National Institute for Health and Care Excellence

IP809– Transcranial direct current stimulation (tDCS) for depression
Consultation Comments table
IPAC date: Thursday 11th June 2015

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1	Consultee 5 The Royal College of Psychiatrists	**Lay description**	In the first box it says tDCS is applied for "several minutes at a time". I think this is a bit misleading as, to us, 'several' implies 3-5 minutes when in fact typical protocols involve 20 (and sometimes 30) minutes of stimulation. Although we are not sure whether this text is just for reviewers?	Thank you for your comment. The lay description in the overview has been changed to: ' *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.*'
2	Consultee 3 Specialist Adviser	**Title and section 1**	The conventional abbreviation for the procedure is tDCS (rather than TDCS) I support the provisional recommendations which I think would be helpful to clinicians and patients. I have commented separately on the draft audit tool	Thank you for your comment. The abbreviation for the procedure has been changed to tDCS for consistency with the literature.

3	Consultee 5 The Royal College of Psychiatrists	**Title**	The acronym "TDCS" is used throughout. - it is normally written with a lower case t.	Thank you for your comment. The abbreviation for the procedure has been changed to tDCS for consistency with the literature.
4	Consultee 4 The Royal College of Psychiatrists	**1, 6.1 and 6.2**	Evidence is really quite weak at present. Such important variables as where to put the electrodes, duration of current applied, amplitude of current, number of sessions etc. remain unknown so if clinicians start to use it they will make ad hoc decisions on these parameters leading to a plethora of very small scale 'studies' which will add little to our understanding. Need large scale studies therefore.	Thank you for your comment. Section 1.3 of the guidance states that ' *NICE encourages further research into tDCS for depression which should document how patients were selected and any other treatments they were having. It should describe the precise method and regime used for administering tDCS. Outcome measures should include the duration of effect. NICE may update the guidance on publication of further evidence*.'
5	Consultee 2 Overseas Health Researcher	**1.3 and 6**	It should be emphasized that large RCTs are currently being carried out, and this current recommendation will likely change in the next years.	Thank you for your comment. Section 1.3 of the guidance already states that NICE may update the guidance on publication of further evidence: *'NICE encourages further research into tDCS for depression which should document how patients were selected and any other treatments they were having. It should describe the precise method and regime used for administering tDCS. Outcome measures should include the duration of effect. NICE may update the guidance on publication of further evidence.'*

6	Consultee 1 Overseas healthcare professional	**3.2**	Some specific comments: the draft states that tDCS is usually given at 1-2 mA and with cathode on the right frontal cortex - note the field is rapidly evolving, including recent pilot studies of novel electrode placements. recent studies are also using 2.5 mA. It would be better to either 1) state that studies to date used ....[stimulus parameters/ montage] or 2) to give a broader description - tDCS usually uses current of 1-3 mA. The anode is usually placed on the left frontal area and the cathode on the right frontal area or elsewhere	Thank you for your comment. Section 6.2 of the guidance states that '*The Committee noted the inconsistency of the outcomes reported after tDCS for depression between the various studies. Together with the uncertainties about the different modes of administration and number of treatments, this underpinned the recommendation for further research.'* The Committee considered your comment and decided to change section 3.2 of the guidance as follows: '*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.*'

7	Consultee 5 The Royal College of Psychiatrists	**3.2**	In point 3.2 it says "The anode is usually positioned over the left frontal cortex and the cathode over the right frontal cortex". Firstly, we think it should be made clear that they are referring to when tDCS is used to treat depression, as this is not the montage used in all disorders. Secondly, we don't think it's fair to say that the cathode is normally placed over the right frontal cortex as many studies have used an anodal set-up rather than a bilateral one i.e. the anode over the left DLPFC and the cathode over the right supraorbital area. Thirdlywe I think it would be good to be a bit more specific and write 'prefrontal cortex' rather than just "frontal cortex".	Thank you for your comment. Section 6.2 of the guidance states that '*The Committee noted the inconsistency of the outcomes reported after tDCS for depression between the various studies. Together with the uncertainties about the different modes of administration and number of treatments, this underpinned the recommendation for further research.'* Furthermore, the indication of depression in this guidance is specified in the title. The Committee considered your comment and decided to change section 3.2 of the guidance to remove reference to the 'normal' positioning of the electrodes, as follows: '*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.*'
8	Consultee 3 Specialist Adviser	**3.3**	Suggest modify second sentence: Usually treatment is delivered by a trained clinician. Equipment is available to allow self-administration by the patient but the acceptability of this has not been evaluated in clinical trials.	Thank you for your comment. Section 3.3 of the guidance has been changed to: '*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*.'

