678
I had enough time to discuss any concerns I had with my doctor/ nurse since having ECT	.106	.331	.118	-.007	.030	-.060	.578
I think I was properly cared for after the ECT treatment (e.g. people spent time with me if I felt confused or distressed)	.189	.104	-.285	-.061	.012	-.179	.529
Ward staff explained to me what would happen during ECT	-.177	.291	-.062	.082	.104	.081	.506
Ward staff explained the possible side-effects of ECT	-.049	.119	-.014	.004	.084	.137	.483

3.6.3 Interpretation of factors

Factor loadings are considered high if they are greater than 0.6 (the positive or negative sign is irrelevant) and moderately high if they are above 0.3. Loadings below 0.3 are normally ignored because the correlation of the variable with the factor is considered too weak (Kline 1994). There is a clear simple structure to the factor analysis in which variables (the questions) that were inter-correlated and combined to form factors were moderately to highly correlated with 1 factor but uncorrelated with all other factors (Thurstone 1947). Composite scores for further analysis were computed by summing the results of each of the questions contained in each factor presented above and explained below.

Factor 1 – Effectiveness of ECT: 11 statements (items) from the attitudes questionnaire were sufficiently inter-correlated to form factor 1. Ten of these items had factor loadings greater than 0.3 and were combined to form factor 1. Examination of the items included in this factor indicated that this factor addresses the issue of participants' attitudes towards the effectiveness of ECT. A composite score was computed by summing the results of each of the statements contained in this factor. So factor 1 represents the attitudes of participants towards the effectiveness of ECT on a scale that ranges from 10 to 50. Scores above the midpoint of 30 (midpoint is the number of questions multiplied by the neutral value in all questions, 3) can be considered to represent positive attitude towards the effectiveness of ECT, scores around this midpoint can be considered neutral and scores below 30 mean that participants were negative in their attitude towards the effectiveness of ECT.

Factor 2 – Consent: comprised 8 statements that focused on satisfaction with the amount of information participants were given prior to treatment and the consent process. 1 statement was excluded because its factor loading (correlation with the factor) was below

0.3. Factor 2 thus represents the attitudes of participants towards the information and consent associated with the ECT process. This scale ranges from 7 to 35. Scores above the midpoint of 21 can be considered to represent positive attitude towards the consent process, scores around this midpoint can be considered neutral and scores below 21 indicate that participants were negative in their attitude towards the consent process.

Factor 3 – Fear of ECT: comprised 5 statements about specific fears about the actual ECT procedure. All questions were included because factor loadings were above 0.3. This scale ranged from 5 to 25. Scores above the midpoint of 15 can be considered to represent positive attitude towards fears of the procedure, scores around this midpoint can be considered neutral and scores below 15 indicate that participants attitude towards fear of the procedure were negative.

Factor 4 – Memory effects of ECT: comprised 8 statements primarily related to the perceived impact of ECT on memory. All questions were included because factor loadings were above 0.3. This scale ranges from 8 to 40. Scores above the midpoint of 24 can be considered to represent positive attitude towards the memory effects of ECT, scores around this midpoint can be considered neutral and scores below 24 indicate that participants were negative in their attitude towards the memory effects of ECT.

Factor 5 – Experience of ECT: comprised 7 statements about ones experience with the ECT procedure and 1 statement was excluded from the composite score because its factor loading was below 0.3. This scale ranges from 6 to 30. Scores above the midpoint of 18 can be considered to represent a positive attitude towards the ECT procedure, scores around this midpoint can be considered neutral and scores below 18 indicate that participants found the ECT procedure to be a negative experience, and hence their attitude was negative.

Factor 6 – Perception of ECT: comprised 8 statements that related to participants perception of ECT. 1 statement was excluded because its factor loading (correlation with the factor) was below 0.3. This scale ranges from 7 to 35. Scores above the midpoint of 21 can be considered to a represent positive perception of ECT, scores around the midpoint can be considered neutral and scores below 21indicate that participants had a negative perception of ECT.

Factor 7 – Perception of care: comprised 5 statements that related to participants perception of care they received before during and after their course of ECT. All items were included as their factor loadings were above 0.3. This scale ranges from 5 to 25. Scores above the midpoint of 15 can be considered to a represent positive attitude towards the care received, scores around the midpoint can be considered neutral and scores below 15 indicate that participants had a negative attitude towards the care they received.

3.6.4 Composite scores

Values around the midpoint of each factor represent a neutral attitude towards that factor whereas low scores represent a negative attitude and high scores represent a positive attitude. Raw scores for the end of treatment and 3 month assessment are presented visually and levels of positivity or negativity in each factor relative to a neutral attitude can be seen (Figure 3.17 to Figure 3.23). Both groups were above the point of neutrality in their attitudes towards the effectiveness of ECT, the consent process associated with ECT, fear of ECT, perception of ECT and perception of care at end of treatment and 3 months later. The attitude of participants in the RUL group was neutral while the attitude of participants in the bitemporal group was slightly negative towards the memory effects of ECT and experience of ECT composite scores at the end of treatment. 3 months after the end of treatment the attitude of participants in the RUL group was neutral while the

attitude of participants in the bitemporal group was slightly negative towards the memory effects of ECT and both groups were slightly negative about their attitudes towards their experience of ECT.

Figure 3. 17 Effectiveness of ECT attitude scores for both treatment groups at both assessment time-points

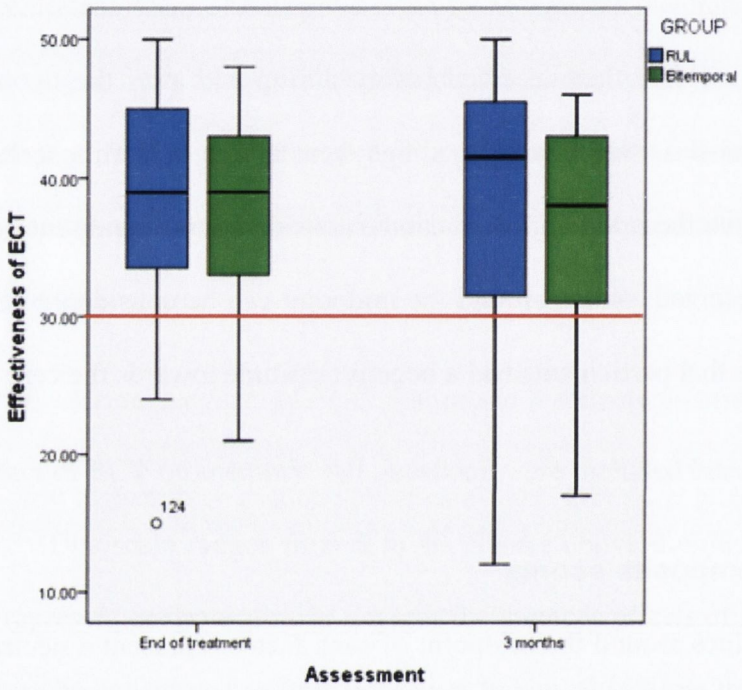


Figure 3. 18 Attitude scores for both treatment groups at both assessment time-points for the consent process associated with ECT

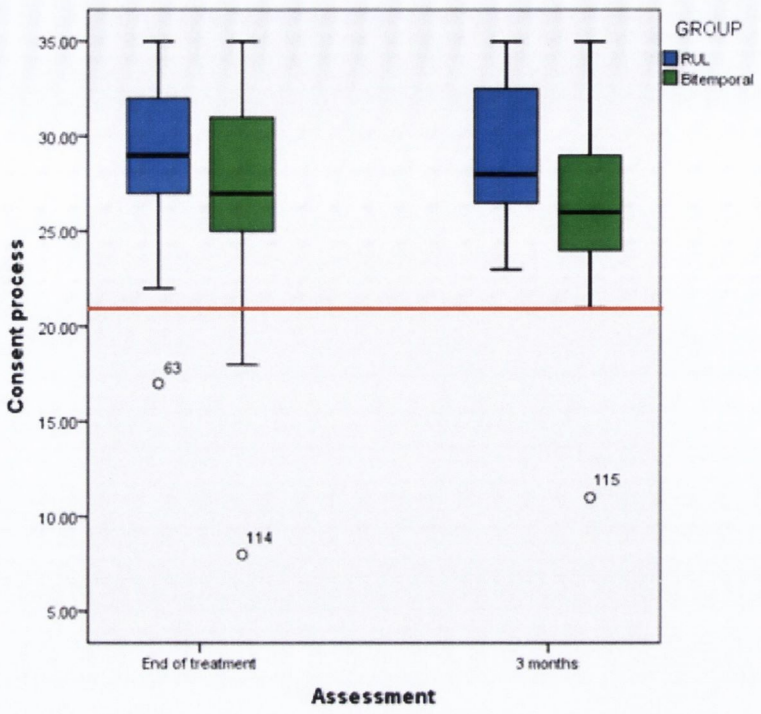


Figure 3. 19 Fear of ECT attitude scores for both treatment groups at both assessment time-points

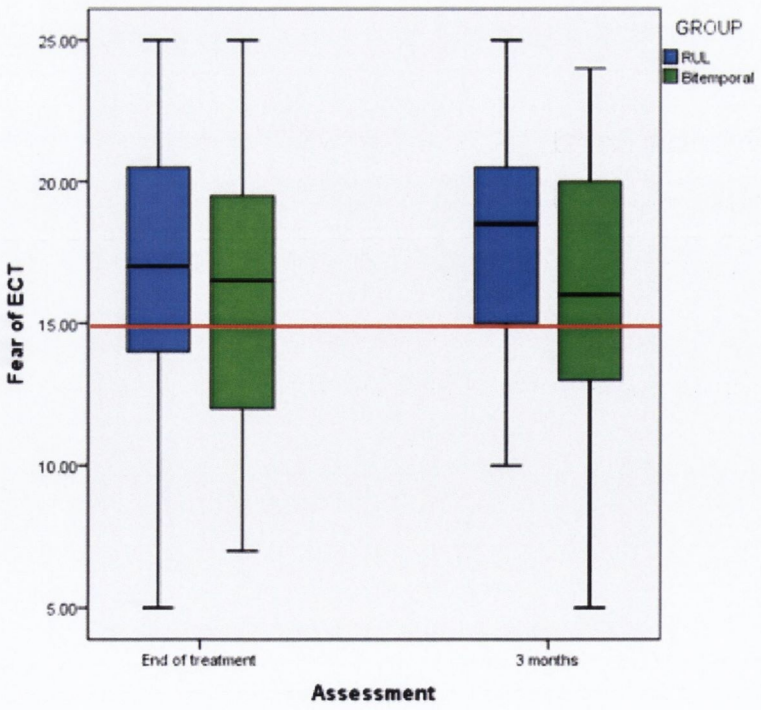


Figure 3. 20 Attitude scores towards the memory effects of ECT for both treatment groups at both assessment time-points

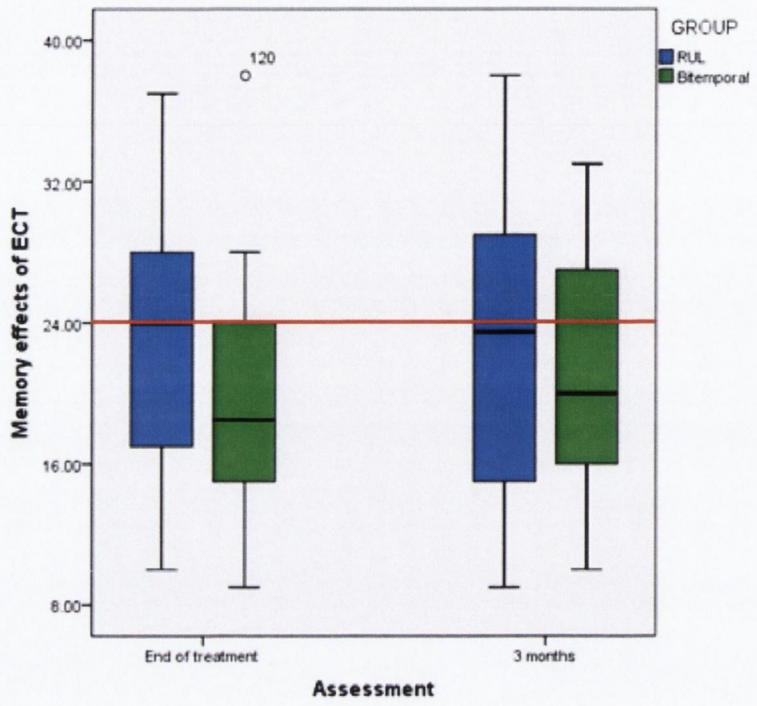


Figure 3. 21 Experience of ECT attitude scores for both treatment groups at both assessment time-points

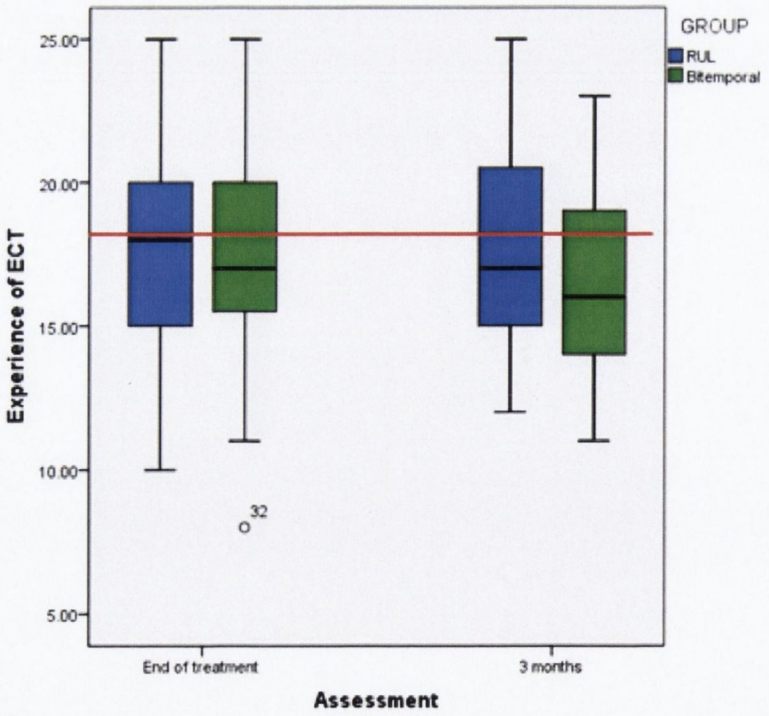


Figure 3. 22 Attitude scores towards the perception of ECT composite score for both treatment groups at both assessment time-points

