Chapter 1

The Place of ECT and Related Treatments in Contemporary UK Psychiatry

I Nicol Ferrier

The previous edition of The ECT Handbook was produced in 2013 and was well received. The current edition updates the 2013 one and attempts to find a similar balance between outlining the scientific literature relating to ECT and related treatment modalities and pragmatic and practical advice on their place in management and delivery in a UK context. This chapter concentrates on the guidelines in the UK for the use of ECT and related treatments. The recommendations of NICE for the use of ECT and related treatments are outlined first, followed by position statements from the Committee. Any differences (which are usually minor and of emphasis rather than substance) are highlighted. The position statements were generated in 2017 and have been ratified by the College. They can be found on the Royal College of Psychiatrists' website at:

www.rcpsych.ac.uk/workinpsychiatry/committeesofcouncil/ectandrelatedtreatments.aspx

Evidence supporting these position statements can be found in individual chapters of the Handbook.

The use of ECT has fallen across the UK in the last few decades although there is some evidence that, in the last few years, the numbers of courses administered each year is falling much more slowly (Buley *et al.*, 2017; SEAN, 2016). There are a myriad of reasons why the numbers of patients receiving ECT have fallen: some relate to attitudes of patients and of staff, others relate to the problems of delivering it in the current service framework. These issues are discussed more fully in subsequent chapters of this Handbook. Paradoxically the evidence base for the efficacy and safety of ECT continues to grow. The Committee feels that it is a valuable treatment that is either not considered at all or left until too late, in the management of many complex and severe cases. The position statement relating to ECT outlines the kind of patients for whom the College believes ECT should be considered. Despite the strong evidence for ECT, it is likely it will continue to be used only for a minority of patients with complex and severe mental illnesses so it is gratifying, given the scale of the clinical problem, that research on other potential physical treatment modalities for some of these patients is active. The position statements, together with the relevant National Institute for Health and Care Excellence (NICE) guideline recommendations, on ECT and the most prominent related treatments are given below, focusing on their use in depression. There are a variety of international guidelines on ECT and other modalities and the College's position is broadly in line with the rest of the world.

ECT

Depression

NICE Guidelines on Use of ECT in Depression

The 2009 NICE Guideline for Depression (CG90, NICE, updated 2016) made the following recommendations about ECT:

1.10.4.1 Consider ECT for acute treatment of severe depression that is life-threatening and when a rapid response is required, or when other treatments have failed.

1.10.4.2 Do not use ECT routinely for people with moderate depression but consider it if their depression has not responded to multiple drug treatments and psychological treatment.

1.10.4.3 For people whose depression has not responded well to a previous course of ECT, consider a repeat trial of ECT only after:

- reviewing the adequacy of the previous treatment course and
- considering all other options and
- discussing the risks and benefits with the person and/or, where appropriate, their advocate or carer.

1.10.4.4 When considering ECT as a treatment choice, ensure that the person with depression is fully informed of the risks associated with ECT, and with the risks and benefits specific to them. Document the assessment and consider:

- the risks associated with a general anaesthetic
- current medical comorbidities
- potential adverse events, notably cognitive impairment
- the risks associated with not receiving ECT.

The risks associated with ECT may be greater in older people; exercise particular caution when considering ECT treatment in this group.

1.10.4.5 A decision to use ECT should be made jointly with the person with depression as far as possible, taking into account, where applicable, the requirements of the Mental Health Act 2007. Also be aware that:

- valid informed consent should be obtained (if the person has the capacity to grant or refuse consent) without the pressure or coercion that might occur as a result of the circumstances and clinical setting
- the person should be reminded of their right to withdraw consent at any time
- there should be strict adherence to recognised guidelines about consent, and advocates or carers should be involved to facilitate informed discussions
- if informed consent is not possible, ECT should only be given if it does not conflict with a valid advance decision, and the person's advocate or carer should be consulted.

1.10.4.6 The choice of electrode placement and stimulus dose related to seizure threshold should balance efficacy against the risk of cognitive impairment. Take into account that:

- bilateral ECT is more effective than unilateral ECT but may cause more cognitive impairment

- with unilateral ECT, a higher stimulus dose is associated with greater efficacy, but also increased cognitive impairment compared with a lower stimulus dose.

