NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of transcranial direct current stimulation (tDCS) for depression

Depression causes low mood or sadness that can last for weeks or months. People with depression often feel hopeless and lose interest in things they used to enjoy. Other symptoms include sleeping badly, and having no appetite or sex drive. Transcranial direct current stimulation aims to treat depression by applying a very weak electric current to the head using electrodes placed on the scalp.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this interventional procedure (IP) overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This IP overview was prepared in October 2014 and updated in June 2015.

Procedure name

- Transcranial direct current stimulation for depression

Specialist societies

- Royal College of Psychiatrists.

Description

Indications and current treatment

Depression is a common disorder, characterised by persistent sadness, loss of interest or pleasure, feelings of guilt, low self-worth, tiredness, poor concentration, and disturbed sleep, appetite and libido. It is often accompanied by feelings of hopelessness and suicidal thoughts. Depression can last from weeks to years, and can be recurrent. It can substantially impair a person's ability to function at work or cope with daily life.

Treatments for depression include a range of psychological therapies, and antidepressant medications. In severe depression that has not responded to other treatments, electroconvulsive therapy is sometimes used.

What the procedure involves

Transcranial direct current stimulation (tDCS) is a non-invasive method of electrical stimulation of the brain using a weak direct current applied to the scalp through electrodes. The aim is to modify cortical excitability and activity in the brain areas under the scalp electrodes. It is thought to work by the depolarisation and hyperpolarisation of cortical neurons. The patient, who remains awake and alert during the procedure, is usually seated while a portable battery-operated stimulator delivers a constant low-strength direct current to 2 saline-soaked sponge electrodes placed on the scalp. Treatment sessions typically last for about 20–30 minutes, and are repeated daily for several weeks. Treatment is usually delivered by a trained clinician, but it can also be self-administered by the patient. tDCS may be used alone or in addition to other treatments for depression.

Outcome measures

There are several scales used to measure depression severity. The Montgomery–Åsberg Depression Rating Scale (MADRS) measures 10 items (including apparent sadness, reported sadness and suicidal thoughts) on a scale of 0 to 6 with low values indicating less depression. The Hamilton Depression Rating Scale (HDRS) uses a semi-structured interview to assess a number of variables (including depressed mood, insomnia, agitation, anxiety and weight loss) measured on 5-point or 3-point scales, with low values indicating less depression.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to transcranial direct current stimulation (tDCS) for depression. The following databases were searched, covering the period from their start to 4 March 2015: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with depression.
Intervention/test	Transcranial direct current stimulation (tDCS).
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on about 2000 patients included in 2 systematic reviews and meta-analyses[1,2], 1 randomised controlled trial (RCT)[3], 1 open-label follow-up study[4], 2 case series[5,6] and 1 case report[7].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on transcranial direct current stimulation (tDCS) for depression

Study 1 Shiozawa P (2014)

Details

Study type	**Systematic review and meta-analysis**
Country	Not reported
Recruitment period	Search from 2006 (first RCT) to 31/01/2014
Study population and number	n=**259** (137 active tDCS versus 122 sham tDCS) patients with a moderate degree of treatment-resistant depression (7 studies) were included in the main analysis.
Age and sex	Mean 44 years; 58% female
Patient selection criteria	Randomised sham-controlled trials, articles written in English, Spanish or Portuguese, studies providing data for depression scores and response remission rates. Exclusion criteria: case reports, case series, non-controlled trials and trials assessing other conditions than major depression disorders or other interventions than tDCS.
Technique	• One or 2 mA direct current was applied over the scalp for 20–30 minutes. Current density (electric current/electrode surface area) varied between 0.28–0.57 A/m2. All studies positioned the anode over the left DLPFC-F3 area, according to the EEG 10/20 system. Cathode was positioned either in contralateral cortex (F4) or over the right supraorbital area. • Sham tDCS was done using a procedure in which a simulated session was preceded by a brief active simulation period of about 5–60 s.
Follow-up	**Not reported**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: None.

Study design issues:

- All studies reported that raters were blinded to the treatment applied.
- One study (Boggio 2008) randomised patients into 3 groups: active tDCS over the left DLPFC, active tDCS over the occipital stimulation and sham tDCS. The authors decided not to include the occipital stimulation group in the analysis because it was either included in the active group or the control group in previous meta-analyses.
- For the Brunoni study (2013), 2 separate datasets (Brunoni-group and Brunoni-factor) were considered in 2 different analyses since a factorial design was used in this study, randomising patients to 4 groups (sham tDCS/placebo, sham tDCS/sertraline, active tDCS/placebo and active tDCS/sertraline). In the main analysis (Brunoni-group), active tDCS/placebo was compared with sham tDCS/placebo. In another analysis (Brunoni-factor), active tDCS (active tDCS/placebo and active tDCS/sertraline) was compared with sham tDCS (sham tDCS/placebo and sham tDCS/sertraline).
- Both continuous and categorical measures analysed.

Study population issues:

- Heterogeneity between studies not significant (I^2=35.3% and p=0.15 for the χ^2 test).
- Risk of publication bias not significant.
- No predictors of response identified.
- All studies allowed the concomitant use of other psychotropic drugs than antidepressants (including benzodiazepines).
- The number of tDCS sessions varied from 5–15.
- tDCS was either used as an add-on therapy to pharmacotherapy (77 active tDCS versus 73 sham tDCS) or as monotherapy in antidepressant-free samples (60 active tDCS versus 49 sham tDCS).

Other issues: This meta-analysis included all the studies from the Berlim (2012) and Kalu (2012) meta-analyses (see Appendix A).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **259 (137 versus 122) although this varies for each outcome from 7 studies**

Improvement in depressive symptoms (based on the change in depression scores using Hedges' g as the measure of the effect size in order to standardise across studies using different depression scales. Hedges' g is calculated from the pooled mean difference between groups divided by the standard deviation, with an adjustment for small sample sizes).

- Active tDCS was significantly superior to sham tDCS:
    - small to medium effect size
    - Hedges' g=0.37; 95% CI 0.04 to 0.7 when the 'Brunoni-group' dataset was used in the pooled analysis (see study design issues).
    - Hedges' g=0.40; 95% CI 0.07 to 0.73 when the 'Brunoni-factor' dataset was used in the pooled analysis (see study design issues).

Treatment response rates (defined as a >50% improvement in depression scores from baseline to end point)

- Active tDCS was significantly superior to sham tDCS:
- OR 1.63, 95% CI 1.26 to 2.12 when the 'Brunoni-group' dataset was used
- OR 1.66, 95% CI 1.32 to 2.10 when the 'Brunoni-factor' dataset was used.

Remission rates (absence of clinically relevant symptoms)

- Active tDCS was significantly superior to sham tDCS:
- OR 2.5, 95% CI 1.26 to 4.99 when the 'Brunoni-group' dataset was used
- OR 2.5, 95% CI 1.2 to 5.08 when the 'Brunoni-factor' dataset was used.

Acceptability of the treatment

- Active tDCS: 8% (12/137) of patients dropped out of studies
- Sham tDCS: 11% (15/122) of patients dropped out of studies

No difference in acceptability: OR 0.73 (95% CI 0.32 to 1.69).

Association between days of stimulation and the effect size

- ≤10 days: Hedges' g=0.37 95% CI 0.22 to 0.96
- >10 days: Hedges' g=0.42 95% CI 0.07 to 0.77
  p=0.09

Longer periods of stimulation might be associated with a larger antidepressant response.

Association between total current electric charge and the effect size

- Association not significant (p=0.09)
- A trend was observed for higher current charges determining larger antidepressant effects.

No safety events reported.

Abbreviations used: CI, confidence interval; DLPFC, left dorsolateral prefrontal cortex; EEG, electroencephalogram; OR, odds ratio; RCT, randomised controlled trial.

Study 2 Brunoni AR (2011)

Details

Study type	**Systematic review and meta-analysis of safety events**
Country	International
Recruitment period	Search from 1998 to August 2010
Study population and number	n=3836 participants from 209 studies were included in their initial assessment. Of these, **n=1851** participants were included in the 117 studies that had assessed adverse events.
Age and sex	Of the 1851 participants who were in studies where adverse events were assessed, mean age was 35.3 years; 50% female
Patient selection criteria	Articles written in English and original articles that reported tDCS effects in humans. Exclusion criteria: animal studies, review articles, articles reporting duplicate data or data extracted from original articles, articles addressing only the effects of other brain stimulation techniques such as alternating current stimulation or transcranial magnetic stimulation.
Technique	Sham tDCS: the initial fade-in phase was induced (the current was increased in order to reach the targeted dose) and the device was turned off after 30–60 s.
Follow-up	**Not reported.**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: None

Study design issues:

- Systematic review conducted according to the recommendations of the Cochrane adverse effects method group.
- No studies were discarded based on risk bias and separate analyses according to study quality were undertaken to identify adverse effects related with tDCS
- The meta-analysis was performed using a random-effects model for the pooling model.

Study population issues:

- Both healthy and non-healthy participants were included in the systematic review.
- Meta-analysis conducted with non-healthy participants reporting itching. It included patients with major depression, fibromyalgia, spinal cord injury pain, nicotine dependence, alcohol dependence, binge-eating disorder or chronic pain. Patients with major depression were only present in 2 studies (out of 8).