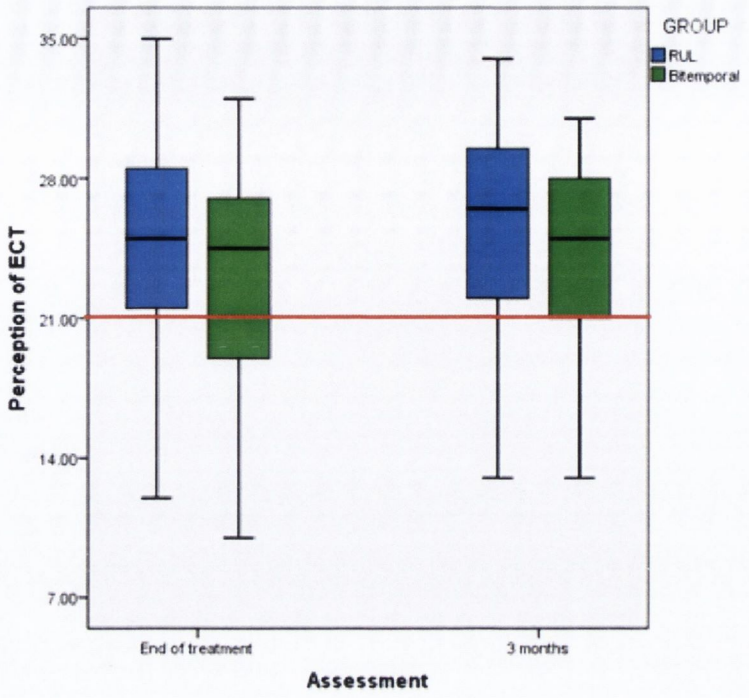


Figure 3. 23 Attitude scores towards the perception of care composite score for both treatment groups at both assessment time-points

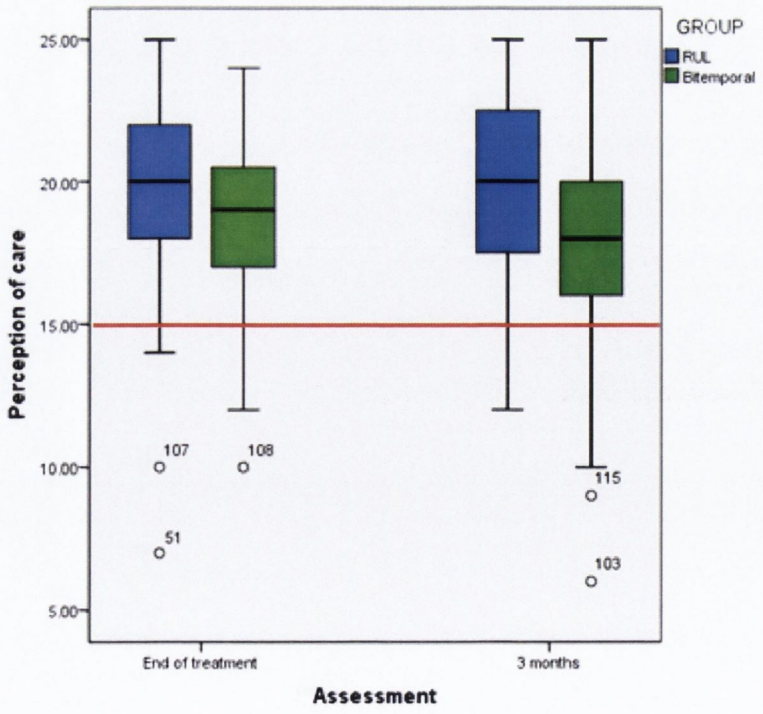


Figure 3.17 to 2.23 Boxplots displaying the level of positivity or negativity expressed from participants in both treatment groups to the 7 factors. The blue box represents the high dose RUL group. The green box represents the bitemporal group. The black line within each box is the median value. The upper end of each box above the median represents the upper quartile or 25% of data greater than the median. The lower end of each box below the median represents the lower quartile or 25% of data less than the median. Whiskers extending above and below the box represent the maximum and minimum values excluding outliers. Dots above and below the whiskers represent scores that were considerably higher or lower than normal for these data. The minimum and maximum scores for each boxplot are specific to each composite score only. The red line indicates the midpoint of the minimum to maximum score range and the point of neutral values. Below the red line represents negative attitude towards each composite score. Above the red line indicates positive attitude towards each composite score.

3.6.5 Group comparison

The primary analysis focused on the comparative attitudes of participants in each treatment group at the end of the treatment course. The seven domains created by the factor analysis were compared between treatment groups using T-Tests (Table 3.29).

Table 3. 29 Comparison of treatment groups for each of the attitude domains at end of treatment course

	High dose RUL Group Mean (sd) N = 43	Bitemporal Group Mean (sd) N = 39	t-test (d.f.)	P
Effectiveness of ECT	38.51 (7.94)	37.44 (7.45)	0.631 (80)	0.530
Informed consent	29.09 (3.92)	26.95 (5.47)	2.054 (80)	0.043
Fears about ECT	16.77 (4.93)	16.51 (4.49)	0.244 (80)	0.808
Memory effects of ECT	22.74 (7.14)	19.26 (6.19)	2.353 (80)	0.021
Experience of ECT	17.30 (3.28)	17.46 (3.29)	- 0.219 (80)	0.827
Perception of ECT	24.60 (5.29)	23.28 (5.22)	1.138 (80)	0.259
Perception of care	19.44 (3.88)	18.62 (3.40)	1.021 (80)	0.310

There was no difference between the treatment groups in the effectiveness of ECT, fears about ECT, experience of ECT, perceptions of ECT and perception of care domains. However, patients treated with high dose RUL ECT were significantly more positive about the consent process (P = 0.043) and were significantly more positive about the memory effects of ECT (P = 0.021) compared with patients treated with bitemporal ECT.

3 months after the treatment course there was no difference between the treatment groups in effectiveness of ECT, fears about ECT, memory effects of ECT, experience of ECT and the perception of ECT domains (Table 3.30). However, the high dose RUL ECT group were statistically significantly more positive about the informed consent process (P = 0.035) and the perception of care domain (P = 0.049) than the bitemporal group.

Table 3. 30 Comparison of treatment groups for each of the attitude domains 3 months after the treatment course

	High dose RUL Group Mean (sd) N = 24	Bitemporal Group Mean (sd) N = 24	t-test (d.f.)	P
Effectiveness of ECT	38.21 (10.03)	35.88 (8.59)	0.866 (46)	0.391
Informed consent	29.08 (3.62)	26.38 (4.92)	2.170 (46)	0.035
Fears about ECT	17.75 (4.28)	16.33 (4.31)	1.143 (46)	0.259
Memory effects of ECT	22.42 (8.33)	20.75 (6.71)	0.764 (46)	0.449
Experience of ECT	17.58 (3.65)	16.50 (3.04)	1.119 (46)	0.269
Perception of ECT	25.63 (5.27)	24.38 (5.06)	0.838 (46)	0.406
Perception of care	19.71 (3.30)	17.42 (4.46)	2.022 (46)	0.049

3.6.6 Attitudes over time

Attitudes have been compared for both treatment groups at both assessment time-points separately above. A subgroup analysis was performed to examine the consistency of attitudes over time. The reduced sample of 24 participants in each treatment group that completed the attitudes questionnaire at both assessment time-points was used in this analysis. Seven separate mixed between-within subjects ANOVA analyses were performed: one for each domain that emerged through factor analysis of the attitudes questionnaire.

3.6.6.1 Main effect for group

There was no difference between the treatment groups in level of positivity expressed towards the effectiveness of ECT, informed consent, fears about ECT, memory effects of ECT, experience of ECT and perception of ECT domains and the effect size was small in each case (Partial Eta Squared ≤ 0.4) (Table 3.31). However, the high dose RUL group expressed more positive attitudes towards the perception of care domain than the bitemporal group ($P = 0.033$) and there was an associated moderate effect size (Partial Eta Squared = 0.095). (Partial Eta Squared is a common effect size statistic that represents the proportion of variance of the dependent variable that is explained by the independent variable. Values for Eta Squared can range from 0 to 1 and standard interpretations are that values around 0.01 represent a small effect, 0.06 represents a moderate effect and greater than 0.14 represents a large effect (Cohen 1988)).

Table 3. 31 Mixed between-within subjects ANOVA results comparing both treatment groups for the 6 domains of the attitudes questionnaire

Attitudes scale domain	F (d.f.)	P	Partial Eta Squared
Effectiveness of ECT	0.736 (1, 46)	0.395	0.016
Informed consent	0.021 (1, 46)	0.886	0.000
Fears about ECT	0.393 (1, 46)	0.534	0.008
Memory effects of ECT	1.733 (1, 46)	0.194	0.036
Experience of ECT	0.766 (1, 46)	0.386	0.016
Perception of ECT	1.298 (1, 46)	0.261	0.027
Perception of care	4.810 (1, 46)	0.033	0.095

3.6.6.2 Main effect for time

There was no significant difference in any domain over time (Table 3.32), i.e. the level of positivity expressed by participants at end of treatment did not increase or decrease significantly by the 3 month assessment in either treatment group (Table 3.32).

Table 3. 32 Mixed between-within subjects ANOVA results comparing the 6 domains of the attitudes questionnaire over time between end of treatment course and 3 months after the treatment course

Attitudes scale domain	F (d.f.)	P	Partial Eta Squared
Effectiveness of ECT	2.123 (1, 46)	0.152	0.044
Informed consent	1.695 (1, 46)	0.199	0.036
Fears about ECT	0.238 (1, 46)	0.628	0.005
Memory effects of ECT	0.058 (1, 46)	0.811	0.001
Experience of ECT	2.550 (1, 46)	0.117	0.053
Perception of ECT	0.012 (1, 46)	0.914	0.000
Perception of care	0.862 (1, 46)	0.358	0.018

3.6.6.3 Interaction effect

There was also no significant interaction effect in any domain (Table 3.33), i.e. there was the same change in scores over time for the two different groups.

Table 3. 33 Table of interaction effects for each domain

Attitudes scale domain	F (d.f.)	P	Partial Eta Squared
Effectiveness of ECT	0.129 (1, 46)	0.721	0.003
Informed consent	0.021 (1, 46)	0.886	0.000
Fears about ECT	0.393 (1, 46)	0.534	0.008
Memory effects of ECT	0.520 (1, 46)	0.474	0.011
Experience of ECT	0.538 (1, 46)	0.467	0.012
Perception of ECT	0.295 (1, 46)	0.589	0.006
Perception of care	0.296 (1, 46)	0.589	0.006

3.6.7 Positive attitude towards ECT

A logistic regression described in section (7.3.6) was used to identify the factors that influenced a participant's level of positive attitude towards ECT. Firstly, a dependent variable was needed. Responses to the question, "I think ECT helped me", at end of treatment was used. This 5 point Likert type question had 82 responses in total (43 RUL and 39 bitemporal). Reponses were strongly disagree = 3, disagree = 7, don't know = 15, agree = 25 and strongly agree = 32. These responses were dichotomized: agree and strongly agree responses were recoded as positive responses and strongly disagree and disagree responses were recoded to negative responses. The 15 don't know responses were excluded from the analysis. The knowledge question, ECT treatment involves inducing a seizure in the brain, was used to represent knowledge of the ECT process in this model. Definitely and probably responses were coded 1 and not sure, probably not and definitely

not responses were coded 0 to create a dichotomous variable. There were 63 participants with complete data included in the logistic regression (35 RUL and 28 bitemporal participants). The Hosmer and Lemeshow Test is a test of model fit and is the most reliable one available in SPSS (Pallant 2005). It assesses whether or not the observed event rates match expected event rates and in this test an insignificant result in positive. The result supports the use of the specified model, χ^2 (8) = 9.503, P = 0.302. The Cox & Snell R Square and the Nagelkerke R Square values indicate the amount of variation in the dependent variable accounted for by the regression. In this case, the Cox & Snell value of 0.195 and the Nagelkerke value of 0.348 indicates that between 20% and 35% of the variance in the dependent variable, I think ECT helped me, yes or no, was explained by this model. Laterality (P = 0.391), ACER at end of treatment (EOT) (P = 0.963), CSSES at EOT (P = 0.834), gender (P = 0.539), treatment resistance (P = 0.568), and age (P = 0.286) had no effect. The only variable that predicted the likelihood of a participant answering positively to the question, "I think ECT helped me", was remission status (P = 0.008). Participants that were remitted at end of treatment course were 24 times more likely to answer positively to this question compared with those that had not achieved remission at the end of treatment.

3.6.8 Negative attitude towards ECT

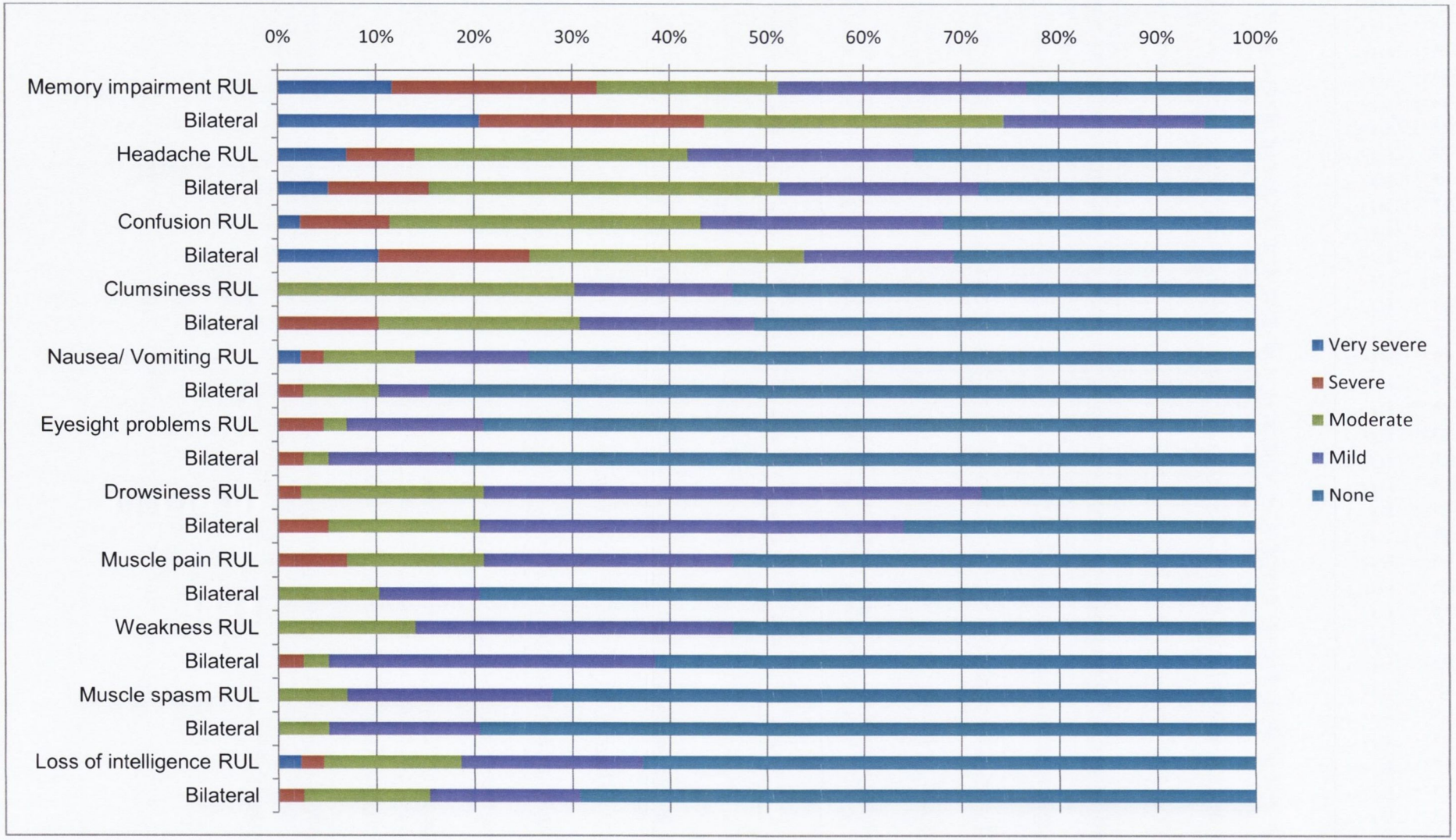
Responses to the question, "I would never have ECT again", at the end of treatment were used for a dependant variable to identify factors associated with a negative attitude of ECT. This 5 point Likert type statement had 82 responses in total (43 RUL and 39 bitemporal). Reponses were strongly disagree = 33, disagree = 27, don't know = 14, agree = 7 and strongly agree = 1. These responses were dichotomized: agree and strongly agree responses were recoded 1 and strongly disagree and disagree responses were recoded 0.

