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REVIEW

Regulatory considerations for the clinical and research use of transcranial direct current stimulation (tDCS): Review and recommendations from an expert panel

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Abstract

The field of transcranial electrical stimulation (tES) has experienced significant growth in the past 15 years. One of the tES techniques leading this increased interest is transcranial direct current stimulation (tDCS). Significant research efforts have been devoted to determining the clinical potential of tDCS in humans. Despite the promising results obtained with tDCS in basic and clinical neuroscience, further progress has been impeded by a lack of clarity on international regulatory pathways. Therefore, a group of research and clinician experts on tDCS were convened to review the research and clinical use of tDCS. This report reviews the regulatory status of tDCS and summarizes the results according to research, off-label, and compassionate use of tDCS in the following countries: Australia, Brazil, France, Germany, India, Iran, Italy, Portugal, South Korea, Taiwan, and the US. Research use, off label treatment, and compassionate use of tDCS are employed in most of the countries reviewed in this study. It is critical that a global or local effort is organized to pursue definite evidence to either approve and regulate or restrict the use of tDCS in clinical practice on the basis of adequate randomized controlled treatment trials.

Keywords

tDCS, regulatory, safety

History

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Introduction

The field of transcranial electrical stimulation (tES) has experienced significant growth as evidenced by the number of peer-reviewed publications on non-invasive Brain Stimulation (NIBS) in the past 15 years, as well as by the exponential increase in the number of laboratories involved with such research. One of the NIBS techniques leading this increased interest is transcranial direct current stimulation (tDCS). The exponential growth of tDCS reflects the ease of use of this method in addition to its so far favorable profile combined with its ability to produce significant effects on human neural plasticity (1).

Significant research efforts have been devoted to determining the clinical potential of tDCS in humans. The data from numerous studies conducted by international teams have

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repeatedly shown that tDCS can provide clinical benefits for several conditions such as major depression (2,3), stroke (4–9), aphasia (10–12), chronic pain (13–15), Alzheimer's (16–19), Parkinson's (20), and schizophrenia (21), with no major side-effects. Further, the research utility of tDCS has proved valuable in elucidating brain circuit function by providing a tool capable of safely modulating neurophysiology and behavior in humans (22–26). Despite these advancements in diverse applications of tDCS in basic and clinical neuroscience, however, further progress in some countries such as, for instance, South Korea, where lack of specific regulations for tDCS research has been slowing down a research development. Also, the lack of a plan for regulatory approvals for trials testing clinical approaches may also decrease future interest. Thus, there has been an increased need for regulations governing the use of tDCS, and this has been called for by practitioners, patients, and regulatory agencies.

As clinical and neuroscience research on tDCS is an international effort, and collective safety and efficacy experience influences ongoing work, it is critical to organize and compare regulatory consideration on a federal and global level. We, therefore, convened a group of research and clinician experts on tDCS to review the research and clinical use of tDCS. In this report we summarize the evidence and review the regulatory status of tDCS in Australia, Brazil, France, Germany, India, Iran, Italy, Portugal, South Korea, Taiwan, and the US. These countries were chosen as some of the productive researchers in tDCS are from these countries. We also include at the end of this article an opinion summary from the group regarding its clinical and research use. The group selected to be part of this article is composed from leaders in tDCS research in each respective country, as evidenced by the scientific production of the members. In addition, all the members are affiliated with leading academic, industrial, and/or regulatory agencies.

There are well-established laws for the regulation of medical device distribution and use in most developed countries, such that it is incorrect to focus on the ''need'' for regulation, but rather clarity and consistency in how standing regulations are applied to tDCS. Ambiguity among clinicians and researchers can lead to lack of access to equipment and unfortunate substitutions such as less suitable devices and accessories being used. This document, therefore, places the use in the tDCS in the context of existing international regulations.

Overview of regulatory process

With regard to this topic, it is important to clarify the definition of a ''Medical Device''. The regulatory bodies and agencies of different countries have adopted various positions and standards in defining a Medical Device. According to the US Food and Drug Administration (FDA) (27), a medical device is defined as: ''An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory'' that is recognized for the use in diagnosis, prevention, and treatment in humans without using chemical pathways.

The FDA has established three different classifications for Medical Devices designated as Class I, Class II, and Class III with different standards and controls ensuring safety and efficacy depending on the risk of the device. For example, dental floss and band aids are Class I Medical Devices, non-invasive blood pressure monitors, and OTC TENS devices for treatment of pain or for esthetic purposes represent examples of Class II Medical Devices, and heart replacement valves or deep-brain stimulating electrodes are exemplars of Class III Medical Devices. It is important to note that nearly all non-invasive or cutaneously administered electrical stimulation devices have been deemed Class II medical devices by the FDA, stemming from more than 40 years of accumulated data on their safe use. Based on the FDA definition of a medical device, and recognizing the spectrum of devices regulated, it is thus logical to include tDCS devices—whether indicated for medical treatments, diagnostic purposes, wellness aids, entertainment devices, or for any other purpose—as a Medical Device according to the FDA.