Other issues: None.

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 1851 from 117 studies reporting some adverse events.

Meta-analysis performed on 8 studies with low risk of bias and adequate data reporting.

No efficacy outcomes reported.</td><td>Frequency of adverse events (% of studies)
<table>
<tr><td>Adverse event*</td><td>Active tDCS group (117 studies)</td><td>Sham tDCS group (82 studies)</td><td>p value</td></tr>
<tr><td>Itching</td><td>39% (46/117)</td><td>33% (27/82)</td><td>NS</td></tr>
<tr><td>Tingling</td><td>22% (26/117)</td><td>18% (15/82)</td><td>NS</td></tr>
<tr><td>Headache</td><td>15% (17/117)</td><td>16% (13/82)</td><td>NS</td></tr>
<tr><td>Burning</td><td>9% (10/117)</td><td>10% (8/82)</td><td>NS</td></tr>
<tr><td>Discomfort</td><td>10% (12/117)</td><td>13% (11/82)</td><td>NS</td></tr>
</table>
*The presence of an adverse event was considered if the study reported its occurrence in at least 1 patient.
Itching (active tDCS versus sham tDCS)
OR 1.06, 95% CI 0.62 to 1.8 (fixed-effect model).
OR 0.95, 95 % CI 0.28 to 3.94 (random-effect model).
Heterogeneity was significant (I^2=65%, p=0.02 in the $\chi 2$ test).
In the funnel plot: all studies except 2 exceeded the limits of the graph.
Publication bias: Egger’s test was not significant (p=0.4) but further, sensitivity analyses showed a wide variation of results when each study was excluded 1 at a time.</td></tr>
<tr><td colspan="2">Abbreviations used: CI, confidence interval; NS, not significant; OR, odds ratio.</td></tr>
</table>

Study 3 Brunoni AR (2013) − *Study included in the Shiozawa (2014) meta-analysis.*

Details

Study type	**RCT double-blind (phase 1 of the SELECT-tDCS study)**
Country	Brazil
Recruitment period	2010–11
Study population and number	n=**120 (30 active tDCS and placebo versus 30 active tDCS and sertraline versus 30 sham tDCS and placebo versus 30 sham tDCS and sertraline)** with moderate to severe, nonpsychotic, unipolar MDD.
Age and sex	Mean 42 years; 68% (82/120) female
Patient selection criteria	Patients with unipolar, nonpsychotic MDD, with a 17-item Hamilton Depression Rating Scale score greater than 17, with low risk of suicide and aged between 18–65 years old. Exclusion criteria: other Axis I disorders including alcohol or substance harmful use or dependence (although patients with anxiety disorders as a comorbidity were allowed), any Axis II disorders, previous neurological conditions (epilepsy, traumatic brain injury, stroke), any severe, life threatening Axis III disorders and specific contraindications for tDCS (such as metallic plates in the head). Patients using or who had used sertraline in the current depressive episode were excluded but those who had used sertraline in past episodes were not necessarily excluded.
Technique	Active tDCS: 6-week treatment of 2-mA anodal left/cathodal right prefrontal tDCS (12 30-minute sessions: 10 consecutive sessions once daily from Monday to Friday plus 2 extra sessions every other week). Two certified nurses administered the tDCS intervention. Sham tDCS: the device was turned off after 1 minute of active stimulation, mimicking the common adverse effects of mild scratching and discomfort that are experienced immediately after stimulation onset. Sertraline hydrochloride: 50 mg/day Placebo pills had the same size, colour and taste as the active drug. All subjects were free of antidepressant, antipsychotic, and anticonvulsant medications for at least 5 half-lives of the drug before study onset. Benzodiazepines were tolerated but tapered to a maximum of 20 mg/day diazepam (or equivalent). Both interventions were started simultaneously on the first day of treatment.
Follow-up	**4 weeks after the 10-session treatment**
Conflict of interest/source of funding	None

Analysis

Follow-up issues:

- The patients were allowed 2 non-consecutive missed visits; in such cases, extra tDCS sessions were performed to complete the total number of sessions.
- 7.5% (9/120) dropped out within the first 2 weeks and 86% (103/120) of patients completed the entire trial.
- Dropouts were balanced between groups. The reasons for dropouts were manic switch (n=2, combined treatment group), suicidal ideation (n=1, placebo; n=1, tDCS only), more than 2 missing visits within the first 2 weeks (n=2, placebo; n=3, sertraline only; n=1, tDCS only), and other reasons.

Study design issues:

- Randomisation using a 2x2 factorial design.
- A research assistant not directly involved in other aspects of the trial performed a 1:1:1:1 permuted block randomisation, and the allocation was concealed using a central randomization method.
- The raters and patients were blinded to the treatment, and contact between participants was avoided to enhance study blinding.
- Intention-to-treat analysis.
- Safety was measured with an adverse effects questionnaire, the Young mania rating scale, and cognitive assessment.

- This study comprised 3 phases: the RCT, an open-label, crossover phase in which sham tDCS non-responders received 10-day active tDCS and a 6-month follow-up phase in which tDCS responders had maintenance tDCS alone or combined with sertraline if they were in the combined treatment group (see Valiengo 2013 in Table 2).
- Pharmacological adherence was assessed by pill count (an acceptable level of adherence was considered if less than 10% of the pills were returned).

Study population issues:

- In the patient population, the prevalence of hypertension was 22.5%, the prevalence of hypothyroidism was 13%, and 17.5% were current smokers.
- The sample had, on average, low treatment resistance (56% of patients had 0 or 1 failed treatment and only 22% had >2 failed episodes), with a median index episode duration of 12 weeks (interquartile range, 5–20 weeks) and a median of 3 past depressive episodes (interquartile range, 2–5 episodes).
- The washout had a mean duration of 18 days.
- 19% (23/120) of patients were using benzodiazepines (mean dosage, 13.4 mg/day diazepam equivalent).

Other issues: None

Key efficacy and safety findings

Efficacy

Number of patients analysed: n=**120 (30 active tDCS/placebo versus 30 active tDCS/sertraline versus 30 sham tDCS/placebo versus 30 sham tDCS/sertraline)**

Improvement in depressive symptoms (MADRS scores at different times)

	Baseline	**Week 2**		**Week 4**		**Week 6**	
Group or factor	**Mean (SD)**	**Mean (SD)**	**% (SD)***	**Mean (SD)**	**% (SD)***	**Mean (SD)**	**% (SD)***
Group							
Active tDCS and sertraline	30.73 (6.72)	15.53 (7.90)	−48.5 (23.5)	15.70 (7.98)	−47 (25.7)	13.17 (8.46)	−56 (27.3)
Active tDCS and placebo	30.76 (5.78)	20.53 (9.59)	−34 (26.8)	19.33 (10.41)	−38 (29.5)	19.07 (12.21)	−39.5 (34.2)
Sham tDCS and sertraline	30.50 (6.81)	22.10 (11.50)	−29 (30.1)	22.83 (11.03)	−25 (34.5)	21.67 (13.14)	−30 (36.7)
Sham tDCS and placebo	30.76 (5.31)	21.37 (10.06)	−30 (30.7)	22.56 (9.50)	−24 (36.1)	24.73 (8.65)	−18 (29.0)
p value**	0.99	0.01		0.01		<0.001	
Factor							
No tDCS	30.63 (6.10)	21.73 (10.71)	−30 (30.9)	22.70 (10.21)	−25 (34.8)	23.20 (11.14)	−24 (33.3)
tDCS	30.75 (6.22)	18.03 (9.02)	−41 (25.6)	17.52 (9.38)	−42 (27.9)	16.11 (10.83)	−48 (31.7)
p value**	0.91	0.04		0.003		0.001	
No sertraline	30.76 (5.51)	20.95 (9.70)	−32 (28.6)	20.95 (10.02)	−31 (33.3)	21.90 (10.88)	−29 (33.3)
Sertraline	30.61 (6.71)	18.81 (10.32)	−39 (28.6)	19.27 (10.20)	−36 (32.5)	17.14 (11.77)	−43 (34.8)
p value**	0.89	0.25		0.36		0.03	

*****Percentage represents percentage of change, calculated as (score at period − score at baseline)/score at baseline.

**p values represent results for the mixed-model analysis of variance time × group interaction (for the main analysis) or time × tDCS and time × sertraline interaction (for the factorial analysis) at each week.

Differences in MADRS scores between treatments after 6 weeks

Treatments compared	**Mean difference (points)**	**95% CI**	**p value**
Active tDCS and sertraline versus sham tDCS and placebo	11.5	6.03 to 17.10	<0.001
Active tDCS and sertraline versus active tDCS and placebo	5.9	0.36 to 11.43	0.03
Active tDCS and sertraline versus sham tDCS and sertraline	8.5	2.96 to 14.03	0.002
Active tDCS and placebo versus sham tDCS and sertraline	2.6	-2.90 to 8.13	0.35
Sham tDCS and sertraline versus sham tDCS and placebo	2.9	-1.50 to 7.10	0.202
Active tDCS and placebo versus sham tDCS and placebo	5.6	1.30 to 10.01	0.01
tDCS versus no tDCS***	7.08	3.16 to 11.01	<0.001
Sertraline versus no sertraline***	4.48	0.57 to 8.39	0.02

Safety

Skin redness after 2 weeks:

- Active tDCS: 25% (13)
- Sham tDCS: 8% (4, p=0.03)

5 episodes of hypomania (Young mania rating scale score >8) and 2 episodes of clinical mania occurred: 5 (including 2 manic episodes) in combined treatment, 1 in tDCS only and 1 in sertraline only.