The 14 don't know responses were excluded from the analysis. There were 66 participants with complete data included in the logistic regression (37 RUL and 29 bitemporal participants). The Hosmer and Lemeshow Test supported the use of the model, χ^2 (7) = 1.398, P = 0.986. The Cox & Snell and Nagelkerke R Square values indicated that between 26% and 49% of the variance in the dependent variable, I would never have ECT again, yes or no, was explained by the model. Cognitive function at end of treatment (P = 0.633), subjectively perceived cognitive side-effects (P = 0.631), gender (P = 0.599), treatment resistance (P = 0.690) and knowledge of ECT (P = 0.533) were not significant predictors of a negative attitude towards ECT. The odds of a person answering yes, I would never have ECT again, were almost 50 times higher for someone who did not remit than for a person who did remit (P = 0.016), all other factors being equal. Increasing years of age were associated with a 13.5% increased likelihood of saying yes, I would never have ECT again (P = 0.010).

3.6.9 Severity of side effects

There were 11 questions included in the attitude questionnaire that were not included in the factor analysis because they were questions and not statements. Responses were therefore answers (very severe, severe, moderate, mild and none) and not level of agreement. Responses for both treatment groups are presented in Figure 3.24. The highest reports of very severe and severe side effects were for questions about memory side-effects. For the majority of questions responses were predominately moderate to no side-effects experienced.

Figure 3. 24 100% stacked bar-chart for responses from both treatment groups to specific questions about side-effects after the course of ECT



3.6.10 Knowledge questions

Participants were asked 5 knowledge questions that were either correct or incorrect (Tables 3.34 and 3.35). Responses were converted to a binomial variable, i.e. questions answered correctly (i.e. definitely or probably) were converted to 1 while questions answered incorrectly (i.e. probably not or definitely not) were converted to a score of 0 and compared between groups using Chi Squared Tests or Fishers Exact Test where the number of responses was too small to use Chi Squares. Question 1: χ^2 (1) = 0.947, P = 0.331, Question 2: χ^2 (1) = 6.108, P = 0.014, Question 3: Fishers Exact test, P = 1.000, Question, 4: Fishers Exact test, P = 1.000 and Question 5: Fishers Exact test, P = 0.331. The only difference between the groups was on the question, "ECT treatment involves inducing a seizure in the brain". More participants in the high dose RUL group answered this question correctly.

Table 3. 34 Responses to knowledge questions for the high dose RUL ECT treatment group

N = 43	Definitely N (%)	Probably N (%)	Not sure N (%)	Probably not N (%)	Definitely not N (%)
ECT treatment involves passing a current of electricity through the brain	25 (58)	11 (26)	6 (14)	0 (0)	1 (2)
ECT treatment involves inducing a seizure in the brain	26 (61)	10 (23)	4 (9)	3 (7)	0 (0)
ECT treatment involves being given an anaesthetic	41 (95)	1 (2)	1 (2)	0 (0)	0 (0)
ECT treatment is used to treat depression	39 (91)	3 (7)	1 (2)	0 (0)	0 (0)
ECT treatment is used to treat anxiety	20 (47)	8 (19)	10 (23)	4 (9)	1 (2)

Table 3. 35 Responses to knowledge questions for the bitemporal ECT treatment group

N = 39	Definitely N (%)	Probably N (%)	Not sure N (%)	Probably not N (%)	Definitely not N (%)
ECT treatment involves passing a current of electricity through the brain	17 (44)	11 (28)	11 (28)	0 (0)	0 (0)
ECT treatment involves inducing a seizure in the brain	16 (41)	6 (15)	13 (33)	1 (3)	3 (8)
ECT treatment involves being given an anaesthetic	38 (97)	0 (0)	1 (3)	0 (0)	0 (0)
ECT treatment is used to treat depression	36 (92)	2 (5)	1 (3)	0 (0)	0 (0)
ECT treatment is used to treat anxiety	16 (41)	10 (26)	10 (26)	1 (3)	1 (3)

3.6.11 Qualitative data report

At the end of the treatment course 20 (40%) of the high dose RUL and 17 (34%) bitemporal participants chose to make a comment on the free-text section of the attitudes questionnaire. The response rate was lower than expected and responses were very limited: they were brief, normally no more than one line and little detail was available for a thorough analysis. In the RUL group there were 9 comments that could be classified as positive, 9 that could be classified as negative and 1 that was unrelated to ECT. In the bitemporal group there were 8 positive comments, 7 that could be classified as negative and 1 that was unrelated to ECT. As discussed in the data analysis section the 7 composite scores derived from factor analysis of the attitudes questionnaire provided an initial template by which to analyse these data. Responses to end of treatment and 3 month follow-up assessments were analysed separately. Responses were read and re-read and any passages that related to one of the existing themes in the initial template were coded as such. Six of the seven themes were maintained after analysis of the data and one theme, fear of ECT, was dropped as it was not relevant or at least was not mentioned by participants.

At the end of treatment the theme of effectiveness of ECT was the one most often referred too. Responses were quite polarized in that some were very positive about the effectiveness of ECT:

"overall, ECT treatment was a positive experience and I would not hesitate if I need it in the future".

"I think I would still be depressed if it weren't for ECT. I have been here for 5 months and it only took 3 goes of ECT to have me "on my way home"! Thanks!"

"Felt ECT helped my mood and my depression".

"I am grateful for the relief from depression which I have received from ECT".

"it worked for me. I feel much better".

"ECT proved very helpful to me and I hope it will be ever more beneficial to patients in the future".

"I am very much relieved that I decided to get ECT because it has made me so well again. I intend to tell everybody how successful it is".

"ECT was very effective treating my depression".

"Very professional treatment and seemingly successful".

However, there were also a number of negative comments about the perceived effectiveness of ECT:

"The sickness, headaches, confusion, disorientation, memory loss and general aesthetic were not worth the result gained from the ECT"

"I have seen people for whom ECT seems to have had a positive effect, however, for me, it has not made any difference. But I still have to suffer the bad side-effects. I will NEVER have ECT again, no matter how sick I become"

"I thought that going through 12 sessions of ECT that it would improve my health. Unfortunately this is not the case and I am sad about this"

The effects of ECT on memory were reported by a number of participants and again these can be summarized as positive:

"With this session of ECT I had so very little memory loss and the only bit I had was really a few days after ECT while still in hospital and it was so minimal (like forgetting a nurses name or something quite small) that it is hardly worth mentioning".

"I was so very happy and surprised when I came home this time on (Date removed) that I had no memory loss at all and everything just fit so perfectly into place".

"I think myself, it must be unilateral as I had no memory loss like before"

"I have had short term problems but the positives outweigh the negatives two-fold".

And negative:

"Memory loss and loss of concentration severe and frightening. I would have to think thoroughly about having it again".

"Memory presently very low but would hope this would clear within next day or two"

"Found it very hard to accept losing my memory over very simple things and make things stack up as to where I was"

"I am sure I received good care pre & post ECT, I just can't remember".

There were only two comments about the consent process and again one was positive and one was negative:

"I was given all the information about the procedure".

"People undergoing ECT should be properly briefed vis-à-vis ECT"

Experience of ECT as a treatment was also mixed from respondents:

"I would definitely have this treatment again if necessary in the future".

"I found the whole experience positive"

And:

"I would not have ECT if there was an alternative"

"I had negative feelings about ECT"

"Counteract the side effects of muscle spasms"

Another theme was perception of ECT as a treatment and comments here were all positive.

"I am happy with ECT and all the treatment and care".

"I would definitely have this treatment again if necessary in the future".

Finally, there were a number of comments made on how participants felt they were cared for during their treatment course. All but one comment was positive:

"I am happy with ECT and all the treatment and care".

"The staff in the ECT Suite were extremely helpful and careful throughout my treatment. Nursing staff on the ward were also pleasant throughout treatment".

"Was treated with respect and helpfulness a thoroughly professional staff".

"I was very impressed by how professional the ECT staff were at doing their job. They were kind and reassuring and listened to any worries or concerns I had about ECT and they did their best to minimise the worries I had. Thank you".

"Staff were friendly and relax which brought down my anxiety".

"The treatment was carried out in a highly professional way and I had every confidence that it was beneficial and in no way harmful".

"I am very grateful to all staff who helped me recover through ECT".

"I was treated with kindness, understanding all through pre-treatment, treatment and recovery. Thank you".

"the staff wonderful and would not hesitate to have ECT again if needed".

"I have been looked after very well here at Edmundsbury and St. Pat's"

The negative comment about perception of care referred to a range of issues:

"I found third party conversation prior to treatment and in recovery area distressing, inconsistency of treatment teams, attention to my sensitivities e.g. not introducing or different anaesthetist, discussions not concerning treatment e.g. accounts of staff, found staff unnerving".

There was a considerable lack of depth and discussion to many of the responses to the open-ended question in the ECT attitudes questionnaire at end of treatment and no new themes were added to the initial template. However, a number of issues are quite clear. Having completed a course of ECT, patients were quite definite about their own personal views on the subject. Those who believed ECT had worked for them in terms of symptomatic remission were positive about ECT and did not make further comments about adverse effects such as memory loss, while those who failed to achieve remission with ECT were quite negative about ECT and their comments focused mainly on the negative effects of ECT. These results are largely in line with the quantitative analysis of the attitudes questionnaire and support the finding that positive and negative attitudes were predictable based on remission status at end of treatment. The memory effects of ECT were commented on and again were polarised: some participants were surprised by how little their memory was affected and others felt that even with negative memory effects the positive effects outweighed these. Others were quite distressed by the negative impact of ECT on memory. The consent process was only mentioned by two participants and both comments were extremely brief and polarised. It was not possible to draw any real conclusions from such a scarcity of data in this area. Experience of ECT and perception of ECT as a treatment are closely linked themes but they were also only briefly mentioned by participants. Again,

experience and perception appeared to be influenced by the positive and negative effects of the treatment. Quite a lot of comments referred to how well participants felt they were cared for by ward based staff and the ECT clinic staff: apart from one comment participants were very pleased with the care they received from staff and with how professional they felt staff were during the course of their treatment. This again is very much reflective of the quantitative analysis.

3 months after the treatment course 5 (10%) high dose RUL and 14 (28%) bitemporal participants made a comment about their experience of ECT. 6 statements were positive, 9 were negative, 3 contained both positive and negative statements about ECT and 1 was unrelated to ECT.

The perceived effectiveness of ECT theme was very prominent at 3 months but again there were positive and negative statements:

"I found ECT worked for me and the care I got was very good"

"I would not hesitate to have it again"

"I would have it again if I had to but hope I don't have same ever again"

"I have had two courses of ECT (1987 and 2009). If necessary I should not hesitate to have it again"

"I found ECT very helpful throughout the past few years"

"ECT definitely helped me and I have no major problem"

Some negative statements were:

"Just feel a little let down as I thought the treatment would be a success. Anyway it was worth a try"

"I am disappointed the treatment did not appear to last"

"Doubtful about the efficacy of ECT for me"

"I certainly never will have ECT again, even if it was my final option. In total I have had 14 sessions of ECT at invervals, always hoping the last one would be the one to "kick in". I have not had even one thing good to happen. More ECT, never ever gain".

Although very few participates made statements about the effects of ECT on memory 3 months after the treatment course those that did were all negative:

"My memory have not returned at all. Most of the medical people I speak to about this just pass it off and say give"

"Just to specify I have lost memories of chunks of time from about 6 months before receiving ECT. I sometimes have to be told what I did, what happened to me during this period and I have no recollection of it when told"

"I found ECT very helpful throughout the past few years. The only deficit in having ECT is memory loss"

"A lot of questions look for definitive answers in and around the period when ECT took place, which is where my memory loss was concentrated mostly"

3 Months after the treatment course there was only one statement about the consent process associated with ECT.

"I was given no information before or after the treatment"

Fear was documented by 1 participant 3 months after the treatment course:

"I was very scared of having ECT but I was not getting any better on tablets I had good results very soon after ECT".

Again, the only comments relating to perceptions of care of care were very positive:

"I find the whole ECT team amazing. They are extremely professional and made me feel totally at ease"

"nurses were very kind and helpful"

Perception of ECT as a treatment is closely linked to perceptions of effectiveness and data were very scarce at this time-point in this area:

"I would have preferred not to have it if medication and counselling were adequate"

Data 3 months after the treatment course were very poor. There were very few comments made and most comments were very brief and a thorough analysis was not possible. Data that was gathered at this point was largely reflective of the previous analysis of

data at end of the treatment course. Participants remained quite polarised in their attitudes towards ECT in areas such as the effectiveness of ECT. Again, participants were very positive about the care they received from ward based staff and staff working in the ECT clinic. However, participants that did write comments at this time were negative about the memory effects of ECT. It is obviously plausible that the negative memory effects of ECT had persisted in this sample but it is not possible to draw any firm conclusions from these data as less than 20% of the sample completed this section of the questionnaire 3 months after receiving ECT. It is possible that only those participants that experienced persistent memory deficits felt compelled to complete this section of the questionnaire and it would be so much more informative if more participants had completed this section. There was one comment about the consent process that is however alarming. One participant felt they were not given any information before or after their course of treatment. This statement is quite strong but given the fact that participants were participating in a randomized controlled trial it must be considered that the memory effects of ECT have hindered the participant's ability to recall the extremely involved consent process prior to receiving ECT.