1.10.4.7 Assess clinical status after each ECT treatment using a formal valid outcome measure, and stop treatment when remission has been achieved, or sooner if side effects outweigh the potential benefits.

1.10.4.8 Assess cognitive function before the first ECT treatment and monitor at least every three to four treatments, and at the end of a course of treatment.

1.10.4.9 Assessment of cognitive function should include:

- orientation and time for reorientation after each treatment
- measures of new learning, retrograde amnesia and subjective memory impairment carried out at least 24 hours after a treatment.

If there is evidence of significant cognitive impairment at any stage consider, in discussion with the person with depression, changing from bilateral to unilateral electrode placement, reducing the stimulus dose or stopping treatment depending on the balance of risks and benefits.

1.10.4.10 If a person's depression has responded to a course of ECT, antidepressant medication should be started or continued to prevent relapse. Consider lithium augmentation of antidepressants.

Royal College of Psychiatrists' Position Statement on ECT for Depression

The Royal College of Psychiatrists similarly holds that ECT is a well-established and safe treatment option for depressed patients who have an inadequate response to, or poor tolerability of, antidepressant treatment. The College concurs with NICE's recommendations for consent and monitoring of ECT. The position statement broadly agrees with NICE's recommendations but is more robust in its recommendations regarding the elderly, more explicit on the place of ECT in management and more up to date regarding the evidence on cognitive side effects. The evidence supporting these assertions is outlined in Chapter 3. Whilst the current evidence base for ECT in depression is not sufficiently detailed to allow certainty about the sequencing of ECT within a patient's management plan, it is sufficiently robust to be confident about efficacy in the clinical situations outlined below. The Committee's position statement recommends:

ECT as a first-line treatment for patients (including the elderly):

- where a rapid definitive response for the emergency treatment of depression is needed
- with high suicidal risk
- with severe psychomotor retardation and associated problems of compromised eating and drinking and/or physical deterioration
- who suffer from treatment-resistant depression that has responded to ECT in a previous episode of illness
- who are pregnant with severe depression and whose physical health or that of the foetus is at serious risk
- who prefer this form of treatment.

ECT as a second-line treatment for patients (including the elderly):

- with treatment-resistant depression
- who experience severe side-effects from medication

- whose medical or psychiatric condition, in spite of other treatments, has deteriorated to an extent that raises concern.

Chapter 3 reviews the evidence about ECT in the treatment of unipolar depression.

Bipolar Disorder

Mania

The NICE Technology Appraisal Guidance on the Use of Electroconvulsive Therapy (ECT) (TA59) was first published in 2003. It was updated in 2009 (NICE, 2009) and, in 2014, NICE decided there was no new evidence which met NICE standards and left the appraisal unchanged. Recommendation 1.1 of TA59 states that it is recommended that electroconvulsive therapy (ECT) is used only to achieve rapid and short-term improvement of severe symptoms after an adequate trial of other treatment options has proven ineffective and/or when the condition is considered to be potentially life-threatening, in individuals with a prolonged or severe manic episode.

The NICE clinical guideline on bipolar disorder (CG185; NICE, 2014) makes no changes to the recommendation of TA59 except to advise stopping or reducing lithium or benzodiazepines before giving ECT, monitoring the length of fits carefully if the patient is taking anticonvulsants and monitoring mental state carefully for evidence of switching to the opposite pole.

The Royal College of Psychiatrists' position statement concurs with this and indicates that ECT should be a second line treatment for those patients with persistent or life-threatening symptoms in severe or prolonged mania.

Bipolar Depression

The NICE clinical guideline on bipolar disorder (CG185; NICE, 2014) made no recommendations about the use of ECT in bipolar depression. However, more recently, a randomised controlled trial (RCT) from Norway showed improved outcomes when patients with treatment-resistant bipolar depression who had failed to respond to antidepressants were given a course of unilateral ECT (Schoeyen *et al.*, 2015). The Committee's position statement reflects this new evidence and states that ECT should be considered in some circumstances for patients with bipolar depression.

Chapters 4 and 5 review the evidence about ECT in the treatment of the various phases of bipolar disorder.