Safety and adverse effects

With the typical current levels and experimental protocols (28), the side-effects of tDCS are mild, benign, and short-lived. In a recent systematic review, Brunoni et al. (29) assembled data from tDCS studies performed up to 2010. Out of 172 articles, 56% mentioned adverse effects and 63% reported at least one adverse effect. Importantly, when they were systematically assessed, the rates of common adverse effects did not differ between the active arms of the studies and the sham arms. These included itching (39.3% vs 32.9%, respectively), tingling (22.2% vs 18.3%), headache (14.8% vs 16.2%), burning sensation (8.7% vs 10%), and discomfort (10.4% vs 13.4%). However, most studies reviewed did not systematically assess adverse effects. Therefore, we suggest that publication of tDCS trials should require systematic assessment and report of the intensity and frequency of adverse effects, even if they are mild or if none are observed.

While it is commonly ignored, tDCS-induced erythema (skin reddening) is an adverse effect significantly more common in active vs sham groups (30–32). The erythema presumably occurs due to an increase in blood flow of dermal vessels accompanying the current application. Although this effect is generally benign, it might compromise study blinding in randomized, sham-controlled trials (30) and, therefore, should be minimized by following the standard procedures regarding tDCS applications. Recently it has also been suggested that the topical pre-treatment with Ketoprofen could reduce the tDCS-induced erythema (33). On rare occasions, tDCS application has led to skin burns (34). However, this appears to occur only when standard procedures regarding tDCS application (such as correct preparation of the skin, humidification of sponges with saline, limit of voltage/current above a maximum impedance, etc.) are not followed (22,35). Therefore, the safety of tDCS is limited to use with appropriate tDCS equipment, accessories, and protocols.

According to the FDA, and similarly to other international regulatory agencies, serious adverse events are those in which the outcome is (i) death, (ii) life-threatening, (iii) hospitalization, (iv) disability/permanent damage, (v) congenital anomaly/birth defect, (vi) required intervention to prevent permanent impairment or damage (for implantable devices),

(vii) and other serious events—e.g. refractory seizures, cardiorespiratory arrest, anaphylactic reaction etc. No serious adverse events attributable to tDCS have been reported in more than 10,000 subjects investigated in the contemporary tDCS literature (1998–2014). Specifically, there have been no reports of cardiorespiratory arrest, seizures, or brain damage. In addition, specific tests have been conducted for serum enolase, a protein associated with neuronal death, with no significant effect (36) and for evidence of structural brain damage (37). Studies have examined and found no significant abnormal changes in electroencephalographic activity (38) or in heart rate variability (39–41). The threshold for adverse effects was suggested in a safety study in rats (42), where the charge density necessary to induce brain damage in rats was found to be at least 100-times higher than the charge density used in tDCS trials. Because skin discomfort and pain are induced with currents even 2–3-times higher than that used in most tDCS experiments, it is highly unlikely that the safety threshold would ever be reached in human tDCS studies.

Interestingly, there is a description of one case report in 1964 of ''respiratory and motor paralysis with cramping of the hands, (. . .) nausea, [and without] loss of consciousness'' during electrical stimulation (35). The authors later acknowledged that a current 10-times higher than the intended amperage was accidentally delivered to this subject (35). Although the conditions of the stimulation in this event, or even the nature of the adverse behavioral response are unclear, this report provides an important reminder of the risk when electrical stimulation is applied outside the range of well-studied parameters. The risk of permanent injury is posed by ''Do It Yourself tDCS'' (DIY-tDCS) (43) that fosters home and un-supervised tDCS applications, outside the controlled settings of laboratories and clinical centers. Importantly, risk designation by the IRB or FDA is specific to *both* the device used and clinical protocol—thus changing any aspect of the device, electrodes, protocol (e.g. increasing dose), or include/exclusion requires re-examination of risk-level. This last point is critical in regards to the so-called ''DIY-tDCS'' movement or ad-hoc commercial products—these cannot claim the benefit of the robust safety record of clinical tDCS precisely because they deviate in these aspects.

Recommendations based on evidence to date

Here we summarize information regarding the safety of tDCS for the benefit of research ethics committees and Institutional Review Boards, as well as in clinical practice. The application of tDCS has presented minimal risk in numerous studies when it has been applied in research or clinical studies within standard parameters. *Minimal risk* means there have been no serious adverse events, that common adverse effects such as reddening of the skin are mild and short-lived, and that reasonable efforts at assessment have determined there is no evidence of brain damage. *Standard parameters* to date mean that (1) the current is less than 2.5 mA, (2) it is applied through electrodes that are known to minimize skin burns at the specific current level, (3) the current application duration is less than 20–60 min per session, and (4) that sessions are not more frequent than twice per day. This does not imply that exceeding these stimulation parameters will result in substantial risk, but that experience with these stimulation parameters is limited, and thus definite statements are not possible to date.

tDCS can be described as a *non-invasive* procedure in the standard medical usage of this term, meaning that it does not involve penetrating the skin or a body cavity. Nonetheless, the application of electrical current to the brain has been shown to induce functional changes (neural plasticity) that, although being the targeted physiological effect, can represent also a potential risk for the patient or participant. Although tDCS has been shown to be safe and effective in many experiments, the stimulation parameters, if chosen incorrectly, might lead to *maladaptive plasticity* rather than adaptive or positive effects on neural plasticity. In fact, this is particularly important when combining with a behavioral therapy. It is important that the given behavioral therapy is associated with adaptive effects.