4 Discussion

The results of this study are based on a randomized controlled trial design with a relatively large sample size. As such this study overcomes many of the methodological limitations of other studies that have reported similar data. 100 participants were recruited and randomly allocated to receive 1.5 × ST bitemporal ECT or high dose (6 × ST) RUL ECT. Results are generalizable to other settings: all participants were referred for the treatment of severe depression which is the major indication for ECT (Lisanby 2007b); 60% of the sample were female which is consistent with depression research studies, ECT studies (Sackeim *et al.* 1993; Sackeim *et al.* 2000; McCall *et al.* 2002b; Sackeim *et al.* 2008; Kellner *et al.* 2010) and epidemiological data for depression (Tsuang & Tohen 2002); age ranged from 21 to 83 years and mean age was 58; which is consistent with previous ECT for depression research. Participants were severely depressed as established objectively using the HDRS and subjectively using the Beck Depression Inventory. Less than 20% of participants in each treatment group exhibited psychotic symptoms so results may not be directly generalizable to samples with psychosis. However, one might well expect ECT to be more effective in patients with psychosis as a study involving 253 patients, conducted by the Consortium for Research in Electroconvulsive Therapy (CORE) group, reported that patients with psychotic depression responded in higher rates to ECT than patients without psychosis (Petrides *et al.* 2001b). All participants had failed at least one course of an antidepressant medication and more than 50% of each group met criteria for treatment resistance; having failed two adequate courses of antidepressant drugs administered for an adequate period of time. This type of treatment resistance is typical of patients referred for ECT. Approximately half of participants had previously had ECT but not within six months of entering this study. Participants that previously had ECT predominantly received bitemporal ECT and may have been more able to identify treatment allocation than those having ECT for the first time.

However, there was no difference between the groups in the number of participants that received ECT in the past. These results provide both valuable and novel evidence based on empirically gathered data from naturalistic conditions, i.e. apart from ECT administration, no other aspect of the patient's treatment were adjusted and patients were treated as they would have been by their independent treating clinical team. As such, results should be generalizable to real world settings where patients remain on or commence other medications before and during their course of treatment. Also, participant's independent treating clinical teams decided when to terminate the treatment course based on clinical presentation and without input from the research team. It is remarkable then that there was no difference in the number of treatments administered to each treatment group, which one assumes supports the hypothesis that both forms of ECT were equally effective in terms of therapeutic effect.

As expected seizure threshold was higher with bitemporal ECT and a greater number of second and third stimulations were needed to establish ST at the first treatment session compared with RUL ECT. Although the high dose RUL group received higher mean stimulus doses throughout the treatment course ST was more easily established with RUL ECT and the need for additional anaesthesia care and less re-stimulations at the first treatment session make RUL ECT a potentially more acceptable form of ECT. Despite these group differences seizure duration was almost identical between the groups. The effectiveness of ECT in terms of symptomatic remission was not examined in this study. However, other aspects of ECT and its effects on severe depression were examined that address significant and clinically relevant gaps in the evidence base.

This is the first study to compare the effects of 1.5 × ST bitemporal ECT with 6 × ST RUL ECT, administered twice weekly, on recovery of orientation after ECT. These data provided a unique opportunity to examine high dose RUL ECT from a relatively large sample size, under randomized conditions, undergoing treatment in naturalistic conditions with 100%

of the recovery data gathered. We know that some treatment parameters (e.g. sine wave ECT) influence time to recovery of orientation but until now we have only had theories that other treatment parameters and certain patient characteristics are associated with slower recovery of orientation. There has been an obvious paucity of evidence in these areas which severely limits our ability to identify those patients that are susceptible to extended periods of disorientation and prolonged disorientation after ECT. Given that acute disorientation immediately following ECT is the most striking side effect of ECT (Royal College of Psychiatrists 2005) and may be associated with persistent retrograde amnesia (Sobin *et al.* 1995), reductions in time to recovery of orientation may be associated with attenuations in persistent amnestic adverse effects but is also an important goal of ECT research in its own right.

RUL ECT was associated with a significantly quicker recovery of orientation at the first treatment session and this was expected based on previous evidence when ECT is administered at ST doses. However, at ST doses compared to supra-threshold doses, bitemporal ECT is less effective and RUL ECT is not effective (Sackeim *et al.* 1993). At therapeutic doses, administered at subsequent treatment sessions, RUL ECT maintained its advantage over bitemporal ECT with respect to recovery of orientation. This is a novel and extremely important finding. Until now all we have known about RUL ECT is that it can be as effective an antidepressant as standard bitemporal ECT if administered at high doses. For the first time we now have evidence that high dose RUL ECT has advantages in terms of reduced time to recovery of orientation after ECT. Also, this finding points to the potential of high dose RUL ECT in terms of reductions in other aspects of the adverse cognitive effect profile compared with bitemporal ECT. It is now even more likely that high dose RUL ECT will be associated with other improvements such as superior retrograde memory performance.

Several other treatment parameters were also identified as modifying factors. It has been previously reported that longer seizure durations are associated with increased time to recovery of orientation (Calev *et al.* 1991a) and results from this study support this finding and contribute valuable evidence in terms of the specific duration of additional time spent disorientated relative to additional seconds of seizure activity. It is advisable that treating teams make every effort to avoid extended seizure durations, especially as seizure duration is unrelated to antidepressant effectiveness. While it has been found that increasing numbers of treatment sessions may influence the extent of deficits in cognitive performance (Sackeim *et al.* 2007) this is the first time that increasing numbers of treatment sessions have been found to directly affect time to recovery of orientation. As such, assessment of the need for additional treatment sessions during the course of treatment is not only good practice in terms of determining the need for continued ECT but will also ensure the avoidance of longer periods of disorientation after additional ECT treatment sessions and potentially lead to attenuations in persistent amnestic effects.

Several patient characteristics were found to be modifying factors that may help clinical teams identify patients at greater risk of prolonged periods of disorientation after ECT. It has previously been hypothesised that older age was associated with slower recovery of orientation (Fraser & Glass 1978) but little evidence has been found to support this hypotheses. For the first time, older age was identified as the most influential patient characteristic associated with slowed time to reorientation after ECT and this effect was independent of electrode placement. Even if high dose RUL ECT does not have advantages over bitemporal ECT in terms of other aspects of cognitive functioning, older patients referred for ECT may be ideal candidates for high dose RUL ECT given its advantages in time to recovery of orientation. Increased cardiac output appears to have an alerting effect on reorientation and is significantly associated with quicker recovery of orientation that was

independent of electrode placement. It may be that an increased cardiac response is a sign of an increased vagal response to ECT and is related to increased release of catecholamine's that promotes a quicker awakening after treatment and an earlier recovery of orientation.

It has been previously hypothesised that deficits in cognitive functioning may contribute to longer recovery of orientation. In this study global cognitive functioning and specific measures of executive function did not modify recovery of orientation. However, prospective participants with an MMSE score of ≤ 18 were excluded from this study and future trials without this restriction may find an association here.

Prior studies have reported competing results with respect to the influence of Lithium on recovery of orientation after ECT. Mukherjee et al (1993) concluded that any potential lithium-ECT interaction with respect to adverse physical or cognitive effects such a slower recovery of orientation were overestimated. Thirthalli et al (2010) reported a positive relationship between higher serum lithium levels and longer time to recovery of orientation after ECT. However, Lithium had no effect on time to recovery of orientation in this study. It may be that there were not enough patients with high serum Lithium levels in this study compared with the Thirthalli et al (2010) study. However, when Lithium is maintained within therapeutic range I found no evidence to support the theory of an ECT-Lithium interaction with regard to recovery of orientation after ECT.

Prolonged disorientation has previously been defined as a failure to answer a checklist of reorientation questions within 90 minutes of resumption of spontaneous breathing (Sobin *et al.* 1995; Sackeim *et al.* 2000; Sackeim *et al.* 2008) This criterion was considered overly protracted and for the purposes of this study prolonged disorientation was defined as failure to correctly answer 4 out of 5 orientation questions within 50 minutes. It was therefore expected that rates of prolonged disorientation might well have been higher in this study.

There were indeed higher rates of prolonged disorientation in this study: 25% of participants in each treatment group experienced prolonged disorientation. However, it is a novel finding that under this criterion there was no difference between the treatment groups in the number of participants that experienced an episode of prolonged disorientation. Comparing these results to studies that used 90 minutes as the criterion for prolonged disorientation, RUL ECT appears to maintain significant advantages over bitemporal ECT; i.e. at 50 minutes after resumption of spontaneous breathing 25% of each group experienced prolonged disorientation but at 90 minutes in other studies considerably less patients treated with high dose RUL ECT experienced prolonged disorientation compared to patients treated with high dose bitemporal ECT. It may be that even in patients that experience prolonged disorientation, recovery of orientation is quicker when treated with high dose RUL ECT.

Older age was once again the most significant patient characteristic to predict prolonged disorientation but high dose RUL ECT may reduce the duration of prolonged disorientation in older patients. The alerting effect of an increased vagal response on recovery of orientation was maintained here also. Future studies that use continuous measurement of cardiac output during ECT may be able to identify the degree of change likely to eliminate prolonged disorientation but it is equally likely that other factors currently unknown (e.g. minor structural abnormalities in specific regions of the brain) play a more contributing role in prolonged disorientation.

Transient increases in blood pressure and HR following ECT have been well documented since the beginning of ECT (Bellet *et al.* 1941). During ECT the vagus nerve is stimulated which produces a parasympathetic response followed by a rebound sympathetic response characterised by surges of catecholamines during and after the seizure (Tess & Smetana 2009). These reactions result in dramatic effects on heart rate such as bradycardia or even a brief period of aystole prior to the seizure and hypertension or tachycardia during and

after the seizure (Tess & Smetana 2009). There is some evidence that vagal response may be sensitive to dose and electrode placement: Nagler et al (2010) found RUL ECT was associated with increased intervals between two consecutive heartbeats (from 0.6 ± 0.0 seconds to 4.1 ± 3.4 seconds) while there was relatively little effect on duration between heartbeats when the same participants were treated with bifrontal ECT. Nagler et al (2011) found a significantly greater proportion of patients treated with RUL ECT developed asystole and asystole lasted significantly longer compared to patients treated with bifrontal placement. Stewart et al (2010) found aystole much more likely with RUL ECT compared with bitemporal or bifrontal ECT (Stewart *et al.* 2010). It is hypothesised that the longer distance between different electrode placements and the vagus nerve result in different levels of stimulation of the vagus nerve and as a result different levels of cardiac response during ECT (Nagler 2010; Stewart *et al.* 2010). These studies only examined the effect of electrode placement on cardiac response during stimulation and the resultant seizure. Continuous assessment of cardiac response throughout the stimulation and seizure was not used in this study and the focus was on the period of recovery once the seizure had terminated. It was hypothesised that cardiac response after the seizure would be significantly different between the treatments groups. If one treatment was associated with an increased risk of adverse cardiac event compared to the other it would supersede any other findings regarding recovery of orientation or HRQOL.

Postictal cardiac response was significantly influenced by electrode placement. It is surprising that RUL ECT had a greater effect on blood pressure while bitemporal ECT had a greater effect on heart-rate. However, these effects were only observed upon resumption of spontaneous breathing and were not maintained throughout the recovery period. One limitation of this study that may explain this is that continuous measurement of cardiac response throughout the seizure was not used. As such it is impossible to say that changes in

BP and HR did not track each-other initially and one reduced more quickly than the other by the time they were first measured in this study. Lane et al (1989) and Takada et al (2005) found the greatest increase in post ECT HR occurred within one minute of stimulation and returned towards pre-treatment levels within 5 minutes of stimulation. The greater impact of RUL ECT on blood pressure is reflected in the number of patients that experienced hypertension that required intervention. Hypertensions that required medical intervention occurred only in the high-dose RUL ECT group and while this was not a statistically significant difference it was certainly a trend-worthy one and requires further investigation. Despite bitemporal ECT being associated with more of an increase in HR after ECT there was no difference in the number of participants in each group that experienced tachycardia.

Researchers in recent years have sought to predict clinical response from an array of physiological responses to ECT. Peak heart-rate submaximality (PHRS) (highest peak heart-rate during the course of treatment minus heart-rate during an individual treatment) (Swartz 2000); Peak HR, motor and EEG seizure duration, systolic and diastolic blood pressure (BP) (Saravanan *et al.* 2002; Azuma *et al.* 2007); and Rate Pressure Product (RPP) (HR × systolic BP) (Saravanan *et al.* 2002) have all been investigated as potential predictors of response or early response to ECT. Swartz et al (2000) found HR responsive to stimulus dose immediately after administration and that patients with the highest PHRS and those that more often reached their own PHRS immediately after treatment remitted quicker than those patients with lower PHRS and those that rarely reached their own PHRS throughout their treatment course (Swartz 2000). Saravanan et al (2002) found that cumulative RPP and percentage change in RPP from baseline was higher in those patients that achieved early remission compared to those that remitted later in their course of treatment (Saravanan *et al.* 2002). Azuma et al (2007) Found that higher postictal BP and HR predicted clinical response measured using the HDRS (Azuma *et al.* 2007). These researchers argue that greater response

in these physiological parameters indicate the presence or absence of an adequate seizure more than current evaluations of seizure adequacy; e.g. duration of the motor or EEG seizure. These studies were observational and all used bitemporal ECT predominantly. RUL ECT administered at ST doses is associated with significantly less of a physiological response compared with ST bitemporal ECT (Mayur *et al.* 1998) and RUL ECT at ST doses is ineffective despite the effective induction of seizures (Sackeim *et al.* 1993). It may be that high dose RUL ECT is as effective as standard bitemporal ECT because it induces a greater cardiac response that is comparable to the effects of standard bitemporal ECT, and in so doing increases the quality of the seizure.

The results of this study would certainly support such a hypothesis. Continuous measurement of the physiological response to ECT was not performed in this study and there was no measure of depression severity used as a dependent variable so it was not possible to compare clinical outcome based on physiological response to the comparative treatments. However, it was found that there was no difference in the number of treatments administered between the treatment groups despite the fact that the decision to stop treatment was made by the patient's independent treating clinical team. As such, the equality of effectiveness of high dose RUL ECT compared with 1.5 × ST bitemporal ECT may be related to the increased quality of seizure associated with RUL ECT administered at high stimulus doses. It would certainly be valuable for future research to use continuous measurement and a measure of depression severity to compare the complete physiological response of both types of ECT and the resultant effects on depression severity.