The frequency of adverse effects did not differ per group (p=0.17, Fisher's exact test).

tDCS had no hazardous cognitive effects (either no change or improvement in cognitive performance was observed between baseline and endpoint).

***Factorial analysis

Factorial analysis

- Interaction between tDCS and sertraline not significant ($F_{116,1}$=0.51; p=0.48)
- Main effect for tDCS significant ($F_{116,1}$= 12.85; p<0.001)
- Main effect for sertraline significant ($F_{116,1}$=5.15; p=0.02)
- Effects of tDCS and sertraline additive

Response rates according to MADRS scores[a]

	% of responders		
Groups	**Week 2**	**Week 4**	**Week 6**
Active tDCS and sertraline	53% (16/30)	53% (16/30)	63% (19/30)
Active tDCS and placebo	30% (9/30)	40% (12/30)	43% (13/30)
Sham tDCS and sertraline	33% (10/30)	27% (8/30)	33% (10/30)
Sham tDCS and placebo	37% (11/30)	30% (9/30)	17% (5/30)
p value	0.25	0.14	<0.001

[a]Response was defined as a score change greater than 50% from baseline. p values represent results for the logistic regression of time × group interaction.

- Significant difference in response rate for tDCS only versus placebo (43%; OR=8.6; 95% CI 2.5 to 29.1; p<0.001).

Significant difference in response rate for active tDCS and sertraline versus placebo (43%; OR=8.6; 95% CI 2.5 to 29.1; p<0.001).

- No significant association for sertraline only versus placebo (33%; OR=2.5; 95% CI 0.7 to 8.5; p=0.14).

Remission rates according to MADRS scores[b]

	% of responders		
Groups	**Week 2**	**Week 4**	**Week 6**
Active tDCS and sertraline	20% (6/30)	23% (7/30)	47% (14/30)
Active tDCS and placebo	13% (4/30)	23% (7/30)	40% (12/30)
Sham tDCS and sertraline	17% (5/30)	13% (4/30)	30% (9/30)
Sham tDCS and placebo	20% (6/30)	10% (3/30)	13% (4/30)
p value	0.89	0.40	0.03

[b]Remission was defined as a MADRS score of 10 or less. p values represent results for the logistic regression of time × group interaction.

- Significant difference in remission rate for tDCS only versus placebo (40%; OR=4.3; 95% CI 1.2 to 15.6; p=0.02)
- Significant difference in remission rate for active tDCS/sertraline versus placebo (47%; OR=5.7; 95% CI 1.6 to 20.3; p=0.007)
- No significant difference in remission rate for sertraline only versus placebo (30%; p=0.12)

Abbreviations used: CI, confidence interval; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, major depressive disorder; OR, odds ratio; RCT, randomised controlled trial; SD, standard deviation.

Study 4 Valiengo L (2013)

Details

Study type	**Naturalistic, open-label follow-up study (follow-up phase of the SELECT-tDCS study)**
Country	Brazil
Recruitment period	2010−2011
Study population and number	n=**42 patients from the SELECT-tDCS study**
Age and sex	Mean 43 years; 71% (30/42) female
Patient selection criteria	Responders who had active tDCS in either phase 1 (RCT) or 2 (cross-over phase) of the SELECT-tDCS study. Response was defined as either a >50% MADRS improvement or an end point MADRS <13.
Technique	The phase 2 sample was composed by non-responders who had sham tDCS in phase 1. These patients were treated by a 12-day course of active tDCS using the same parameters and montage of phase 1.Phase 3 (follow-up phase) was composed from all active-tDCS responders from phases 1 and 2. Patients were treated by tDCS every other week for 3 months (6 sessions), and thereafter once a month for the next 3 months. People taking placebo were maintained medication free throughout phases 2 and 3. Patients initially randomised tor sertraline were allowed to choose whether they wanted either to maintain the dose of 50 mg/day of sertraline or enter in the follow-up phase with no antidepressant therapy.
Follow-up	**24 weeks**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues:

- The follow-up was interrupted earlier if the patients had a relapse of depressive symptoms.
- There were 17 dropouts in the follow-up study. The main reasons were protocol violation (12% [2/17]); request to leave the study either for 'feeling better' or 'feeling worse' (24% [4/17]); and failure to return to the research centre (65% [11/17]).

Study design issues: Relapse was assessed by a Kaplan–Meier survival analysis.

Study population issues:

- 30 phase 1 tDCS responders and 12 tDCS responders from phase 2 were enrolled into phase 3.
- Phase 3 patients had a greater prevalence of melancholic depression and a lower prevalence of atypical depression as compared with phase 1 patients.
- 19% (8/42) of patients were using sertraline 50 mg/day in association with tDCS at the beginning of the follow-up phase.

Other issues: None.

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 42

Mean response duration: 11.7 weeks.

Relapse**
<table>
<tr><th>Length of treatment</th><th>Survival rate*</th><th>95% CI</th></tr>
<tr><td>12 weeks</td><td>60%</td><td>40–75%</td></tr>
<tr><td>24 weeks</td><td>47%</td><td>27–64%</td></tr>
</table>
*Kaplan–Meier survival analysis
**Relapse occurred if the patient presented with 2 consecutive MADRS>12, any MADRS>15, suicidal attempt, severe suicidal ideation or psychiatric hospitalisation.

• Number of patients who relapsed: 15; 80% (12/15) had a single MADRS score>15 and 20% (3/15) had 2 consecutive MADRS scores>12.
• None of the relapses were due to hospitalisation, suicidal ideation or suicidal attempt.
• Patients with treatment-resistant depression had a much lower 24-week survival rate than non-refractory patients: 10% versus 77%, OR 5.52; p<0.01.
• Of the 19% (8/42) of patients who were treated by sertraline and tDCS, 62.5% (5/8) finished the follow-up phase.</td><td>• Similar incidence of adverse effects was reported as in phase 1.

Adverse effects reported during phases 2 and 3
<table>
<tr><th>Adverse effect</th><th>% (n)</th></tr>
<tr><td>Itching</td><td>42 (18/42)</td></tr>
<tr><td>Skin redness</td><td>23 (10/42)</td></tr>
<tr><td>Headache</td><td>19 (8/42)</td></tr>
<tr><td>Somnolence</td><td>16 (7/42)</td></tr>
</table></td></tr>
<tr><td colspan="2">Abbreviations used: CI, confidence interval; MADRS, Montgomery–Åsberg Depression Rating Scale; OR, odds ratio; RCT, randomised controlled trial.</td></tr>
</table>

Study 5 Martin DM (2013)

Details

Study type	**Case series**
Country	Australia
Recruitment period	Not reported
Study population and number	n=**26 patients pooled from 2 studies with different tDCS protocols, who had responded to acute tDCS treatment.**
Age and sex	Mean 47 years; 58% (15/26) female
Patient selection criteria	Inclusion criteria: Responders to acute tDCS treatment (who had a 50% reduction in MADRS scores compared against baseline) were eligible to receive continuation tDCS. Before receiving the acute course of tDCS, all participants met DSM-IV criteria for an MDE and had a score of 20 or more on the MADRS. Exclusion criteria: drug or alcohol abuse or dependence, other Axis I disorders, neurological disorders, or failure to respond to electroconvulsive therapy in the current episode of depression.
Technique	The same form of tDCS treatment was given during the continuation treatment phase as had been administered during the acute treatment course. tDCS treatments were given continuously for 20 min at 2 mA using an Eldith DC-stimulator (Neuro- Conn GmbH, Germany). Patients pooled from the Loo (2012) study were treated by anodal tDCS administered over the left DLPFC and the cathode placed over F8. Patients polled from the Martin (2011) study were treated by anodal tDCS administered over the left DLPFC and the cathode placed over the upper right arm. Continuation tDCS was administered **weekly for the first 3 months** and **once per fortnight for the final 3 months**.
Follow-up	**6 months from the start of continuation tDCS**
Conflict of interest/source of funding	This study was supported by an Australian National Health and Medical Research Council (NHMRC) Project Grant. The NHMRC had no further role in study design, in the collection, analysis and interpretation of data, in the writing of the report, and in the decision to submit the paper for publication.

Analysis

Follow-up issues:

- Mood was assessed using the MADRS at 3 and 6 months.

Study design issues:

- 15% (4/26) of patients received 2 different courses of continuation tDCS, each 1 following a separate acute course of tDCS from the 2 different studies. Therefore, the final analysis included 30 courses of continuation tDCS.
- During each acute course, all participants were either medication free or remained on antidepressant medications to which they had failed to respond and continued at stable doses that had not been altered for at least 4 weeks before the treatment.
- During continuation treatment (this study), patients either continued to remain medication free (n=7, 10 courses), continued on the same antidepressant medication taken during the acute treatment course (n=16, 17 courses), or started a new antidepressant treatment during continuation treatment (n=3, 3 courses).
- Open label study.
- Relapse was defined as' the re-emergence of depressive symptomology of sufficient severity to warrant either withdrawal from the continuation study to commence a new acute tDCS course, or commencement of an alternative treatment.
- Data was censored from patients who did not withdraw from the study because of relapse.
- Patients received 2 different forms of tDCS treatment.