Schizophrenia

Recommendation 1.9 of the NICE Technology Appraisal Guidance on the Use of Electroconvulsive Therapy (TA59; NICE, 2009) states that 'The current state of the evidence does not allow the general use of ECT in the management of schizophrenia to be recommended' and the Committee's position statement concurs with that view. However it may have a place in the management of some patients. A recent systematic review and meta-analysis assessed the proportion of patients with Treatment Resistant Schizophrenia (TRS) that responded to ECT augmentation of clozapine and concluded that ECT may be an effective and safe augmentation strategy in TRS. A higher number of ECT treatments may be required than is standard for other clinical indications (Lally *et al.*, 2016). In the light of

this the position statement indicates that ECT should be considered in some circumstances for patients with TRS.

Catatonia

Recommendation 1.1 of the NICE Technology Appraisal Guidance on the Use of Electroconvulsive Therapy (TA59; NICE, 2009) recommends that ECT is used only to achieve rapid and short-term improvement of severe symptoms after an adequate trial of other treatment options has proven ineffective and/or when the condition is considered to be potentially life-threatening in individuals with catatonia. NICE also states (recommendation 1.7) that:

> A repeat course of ECT should be considered under the circumstances indicated in 1.1 only for individuals who have catatonia or mania and who have previously responded well to ECT. In patients who are experiencing an acute episode but have not previously responded, a repeat trial of ECT should be undertaken only after all other options have been considered and following discussion of the risks and benefits with the individual and/or where appropriate their carer/advocate.
>
> (NICE TA59, 1.7, 2009)

The College's position statement is more robust and states that ECT may be considered as a first line treatment in life threatening catatonia and that it is effective in less severe cases of catatonia that have not responded to medication, where it is a second line treatment.

Chapters 10 and 11 review the evidence about ECT in the treatment of schizophrenia and catatonia.

Severe mental illness in pregnancy and the puerperium

In 2014 the NICE Guidelines for antenatal and postnatal mental health were published (CG192; NICE, 2014). It was recommended that ECT be considered for pregnant women with severe depression, severe mixed affective states or mania, or catatonia, whose physical health or that of the foetus was at serious risk. The Guideline stated that if a pregnant woman with bipolar disorder developed mania while taking prophylactic medication, the dose of the prophylactic medication and adherence should be checked, the dose increased if the prophylactic medication was an antipsychotic and the medication changed to an antipsychotic if she was taking another type of prophylactic medication. If there was no response and the woman had severe mania, lithium should be considered and then ECT considered if there was no response to lithium.

Anderson and Reti (2009) reviewed the use of ECT in pregnancy in 339 published cases. They reported at least partial response of depressive symptoms in 84% of cases and concluded that the risks to foetus and mother are low. There is evidence that depression may respond better to ECT in the post-natal period than in other circumstances, with more rapid and complete remission of mood and psychotic symptoms (Reed *et al.*, 1999). These observations led the Committee to indicate in its position statement that ECT should be used as first line treatment in women who are pregnant with severe depression, or severe mixed affective states, mania or catatonia and whose physical health or that of the foetus is at serious risk. ECT should be considered in some circumstances for those women with post-natal psychosis.

Chapter 8 reviews the evidence about ECT in the treatment of severe mental illness in pregnancy and in the puerperium.

Transcranial Magnetic Stimulation

Transcranial Magnetic Stimulation (TMS) is a non-invasive technique used to stimulate neuronal tissue. This technique involves placement of an electromagnetic coil to deliver a rapidly changing magnetic field which alters the electrical properties of the cortical neurons. Repetitive Transcranial Magnetic Stimulation (rTMS) is a relatively new treatment modality for psychiatric disorders where the stimulus train is repeated at pre-set intervals.

The most recent NICE interventional procedure guidance (IPG542; NICE, 2015) on rTMS for depression recommends that rTMS may be used for depression with normal arrangements for clinical governance and audit. It states:

- The evidence on repetitive transcranial magnetic stimulation for depression shows no major safety concerns. The evidence on its efficacy in the short term is adequate, although the clinical response is variable. Repetitive Transcranial Magnetic Stimulation for depression may be used with normal arrangements for clinical governance and audit.
- During the consent process, clinicians should, in particular, inform patients about the other treatment options available, and make sure that patients understand the possibility the procedure may not give them benefit.