There was no difference between the treatment groups in the number of participant's that complained of headaches, nausea or muscle discomfort. However, each potential adverse physical effect was associated with different modifying factors. 50% of the sample complained of at least one post ictal headache which was almost identical to the findings of

Sackeim et al (1987) where ECT was administered at ST doses. It is interesting that headaches were not more likely at doses above ST and it is also positive that headaches were at least no more likely following high dose RUL ECT than with bitemporal ECT. Women were twice as likely as men to experience a post-ictal headache which has not previously been reported. Epidemiological studies report that women are twice as likely as men to complain of migraine and tension-type headache which has been attributed to female hormones (Rasmussen 2001) which may also play a role in the preponderance of headache amongst women after ECT. There is now a need to inform treating clinical teams about this finding and examine further the need to develop strategies to address this issue; for e.g. treating teams should include this when delivering information to prospective patients, especially women, and there may be a need to implement prophylactic interventions such as pre-treatment with analgesia for women, at least for the initial number of treatments at which headaches are more likely. Longer seizure duration has previously been reported to be associated with increased severity of headache (Dinwiddie *et al.* 2010) but this is the first time that longer seizure duration has been found to be associated with an increased risk of headache after treatments. Factors that regulate seizure duration are currently unknown but given its influence on recovery of orientation and headaches it may be necessary to examine this area in future studies.

20% of participants complained of post-ictal nausea which is also very similar to previous findings when ECT was administered at ST doses (Sackeim *et al.* 1987c). Women were twice as likely to complain of nausea after the first treatment session but not thereafter. The administration of Ondansetron prior to treatment when patients had complained of nausea after previous treatment sessions in this course of treatment is a significant confounder here. Although not all patients that complained of nausea accepted Ondansetron on subsequent treatment sessions a large proportion did. This is most likely the reason why

nausea was more prevalent at earlier treatment sessions and may account for why women complained of nausea more than men at the 1st treatment session but not thereafter. Longer seizure duration was again the most likely predictor of nausea and further highlights the need to ensure an adequate seizure but avoid lengthy ones. Being on Lithium also had a protective effect throughout the treatment course. Anecdotally, small increases in salt intake has been recommended as an antiemetic, especially during pregnancy, and it may be that taking regular Lithium reduced the likelihood of nausea after ECT.

Muscle discomfort was not a significant feature in this study and occurred in less than 12% of participant's and after less than 2% of treatments. Myalgia rarely occurred after the first treatment. This may be because doses of the muscle relaxant medication were adjusted at subsequent treatment sessions if there were complaints of myalgia at earlier treatment sessions. The low rate of myalgia and rare occurrence after the first treatment session can be seen as a result of optimized anaesthesia practice as the Anaesthetist's working in the ECT department in this study were experienced in ECT practice and provided a consistent service throughout the data collection period. The use of regular Anaesthetist's attending purpose built ECT centres is in line with recommended best practice.

Longer term functional outcomes were assessed one, three and six months after the treatment course ended. Over 80% of data were collected 1 month after the treatment course ended but there was a loss of data at three and six months where approximately 60% and 50% of data were collected respectively. Although these data were not collected from participants it may be that their designated next of kin (NOK) experienced a significant participant burden as they were repeatedly contacted to provide this information throughout the follow-up period. Also, the inclusion of participants NOK as another group of participants increased the number of participants that had to be contacted on follow-up assessments and therefore increased the chance of not being able to contact participants. It may also be

possible that NOK of participants that recovered or failed to achieve remission lost motivation to participate in on-going research as time progressed passed the time of the index episode of depression. Due to this loss of data the primary analyses focused on the comparative effects of the two treatments on recovery of basic and instrumental functioning up to four weeks after the treatment course ended with a subgroup analysis of functional outcomes at six months.

Severe depression had only a minor impact on ability to perform basic ADL. This is not uncommon when the ability to perform the most basic ADL are assessed in populations that are not the most severely physically unwell, such as outpatient samples (Gompertz *et al.* 1994). The cognitive effort hypothesis suggests that depression more severely impacts ability to perform effortful tasks requiring additional cognitive capacities than automatic processes that are less cognitively demanding and is a good explanation for this finding (Hammar *et al.* 2010). There was a considerable recovery of ability to perform basic ADL that occurred within four weeks of the treatment course ending that is consistent with previous reports (McCall *et al.* 2001; McCall *et al.* 2002c; McCall *et al.* 2004). A subgroup analysis of the reduced sample indicated that this improvement was maintained throughout the six month follow-up period which is also consistent with previous analysis (McCall *et al.* 2001). Performance of IADL was much more severely effected in this sample, the extent of which was comparable to previous samples referred for ECT (McCall *et al.* 1999a; McCall *et al.* 2001; McCall *et al.* 2002a; McCall & Dunn 2003). There was a significant recovery of ability to perform IADL in both treatment groups 4 weeks after the treatment course that was comparable to improvements in other studies (McCall *et al.* 2001; McCall *et al.* 2004). Analysis of the reduced sample at 6 months after the treatment course indicates that the improvement was maintained over time.

It is a novel finding that there was no difference between the treatment groups in performance of basic or instrumental ADL 4 weeks after treatment and analysis of the reduced dataset at 6 months after treatment is consistent with this. While it was hypothesised that high dose RUL ECT would be associated with less executive dysfunction after ECT there was no difference between the treatment groups which may account for the lack of difference in functioning. However, it is positive that high dose RUL ECT is at least as effective as standard bitemporal ECT on functional outcomes and advantages in other areas would support the regular use of RUL ECT at high doses.

HRQOL is a multidimensional concept that is subjective and complex. People can report a varying state of HRQOL depending upon their perception of ill-health and the effects of treatments administered. As such, ones perception of the effects of depression, their beliefs about how it affects them and their perception of the treatments administered, including positive and negative effects, influences ones perception of their own HRQOL. HRQOL can improve independently of remission from depressive symptoms (Hirschfeld *et al.* 2002) and remission from depression does not always produce an improvement in HRQOL (Simon *et al.* 1998). Measurement of illness severity and the impact of interventions can be based on disease specific measures (e.g. the HDRS) or generic measures (e.g. the SF-36). Disease specific measures focus on severity of symptoms and rate the change in severity over time. These measures are limited in scope and often don't measure other aspects of life important to patients (Rapley 2003). Generic outcome measures focus on the impact of illness and interventions on multiple domains of well-being and functioning. It is a strength of this study that a subjective and generic outcome measure was also used to evaluate the impact of ECT as an intervention for depression.

Participants in this study rated their own HRQOL worse than those previously reported for a comparative normal population (Jenkinson *et al.* 1996), a depressed community

sample (Duggan 1999), and normative data for a depressed population (Wells *et al.* 1989; Ware *et al.* 2007) but equally as affected as other samples referred for ECT (Fisher *et al.* 2004; McCall *et al.* 2006; McCall *et al.* 2011). ECT is normally withheld until a patient has not responded to antidepressant drugs, where there may be significant physical deterioration, where a rapid response is required or acute suicidality is a feature (Kavanagh & McLoughlin 2009). It is therefore not surprising that those referred for ECT are significantly more affected in terms of HRQOL than those not referred for ECT.

There were no differences between the treatment groups in severity of depression, cognitive performance or any domain of the SF-36 Health Survey prior to treatment. There were 4 important findings from this study with regard to ECT for major depression and HRQOL: (1) subjectively perceived physical functioning and wellbeing improved 6 months after ECT; (2) subjectively perceived mental wellbeing and functioning improved significantly 6 months after ECT; (3) After controlling for pre-intervention scores, there was no significant difference between the treatment groups in any of the SF-36 health and well-being domains; and (4) six months after the course of ECT both groups had persistently low HRQOL.

This is the first time that different types of ECT have been compared for their effects on HRQOL and it is a novel and significant finding that both treatments were equally effective regarding subjectively rated HRQOL outcomes. Although high dose RUL ECT was not superior to bitemporal ECT in terms of HRQOL outcomes it is expected that high dose RUL ECT will further optimize ECT practice based on: current evidence that high dose RUL ECT is as effective as standard bitemporal ECT in terms of antidepressant effect; the findings of this study in terms of HRQOL outcomes and time to reorientation; and it is hoped that future evidence will find advantages for high dose RUL ECT over bitemporal ECT in terms of other cognitive outcomes.

Persistent deficits in HRQOL and functioning after symptomatic recovery from depression are common and this highlights the need for holistic interventions rather than treating just the symptoms of depression alone (IsHak *et al.* 2011). However, this study found the only factor that predicted superior HRQOL 6 months after ECT was remission status at the end of treatment. Thus, symptomatic remission should remain the primary goal of depression treatment and additional holistic interventions should be implemented to compliment this aim.

While some have argued that ECT is not only not effective but globally harmful (Breggin 1991; Barker 2011), these findings support the findings of others that ECT is not associated with decrements HRQOL in any domain and this is true in remitters and non-remitters alike (Fisher *et al.* 2004; McCall *et al.* 2011). In fact, those that failed to achieve remission criteria made improvements in depression severity from pre-treatment but failed to attain enough improvement to achieve remission criteria for this study (HDRS score $\leq$ 10). Also, global cognitive functioning after treatment was at least no worse than pre-treatment in remitters and non-remitters alike. The extent of improvements in HRQOL was remarkably consistent with previous reports (Fisher *et al.* 2004; McCall *et al.* 2011). However, this evidence addresses many of the limitations of previous work in this area which has inhibited NICE from providing further guidance with regard to ECT: these findings are based on a randomized controlled trial design; provide longitudinal evidence supporting the effectiveness of ECT in major depression; are based on data gathered from a relatively large sample; are based on data collected using a rigorous and psychometrically sound HRQOL outcome measure; were gathered from a trial where ECT was administered at effective doses relative to electrode placements and at a frequency schedule consistent with practice in Europe; and data were collected at time-points that allowed participants to engage fully with activities considered integral to HRQOL and allowed participants time to consider their own

HRQOL before providing such data (i.e. 6 months after the treatment course ended). It is intended that this evidence will inform future NICE guidance regarding the effect of ECT on HRQOL, and not just with standard bitemporal ECT but also for high dose RUL ECT. Also, this type of evidence adds directly to the ability of NICE to compare the cost effectiveness, in terms of health quality gained for money spent, and to calculate quality adjusted life years which NICE bases its guidance on (Drummond *et al.* 2005).

However, not all participants achieved remission by the end of the treatment course and this cohort of patients provides the greatest challenge to modern Psychiatry. All of the participants in this study had previously failed to remit with at least one adequate antidepressant drug treatment course and over half of the participants had failed two adequate courses of antidepressant drugs. It may be that certain types of depression, specific comorbid psychiatric illness or certain patient characteristics are associated with ECT being less effective and future research should consider this area of study.

The ECT attitudes questionnaire was administered to participants at the end of their treatment course and again 3 months later. It was intended to address a number of key research questions: (1) did participants have negative or positive attitudes towards ECT? (2) At the end of treatment course and at 3 months after the treatment course was there a difference in attitude between those administered 1.5 × ST bitemporal ECT and those administered 6 × ST RUL ECT and were attitudes consistent over time? And (3) what factors contribute to a positive attitude and a negative attitude towards ECT?

Participants in this trial were happy with the explanation of ECT prior to commencing treatment and the level of satisfaction with information given prior to commencing ECT exceeded that of many other studies (Freeman & Kendell 1980; Baxter *et al.* 1986; Szuba *et al.* 1991; MIND 1995; Sestoft *et al.* 1995; UKAN 1995; Wheeldon *et al.* 1999; Sienaert *et al.*

2005; Myers 2007; Virit *et al.* 2007; Malekian *et al.* 2009). Participants were happy that they had made an informed decision to have ECT and less than 5% of participants felt pressurised or forced to have ECT. These are exceptionally low rates of perceived coercion compared to other studies (Freeman & Kendell 1980; Benbow 1988; Malcolm 1989; UKAN 1995; Pedler 2000; Tang *et al.* 2002; Philpot *et al.* 2004; Myers 2007; Malekian *et al.* 2009). Participants were very positive that ECT had helped them and felt that ECT had relieved their depression. However, 66% of bitemporal participants and 53% of RUL participants complained of problems with their memory after the course of treatment which is consistent with other studies (Freeman & Kendell 1980; Malcolm 1989; Riordan 1993; Pettinati *et al.* 1994; UKAN 1995; Walter *et al.* 1999; Pedler 2000; Taieb *et al.* 2001; Philpot *et al.* 2004; Sienaert *et al.* 2005; Rush *et al.* 2007; Malekian *et al.* 2009; Rayner *et al.* 2009). Despite the memory effects of ECT 81% of participants would readily have the treatment again if needed.

Responses to the ECT attitudes questionnaire were factor analysed to create statistically rigorous composite scales to reduce the number of comparisons made and facilitate rigorous statistical analysis of these data. Seven latent variables emerged from the factor analysis: effectiveness of ECT, informed consent, fears about ECT, memory effects of ECT, experience of ECT, perception of ECT and perception of care.

The primary analysis focused on the attitudes of participants at the end of the treatment course. The RUL group were significantly more positive about the consent process and the memory effects of ECT than participants in the bitemporal group. Both groups were recruited the same way, by the same researcher and were given the same written and verbal information prior to consenting to take part in the trial. Also, participants were not randomized until immediately before their first treatment session; until after they had consented to the course of ECT; until after they had consented to the individual treatment session; and until after they had consented to the EFFECT-DEP TRIAL. It may be that the

memory effects of RUL ECT were less severe at the end of treatment (and certainly the RUL group were more positive than the bitemporal group in this regard) and patients treated with RUL ECT were better able to recollect the consent process and were therefore more positive towards it. It would be of great benefit if future studies were to include an objective measure of anterograde memory that may confirm this disparity between the groups.

The consistency of attitudes over time between the treatment groups was examined with the reduced sample of 24 (48%) participants in each group that completed questionnaires at both assessment time-points. In this analysis the RUL group were more positive than the bitemporal group in the perceptions of care domain but in no other domain. The loss of data in this analysis compared with analysis of data for the end of treatment may explain the lack of consistency between both analyses. However, what is clear is that there was no change in attitudes over time in either group in any domain.

Although more than half of participants complained of negative memory effects associated with ECT, objective global cognitive function or subjective cognitive side effects did not predict attitude towards ECT. Prediction of a positive or negative attitude towards ECT was based on remission status. Participants that remitted at end of treatment were more likely to be positive about ECT while participants that failed to achieve remission at end of treatment where more likely to be negative about ECT. It may be the case that those participants that achieve remission are less concerned with transient or more persistent memory impairment than those that failed to achieve remission. Failure to achieve remission and the presence of unwanted adverse effects would certainly negatively influence one attitude towards any treatment.