Study population issues: The majority of patients in this study had failed at least 1 adequate course of antidepressant treatment before being treated by the acute tDCS course.

Other issues: Patients were pooled from 2 previous studies: Loo (2012) and Martin (2011) which can be found in Appendix A.

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 26

Relapse
<table>
<tr><th>Length of treatment</th><th>Cumulative probability of surviving without relapse</th><th>Cumulative probability of surviving without relapse (when the patients who started a new antidepressant during continuation tDCS were excluded from the analysis)</th></tr>
<tr><td>3 months (tDCS once weekly)</td><td>84%</td><td>81%</td></tr>
<tr><td>6 months (tDCS once fortnightly)</td><td>51%</td><td>60%</td></tr>
</table>
• Medication resistance was found to be the only predictor of relapse during continuation tDCS (Hazard ratio=1.61; 95% CI, 1.10-2.36, p<0.05).

Treatment response rates
<table>
<tr><th>Length of treatment</th><th>Survivors who continued to meet the criterion for response</th></tr>
<tr><td>3 months (tDCS once weekly)</td><td>56% (10/18)</td></tr>
<tr><td>6 months (tDCS once fortnightly)</td><td>80% (8/10)</td></tr>
</table></td><td>• Most common side effects reported during both weekly and fortnightly continuation tDCS: feelings of tingling/ itching or burning during stimulation, and transient skin redness.
• During weekly continuation tDCS
o Light-headedness/ dizziness: 40%
o Headache: 23%
o Fatigue: 10%
o Nausea: 10%
o Blurred vision on more than 1 occasion: 7%
• During fortnightly continuation tDCS
o Light-headedness: 17%
o Headache: 11%
o Blurred vision: 11%
o Nausea on more than 1 occasion: 6%

Authors stated the ‘the side effects were mild, did not result in distress, and did not require any medical intervention.’</td></tr>
<tr><td colspan="2">Abbreviations used: CI, confidence interval; DLPFC, dorsolateral prefrontal cortex; DSM-IV, diagnostic and statistical manual of mental disorder; MADRS, Montgomery–Åsberg Depression Rating Scale; MDE, major depressive episode.</td></tr>
</table>

Study 6 Palm U (2008) [letter to the editor]

Details

Study type	**Case series**
Country	Not reported
Recruitment period	Not reported
Study population and number	n=**15** patients
Age and sex	Not reported
Patient selection criteria	Not reported
Technique	• 10 patients were treated by 1 mA tDCS. • 5 patients were treated by 2 mA tDCS. • Each active tDCS was applied over 20 minutes on 5 days per week during 2 weeks. • Eldith DC-stimulator (NeuroConn) with 2 water-soaked sponges was used. The anode was placed over the left DLPFC with the centre over F3 and the cathode over the right supraorbital region.
Follow-up	**Not reported**
Conflict of interest/source of funding	Not reported.

Analysis

Follow-up issues: None.

Study design issues: None.

Study population issues: None.

Other issues: None.

Key efficacy and safety findings

Efficacy	Safety
Non-peer-reviewed efficacy findings from letters are not selected for presentation in the overview.	• In the tDCS 1 mA group, 1 patient had a large erythema and small brown crusts after 4 days of tDCS that persisted until the end of tDCS treatment. • In the tDCS 2 mA group, all patients (5/5) had **skin lesions** with extensive redness and brown crusty intracutaneous changes with irregular but overall round shapes. The extension of the lesions ranged from 2–3 mm up to 2 cm and was proportional to the skin impedance measured while connecting the DC-stimulator. Generally, the lesions occurred after the fourth or fifth stimulation, showed stable superficial extensions during further tDCS and healed without scars about 1–3 weeks after the end of the tDCS treatment.
Abbreviations used: DLPFC, left dorsolateral prefrontal cortex.	

Study 7 Shiozawa P (2014)

Details

Study type	**Case report**
Country	Brazil
Recruitment period	Not reported
Study population and number	**n=1** patient with major depressive disorder
Age and sex	66-year-old male
Patient selection criteria	Patient with major depressive disorder for 6 months. Patient had dyslexia and was left-handed. The patient had been previously treated by venlafaxine 150 mg daily for 2 months with no clinical improvement.
Technique	10 consecutive daily tDCS sessions. The cathode was positioned over the right DLPFC and the anode over the left DLPFC. A direct current of 2 mA for 20 minutes per session was used. The rubber electrodes were wrapped in cotton which was moistened with saline.
Follow-up	**Not reported**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: None.

Study design issues: None.

Study population issues: None.

Other issues: None.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **1**	The patient presented with intensification of depressive symptoms and panic attacks after 5 days of treatment. It was hypothesised that the patient had a right hemispheric dominance (he was left-handed and dyslexic). This was corroborated by the Edinburgh handedness scale. The patient was then treated by transcranial magnetic stimulation for 10 days over the left DLPFC to inhibit the area, which was hypothetically hyperactivated following the rationale of right dominance. The patient presented amelioration of depressive and anxious symptoms.
Abbreviations used: DLPFC, left dorsolateral prefrontal cortex.	

Efficacy

Improvement in depressive symptoms

A systematic review and meta-analysis of 7 randomised controlled trials (RCTs) including 259 patients treated by active transcranial direct current stimulation (tDCS, n=137) or sham tDCS (n=122) reported a significantly greater improvement in depressive symptoms in the active tDCS group using Hedges' g as the measure of the effect size, which standardises studies using different depression scales (Hedges' g=0.37; 95% confidence interval [CI] 0.04 to 0.7) compared against the sham tDCS group[1].

An RCT of 120 patients treated by active tDCS plus sertraline (n=30), active tDCS plus placebo (n=30), sham tDCS plus sertraline (n=30) or sham tDCS plus placebo (n=30) reported significantly lower Montgomery–Åsberg Depression Rating Scale (MADRS) scores (10 items measured on a scale of 0 to 6 with low values indicating less depression) after 6 weeks in patients treated by active tDCS plus sertraline compared against patients treated by sham tDCS plus sertraline (mean difference 8.5 points; 95% CI 2.96 to 14.03; p=0.002). Significantly lower MADRS scores after 6 weeks were also reported in patients treated by active tDCS plus placebo compared against patients treated by sham tDCS plus placebo (mean difference 5.6 points; 95% CI 1.30 to 10.01; p=0.01)[3].

Treatment response rates

The systematic review of 7 RCTs including 259 patients reported significantly better treatment response rates (defined as an improvement greater than 50% in depression scores from baseline to end point) in the active tDCS group compared against the sham tDCS group (odds ratio [OR] 1.63; 95% CI 1.26 to 2.12)[1].

In the RCT of 120 patients, response rates after 6 weeks were 63% (19/30) for the patients treated by active tDCS and sertraline, 43% (13/30) for the patients treated by active tDCS and placebo, 33% (10/30) for the patients treated by sham tDCS and sertraline and 17% (5/30) for the patients treated by sham tDCS and placebo (p<0.001)[3].

A case series of 26 patients treated by tDCS for up to 6 months after an acute course of tDCS once weekly for 3 months and then once every other week for the following 3 months, reported treatment response rates among the 'survivors' of 56% (10/18) at 3 months and 80% (8/10) at 6 months[5].

Remission rates

The systematic review of 7 RCTs including 259 patients reported significantly better remission rates in the active tDCS group compared against the sham tDCS group, with scores lower than 8 in the Hamilton Depression Rating Scale (several variables assessed and measured on 5-point or 3-point scales, with low values

indicating less depression), or lower or equal to 10 in the MADRS (OR 2.5; 95% CI 1.26 to 4.99)[1].

In the RCT of 120 patients, remission rates (according to MADRS scores) after 6 weeks were 47% (14/30) for patients treated by active tDCS plus sertraline, 40% (12/30) for patients treated by active tDCS plus placebo, 30% (9/30) for patients treated by sham tDCS plus sertraline and 13% (4/30) for patients treated by sham tDCS plus placebo (p=0.03 between groups)[3].

Relapse

A follow-up study of 42 patients whose depression had responded ('responders') to tDCS treatment in the RCT of 120 patients reported a sustained response rate at 24 weeks in these 'responders' of 47% (95% CI, 27 to 64, measured by Kaplan–Meier survival analysis). Patients with treatment-resistant depression had a much lower 24-week sustained response rate than patients with non-refractory depression (10% versus 77%, OR 5.52; p<0.01). The same study reported a mean response duration (for 'responders', n=42) of 11.7 weeks[4].

The case series of 26 patients treated by tDCS for up to 6 months after an acute course of tDCS once weekly for 3 months and then once every other week for the following 3 months, reported cumulative probabilities of surviving without relapse of 84% at 3 months and 51% at 6 months. Medication resistance was found to be the only significant predictor of relapse during continuation tDCS (hazard ratio=1.61; 95% CI 1.10–2.36; p<0.05)[5].