9	Consultee 1 Overseas healthcare professional	**4**	As persistence of effect in treating depression is a key issue and there are only 2 studies which have reported on this, it would be important to consider the results of both studies.	Thank you for your comment. Valiengo (2013) and Martin (2013) are the 2 studies with the longest follow-up (6 months). Valiengo (2013) is included in the main extraction table (Table 2) and sections 4.4 and 4.5 of the draft guidance report on its results. Martin (2013) was listed in Appendix A of the draft guidance but the Committee considered your comment and decided to include this study in Table 2.
10	Consultee 1 Overseas healthcare professional	**4 and 5**	General comments: focussing on mainly 1 RCT limits the core information on which the consultation is based. the review should at least consider as key information the RCT of Loo et al 2012, which represents the largest sample of depressed patients in whom tDCS alone was compared with sham tDCS. Given there are only a few RCTs in the field, including the key findings of these studies would also enrich the consultation. For example, earlier studies using lower stimulation parameters and fewer sessions tended to have less efficacy (Eg Loo et al, 2010, Palm et al 2012). Studies which enrolled highly treatment resistant patients (Blumberger eg al) had poorer outcomes. These perspectives would provide useful information informing on stimulus parameters and patient samples.	Thank you for your comment. Loo (2012), Palm (2012) and Blumberger (2012) are all included in the Shiozawa (2014) meta-analysis which is included in the main extraction table (Table 2). The 3 studies are also listed in Appendix A. Studies included in a systematic review which is already included in Table 2 are usually only added separately in Table 2 if they bring important additional information on the efficacy and safety of the procedure. The Committee considered your comment and decided not to change the guidance.

11	Consultee 2 Overseas healthcare professional	**4 and 5**	A PubMed search using the keywords â€œtranscranial direct current stimulationâ€• and â€œmajor depressive disorderâ€• yielded 84 references. Among these studies, 9 sham-controlled, randomized clinical trials were identified (1-9). Also of interest, three meta-analyses for tDCS and depression were identified, two of them with positive results (10-12). Finally, all identified RCTs investigated unipolar depression â€“ no RCT for bipolar disorder was found.	Thank you for your comment. The IP overview is based on a rapid review of the literature and is not a comprehensive systematic review. A meta-analysis was included in Table 2, and other relevant studies listed in Appendix A. Please refer to comment 12 for details.

12	Consultee 2 Overseas healthcare professional	**4 and 5**	In the first study, Fregni et al. (1), found a significant decrease in the Hamilton Depression Rating Scale and Beck Depression Inventory after 5 days of active 20-min, 1mA tDCS in 10 patients, with a mean reduction in depression scores of 60-70%. Similar results were later demonstrated by the same group, recruiting 18 antidepressant-free using a similar protocol (2). After that, Boggio et al. (3) recruited 40 patients with moderate to severe depression, evaluating depression improvement after 30 days of stimulation (patients received 10 tDCS sessions), observing depression improvement after prefrontal tDCS Despite these initial, positive findings, three subsequent studies reported negative findings: (1) the study of Loo et al. (4) , which recruited 40 patients, although treatment was provided every other day (total of 5 sessions) and personality disorders were not excluded; (2) the study of Palm et al. (5), which 22 patients with depression, in a cross-over design, comparing two active stimulation protocols (1mA and 2mA) vs. placebo and; (3) Blumberger et al. (7) that recruited 24 refractory patients. All these studies acknowledged methodological limitations (notably small sample sizes) that could have undermined the efficacy of tDCS.	Thank you for your comment. The Committee is grateful for this comprehensive summary of the evidence base. Of the papers cited: Shiozawa (2014) and Brunoni (2013) are included in the main extraction table. Kalu (2012), Berlim (2012), Palm (2012), Loo (2012), Blumberger (2012), Boggio (2008) and Loo (2010) are all listed in Appendix A. The 2 Fregni (2006) studies were identified originally but were not included in the overview as Letters to the Editors are not normally considered adequate to support decisions on efficacy and are not generally selected for presentation in the overview, unless they contain important safety data. Bennabi (2014) was identified during the post-consultation literature search and has been included in Appendix A.