There were significant limitations to the qualitative data gathered as: only 37% of participants responded at end of treatment and only 19% of participants responded 3 months

later; most responses were extremely brief and lacked any depth or dialog; and with such a loss of data and with such limited quality of responses results may not be representative of the entire sample that participated in this study. Results of the qualitative analysis of the end of treatment responses were largely supportive of the quantitative analysis. However, there was considerable polarization between respondents. Some participants were positive about the effectiveness of ECT, memory effects of ECT and perception of ECT domains while others were quite negative about these domains. This is not unusual in other literature as most people are either positive or negative about ECT and very few are ambiguous. However, it was very encouraging that the majority of participants were positive about the level of care they received from Nurses and Staff in the ECT department. The amount of data collected at 3 months follow-up was very disappointing and severely limited the analysis that could be performed. However, these data tended to replicate the results of the end of treatment data.

These results add significantly to the current ECT for severe depression evidence base. The effectiveness of high dose RUL ECT as an antidepressant treatment was already established (Kellner *et al.* 2010). Now for the first time high dose RUL ECT has been found to have significant advantages over standard bitemporal ECT in terms of quicker recovery of orientation; potentially a quicker return to orientation when patients experience prolonged disorientation after ECT; and these results indicate that the extent of persistent retrograde amnesia may also be reduced with high dose RUL ECT. Although there were no assessments of memory used in this study, RUL participants were significantly more positive about the memory effects of ECT and the informed consent process associated with ECT, which may support the hypothesis that RUL participants experienced less negative memory effects after the course of treatment and as a result remember the consent process in more detail. While there were no differences in basic functioning or subjective HRQOL between the groups it is very positive that there were improvements in these areas, that high dose RUL

ECT is at least as effective at standard bitemporal ECT in these areas and that superiority in these areas was based on remission status and not level of cognitive functioning, which also improved after ECT.

Although ECT remains controversial in some areas the evidence base demonstrating its effectiveness as an antidepressant treatment is based on over 70 years of empirical research. Much of the evidence on the adverse cognitive effect profile of ECT has been conducted by proponents of ECT and must be viewed as consistent attempts to optimise ECT in the best interests of patient's. The therapeutic value of ECT to persons with severe depression or treatment resistant depression is epitomised in the objective and subjective results of this study.

5 Summary of findings

The hypotheses that were tested were:

I. Time to recovery of orientation will be shorter with high dose RUL ECT (6 × ST) compared with standard (1.5 × ST) bitemporal ECT.

II. High dose RUL ECT will be associated with fewer complaints of physical side-effects immediately after ECT and there will be less of an impact on the physical effects immediately following treatment compared with bitemporal ECT.

III. High dose RUL ECT will be associated with superior performance of activities of daily living compared with 1.5 × ST bitemporal ECT.

IV. High dose RUL ECT six months after treatment will be associated with superior health related quality of life (HRQOL) compared with bitemporal ECT.

V. Patients' treated with high dose RUL ECT will have a more positive attitude towards ECT compared with those treated with bitemporal ECT.

First and subsequent treatment sessions were analysed separately because the first treatment session is used to establish an individual's seizure threshold. Also, the actual treatment dose administered at subsequent treatment sessions was 1.5 × ST for the bitemporal group and 6 × ST for the RUL group. The first hypothesis was accepted. Using a Cox Mixed Effects Survival model (Therneau *et al.* 2003) I found that high dose RUL ECT was associated with a quicker reorientation of approximately 65% for the first treatment session and 44% quicker recovery of orientation at subsequent treatment sessions compared with bitemporal ECT.

Other factors that modify time to reorientation following ECT were also identified. At the first treatment session increasing decades of age were associated with longer times to reorientation. At subsequent treatments the effect of age was maintained while treatment factors associated with increased time to reorientation, such as longer seizure duration and a consistent increase in disorientation time for each additional treatment session, were also identified. Increased heartrate and blood pressure were associated with an alerting effect on reorientation that may be as a result of an increased vagal response to ECT. The associated increased release of catecholamine's may promote a quicker awakening after treatment and an earlier recovery of orientation

There was no difference between the treatment groups in the number of participants that experienced prolonged disorientation following ECT (i.e. failure to answer four of the five orientation questions within 50 minutes of resumption of spontaneous breathing). Increasing decades of age was the most significant predictor of prolonged disorientation but, contrary to a number of case reports in the literature, Lithium therapy was not (Thirthalli *et al.* 2010). Once again, increased heartrate and blood pressure were associated with a protective effect on the likelihood of prolonged disorientation after ECT.

The second hypothesis was tested in two separate analyses: The first analysis tested the hypothesis that high dose RUL ECT would be associated with fewer complaints of physical side-effects (headaches, nausea and myalgia) immediately after ECT. This hypothesis was rejected. There was no difference in the number of people complaining of headache, nausea or myalgia between the treatment groups. Post ECT myalgia rarely occurred after the first treatment and occurred after less than 2% of treatments in total. Women were twice as likely as men to complain of post ECT headaches and longer seizure duration was associated with a substantially increased risk of headache and nausea after ECT.

The second analysis tested the hypothesis high dose RUL ECT would be associated with less of an impact on physical effects (cardiac response) immediately following treatment compared with bitemporal ECT. This hypothesis can be neither accepted nor rejected. Bitemporal ECT was associated with an increased impact on heart-rate compared with RUL ECT but RUL ECT was associated with an increased impact on blood pressure. However, without the use of continuous measurement it is impossible to say whether both blood pressure and heart-rate initially tracked each other but one returned towards pre-treatment levels quicker than the other by the time of first measurement in this study.

In general, ECT was associated with relatively little change in heart-rate after 5 minutes which is consistent with previous findings. Tachycardia that required intervention was also rare and there was no difference in the rate of occurrence or requirement of intervention between the treatment groups. High dose RUL ECT was associated with a greater transient increase in blood pressure than bitemporal ECT but blood pressure decreased to pre-treatment levels in unison for both treatment groups. However, transient hypertension that required medical intervention occurred only in the high-dose RUL ECT group.

The third hypothesis was rejected. There was a considerable recovery of ability to perform basic and instrumental ADL but there was no difference between the treatment groups at any time-point after treatment.

There were mild deficits in ability to perform basic ADL which is best explained by the cognitive effort hypothesis: depression was associated with significantly more impairment in ability to perform IADL than basic ADL because depression effects ability to perform more complex roles and activities than more basic automatic behaviours such as dressing and feeding for example (Hammar *et al.* 2010).

Executive function has been found to best predict ability to perform IADL and executive function improved significantly in the high dose RUL group from pre-treatment but not in the bitemporal group. However, there was no statistically significant difference in executive function between the treatment groups at the end of treatment. Controlling for the effect of executive function between the groups there was no difference between the treatment groups in performance of IADL at 4 weeks after treatment and analysis of the reduced dataset at 6 months after treatment was consistent with this. Remission status at the end of the treatment course was the only significant predictor of ability to perform IADL 4 weeks and 6 months after treatment.

The fourth hypothesis was rejected. Prior to treatment there were no significant differences between the treatment groups in any of the SF-36 health and well-being domains. Participants reported less of a deficit in the four physical component domains (physical function, role physical, pain and health perception) and more severe deficits on mental component domains (role mental, social functioning, mental health and energy). Although there were improvements in the physical domains by end of treatment these improvements were not statistically significant. This was most likely due to the fact that there was much less of an improvement to be made in these areas. There was a statistically significant improvement in all four mental component domains in both treatment groups. To compare the effectiveness of the two treatments ANCOVA was used to control for difference in pre-treatment scores. After adjusting for pre-intervention scores, there was no significant difference between the two treatment groups on change scores on any of the SF-36 Health and Well-being domains. Six months after treatment participants continued to report persistent deficits in HRQOL compared with normative data. Achieving remission at the end of the treatment course was the only explanatory variable that predicted superior HRQOL 6 months after treatment. In fact, remitters at end of treatment were at, or above, average levels

of HRQOL 6 months after treatment while non-remitters were below average in the mental components of the mental health summary score of the SF-36.

The fifth hypothesis was accepted. In general terms participants in this study expressed very positive attitudes towards the explanation of ECT prior to commencing treatment; the informed consent process; and perceptions of coercion. Participants were generally very positive that ECT had helped them and had relieved their depression. However, participants complained significantly of problems with their memory after the course of treatment. Despite this over 75% of participants would have ECT again if needed.

Seven latent variables emerged from factor analysis of the attitudes questionnaire. These composite scores were used to (1) establish the level of positivity of each group towards ECT and (2) form composite scores that could be compared between groups. Both groups were positive in their attitudes towards the effectiveness of ECT, the consent process associated with ECT, fear of ECT, perception of ECT and perception of care at end of treatment and 3 months later. RUL participants were neutral while bitemporal participants were slightly negative towards the memory effects of ECT and experience of ECT composite scores at the end of treatment. 3 months after treatment RUL participants were neutral while bitemporal participants were slightly negative towards the memory effects of ECT and both groups were slightly negative in their attitudes towards their experience of ECT.

There was no difference in intensity of attitude in any domain over time between the treatment groups. Cognitive function at end of treatment, subjectively perceived cognitive side-effects, gender, treatment resistance and knowledge of ECT were not significant predictors of attitude towards ECT. Remission status at the end of treatment was the only explanatory variable that predicted a positive and a negative attitude towards ECT: remitted participants were positive about ECT while those that failed to achieve remission after a course of ECT had a negative attitude towards the treatment.

6 Strengths and limitations

6.1 Strengths

Although this study is not a randomized controlled trial it was carried out in the context of one as such maintains many of the benefits of the design. Participants were randomly allocated and there were no differences between the groups that may have affected the outcome; participants and raters were blind to group allocation so neither group could have influenced outcomes due to preconceived ideas; and the design facilitated rigorous statistical analysis. In much of the existing evidence base bitemporal ECT was administered at 2.5 × ST (Sackeim *et al.* 2000; Sackeim *et al.* 2008) which is considered supramaximal stimulation in Europe. RUL ECT has frequently been administered at suboptimal stimulus treatment doses (McCall *et al.* 2001) or supramaximal doses (McCall *et al.* 2002b). ECT in this study was administered at effective doses in terms of antidepressant effect (Kellner *et al.* 2010) and these doses are directly comparable to standard ECT practice in Europe, some recent evidence from the USA and the Southern Hemisphere. In previous ECT studies treatment has been administered three times a week. Treatment twice weekly is standard practice in Europe and results from this study are the first to examine the relevant areas with a twice weekly treatment schedule. The sample size of 100 participants in this study is relatively large compared to many ECT studies: e.g Sobin et al (1995) had N = 71 allocated to 4 treatment groups, Sackeim et al (2000) had 80 people divided into 4 treatment groups, Sackeim et al (2008) had N = 90 allocated to 4 treatment groups and Kellner et al (2010) had 230 in three treatment groups but there was an attrition rate of over 30% before the end of the treatment group. By the end of the treatment course no participants had dropped out of this study, 100% of recovery data were collected and at the end of the treatment course data were collected from all participants. There were a large number of outcome measures used in this

study examining a wide and diverse range of health, wellbeing and functioning and all of these outcome measures have established validity and reliability. The data gathered in this study presented a multitude of analytical complications: recovery of orientation and physical response to ECT data were repeated measurements taken at a varying number of repeated time-points; adverse physical effects data were repeated measurements of a binomial outcome; basic functioning data were severely negatively skewed with minimal variation and were repeated measurement comparisons between groups; attitudes of different groups to different treatments have rarely been compared using such a comprehensive scale that required factor analysis before group comparisons could be made. All statistical analyses used in this project accounted for these challenges and were appropriate for the type of data presented. It is viewed as a strength of this project that participants subjective evaluation of their own health related quality of life was a central area of focus rather than an objectively rated disease specific outcome measure only. It is also seen as a strength that this assessment of HRQOL did not take place until sufficient time had passed since the end of the treatment course to allow participants time to engage with those activities that are central to HRQOL. All participants that entered this study had the same opportunity to complete all assessments, including the ECT attitudes questionnaire, so there was no selection bias or other distortion of results.

6.2 Limitations

Physiological response to ECT (blood pressure and heart-rate data) were collected before and after treatment but much of the physiological response to ECT may have subsided prior to the first point of collection after ECT in this study. Future studies should use continuous measurement of these parameters to comprehensively follow their trajectory throughout the treatment session. Data regarding the presence of adverse physical effects (headache, nausea, and myalgia) were gathered from participants at recovery of orientation at each treatment session but there was no severity scale included which may contributed additional information and data to compare between the treatment groups. Also, there were no a priori criteria of adverse cardiac effect (e.g. hypertension, tachycardia) that would require medical intervention and intervention was provided on the basis of clinical judgement and best Anaesthesia practice. Thus, data in this area may reflect naturalistic treatment conditions but lack rigor. Although all participants completed assessments at the end of the treatment course there was a loss of data at subsequent follow-up assessments. As a result longitudinal analysis functioning was limited. The qualitative attitudes data collected in this study were extremely limited in depth and scope. Answers on the free-text section of the ECT attitudes questionnaire were scare at end of treatment and rare at 3 months follow-up. This is most likely because of the significant participant burden associated with completion of such an extensive battery of assessments at each of the 4 major assessment time-points: prior to treatment, at the end of treatment, 3 month and 6 month follow-up. However, the data that were available did largely support the quantitative assessment of the attitudes data.

7 Implications and recommendations

The findings from this study have a number of implications that are relevant to a number of different groups. These are discussed and suitable recommendations are made in each case:

7.1 Clinicians

1.5 × ST bitemporal ECT remains the most commonly used method of administration internationally (Lieiknes *et al.* 2011). Clinicians need to be made aware of the fact that RUL ECT administered at high doses can be as effective as standard bitemporal ECT. Clinicians also need to be made aware of the findings of this study: that high dose RUL ECT is associated with significant reductions in time to recovery of orientation after ECT. Clinicians should then consider a change in routine administration practice to high dose RUL ECT as swifter time to recovery of orientation is a significant improvement in the adverse cognitive effect profile associated with ECT in its own right but may also lead to reductions in persistent memory effects associated with ECT. It is also important that clinicians are made aware of the findings that older age has been confirmed as the most significant predictor of longer disorientation time and prolonged disorientation after ECT. Clinicians should then administer high dose RUL ECT routinely to older patients in particular, especially given the finding that there was no difference in the number of treatments prescribed to participants in this study, supporting the equivalence of effectiveness between both types of ECT. Given that additional treatments were found to be associated with slower recovery of orientation there is also an onus on clinicians to evaluate the need for further ECT after every treatment to ensure that patients are administered no more treatments than is absolutely necessary. Clinicians also need to be made aware that longer seizure duration is predictive of adverse physical effects such as headaches and nausea after ECT and while continuing to ensure an adequate seizure

is achieved at treatment sessions ensure that prolonged seizures are avoided. Finally, clinicians should use the findings from this study to amend their pre-treatment information booklets to include the evidence that headaches are twice as likely in women after ECT. Now that we have this evidence it is important that service users are provided with it prior to treatment.