Acceptability of the treatment

The systematic review of 7 RCTs including 259 patients reported dropout rates of 8% (12/137) in the active tDCS group and 11% (15/122) in the sham tDCS group, with no difference in treatment acceptability (OR 0.73; 95% CI 0.32 to 1.69)[1].

Safety

Mania

Six episodes of either treatment-emergent mania or hypomania (Young Mania Rating Scale score greater than 8) were reported in a randomised controlled trial (RCT) of 120 patients treated by active transcranial direct current stimulation (tDCS) plus sertraline, active tDCS plus placebo, sham tDCS plus sertraline or sham tDCS plus placebo. Five episodes (including 2 manic episodes) were from the active tDCS plus sertraline group and 1 from the tDCS-only group (no further details provided)[3].

Skin lesions

Skin lesions were reported in all (5/5) patients treated by 2 mA tDCS and in 1 (1/10) patient treated by 1 mA tDCS in a case series of 15 patients treated by 1 mA or 2 mA tDCS. Generally, the lesions occurred after the fourth or fifth

stimulation, showed stable superficial extensions during further tDCS and healed without scars about 1–3 weeks after the end of the tDCS treatment[6].

Burning sensation

A burning sensation was reported in 9% of the studies in the active tDCS group and in 10% of the studies in the sham tDCS group in a systematic review of 117 studies (p value not significant)[2].

Skin redness

Skin redness 2 weeks after treatment was reported in 25% (13/60) of patients in the active tDCS group and in 8% (4/60) of patients in the sham tDCS group in the RCT of 120 patients (p=0.03)[3].

Skin redness was reported in 23% (10/42) of patients in a follow-up study of 42 patients whose depression had responded to tDCS treatment in the RCT of 120 patients[4].

Itching and tingling

Itching was reported in 39% of the studies in the active tDCS group and in 33% of the studies in the sham tDCS group in the systematic review of 117 studies (p value not significant and no details of timing provided)[2]. Itching was reported in 42% of patients in the follow-up study (n=42) of the RCT of 120 patients[4].

Tingling was reported in 22% of the studies in the active tDCS group and in 18% of the studies in the sham tDCS group in the systematic review of 117 studies (p value not significant and no details of timing provided)[2].

Headache

Headache was reported in 15% of the studies in the active tDCS group and in 16% of the studies in the sham tDCS group in the systematic review of 117 studies (p value not significant)[2].

Headache was reported in 19% (8/42) of patients in the follow-up study of 42 patients whose depression had responded to tDCS treatment in the RCT of 120 patients[4].

Headache was reported in 23% of patients when tDCS was administered weekly and in 11% when tDCS was administered once every 2 weeks in a case series of 26 patients treated by tDCS for up to 6 months after an acute course of tDCS (absolute numbers not reported)[5].

Light-headedness

Light-headedness was reported in 40% of patients when tDCS was administered weekly and in 17% when tDCS was administered once every 2 weeks in the case series of 26 patients treated by tDCS for up to 6 months after an acute course of tDCS (absolute numbers not reported)[5].

Somnolence

Somnolence was reported in 16% (7/42) of patients in the follow-up study of 42 patients whose depression had responded to tDCS treatment in the RCT of 120 patients[4].

Fatigue was reported in 10% of patients when tDCS was administered weekly in the case series of 26 patients treated by tDCS for up to 6 months after an acute course of tDCS (absolute numbers not reported)[5].

Blurred vision

Blurred vision was reported in 7% of patients when tDCS was administered weekly and in 11% when tDCS was administered once every 2 weeks in the case series of 26 patients treated by tDCS for up to 6 months after an acute course of tDCS (absolute numbers not reported)[5].

Panic attacks

Panic attacks were reported in a single case report 5 days after starting tDCS treatment. It was hypothesised that the patient, who was left-handed and dyslexic, had right hemispheric dominance[7].

Nausea

Nausea was reported in 10% of patients when tDCS was administered weekly and in 6% when tDCS was administered once every 2 weeks in the case series of 26 patients treated by tDCS for up to 6 months after an acute course of tDCS (absolute numbers not reported)[5].

Discomfort

Discomfort was reported in 10% and 13% of the studies in the active tDCS and sham tDCS groups respectively in the systematic review of 117 studies (p value not significant)[2].

Validity and generalisability of the studies

- The maximum number of patients treated by tDCS included in the studies is 60.
- No studies with long-term follow-up (maximum is 6 months follow-up).
- Different strategies for positioning the electrodes on the scalp are used in the studies.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Vagus nerve stimulation for treatment-resistant depression. NICE interventional procedure guidance 330 (2009). Available from http://www.nice.org.uk/guidance/IPG330
- Transcranial magnetic stimulation for severe depression. NICE interventional procedure guidance 242 (2007). Available from http://www.nice.org.uk/guidance/IPG242

Technology appraisals

- Computerised cognitive behaviour therapy for depression and anxiety: Review of Technology Appraisal 51. NICE technology appraisal 97 (2006). Available from http://www.nice.org.uk/guidance/TA97
- Guidance on the use of electroconvulsive therapy. NICE technology appraisal 59 (2003). Available from http://www.nice.org.uk/guidance/TA59

NICE guidelines

- Antenatal and postnatal mental health: Clinical management and service guidance. NICE clinical guideline 192 (2014). Available from http://www.nice.org.uk/guidance/CG192
- Common mental health disorders: Identification and pathways to care. NICE clinical guideline 123 (2011). Available from http://www.nice.org.uk/guidance/CG123
- Depression in adults with a chronic physical health problem: Treatment and management. NICE clinical guideline 91 (2009). Available from http://www.nice.org.uk/guidance/CG91
- Depression in adults: The treatment and management of depression in adults. NICE clinical guideline 90 (2009). Available from http://www.nice.org.uk/guidance/CG90

- Depression in children and young people: Identification and management in primary, community and secondary care. NICE clinical guideline 28 (2005). Available from http://www.nice.org.uk/guidance/CG28

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to where comments are considered voluminous, or publication would be unlawful or inappropriate. Three Specialist Advisor Questionnaires for transcranial direct current stimulation (TDCS) for depression were submitted and can be found on the NICE website; https://www.nice.org.uk/guidance/GID-IP809/documents/transcranial-direct-current-stimulation-tdcs-for-depression-saqs2;

Patient commentators' opinions

NICE's Public Involvement Programme sent 2 questionnaires to 1 NHS trust for distribution to patients who had the procedure (or their carers). NICE received 1 completed questionnaire.

The patient commentators' views on the procedure were consistent with the published evidence and the opinions of the specialist advisers.

Issues for consideration by IPAC

Ongoing studies:

- NCT02116127 Transcranial Direct Current Stimulation (tDCS) for Depression in Pregnancy: A Pilot Study. Location: Canada. Ongoing. Enrolment: 36 patients. Estimated Completion Date: December 2015.
- NCT02152878 Transcranial Direct Current Stimulation for the Treatment of Bipolar Depression (tDCS-BD). Location: Brazil. Phase 2/3. Ongoing. Enrolment: 60 patients. Estimated Completion Date: February 2017.

- NCT02141776 Comparison of Anodal Transcranial Direct Current Stimulation (t-DCS) and Sham Stimulation in Patients With Treatment-resistant Depression. Location: USA. Phase 4. Ongoing. Enrolment: 24 patients. Estimated Completion Date: November 2014.
- NCT01894815 Escitalopram, Placebo and tDCS in Depression: a Non-inferiority Trial (ELECT-tDCS). Location: Brazil. Phase 3. Ongoing. Enrolment: 240 patients. Estimated Completion Date: January 2018.
- NCT01263275 Trial of Transcranial Direct Current Stimulation (tDCS) for Depression. Location Australia. Phase 2. Ongoing. Enrolment: 20 patients. Estimated Completion Date: December 2015.
- NCT02212366 To Enhance Cognition in Late Life Depression Using Transcranial Direct Current Stimulation. Location: Canada. Phase 2. Ongoing. Enrolment: 36 patients. Estimated Completion Date: April 2017.
- -NCT01644747 Transcranial Direct Current Stimulation as an add-on Treatment for Resistant Major Depression in Uni- or Bipolar Patients (STICODEP). Location: France. Phase 2. Ongoing. Enrolment: 120 patients. Estimated Completion Date: July 2016.
- NCT01974076 Transcranial Direct Current Stimulation (tDCS) as an Adjunct to Cognitive Behaviour Therapy (CBT). Location: Australia. Ongoing. Enrolment: 135 patients. Estimated Completion Date: September 2018.
- NCT01346306 Trial of Transcranial Direct Current Stimulation (tDCS). Location: Australia. Phase 2. Ongoing. Enrolment: 120 patients. Estimated Completion Date: April 2015.
- NCT01021709 Trial of Transcranial Direct Current Stimulation (tDCS) Using Alternative Electrode Montages. Location: Australia. Phase 2. Ongoing. Enrolment: 20 patients. Estimated Completion Date: November 2014.
- NCT01875419 Non-invasive Brain Stimulation and Cognitive Processing in Depression. Location: England. Ongoing. Enrolment: 60 patients. Estimated Completion Date: January 2019.