NICE recommends rTMS for the treatment of depression but the evidence cited in the IPG comes from RCTs and meta-analyses of patients with both primary depressive disorder and treatment resistant depression (TRD). The Committee's position statement therefore opined that rTMS could also be considered in patients with TRD and in those with severe depression who do not want to consider, or have contraindications to, the use of ECT. However it was noted that a meta-analysis (Slotema *et al.*, 2010) found that rTMS was not as effective as ECT. This was confirmed in a subsequent meta-analysis by Chen and colleagues although they also found that TMS was better tolerated than ECT (Chen *et al.*, 2017). Hence it should not be considered as a replacement for ECT unless acceptability or tolerability issues dictate this. It was also pointed out that while there are no contraindications for concomitant use of rTMS and neurotropic medications, clinicians should be aware of medications which reduce seizure threshold as there may be a theoretical risk of inducing seizure during stimulation for these patients. Most studies of rTMS involve working age adults hence there is limited safety and efficacy data in child and adolescent populations and pregnant women. The position statement concluded that there should be a protocol in place in each treatment unit which is approved by the local trust governance process. There should also be procedures and policies to ensure the smooth running of the unit and a clear role and responsibility for prescribing clinicians and treating clinicians should be established. A qualified nurse with adequate training and competencies can administer the rTMS and monitor for side-effects during the treatment. They can also assess the patients' progress using appropriate rating scales. The College will look to develop a national training programme for TMS practitioners which will include assessment of competencies and accreditation for rTMS centres along similar lines to ECTAS accreditation.

Chapter 15 reviews the evidence about rTMS in the treatment of depression and outlines the training required for practitioners who wish to deliver rTMS.

Ketamine

There are currently no NICE recommendations on the use of ketamine infusions for the management of depression. Despite clinical trials showing rapid improvement in mood after ketamine infusion, there are still significant gaps in our knowledge about dosage levels, treatment protocols and the effectiveness and safety of long-term use (see Chapter 17). Before ketamine can be recommended for use in clinical practice, extensive research is required to understand how to optimally use ketamine for treating depression. The Royal College of Psychiatrists has concerns for patient safety and hence recommends mental health practitioners to proceed with caution when treating patients with ketamine.

Ketamine is currently approved as an anaesthetic drug by the Medicines and Healthcare Products Regulatory Agency (MHRA) but is not currently approved for use in treating depression.

The antidepressant properties of ketamine were first described over a decade ago (Berman *et al.*, 2000). Since then, ketamine administration has been assessed in treatment of resistant depression, bipolar depression and in ECT induction. Supportive evidence showing rapid antidepressant effect of ketamine has encouraged some clinicians to use 'off label' ketamine in treating patients with depression.

Research investigating the antidepressant effects of ketamine has consistently reported rapid and robust improvement in suicidal depressive symptoms in patients with bipolar disorder. Significant reduction is also seen in depressive symptoms in patients suffering from treatment resistant depression (McGirr *et al.*, 2015). However, most researchers have measured the effects of ketamine for only 72 hours after infusion although there have been a few studies that have shown persistence of the effect for 15–28 days (Singh *et al.*, 2016; Hu *et al.*, 2016). Therefore information about the long-term effects of ketamine prescribed in patients with depression is limited. There is also limited information on ketamine dose-response relationship and the optimal mode of administration (Katalinic *et al.*, 2013).

In the absence of a strong evidence base, there are risks associated with treating depression with ketamine at this stage. Use of low dose ketamine (up to 0.5mg/kg) can produce a variety of psychotomimetic, cognitive or physical adverse effects.

The most common physical adverse effects of ketamine are dizziness, blurred vision, headache, nausea or vomiting, dry mouth, poor coordination, poor concentration and restlessness. These effects have mostly been restricted to the time of administration, usually resolving within 60 minutes. In some studies participants reported transient elevation in blood pressure and heart rate during the period of ketamine infusion and the effect lasted for 80 minutes after dosing. Additionally, ketamine is known for producing psychotomimetic effects, such as hallucinatory behaviour, suspiciousness/paranoia, disorganised thought, unusual thought, blunted affect and emotional withdrawal. There is no clear evidence showing long-term psychotomimetic effect of ketamine when used in repeated doses in depression treatment. Hepatotoxicity and bladder dysfunction have been reported after repeated use of ketamine (Katalinic *et al.*, 2013).