7.2 Researchers

ECT research has progressed in recent years from an attempt to establish the effectiveness of ECT to attempts to optimise ECT, i.e. to maintain the established effectiveness but improve the side-effect and adverse-effect profile associated with ECT. Evidenced based improvements have been made in a number of areas such as a move to brief pulse from sine wave stimulation, treatment twice weekly to thrice weekly in many countries, the use of stimulus dosing protocols instead of using fixed stimulus doses and recent evidence that RUL ECT administered at high doses can be as effective in terms of antidepressant effect as standard bitemporal ECT. The findings of this study that high dose RUL ECT is associated with such a reduction in time to recovery of orientation is significant and proves that further optimisation of ECT is possible, e.g. there may also be associated improvements in persistent memory effects associated with RUL ECT as a result and future research should include tests of antergrade and retrograde memory. Future ECT research should continue to focus on optimising ECT. One area of interest should be to establish the effectiveness of ultra-brief pulse ECT with respect to electrode placement and stimulus doses needed for UBP to be as effective as brief pulse ECT. If UBP ECT can be developed to a stage where it is as effective as brief pulse ECT it may lead to even further reductions in the adverse cognitive effect profile, specifically time to reorientation and persistent memory impairment.

7.3 Nursing

The actual ECT treatment session is a very medical procedure (Kavanagh & McLoughlin 2009). Nurses are mostly involved in preparing patients for treatment, caring for patients during recovery and caring for patients at ward level after treatments and after the treatment course. This study was conducted in the context of a randomized controlled trial and it was therefore expected that there would be high rates of satisfaction with the amount of information given to patients prior to treatment and it was also expected that there would be low rates of perceived coercion. However, in other observational studies there continues to be higher rates of dissatisfaction in these areas. The results of this study demonstrate that it is possible to provide patients with sufficient information prior to treatment and Nurses are in a key position at the care-face to ensure this is done. However, in order to do so Nurses need to be aware of all of the information relevant to ECT practice, positive and negative (Kavanagh & McLoughlin 2009).

There was an extremely low rate of perceived coercion in this study. However, no voluntary patient should feel coerced into accepting any treatment. Nurses are primly placed within the care setting to build relationships with patients based on honesty and trust. If some patients are consenting to ECT and for some reason feel coerced Nurses need to make every effort to identify this and act as: (i) educators for these patients so they can clarify anything that the atient does not understand and facilitate their co-operation with treatment or (ii) act as advocates for these patients to inform the treating team that treatment should not proceed until the patient in happy to proceed.

Also, over 50% of participants in this study communicated their experience of negative memory effects. Currently the evidence has severe limitations and we do not know how many patients we can expect to develop persistent memory impairment (retrograde

amnesia). Nurses at ward level need to be more aware of the potential for memory impairment and the types of memory impairment that can occur after ECT in order to support and understand the experiences of their patients. There is a role here for educators at academic and clinician levels to educate students and qualified staff about ECT so that they have the necessary knowledge to fulfil this role in the practice setting.

7.4 Policy makers

The Mental Health Commission (MHC) provides rules and a code of practice on the use of ECT in Ireland. Rules Governing the Use of Electroconvulsive Therapy state in Section 5.3 that, "The initial stimulus dose of electricity to be delivered to each patient must be discussed and considered by the treating consultant psychiatrist and the consultant psychiatrist responsible for the administration of ECT in advance of ECT and prescribed accordingly" (MHC 2009). In light of recent evidence regarding the effectiveness of high dose RUL ECT (Kellner *et al.* 2010) and the findings of this study regarding recovery of orientation and that high dose RUL ECT was at least as effective as bitemporal ECT in terms of functioning and HRQOL, this rule should be amended to include a discussion on electrode placement also.

The MHC has expressed a desire to see a national mental health information system that would require approved centres to electronically record information that would "facilitate enhanced patient and outcomes focused reporting" (Mental Health Commission 2012). Data of this type collected nationally as part of routine practice would exceed what can be done in a research study and would facilitate direct comparisons of ECT practice in Ireland with other jurisdictions. The MHC should pursue this objective as its use would further enhance the evidence base across all aspects of mental health care, not just in relation to ECT.

7.5 Service users

RUL ECT has long been considered ineffective as an antidepressant treatment compared to bitemporal ECT (Sackeim *et al.* 1993). Service users can now be reassured that if RUL ECT is administered at high doses: it can be at least as effective as bitemporal ECT in terms of antidepressant effect (Kellner *et al.* 2010) and now we have evidence that it is as effective as bitemporal ECT in its effects on recovery of functioning and HRQOL. Service users can also gain from improvements in the adverse cognitive effect profile of RUL ECT with the associated quicker time to reorientation compared to bitemporal ECT. It is also likely that improvements made in this area indicate the potential for improvements in persistent amnestic effects but this needs further investigation. The attitudes research in this study indicates that patients may remember the consent process more after RUL ECT than with bitemporal ECT. This highlights the memory effects of ECT on the most important part of any treatment and highlights the need for mental health professionals to do more with regard to consent and continued assent throughout the treatment course.

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Appendix 1

	N	Depression severity scale	Random allocation	Blinding	Sham comparison group	Remission criteria	Medication use during trial	Wave form	Treatment terminated by	Frequency of treatment	Laterality
Freeman et al (1978)	40	HDRS	✓	Double blind	Partial course	✗	Regular medications maintained during trial	Sine wave	Treating clinical team	Twice weekly	Bilateral
Lambourn & Gill (1978)	32	HDRS	✓	Double blind	✓	✗	Benzodiazepines only	Brief pulse	Treating clinical team	Thrice weekly	Right Unilateral
Johnstone et al (1980)	70	HDRS	✓	Double blind	✓	✗	Benzodiazepines only	Sine Wave	Treating clinical team	Twice weekly	Bifrontal
West (1981)	22	Visual analogue scale	✓	Double blind	✓	✗	50mg amitriptyline at night	Sine wave	Treating clinical team	Twice weekly	Bilateral
Brandon et al (1984)	77	HDRS & MADRS	✓	Double blind	✓	✗	Benzodiazepines only	Sine wave	Treating clinical team	Twice weekly	Bilateral
Gregory et al (1985)	69	MADRS & HDRS	✓	Double blind	✓	✗	Benzodiazepines only	Sine wave	Treating clinical team	Twice weekly	Bilateral and right unilateral groups

Appendix 2

EFFECT-*Dep Study Patient Information*

Please Circle or Fill as Appropriate

Surname: _____

First Name: _____

Insert Patient Label Here

Date of Birth: ___/___/_____

Age: _____

Date Filed___/___/__

_____

_____

Educational Attainment:

Primary Secondary Tertiary

Quaternary

Marital Status:

Married ☐
Unmarried ☐
Divorced ☐
Widowed ☐

Socioeconomic Group_____

1	Professional
2	Managerial & Technical
3N	Skilled Occupations – Non-Manual
3M	Skilled Occupations - Manual
4	Partly skilled
5	Unskilled Occupations

Address:

_____
_____
_____
_____
_____
_____
_____
_____

_____

Phone:_____

Mobile:_____

Weight (kg):_____
1kg = 2.205 lbs, 1 stone = 14lbs

Height (m):_____

Next of Kin :
Name _____

Relation to Patient:_____

Contact Details:

_Phone:_____
_Mobile:_____
_email:_____

Address:

_____
_____
_____
_____
_____
_____

Previous ECT: YES / NO

Date of Last ECT : ____/____/____

Source of Referral: St.JH / St.EH / St.PH

Smoker Y / N

Alcohol : Regular Alcohol Intake: _____U/wk

Family History of Mental Illness:

Relation to patient

Occupation:_____

_____
_____
_____

Appendix 3

Experience of ECT Questionnaire

Below you will find a series of statements which are opinions/ attitudes relating to Electroconvulsive Therapy (ECT).
For each statement please circle the answer which best describes your attitude towards ECT based on the treatment you received. Remember there is no right or wrong answer; we are simply interested in *your experience* of ECT.

Sample Questions
Here are some sample questions and answers to show you how this questionnaire works:

A- I enjoy waiting a long time for the bus:

Strongly disagree disagree don't know agree strongly agree

B- I would like to win the lottery:

Definitely probably not sure probably not definitely not

C- I think it would be better if the world was flat instead of round:

Strongly disagree disagree don't know agree strongly agree

Please circle the response that best describes your experience of ECT for all the following questions:

1- The explanation of ECT given before treatment was adequate:

Strongly disagree disagree don't know agree strongly agree

2- I felt anxious/ frightened before my first ECT treatment:

Strongly disagree disagree don't know agree strongly agree

3- I felt pleased the treatment was starting before my first ECT treatment:

Strongly disagree disagree don't know agree strongly agree

4- Experience of various parts of the treatment:

Please rate each of the following aspects of treatment on how pleasant you found them:

a) Premedication

very pleasant pleasant neutral unpleasant very unpleasant

b) Waiting for treatment

very pleasant pleasant neutral unpleasant very unpleasant

c) ECT staff

very pleasant pleasant neutral unpleasant very unpleasant

d) Anaesthetic injections

very pleasant pleasant neutral unpleasant very unpleasant

e) Falling asleep

very pleasant pleasant neutral unpleasant very unpleasant

f) Waking up

very pleasant pleasant neutral unpleasant very unpleasant

g) Recovery period for a few hours after treatment

very pleasant pleasant neutral unpleasant very unpleasant

5- Experience of ECT

a) I was so upset by the treatment I'd be reluctant to have it again:

Strongly agree agree don't know disagree strongly disagree

b) If necessary I'd readily have the treatment again:

Strongly agree agree don't know disagree strongly disagree

c) More explanation should be given to the patients about the treatment:

Strongly agree agree don't know disagree strongly disagree

d) ECT is a frightening treatment to have:

Strongly agree agree don't know disagree strongly disagree

e) ECT was more upsetting than going to the dentist:

Strongly agree agree don't know disagree strongly disagree

f) How frightening or upsetting was ECT compared with what you expected?

A lot more upsetting A little more upsetting The same as expected A little less upsetting A lot less upsetting

6- Fears and worries about ECT:

Please rate how worried you were about the following:

a) About being made unconscious

Very worried worried neutral unconcerned very unconcerned

b) About losing control of bladder or embarrassing things happening whilst unconscious

Very worried worried neutral unconcerned very unconcerned

c) That electricity was used in treatment

Very worried worried neutral unconcerned very unconcerned

d) About having a fit or turn

Very worried worried neutral unconcerned very unconcerned

e) Of possible brain damage as a result of the treatment

Very worried worried neutral unconcerned very unconcerned

7- Severity of side-effects of ECT

Please rate the severity of the following symptoms:

a) Memory impairment

Very severe severe moderate mild none

b) Headache

Very severe severe moderate mild none

c) Confusion

Very severe severe moderate mild none

d) Clumsiness

Very severe severe moderate mild none

e) Nausea/ Vomiting

Very severe severe moderate mild none

f) Eyesight problems

Very severe severe moderate mild none

g) Drowsiness

Very severe severe moderate mild none

h) Muscle pain

Very severe severe moderate mild none

i) Weakness

Very severe severe moderate mild none

j) Muscle spasm

Very severe severe moderate mild none

k) Loss of intelligence

Very severe severe moderate mild none

8- Memory function after ECT

a) My memory has never returned to normal after ECT

Strongly agree agree don't know disagree strongly disagree

b) My memory now is better than it has ever been

Strongly agree agree don't know disagree strongly disagree

c) ECT is helpful but the side effects are severe

Strongly agree agree don't know disagree strongly disagree

d) ECT has no effect on memory at all

Strongly agree agree don't know disagree strongly disagree

e) ECT causes permanent changes to memory

Strongly agree agree don't know disagree strongly disagree

9- How helpful was the treatment?

a) How much did ECT help you?

A lot A little No change A little worse A lot worse

b) ECT made me less depressed:

Strongly agree agree don't know disagree strongly disagree

c) ECT made me less anxious:

Strongly agree agree don't know disagree strongly disagree

d) ECT made me forget what was bothering me:

Strongly agree agree don't know disagree strongly disagree

e) How long has the effect of ECT lasted:

1 year Or more 6-12 months less than 6 months Immediate relapse No effect

f) ECT is a helpful and useful procedure:

Strongly agree agree don't know disagree strongly disagree

g) ECT works for a short while but the effects don't last:

Strongly agree agree don't know disagree strongly disagree

h) ECT gets you better quicker than drugs:

Strongly agree agree don't know disagree strongly disagree

10- How ECT works:

a) ECT treatment involves passing a current of electricity through the brain:

Definitely probably not sure probably not definitely not

b) ECT treatment involves inducing a seizure in the brain

Definitely probably not sure probably not definitely not

c) ECT treatment involves being given an anaesthetic

Definitely probably not sure probably not definitely not

d) ECT treatment is used to treat depression:

Definitely probably not sure probably not definitely not

e) ECT treatment is used to treat anxiety:

Definitely probably not sure probably not definitely not

11- Consent procedure

a) I was offered other treatments before I had ECT (medications/ talking therapy etc):

Strongly agree agree don't know disagree strongly disagree

b) I felt that I had no alternative but to have ECT:

Strongly agree agree don't know disagree strongly disagree

c) Ward staff explained to me what would happen during ECT:

Strongly agree agree don't know disagree strongly disagree

d) Ward staff explained the possible side-effects of ECT:

Strongly agree agree don't know disagree strongly disagree

e) I received written information about ECT (e.g. hospital booklet etc) before the treatment:

Strongly agree agree don't know disagree strongly disagree

f) I had enough time to think about ECT and discuss it with my doctor or nurse before agreeing to the treatment:

Strongly agree agree don't know disagree strongly disagree

g) I discussed my decision with others (e.g. family, friends or other patients):

Strongly agree agree don't know disagree strongly disagree

h) I think I made a fully informed decision to have ECT:

Strongly agree agree don't know disagree strongly disagree

i) I felt pressurised or forced to have ECT:

Strongly agree agree don't know disagree strongly disagree

j) I think ECT helped me:

Strongly agree agree don't know disagree strongly disagree

k) I think I was properly cared for after the ECT treatment (e.g. people spent time with me if I felt confused or distressed):

Strongly agree agree don't know disagree strongly disagree

12- Side effects of ECT treatment

a) I still have side effects from the ECT treatment

Strongly agree agree don't know disagree strongly disagree

b) Those caring for me took my side-effects seriously

Strongly agree agree don't know disagree strongly disagree

c) I had enough time to discuss any concerns I had with my doctor/ nurse since having ECT

Strongly agree agree don't know disagree strongly disagree

d) I felt some stigma as a result of having ECT

Strongly agree agree don't know disagree strongly disagree

e) I would never have ECT again

Strongly agree agree don't know disagree strongly disagree

13- Additional information:

a) Did ECT relieve your depression?