- NCT01562184 Investigating tDCS as a Treatment for Unipolar and Bipolar Depression. Location: Australia. Ongoing. Phase 2/3. Enrolment: 120 patients. Estimated Completion Date: March 2015.
- NCT01201148 Open Pilot Trial of TES for Depression. Location: Australia. Ongoing. Phase 2. Enrolment: 20 patients. Estimated Completion Date: September 2015.
- NCT01849367 Trial of Bilateral tDCS for Depression. Location: Australia. Ongoing. Phase 1/2. Enrolment: 40 patients. Estimated Completion Date: May 2018.

References

1. Shiozawa P, Fregni F, Bensenor IM et al. (2014) Transcranial direct current stimulation for major depression: An updated systematic review and meta-analysis. International Journal of Neuropsychopharmacology.17 (9) (pp 1443-1452), 2014.Date of Publication: September 2014. 1443-1452.
2. Brunoni AR, Amadera J, Berbel B et al. (2011) A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. International Journal of Neuropsychopharmacology.14 (8) (pp 1133-1145), 2011.Date of Publication: September 2011. 1133-1145.
3. Brunoni AR, Valiengo L, Baccaro A et al. (2013) The sertraline vs. electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial. JAMA Psychiatry 70:383-391.
4. Valiengo L, Bensenor IM, Goulart AC et al. (2013) The sertraline versus electrical current therapy for treating depression clinical study (select-tDCS): results of the crossover and follow-up phases. Depression & Anxiety 30:646-653.
5. Martin DM, Alonzo A, Ho KA et al. (2013) Continuation transcranial direct current stimulation for the prevention of relapse in major depression. Journal of Affective Disorders 144:274-278.
6. Palm U, Keeser D, Schiller C et al. (2008) Skin lesions after treatment with transcranial direct current stimulation (tDCS).[Erratum appears in Brain Stimul. 2009 Jul;2(3):183]. Brain Stimulation 1:386-387.
7. Shiozawa P, Da Silva ME, and Cordeiro Q. (8-9-2014) Transcranial Direct Current Stimulation for Treating Depression in a Patient With Right Hemispheric Dominance: A Case Study. J ECT

Appendix A: Additional papers on transcranial direct current stimulation (tDCS) for depression

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Alonzo A, Chan G, Martin D et al. (2013) Transcranial direct current stimulation (tDCS) for depression: analysis of response using a three-factor structure of the Montgomery-Asberg depression rating scale. Journal of Affective Disorders 150:91-95.	RCT n=64 (33 active tDCS versus 31 sham tDCS) Patients from Loo (2012) RCT. FU=6 weeks	tDCS appears to be particularly effective in treating dysphoria and retardation, but not vegetative symptoms of depression. This may have implications for selection of types of depression most likely to respond to this treatment.	Patients already included in the Shiozawa (2014) meta-analysis.
Arul-Anandam AP, Loo C, and Mitchell P. (2010) Induction of hypomanic episode with transcranial direct current stimulation. Journal of ECT 26:68-69.	Single case report	First report of mania after transcranial direct current stimulation to the dorsolateral prefrontal cortex.	Studies with more patients or longer follow-up are included.
Bennabi D, Nicolier M, Monnin J et al. (2014) Pilot study of feasibility of the effect of treatment with tDCS in patients suffering from treatment-resistant depression treated with escitalopram. Clin Neurophysiol. http://dx.doi.org/10.1016/j.clinph.2014.09.026	RCT (active tDCS versus sham TDCS) n=24 FU=30 days after the end of the treatment	tDCS efficacy on specific symptom profiles in pharmacotherapy-resistant depression is limited. The use of optimised stimulation protocol and longer period of follow-up may valuably contribute to specify the place of tDCS in treatment-resistant depression.	Larger studies or studies with longer follow-up are already included in table 2.
Berlim MT, Van den Eynde F, and Daskalakis ZJ. (2013) Clinical utility of transcranial direct current stimulation (tDCS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. [Review]. Journal of Psychiatric Research 47:1-7.	Systematic review and meta-analysis n=200 (103 active versus 97 sham) from 6 RCTs	No significant difference was found between active and sham tDCS in terms of both response and remission. Also, no difference between mean baseline depression scores and dropout rates in the active and sham tDCS groups was found. Furthermore, sensitivity analyses excluding RCTs that involved less than 10 treatment sessions or stimulus intensity of less than 2 mA did not alter the findings. However, tDCS used as monotherapy was associated with higher response rates when compared to sham	A more recent meta-analysis with more patients is already included.

		tDCS (p = 0.043). Finally, the risk of publication bias in this meta-analysis was found to be low.	
Blumberger DM, Tran LC, Fitzgerald PB et al. (2012) A randomized double-blind sham-controlled study of transcranial direct current stimulation for treatment-resistant major depression. Frontiers in psychiatry Frontiers Research Foundation 3:74-	RCT n=24 (13 active versus 11 sham tDCS) FU=3 weeks	The remission rates did not differ significantly between the 2 groups using an intention to treat analysis. More subjects in the active tDCS group had failed a course of electroconvulsive therapy in the current depressive episode. Side effects did not differ between the 2 groups and in general the treatment was very well tolerated.	Patients already included in the Shiozawa (2014) meta-analysis.
Boggio PS, Rigonatti SP, Ribeiro RB et al. (2008) A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression. International Journal of Neuropsychopharmacology 11:249-254.	RCT n=40 (21 DLPFC versus 9 occipital versus 10 sham tDCS) FU=30 days	The treatment was well tolerated with minimal side-effects that were distributed equally across all treatment groups. Significantly larger reductions in depression scores after DLPFC-tDCS compared with occipital tDCS and sham tDCS were reported. The beneficial effects of tDCS in the DLPFC group persisted for 1 month after the end of treatment.	Patients already included in the Shiozawa (2014) meta-analysis.
Brunoni AR, Ferrucci R, Bortolomasi M et al. (2013) Interactions between transcranial direct current stimulation (tDCS) and pharmacological interventions in the Major Depressive Episode: findings from a naturalistic study. European Psychiatry: the Journal of the Association of European Psychiatrists 28:356-361.	Naturalistic study n=82 FU=5 days	tDCS over the DLPFC acutely improved depressive symptoms. tDCS effects might vary according to prior pharmacological treatment, notably benzodiazepines and some antidepressant classes.	Studies with more patients or longer follow-up are included.
Brunoni AR, Boggio PS, De RR et al. (2014) Cognitive control therapy and transcranial direct current stimulation for depression: a randomized, double-blinded, controlled trial. Journal of Affective Disorders 162:43-49.	RCT n=37 (20 active tDCS/ CCT versus 17 sham tDCS/ CCT) FU=4 weeks	Both CCT alone and combined with tDCS ameliorated depressive symptoms after the acute treatment period and at follow-up, with a response rate of approximately 25%. Older patients and those who presented	Studies with more patients or longer follow-up are included.

		better performance in the task throughout the trial had greater depression improvement in the combined treatment group	
Bueno VF, Brunoni AR, Boggio PS et al. (2011) Mood and cognitive effects of transcranial direct current stimulation in post-stroke depression. Neurocase 17:318-322.	Single case report	A patient with significant mood and cognitive impairment showed marked amelioration of these symptoms following anodal stimulation over the left dorsolateral prefrontal cortex.	Studies with more patients or longer follow-up are included.
Chan HN, Alonzo A, Martin DM et al. (2013) Augmenting transcranial direct current stimulation with (D)-cycloserine for depression: a pilot study. Journal of ECT 29:196-200.	Case series n=5 FU=1 month	The change in MADRS scores was not greater with the combination of D-Cycloserine and tDCS than had previously been produced by tDCS alone. No significant additional adverse effects were reported	Studies with more patients or longer follow-up are included.
Dell'Osso B, Zanoni S, Ferrucci R et al. (2012) Transcranial direct current stimulation for the outpatient treatment of poor-responder depressed patients. European Psychiatry: the Journal of the Association of European Psychiatrists 27:513-517.	Case series n=23 FU=1 week	Findings support the efficacy and good tolerability of tDCS in the acute treatment of patients with treatment resistant depression with clinical benefit being progressive and extended to the first week of follow-up.	Studies with more patients or longer follow-up are included.
Dell'Osso B, Dobrea C, Arici C et al. (2014) Augmentative transcranial direct current stimulation (tDCS) in poor responder depressed patients: a follow-up study. Cns Spectrums 19:347-354.	Naturalistic study n=23 FU=3 months	Even though a progressive reduction of follow-up completers was observed from T2 to T4, the antidepressant effects of acute tDCS persisted over 3 months in almost half of the sample. No post-acute side effects emerged during the follow-up observation. The most frequent causes of drop-out from this study included major modifications in therapeutic regimen and poor adherence to follow-up visits.	Studies with more patients or longer follow-up are included.
Ferrucci R, Bortolomasi M, Vergari M et al. (2009) Transcranial direct current stimulation in	Case series n=14 patients	After 5 days of treatment although	Studies with more