		4 and 5	In fact, two larger, recent tDCS trials observed that tDCS was an effective treatment for depression: (1) the study of Loo et al. (6), which randomized 64 patients to 15 2mA tDCS sessions over 3 weeks and (2) the study of Brunoni et al. (8) , which enrolled 120 antidepressant-free patients with moderate and severe depression who were randomized in four arms (2x2 design): sham tDCS and placebo pill, sham tDCS and sertraline, active tDCS and placebo pill and active tDCS and sertraline. In this study, not only active tDCS was superior to sham tDCS but also the combined tDCS / sertraline was significantly more effective than in the other treatment groups in reducing depressive symptoms. Finally, in the most recent RCT to date, Bennabi et al. (9) recruited 23 refractory patients, observing no difference between active and sham tDCS after 10 days of stimulation. The studies presented, overall, good methodological quality. All of them were sham-controlled trials that either employed automated sham devices or kept raters blinded regarding the intervention status as the sessions were performed by nurses not involved in any other aspect of the trial. The study adequately randomized and allocated participants, reporting in sufficient details the methodology used. Eligibility criteria were also mainly homogenous, chiefly recruiting patients with moderate-to-severe depression.	

		4 and 5	Nonetheless, some studies also included small samples of bipolar depression patients. Regarding tDCS protocol, all studies placed the anode over the left DLPFC, cathode position varied between the right DLPFC and the supraorbital area. Stimulation protocols were more diverse along studies, with stimulation sessions ranging between 5 to 15, stimulation frequency between every other day to twice a day, and dose varying between 1 to 2 mA. Nonetheless, studies mainly differed regarding the sample size, with many pilot studies. Critical to our review purposes, only two studies recruited more than 25 patients per arm and were considered class I studies (18, 20). According to our methodology, a â€œconvincingâ€• positive study should present a positive outcome in all outcomes â€“ in fact, only Brunoni et al. (20) reported that active was superior to sham tDCS in both depression improvement and response/remission rates, as the study of Loo et al. (18) demonstrated that active tDCS was superior to sham in terms of depression improvement, but not response or remission rates. Therefore, the efficacy of anodal tDCS over the left DLPFC to treat depression is probable (but not definite), with a level B recommendation. 1. Fregni F, Boggio PS, Nitsche MA, Marcolin MA, Rigonatti SP, Pascual-Leone A. Treatment of major depression with transcranial direct current stimulation. Bipolar disorders. 2006; 8(2): 203-4. 2. Fregni F, Boggio PS, Nitsche MA, Rigonatti SP, Pascual-Leone A. Cognitive effects of repeated sessions of transcranial direct current stimulation in patients with depression. Depress Anxiety. 2006; 23(8): 482-4.	

		4 and 5	3. Boggio PS, Rigonatti SP, Ribeiro RB, Myczkowski ML, Nitsche MA, Pascual-Leone A, et al. A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression. Int J Neuropsychopharmacol. 2008; 11(2): 249-54. 4. Loo CK, Sachdev P, Martin D, Pigot M, Alonzo A, Malhi GS, et al. A double-blind, sham-controlled trial of transcranial direct current stimulation for the treatment of depression. Int J Neuropsychopharmacol. 2010; 13(1): 61-9. 5. Palm U, Schiller C, Fintescu Z, Obermeier M, Keeser D, Reisinger E, et al. Transcranial direct current stimulation in treatment resistant depression: a randomized double-blind, placebo-controlled study. Brain Stimul. 2012; 5(3): 242-51. 6. Loo CK, Alonzo A, Martin D, Mitchell PB, Galvez V, Sachdev P. Transcranial direct current stimulation for depression: 3-week, randomised, sham-controlled trial. Br J Psychiatry. 2012; 200(1): 52-9. 7. Blumberger DM, Tran LC, Fitzgerald PB, Hoy KE, Daskalakis ZJ. A randomized double-blind sham-controlled study of transcranial direct current stimulation for treatment-resistant major depression. Front Psychiatry. 2012; 3: 74. 8. Brunoni AR, Valiengo L, Baccaro A, Zanao TA, Oliveira AC, Goulart AC, et al. The Sertraline versus Electrical Current Therapy for Treating Depression Clinical Study: Results from a factorial, randomized, controlled trial. JAMA Psychiatry. 2013; 70(4): 383-91.	