Definitely probably not sure probably not definitely not

b) Did ECT cause side-effects?

Definitely probably not sure probably not definitely not

c) Did ECT cause problems with your concentration?

Definitely probably not sure probably not definitely not

d) Did ECT cause problems with your memory?

Definitely probably not sure probably not definitely not

Do you have any other comments you would like to add about your ECT treatment?

_____

_____

_____

_____

_____

_____

_____

Thank you for taking part in our study.

Appendix 4

Timeline of assessments

	Baseline	EOT	4 Weeks	3 Months	6 Months
Demographic details	✔				
HDRS	✔	✔	✔	✔	✔
BDI-II	✔	✔		✔	✔
ACE-R	✔	✔		✔	✔
Trail making test A & B	✔	✔		✔	✔
PSMS	✔		✔	✔	✔
IADL	✔		✔	✔	✔
SF-36	✔				✔
Attitudes		✔		✔	
CSSES	✔	✔		✔	✔

HDRS Hamilton Depression Rating Scale

BDI-II Beck Depression Inventory version two

ACE-R Addenbrookes Cognitive Exam – revised edition

PSMS Physical Self Maintenance Scale

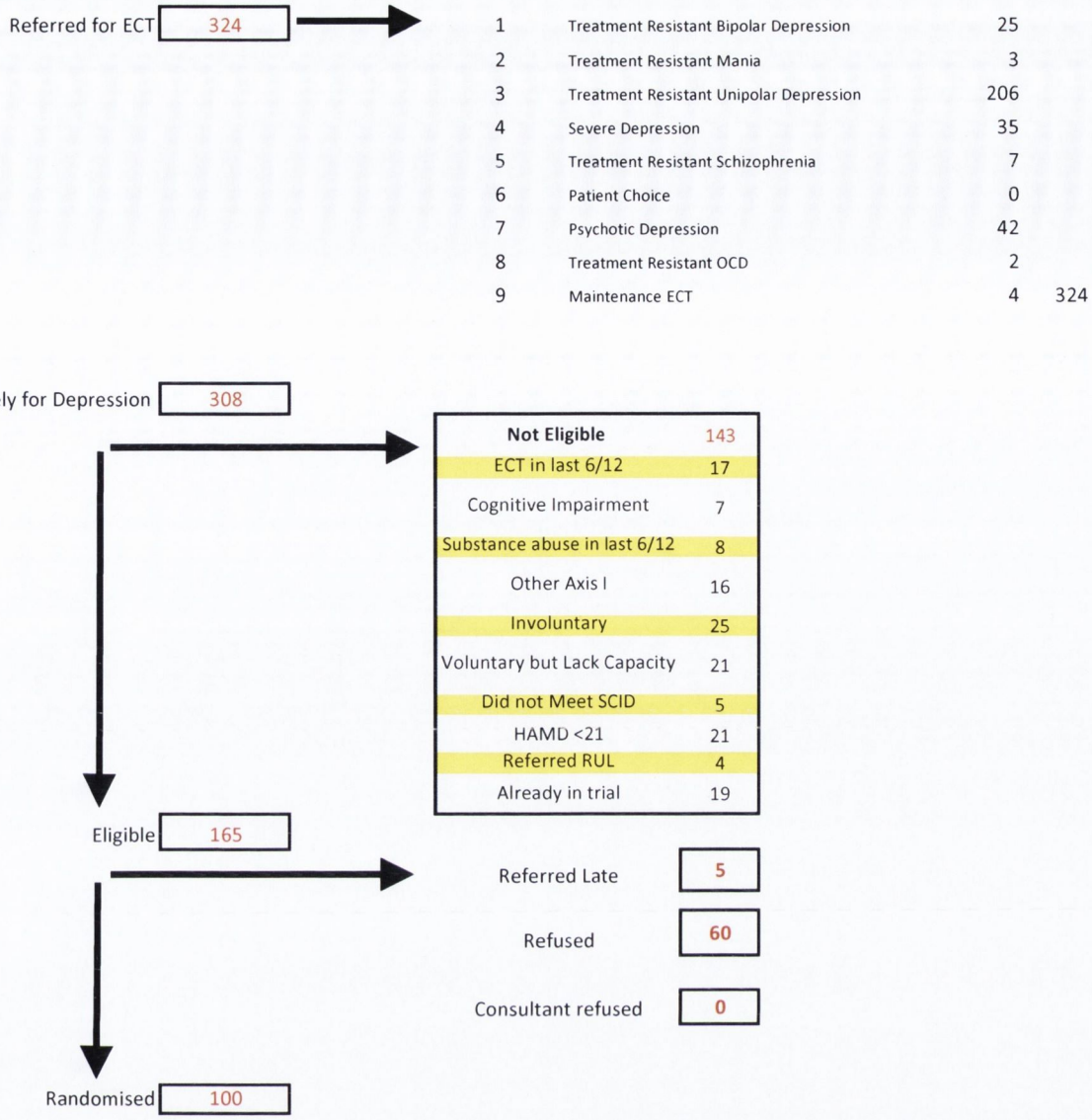
IADL Instrumental Activities of Daily Living Scale

SF-36 Medical Outcomes Study, Short Form 36-item Health Questionnaire

Attitudes ECT Attitudes Questionnaire

CSSES Columbia ECT Subjective Side-Effects Schedule

Appendix 5


Referred for ECT
324
1 Treatment Resistant Bipolar Depression 25
2 Treatment Resistant Mania 3
3 Treatment Resistant Unipolar Depression 206
4 Severe Depression 35
5 Treatment Resistant Schizophrenia 7
6 Patient Choice 0
7 Psychotic Depression 42
8 Treatment Resistant OCD 2
9 Maintenance ECT 4
324
Referred Acutely for Depression
308
Not Eligible 143
ECT in last 6/12 17
Cognitive Impairment 7
Substance abuse in last 6/12 8
Other Axis I 16
Involuntary 25
Voluntary but Lack Capacity 21
Did not Meet SCID 5
HAMD <21 21
Referred RUL 4
Already in trial 19
Eligible
165
Referred Late
5
Refused
60
Consultant refused
0
Randomised
100

Appendix 6

Interpretation of the SF-36

A guide for the interpretation of very high and very low scores on the SF-36 (adapted from Ware and Sherbourne (1992) (Ware & Sherbourne 1992).

Physical functioning:

- Low scores indicate severe limitations in performing activities including bathing and dressing
- High scores indicate an ability to perform all types of physical activities without health related limitations

Role physical:

- Low scores indicate problems with work or other daily activities' as a result of physical health
- High scores indicate no problems with work or other daily activities' as a result of physical health

Role emotional:

- Low scores indicate problems with work or other daily activities' as a result of emotional health
- High scores indicate no problems with work or other daily activities' as a result of emotional health

Social functioning:

- Low scores indicate extreme and frequent interference with normal social activities due to physical or emotional problems.

- High scores indicate no problems with normal social activities due to physical or emotional problems

Mental health:

- Low scores indicate feelings of nervousness and depression all of the time
- High scores indicate that the person feels peaceful, happy and calm all of the time

Energy:

- Low scores indicate feeling tired and worn out all of the time
- High scores indicate that the person feels full of energy all of the time

Pain:

- Low scores indicate severe and limiting bodily ain
- High scores indicate no pain or limitations due to pain

General health perception:

- Low scores indicate that the person believes their personal health is poor and likely to get worse
- High scores indicate that the person believes their personal health is excellent

Appendix 7

Assessment Schedule EFFECT-Dep Study

Pre-treatment		Within treatment assessments						Followup Assessments								
Assessment	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	End	2 weeks	4 weeks	6 weeks	8 weeks	3 months	4 months	6 months	9 months	12 months
Exclusion Criteria, Diagnosis & Treatment Review																
Treatment Review	✓						✓					✓		✓		✓
Criteria	✓															
SCID-I	✓															
ATHF	✓															
Clinical Outcomes																
HDRS[24]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
BDI-II	✓						✓					✓		✓		✓
BPRS	✓						✓					✓		✓		✓
Cognitive outcomes																
NART	✓															
ACE-R	A						B					C		D		A
AMI-SF	✓						✓					✓		✓		✓
Events Questionnaire	✓						✓					✓		✓		✓
Pegboard	✓						✓					✓		✓		✓
Buschke SRMT	1						2					3		1		2
Complex Figure MT	A						B					C		D		A
Trails	✓						✓					✓		✓		✓
Digit Span	I						II					III		I		II
Subjective Side Effects																
CSSES	✓						✓					✓		✓		✓
Functional Outcomes																
IADL	✓								✓			✓		✓		✓
PSMS	✓								✓			✓		✓		✓
Costs & Quality of life																
CSRI	✓													✓		✓
SF-36	✓													✓		✓
Attitudes																
Attitudes questionnaire							✓					✓				✓
Blood Samples																
Phlebotomy	✓						✓					✓		✓		✓

SCID-I : Structured clinical interview for DSM-IV disorders 1996 version. ATHF : Antidepressant treatment history form, developed by Harold Sackeim. BPRS: Brief Psychiatric Rating Scale, HDRS(24): Hamilton Depression Rating Scale - 24 Item version developed by William Guy 1976; ECDEU Manual for Psychopharmacology. NART: National adult reading test. ACE-R: Addenbrooke's Cognitive examination - Revised (Hodges et. Al). AMI-SF: Autobiographical Memory Interview - Short Form. Pegboard : Grooved Pegboard. Buschke SRMT: , Complex Figure: Rey-Osterreith with 4 different figures used. Trails A and B. Digit Span. CSSES: Columbia Subjective Side-effect scale. IADL: Instrumental Activities of Daily living scale. PSMS: Physical Self-Maintenance scale. CSRI: Client service receipt interview. SF-36: Short Form-36 general health questionnaire. Attitudes Questionnaire. Phlebotomy is performed for samples for proteomics and genotyping at the above intervals but also upon relapse or readmission.

Appendix 8

Details of contribution of work to the EFFECT-DEP TRIAL and assessments completed from May 2008 to March 2011

From January 2008 to March 2011:

- I developed this study in consultation with my supervisor. I commenced work on the EFFECT-DEP TRIAL as a research assistant in January 2008. Large amounts of data were being collected as part of the trial across neurocognitive, biochemical, clinical and functional domains. There were a number of these areas that were of particular interest to me as a Registered Psychiatric Nurse and my reading on ECT and depression focused predominantly on these areas: recovery of orientation; physical functioning; HRQOL; and attitudes towards ECT. It became obvious that there were a number of deficits in the ECT-Depression knowledge base in these areas and the trial provided an excellent opportunity to address these deficits. I devised the current study, which was conducted in the context of the EFFECT-DEP TRIAL, to address these deficits in the knowledge base.
- Prior to the trial commencing I redesigned the St. Patricks University Hospital ECT Booklet to make it more efficient and more useable as a data collection tool. 100% of the recovery of orientation and physiological data were collected using this booklet.
- I collected all of the recovery data on the first 100 participants recruited to the EFFECT-DEP TRIAL.
- I entered all of the recovery data on the first 100 participants recruited to the EFFECT-DEP TRIAL into SPSS version 18.0. There were 142,476 data points; 186 data points per patient from 100 participants who had a total of 766 treatments.
- I travelled 3734.4 miles across Ireland conducting follow-up assessments with participants that were unable to attend St. Patricks University Hospital for assessment.

- I created the data entry sheet in SPSS Data Entry Builder 4.0 through which the attitudes data were entered.
- I successfully completed the Post Graduate Diploma in Statistics from Trinity College Dublin, School of Computer Science and Statistics in order that I would be able to independently analyse data for my study.
- I gained a considerable amount of knowledge of the quantitative methodology and valuable experience working on a randomized controlled trial.
- I learned how to use the statistical software package SPSS version 18.0.
- I learned how to use the statistical software package R.
- I devised rigorous statistical analysis methods to appropriately analyse all types of data collected including correlated data and repeated measures data within clusters of participants. Due to the nature of this longitudinal data a significant amount of time and research was dedicated to this aspect of the project to ensure rigor.
- From May 2008 to March 2011, 100 participants were recruited to the EFFECT-DEP TRIAL. 1263 assessments were completed by all 9 members of the research team including 100 pre-treatment assessments, 100 end of treatment assessments, 100 3 month and 100 6 month assessments. I completed 10 (10%) of pre-treatment assessments, 29 (29%) of end of treatment assessments, 26 (26%) of 3 month assessments and 25 (25%) of 6 months assessments. I also completed 23 12 month assessments during this time. I also completed 77 intra-treatment assessments (HDRS only) and 178 Follow-up HDRS assessments (includes: 2 weeks F/U, 4 weeks F/U, 6 weeks F/U, 8 weeks F/U, 4 months F/U and 9 months F/U). In total I completed 368 assessments representing 29.14% of all assessments completed during this time by 9 researchers. Please see Appendix 7 for Schedule of Assessments at each time-point for the EFFECT-DEP TRIAL, Appendix 4 for a Schedule of Assessments at each

time-point for this study and Appendix 8 for a breakdown of the number of assessments I completed during my time working on the EFFECT-DEP TRIAL.

- I was involved in the assessment of more participants than any other researcher.
- On average I conducted more assessments per month than any other researcher involved in the trial (10.2 assessments per month).
- I had the lowest refusal rate or highest retention rate of all researchers involved in the trial.

Assessments	Number completed
Pre-treatment (Full battery)	10
Intra-treatment (HDRS after every 2 treatments)	77
End of treatment (Full battery)	29
Follow-up assessments (Includes: 2 weeks F/U, 4 weeks F/U, 6 weeks F/U, 8 weeks F/U, 4 months F/U and 9 months F/U	178
3 month follow-up (Full battery)	26
6 month follow-up (Full battery)	25
12 month follow-up (Full battery)	23
Total Assessments completed	**368**

Full battery includes:
Criteria – Assessment of suitability for trial (inclusion & exclusion criteria)
SCID – Structured Clinical Interview
ATHF – Antidepressant Treatment History Form
HDRS – 24 item Hamilton Depression Rating Scale
BDI – Beck Depression Inventory
BPRS – Brief Psychiatric Rating Scale
NART – National Adult Reading Test
ACE-R – Addenbrookes Cognitive Exam –Revised
AMI-SF – Autobiographical Memory Interview – Short Form
Events Questionnaire – Anterograde Memory Assessment
Pegboard – Grooved Pegboard
Buschke - 16-item Buschke Memory Test
Complex figure - Rey-Osterrieth Complex Figure Test
Trails – Trail Making Test A & B
Digit span – Digit Span Test
CSSES – Columbia ECT Subjective Side-Effects Schedule
PSMS – Physical Self Maintenance Scale
IADL – Instrumental Activities of Daily Living Scale
CSRI – Client Service Receipt Interview
SF-36 – Short Form 36 Item Health Questionnaire
Attitudes – ECT Attitudes Questionnaire