severe, drug-resistant major depression. Journal of Affective Disorders 118:215-219.	FU=4 weeks	cognitive performances remained unchanged, the BDI and HDRS scores significantly improved more than 30%. The mood improvement persisted and even increased at 4 weeks after treatment ended. The feeling of sadness and mood as evaluated by VAS significantly improved after tDCS.	patients or longer follow-up are included.
Ferrucci R, Bortolomasi M, Brunoni A et al. (2009) Comparative benefits of transcranial direct current stimulation (TDCS) treatment in patients with mild/moderate vs. severe depression. Clinical Neuropsychiatry.6 (6) (pp 246-251), 2009.Date of Publication: December 2009. 246-251.	Open-label non-randomised comparative trial n=32 (19 severe depression versus 13 mild/moderate depression) FU=35 days	tDCS is especially effective in patients with severe MDD, providing sustained antidepressant effects after one month of intervention.	Studies with more patients or longer follow-up are included.
Galvez V, Alonzo A, Martin D et al. (2011) Hypomania induction in a patient with bipolar II disorder by transcranial direct current stimulation (tDCS). Journal of ECT 27:256-258.	Single case report	Frontoextracephalic tDCS has antidepressant properties and the potential to induce hypomanic symptoms. It raises the question of whether frontoextracephalic tDCS requires additional precautions when administered to bipolar patients compared with bifrontal tDCS.	Studies with more patients are included.
Kalu UG, Sexton CE, Loo CK et al. (2012) Transcranial direct current stimulation in the treatment of major depression: a meta-analysis. [Review]. Psychological Medicine 42:1791-1800.	Systematic review and meta-analysis n=176 (96 active versus 80 sham) from 6 RCTs	Active tDCS was found to be more effective than sham tDCS for the reduction of depression severity, although study results differed more than expected by chance. Meta-regression did not reveal any significant correlations.	A more recent meta-analysis with more patients is already included.
Knotkova H, Rosedale M, Strauss SM et al. (2012) Using Transcranial Direct Current Stimulation to Treat Depression in HIV-Infected Persons: The Outcomes of a Feasibility Study. Frontiers in psychiatry Frontiers Research Foundation 3:59-	Case series n=10 FU=2 weeks	Findings support feasibility and clinical potential of tDCS for HIV-MDD patients and justify larger-sample, sham-controlled trials.	Studies with more patients or longer follow-up are included.
Loo CK, Sachdev P, Martin D et al. (2010) A double-blind, sham-controlled trial of transcranial direct current stimulation for the	RCT n=40 (20 active	Overall depression scores improved significantly over 10	Study included into the

treatment of depression. International Journal of Neuropsychopharmacology 13:61-69.	versus 20 sham tDCS) FU=1 month	tDCS treatments, but there was no between-group difference in the five-session, sham-controlled phase. tDCS was found to be safe, with no adverse effects on neuropsychological function, and only minor side-effects.	Shiozawa (2014) meta-analysis.
Loo CK, Alonzo A, Martin D et al. (2012) Transcranial direct current stimulation for depression: 3-week, randomised, sham-controlled trial. British Journal of Psychiatry 200:52-59.	RCT n=64 (33 active tDCS versus 31 sham tDCS) FU=6 weeks	There was significantly greater improvement in mood after active than after sham treatment (P<0.05), although no difference in responder rates (13% in both groups). Attention and working memory improved after a single session of active but not sham tDCS (P<0.05). There was no decline in neuropsychological functioning after 3-6 weeks of active stimulation. One participant with bipolar disorder became hypomanic after active tDCS.	Study included into the Shiozawa (2014) meta-analysis.
Martin DM, Alonzo A, Mitchell PB et al. (2011) Fronto-extracephalic transcranial direct current stimulation as a treatment for major depression: an open-label pilot study. Journal of Affective Disorders 134:459-463.	Case series n=11 FU=3 weeks.	F-EX tDCS appears to be safe and to have antidepressant effects, and may lead to more rapid improvement than tDCS with a bifrontal montage	Studies with more patients or longer follow-up are included.
Minichino A, Bersani FS, Spagnoli F et al. (2014) Prefronto-cerebellar transcranial direct current stimulation improves sleep quality in euthymic bipolar patients: a brief report. Behavioural Neurology 2014:876521.	Case series n=25 FU=30 days after the end of the treatment	Pittsburgh Sleep Quality Index (PSQI) total score and all PSQI subdomains, with the exception of "sleep medication" significantly improved after treatment. As both prefrontal cortex and cerebellum may play a role in regulating sleep processes, concomitant cathodal (inhibitory) stimulation of cerebellum and anodal (excitatory) stimulation of DLPFC may have the potential to modulate prefrontal-thalamic-cerebellar circuits leading to	Larger studies or studies with longer follow-up are already included in table 2.

		improvements of sleep quality.	
Oliveira JF, Zanao TA, Valiengo L et al. (2013) Acute working memory improvement after tDCS in antidepressant-free patients with major depressive disorder. Neuroscience Letters 537:60-64.	RCT n=28 (14 active versus 14 sham tDCS) patients from the SELECT-tDCS study FU=none	One session of tDCS acutely enhanced working memory in depressed subjects, suggesting that tDCS can improve "cold" (non affective-loaded) working memory processes in major depressive disorder.	Patients from the Brunoni (2013) RCT.
Palm U, Keeser D, Schiller C et al. (2009) Transcranial direct current stimulation in a patient with therapy-resistant major depression. World Journal of Biological Psychiatry 10:t-5.	Single case report	Though tDCS over 4 weeks did not exert clinically meaningful antidepressant effects in this case of therapy-resistant depression, the findings for cognitive measures and EEG suggest that beneficial effects may occur in depressed subjects and future studies need to further explore this approach also in therapy-resistant major depression.	Studies with more patients or longer follow-up are included.
Palm U, Schiller C, Fintescu Z et al. (2012) Transcranial direct current stimulation in treatment resistant depression: a randomized double-blind, placebo-controlled study. Brain Stimulation 5:242-251.	RCT n=22 (11 active tDCS versus 11 sham tDCS) FU=4 weeks	There was no significant difference in depression scores after 2 weeks of active compared with 2 weeks of sham tDCS. Scores on the Hamilton Depression Rating Scale were reduced from baseline by 15% for active tDCS and 10% for sham tDCS. In contrast, subjective mood ratings showed an increase in positive emotions after real tDCS compared with sham tDCS.	Study included into the Shiozawa (2014) meta-analysis.
Segrave RA, Arnold S, Hoy K et al. (2014) Concurrent cognitive control training augments the antidepressant efficacy of tDCS: a pilot study. Brain Stimulation 7:325-331.	RCT n=27 (9 tDCS/CCT versus 9 sham tDCS/CCT versus tDCS/sham CCT) FU=3 weeks	All 3 treatment conditions were associated with a reduction in depression severity at the end of 5 treatment sessions. However, only administration of tDCS + CCT resulted in sustained antidepressant response at follow up,	Studies with more patients or longer follow-up are included.

		the magnitude of which was greater than that observed immediately following conclusion of the treatment course.	
Shiozawa P, Da Silva ME, Dias DR et al. (2014) Transcranial direct current stimulation for depression in a 92-year-old patient: a case study. Psychogeriatrics:The Official Journal of the Japanese Psychogeriatric Society 14:269-270.	Single case report n=1 FU=3 weeks	After 10 sessions, the patients presented with satisfactory clinical response. The HDRS score decreased by 17 point (94.4%) from baseline and the decrease was maintained during the 3-week follow-up. There were no significant changes for anxiety or cognitive symptoms. The intervention was well tolerated and no adverse effects were reported.	Larger studies or studies with longer follow-up are already included in table 2.
Tortella G, Selingardi PM, Moreno ML et al. (2014) Does non-invasive brain stimulation improve cognition in major depressive disorder? A systematic review. CNS & Neurological Disorders Drug Targets 13:1759-1769.	Systematic review without meta-analysis.	Non-invasive brain stimulation (NIBS) interventions, such as repetitive transcranial magnetic stimulation and tDCS seem to be a promising tool for cognitive enhancement in major depressive disorder, although several issues and biases (such as blinding issues, tests without correction for multiple comparisons, placebo effects and exploratory analyses, practice effects) hinder the authors to conclude that NIBS techniques improve cognition in patients with depression. Further studies are still warranted to disentangle whether NIBS techniques induce positive effects on cognition beyond their antidepressant effects.	No meta-analysis. Includes both transcranial magnetic stimulation and tDCS techniques.
Zanao TA, Moffa AH, Shiozawa P et al. (2014) Impact of two or less missing treatment sessions on tDCS clinical efficacy: results from a factorial, randomized, controlled trial in major depression. Neuromodulation 17:737-742.	RCT n=120 FU= 6 weeks	Granting 1 to 2 absences during the acute treatment phase did not impact on tDCS antidepressant efficacy. Moreover, out of 103 completers,	Same patient population as in Brunoni (2013) study which

		only 40% (41/103) patients presented no missing visits and 24 % (25/103) presented 2 absences. Absences during the acute tDCS treatment phase are common, which support the use of flexible schedules in future tDCS trials as to minimize attrition. Also, further studies should access whether higher number of absences can compromise optimal tDCS efficacy.	is already included in table 2.