		4 and 5	9. Bennabi D, Nicolier M, Monnin J, Tio G, Pazart L, Vandel P, et al. Pilot Study of Feasibility of the Effect of Treatment With tDCS in Patients Suffering From Treatment-Resistant Depression treated with Escitalopram. Clinical Neurophysiology. 2014. 10. Kalu UG, Sexton CE, Loo CK, Ebmeier KP. Transcranial direct current stimulation in the treatment of major depression: a meta-analysis. Psychol Med. 2012; 42(9): 1791-800. 11. Berlim MT, Van den Eynde F, Daskalakis ZJ. 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. J Psychiatr Res. 2013; 47(1): 1-7. 12. Shiozawa P, Fregni F, Bensenor IM, Lotufo PA, Berlim MT, Daskalakis JZ, et al. Transcranial direct current stimulation for major depression: an updated systematic review and meta-analysis. The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum. 2014: 1-10.	
13	Consultee 3 Specialist Adviser	**4.1 and 4.3**	In discussion of efficacy, data from meta-analysis (Shiozawa 2014) and largest study (Brunoni 2013) are presented alongside each other. Could this be mistakenly interpreted to signify that the Brunoni study was not included in the meta-analyis?	Thank you for your comment. The overview has been changed to state that the Brunoni (2013) study is included in the Shiozawa (2014) meta-analysis.

14	Consultee 5 The Royal College of Psychiatrists	**4.4**	Point 4.4 - It should be noted that not all 120 participants took part in this follow-up study (phase III of the trial). Only those who responded to the acute course of tDCS in phase I or II of the trial were eligible, and 42 people agreed to take part.	Thank you for your comment. The details of the study can be found in the overview. Section 4.4 of the guidance has been changed to: '*A follow-up study of 42 patients who had responded 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*'.
15	Consultee 3 Specialist Adviser	**5**	Might be clearer to separate out data from the large meta-analysis and data from individual studies?	Thank you for your comment. In Sections 4 and 5 the data on efficacy and safety extracted in Table 2 is summarised together regardless of study design. We aim to indicate the source of each finding (by study, and by study design) as it is presented. We aimed to ensure this was clear in the final guidance document.
16	Consultee 3 Specialist Adviser	**5.2**	In this report, the electrodes were soaked in water. Use of saline electrodes with preparation of the skin with alcohol and abrasive saline gel will reduce impedance and should reduce the risk of skin burns. Setting impedance limits on the device will also reduce the risk.	Thank you for your comment.

17	Consultee 5 The Royal College of Psychiatrists	**6**	Also, it might be worth stating that other research has suggested people with severe depression actually respond better to tDCS than those with mild/moderate depression (Ferrucci R, Bortolomasi M, Brunoni AR, Vergari M, Tadini L, Giacopuzzi M, et al. Comparative benefits of transcranial direct current stimulation (tDCS) treatment in patients with mild/moderate vs. severe depression. Clinical Neuropsychiatry. 2009;6(6):246-51)	Thank you for your comment. Ferrucci (2009) study is listed in Appendix A and was not included in the main extraction table because this case series only includes 14 patients with a 4-week follow-up. The committee considered that there was not sufficient evidence to state that the response to tDCS might be better in patients with severe depression. The Committee considered your comment but decided not to change the guidance.
18	Consultee 1 Overseas healthcare professional	**General comment**	Overall i think the document contains sensible conclusions and recommendations.	Thank you for your comment.
19	Consultee 4 The Royal College of Psychiatrists	**General comment**	By contrast the TMS evidence seems to be increasing somewhat in robustness. It is quite widely used in the USA, two systems having been given approval with a third perhaps being approved within a few weeks. I've attached a paper that appeared last week as an example (World Psychiatry 14:1 - February 2015). It uses a 'magic' coil (being sold by an Israeli company who funded and co-authored the study) which isn't really magic but just acts like a large conventional coil. Their results show a clear placebo effect but they claim a real effect on top of this.	Thank you for your comment. NICE is currently reviewing the evidence on transcranial magnetic stimulation for severe depression and the guidance may be updated in light of further evidence.

20	Consultee 1 Overseas healthcare professional	**NOTE**	i lead current research trials funded by competitive research grants (Australian NHMRC, Stanley Medical Research Foundation). For one of these trials, tDCS equipment is supplied by the Soterix company - the company is not involved in study design, conduct, analysis or reporting of results	Thank you for your comment.
21	Consultee 3 Specialist Adviser	**NOTE**	NICE specialist adviser on this technology.	Thank you for your comment.

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