In the light of the above information (which is discussed in further detail in Chapter 17), the Committee's position statement recommended that:

- The use of ketamine for the treatment of depression is considered a novel treatment.
- Ketamine should be used under research trial conditions that include oversight by an institutional research or clinical ethics committee and careful monitoring and reporting of outcomes.

- For persons with treatment resistant depression who are not participating in a research trial but are able and willing to consent to treatment with ketamine, the treating psychiatrist should consider such treatment as a novel or innovative treatment, which should include discussion with peers (preferably including a second opinion) and institutional review by the relevant NHS Trust Drugs and Therapeutic Committee or its equivalent.
- People considering ketamine as a treatment and their carers should be provided with clear information and an explanation that this is a novel treatment. This should include a detailed explanation of the current evidence and potential risks, and be documented in the clinical notes.
- Ketamine treatment for depression occurring outside formal research studies should be collated across centres using a regular mood monitoring framework.
- Practice outside these recommendations should not occur.

Further information on ketamine can be found in Chapter 17. Its use in anaesthesia for ECT is considered in Chapter 23.

Transcranial Direct Current Stimulation

Transcranial direct current stimulation (tDCS) is a novel neuro-modulatory treatment modality for depression and represents a potential alternative to existing pharmacological/psychological treatment options. tDCS is a non-invasive brain stimulation modality, which changes cortical tissue 'excitability' as a result of applying a weak (0.5–2mA) direct current via scalp electrodes overlying targeted cortical areas. In contrast to other neurostimulation modalities, tDCS does not directly trigger action potentials in neuronal cells, but instead changes overall tissue excitability, and therefore may be more aptly regarded as a 'neuro-modulatory' rather than a neuro-stimulatory approach.

In 2015, NICE made the following recommendations in its interventional procedure guidance on tDCS for depression (IPG 530; NICE, 2015):

1. The evidence on tDCS for depression raises no major safety concerns. There is evidence of efficacy but there are uncertainties about the specific mode of administration, the number of treatments needed and the duration of effect. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research.
2. Clinicians wishing to do tDCS for depression should inform the clinical governance leads in their NHS trusts, and ensure that patients understand the uncertainty about the procedure's efficacy and provide them with clear written information – the use of information for the public published by NICE is recommended: www.nice.org.uk/guidance/IPG530/InformationForPublic.
3. Audit and review is recommended of clinical outcomes of all patients having tDCS for depression (NICE developed an audit tool: www.nice.org.uk/Guidance/IPG530/Resources).

A meta-analysis of tDCS for the treatment of major depressive episodes identified 10 RCTs (n = 393) of tDCS, either as monotherapy or as adjunctive treatment alongside antidepressant medication and/or Cognitive Control Training (CCT) (Meron *et al.*, 2015). tDCS was superior to sham tDCS. Adjunctive antidepressant medication and cognitive control training negatively impacted on the treatment effect. However, the pooled log odds

ratios (LOR) for response and remission were statistically non-significant. There were no statistically significant differences in the dropout rates due to adverse effects between the active and sham tDCS treatment groups.

Based on this evidence, the following conclusions were drawn in the Committee's position statement in 2016:

1. tDCS may represent an effective treatment option for patients presenting with major depressive episodes.
2. tDCS offers a generally acceptable tolerability profile, which may make it a useful alternative to antidepressant medication in patients who do not wish to take medication and for those who cannot tolerate antidepressant medication.
3. The current body of evidence does not support the use of tDCS in treatment resistant depression.
4. The current body of evidence does not support the use of tDCS as an add-on augmentation treatment for depressed patients who are already taking an antidepressant or undergoing cognitive control training.
5. Further research is needed, in particular, involving larger sample sizes over longer periods of treatment.