Appendix B: Related NICE guidance for transcranial direct current stimulation (tDCS) for depression

Guidance	Recommendations
Interventional procedures	**Vagus nerve stimulation for treatment-resistant depression. NICE interventional procedure guidance 330 (2009)** 1.1 Current evidence on the safety and efficacy of vagus nerve stimulation (VNS) for treatment-resistant depression is inadequate in quantity and quality. Therefore this procedure should be used only with special arrangements for clinical governance, consent and audit or research. It should be used only in patients with treatment-resistant depression. 1.2 Clinicians wishing to undertake VNS for treatment-resistant depression should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients and/or their parents/carers understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. In addition, the use of NICE's information for patients ('Understanding NICE guidance') is recommended. • Audit and review clinical outcomes of all patients having VNS for treatment-resistant depression (see section 3.1). 1.3 Patient selection and management should be carried out by a multidisciplinary team including a psychiatrist and a surgeon (usually a neurosurgeon), with other relevant specialists (for example, a clinical psychologist and an appropriately trained technician). 1.4 NICE encourages further research into VNS for treatment-resistant depression. Research outcomes should include depression rating scales, objective measures of depressive symptoms and patient-reported quality of life. NICE may review the procedure on publication of further evidence.
Interventional procedures	**Transcranial magnetic stimulation for severe depression. NICE interventional procedure guidance 242 (2007)** 1.1 Current evidence suggests that there are no major safety concerns associated with transcranial magnetic stimulation (TMS) for severe depression. There is uncertainty about the procedure's clinical efficacy, which may depend on higher intensity, greater frequency, bilateral application and/or longer

	treatment durations than have appeared in the evidence to date. TMS should therefore be performed only in research studies designed to investigate these factors. 1.2 Future research should aim to address patient selection criteria, the optimal use of this procedure in relation to other treatments, and the duration of any treatment effect. Clinicians should collaborate to ensure that studies are sufficiently large to be adequately powered. The Institute may review the procedure upon publication of further evidence.
Technology appraisals	**Computerised cognitive behaviour therapy for depression and anxiety: Review of Technology Appraisal 51. NICE technology appraisal 97 (2006)** This review concerns five specific packages for the delivery of computerised cognitive behaviour therapy (CCBT) accessed via a referral from a general practitioner (GP): three for depression (Beating the Blues, COPE and Overcoming Depression), one for panic/phobia (FearFighter) and one for obsessive-compulsive disorder (OCD; OCFighter, previously known as BTSteps). This guidance should be read in the context of the clinical guidelines on depression, anxiety and OCD). 1.1 This recommendation has been replaced by recommendations in the two depression clinical guidelines (CG90 and CG91) published in October 2009. 1.2 This recommendation has been replaced by recommendations in the two depression clinical guidelines (CG90 and CG91) published in October 2009. 1.3 This recommendation has been replaced by the generalised anxiety disorder and panic disorder guideline (CG113), published in January 2011, and by the social anxiety disorder guideline (CG159), published in May 2013. 1.4 OCFighter (previously known as BTSteps) is not recommended as an option for delivering CBT in the management of OCD. 1.5 People currently using OCFighter, whether as routine therapy or as part of a clinical trial, should have the option to continue on therapy until the person, or the GP and/or specialist, consider it appropriate to stop.
Technology appraisals	**Guidance on the use of electroconvulsive therapy. NICE technology appraisal 59 (2003)**

	The recommendations in this technology appraisal relating to the treatment of depression have been replaced by recommendations in 'Depression in adults (update)' (NICE clinical guideline 90) published in October 2009. Note that the recommendations in this technology appraisal relating to the treatment of catatonia-prolonged or severe manic episodes and schizophrenia have not changed. The recommendations relating to depression have been removed from this web viewer version. 1.1 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: • catatonia • a prolonged or severe manic episode. 1.2 The decision as to whether ECT is clinically indicated should be based on a documented assessment of the risks and potential benefits to the individual, including: the risks associated with the anaesthetic; current co-morbidities; anticipated adverse events, particularly cognitive impairment; and the risks of not having treatment. 1.3 The risks associated with ECT may be enhanced during pregnancy, in older people, and in children and young people, and therefore clinicians should exercise particular caution when considering ECT treatment in these groups. 1.4 Valid consent should be obtained in all cases where the individual has the ability to grant or refuse consent. The decision to use ECT should be made jointly by the individual and the clinician(s) responsible for treatment, on the basis of an informed discussion. This discussion should be enabled by the provision of full and appropriate information about the general risks associated with ECT (see section 1.9) and about the risks and potential benefits specific to that individual. Consent should be obtained without pressure or coercion, which may occur as a result of the circumstances and clinical setting, and the individual should be reminded of their right to withdraw consent at any point. There should be strict adherence to recognised guidelines about consent and the involvement of patient advocates and/or carers to facilitate informed discussion is strongly encouraged.

	1.5 In all situations where informed discussion and consent is not possible advance directives should be taken fully into account and the individual's advocate and/or carer should be consulted. 1.6 Clinical status should be assessed following each ECT session and treatment should be stopped when a response has been achieved, or sooner if there is evidence of adverse effects. Cognitive function should be monitored on an ongoing basis, and at a minimum at the end of each course of treatment. 1.7 It is recommended 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. 1.8 This recommendation has been updated and replaced by NICE clinical guideline 90. 1.9 The current state of the evidence does not allow the general use of ECT in the management of schizophrenia to be recommended. 1.10 National information leaflets should be developed through consultation with appropriate professional and user organisations to enable individuals and their carers/advocates to make an informed decision regarding the appropriateness of ECT for their circumstances. The leaflets should be evidence based, include information about the risks of ECT and availability of alternative treatments, and be produced in formats and languages that make them accessible to a wide range of service users.
Clinical guidelines	**Antenatal and postnatal mental health: Clinical management and service guidance. NICE clinical guideline 192 (2014)** Guideline includes recommendations on the use of electroconvulsive therapy (ECT) but does not include tDCS.
Clinical guidelines	**Common mental health disorders: Identification and pathways to care. NICE clinical guideline 123 (2011)** 1.1 Improving access to services 1.2 Stepped care

	1.3 Step 1: Identification and assessment 1.4 Steps 2 and 3: Treatment and referral for treatment 1.5 Developing local care pathways
Clinical guidelines	**Depression in adults with a chronic physical health problem: Treatment and management. NICE clinical guideline 91 (2009)** 1.1 Care of all people with depression 1.2 Stepped care 1.3 Step 1: recognition, assessment and initial management in primary care and general hospital settings 1.4 Step 2: recognised depression in primary care and general hospital settings – persistent subthreshold depressive symptoms or mild to moderate depression 1.5 Step 3: recognised depression in primary care and general hospital settings – persistent subthreshold depressive symptoms or mild to moderate depression with inadequate response to initial interventions, and moderate and severe depression 1.6 Step 4: complex and severe depression
Clinical guidelines	**Depression in adults: The treatment and management of depression in adults. NICE clinical guideline 90 (2009)** 1.10.4 Electroconvulsive therapy (ECT) 1.10.5 Transcranial magnetic stimulation
Clinical guidelines	**Depression in children and young people: Identification and management in primary, community and secondary care. NICE clinical guideline 28 (2005)** Guideline includes recommendations on the use of electroconvulsive therapy (ECT) but does not include tDCS.

Appendix C: Literature search for transcranial direct current stimulation (tDCS) for depression

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	04/03/2015	Issue 3 of 12, March 2015
Database of Abstracts of Reviews of Effects – DARE (Cochrane Library)	04/03/2015	Issue 1 of 4, January 2015
HTA database (Cochrane Library)	04/03/2015	Issue 1 of 4, January 2015
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	04/03/2015	Issue 2 of 12, February 2015
MEDLINE (Ovid)	04/03/2015	1946 to February Week 4 2015
MEDLINE In-Process (Ovid)	04/03/2015	March 03, 2015
EMBASE (Ovid)	04/03/2015	1974 to 2015 Week 09
PubMed	04/03/2015	n/a
JournalTOCS	04/03/2015	n/a

Trial sources searched on 25/09/2014

- Current Controlled Trials *meta*Register of Controlled Trials – *m*RCT
- Clinicaltrials.gov
- WHO International Clinical Trials Registry

Websites searched on 25/09/2014

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	Depression/
2	exp Mood Disorders/
3	Depression, Postpartum/
4	((Depress* or Mood* or Bipolar* or Bi-polar* or Manic* Neurotic* or Neuros* or Affect* or Season* or SAD* or Dysthymic*) adj4 (Disorder* or Episode* or Syndrome* Postpartum* or Post-partum* or Postnatal or Post-natal)).tw.
5	melancholia*.tw.
6	(depression or depressed).tw.
7	1 or 2 or 3 or 4 or 5 or 6
8	((transcranial or head or brain) adj4 direct adj4 current* adj4 stimul*).tw.
9	tDCS.tw.
10	((direct or electric*) adj4 current* adj4 (therap* or stimul*)).tw.
11	((non-invasive or non invasive) adj4 brain adj4 stimul*).tw.
12	Electric Stimulation Therapy/
13	(electric* adj4 stimul* adj4 therap*).tw.
14	Electrotherap*.tw.
15	(HDCstim or HDCstimPro or HDC or Magstim or DVkit or Neuroconn).tw.
16	or/8-15
17	7 and 16
18	animals/ not humans/
19	17 not 18
20	limit 19 to english language