However two large randomised clinical trials have recently presented results showing either modest or negative tDCS efficacy (Brunoni *et al.*, 2017; Loo *et al.*, 2018) and a recent systematic review concluded that robust efficacy has not been consistently demonstrated (Borrione *et al.*, 2018). tDCS is not discussed further in this Handbook due to the early stage of the research and associated uncertainty. For further details, please refer to the referenced NICE guideline and the cited 2018 systematic review.

Neurosurgery for Mental Disorder

The College position statement on neurosurgery for mental disorder (NMD) is that, for carefully selected patients, with difficulties in specific symptom domains – specifically those with Depressive Disorders and Obsessive Compulsive Disorders – neurosurgical therapies may reasonably be considered. In each individual case, consideration of the appropriateness of offering any form of NMD must balance the risks and benefits of surgery with the risks and benefits of continuing with 'treatment as usual' and should also acknowledge patient preference.

The evidence base to support this College position is derived from an accumulated literature comprising open case series evaluations, some of prolonged duration and high quality. There is limited evidence from randomized, controlled trials, but this is available for some lesion surgical approaches and for deep brain stimulation (DBS) for obsessive compulsive disorder (OCD).

The position statement set out the core principles for ethical, safe and effective NMD. These are:

1. NMD procedures must only ever be performed with a specific therapeutic intention, i.e. for symptom relief and restoration of function.
2. NMD provision (lesion procedures **and** invasive stimulation methods) should be subject to ethical and clinical governance oversight by an independent body. Special attention must be paid to the processes of patient advocacy, the assessment of capacity and the nature of informed consent.

3. NMD should only be provided by neurosurgeons familiar in functional stereotactic surgery within specialist centres, and the clinical programme should be led by experienced psychiatrists with relevant expertise in the target disorders.
4. All patients who are considered as candidates for NMD must be informed that neurosurgery is only one component of a more comprehensive psychiatric management plan that will also include attention to wider aspects of psychological, social and occupational functioning.
5. Relevant mental health legislation (there are regional variations within the UK) must be adhered to.
6. Candidates for all forms of NMD (including lesion procedures and invasive stimulation methods) must be robustly evaluated by clinicians with specific expertise in the management of the target disorder and confirmed to meet consensus criteria with respect to the severity and refractoriness of the presenting condition.
7. Patient selection procedures and any discussions about possible NMD should be conducted by experienced multidisciplinary teams with close working between – as a minimum – stereotactic and functional neurosurgeons, psychiatrists, mental health nurses and expert psychological therapists. Where DBS is the surgical method proposed, this must also involve neurologists and specialist nurses familiar with the management of DBS systems and their programming.
8. Comprehensive pre- and post-operative evaluation – with specific attention to disorder-specific symptom outcomes, cognition, social and interpersonal functioning and health-related quality of life measures – must take place, with an identified mechanism for reporting the immediate and longer-term outcomes within a robust clinical governance structure.
9. Post-operative care plans should be developed collaboratively, should cover a period of at least 12 months, and should include the full participation of locality mental health services. Surgery should not take place unless a detailed, collaborative, patient-centred post-operative care plan has been agreed.

The position statements on individual NMD treatments are briefly set out below. Further details are available in Chapter 16.

Ablative neurosurgery (the creation of small targeted lesions by focal applications of radiofrequency induced heat, by radiation or by ultrasound) is the form of NMD with the strongest evidence base and longest reported follow-up. In particular, this relates to the two procedures most commonly offered as treatments for patients with otherwise refractory and disabling depression and OCD – anterior cingulotomy and anterior capsulotomy. Both procedures have been considered as representing acceptable, safe and effective established clinical practice in the UK for many years, including following review by independent, multidisciplinary, expert groups. The position statement takes the view that the delivery of safe and effective ablative NMD – subject to the general caveats above – represents an important element of the ethical and optimised management of patients with chronic, otherwise treatment refractory depression and OCD. There is currently no compelling evidence to support ablative NMD for any other psychiatric indication.

DBS is a surgical approach whereby deep structures of the brain can be directly stimulated electrically using permanently implanted electrodes and an externally programmed, implantable pulse generator. Recent pivotal blinded controlled comparisons of active DBS with sham stimulation have failed to demonstrate efficacy for the two most