The safety of tDCS has been demonstrated primarily for short-term use. The effects of long-term use are largely unknown, and there are not enough follow-up studies to understand the effects of continued tDCS over the long-term (44). There are few studies assessing chronic use of tDCS. The safety and efficacy of daily to twice-daily, domiciliary, 30-min, 1–3-mA tDCS sessions across nearly 3 years was reported in a patient with schizophrenia (45). The longest acute treatment trials to date have delivered $\sim$ 6 weeks of tDCS, with up to 30 sessions of tDCS (41, 46). These studies show no increased incidences of adverse events; although data is still limited.

Finally, tDCS is a complex and as yet poorly understood method of manipulating the physical properties of neural tissue. Ethical use requires that the researcher or clinician has current scientific knowledge of the rapidly developing literature, such that research or clinical practice is guided by new evidence on safety and efficacy as it becomes available.

Efficacy

A fundamental effect of tDCS is that it is able to modulate cortical excitability (47–51); therefore, tDCS has been examined as a potential therapeutic intervention in multiple clinical disorders, including depression, chronic pain, stroke, Alzheimer's, and Parkinson's disease (17, 18, 46, 52–60).

One of the main clinical applications being tested with tDCS is stroke. For instance, daily sessions of tDCS improve upper limb function in stroke patients (61), as well as increase scores on activities of daily living (ADLs). These findings have been confirmed by meta-analysis where various montages of tDCS—with or without adjunct physical therapy—improve motor function in mild to-moderate stroke patients (61).

Besides motor function in stroke, language recovery has also been explored with tDCS. Anodal tDCS over perilesional areas improves language function, but the effect was found to persist over time only when tDCS was coupled with language training (62, 63). More research is required to evaluate the effectiveness of tDCS for practical language rehabilitation (anodal/cathodal/dual), primarily through examining the stability of the improvement over clinically significant intervals

of time (64). For example, using cathodal stimulation over the injured cortex, Monti et al. (62) showed that, although the tDCS treatment in aphasia induces a gain in speech performance of ~25%, this effect was transient.

There has been considerable interest in treating depression with tDCS applied asymmetrically to the frontal lobes (typically with anodal electrode over left dorsolateral prefrontal cortex and cathode over right supraorbital cortex). The most recent meta-analysis, incorporating all RCTs to date, found that active tDCS was more effective than a sham stimulation comparator (65). However, given the limited number of RCTs available ($n = 7$), evidence for the antidepressant efficacy of tDCS cannot be considered conclusive, and further trials are required. Earlier meta-analyses reported mixed findings, likely because of heterogeneity in the evidence base (66, 67). An important consideration may be concurrent antidepressant drug treatment. When tDCS was used as monotherapy, a 63% response rate was observed, with more than doubling of the remission over sham control (66). In other reviews of tDCS and depression, the odds ratio for (OR) favorable symptom response was 1.63 (95% CI = 1.26–2.12) and the OR for remission was 2.50 (95% CI = 1.26–2.49) (65). When an acute course of tDCS was followed by weekly-to-fortnightly maintenance tDCS sessions, the cumulative probability to avoid relapse was 83.7% at 3 months, and 51.1% at 6 months (68). When Major Depressive Disorder (MDD) and Bipolar Depressive Disorder (BDD) were examined separately, five sessions of anodal stimulation induces a beneficial effect that persists at 1 week and 1 month in both groups (3).

There has also been an effort to use tDCS for enhancing cognitive function in patients with Alzheimer's, suggesting that tDCS can positively improve memory performance (16, 17, 19); and that the after effects of repetitive sessions of tDCS seem to outlast for at least 4 weeks (17).

In patients with schizophrenia that were refractory to medication, cathodal tDCS over the left temporoparietal junction (TPJ) coupled with anodal tDCS over the left dorsolateral prefrontal cortex (DLPFC) reduces auditory verbal hallucinations on 31%, lasting for up to 3 months. Also, general severity of illness improves on the Positive and Negative Syndrome Scale (ES = 0.98, 95% CI = 0.22–1.73) (21).

In studies of tDCS effects on pain sensitivity in healthy subjects, anodal stimulation leads to an increment in pain threshold and better tolerance compared to sham stimulation (69). The cathodal stimulation reduces the sensitivity to Aδ-fiber-mediated cold sensation and C-fiber-mediated warm sensation compared with baseline, whereas Aβ-fiber-mediated somatosensory inputs were less affected (70). In patients undergoing the total knee arthroplasty, tDCS reduces opioid consumption and pain level (71). For treating chronic pain regardless of etiology, the ES of tDCS has been estimated between −2.29 (95% CI= −3.5 to −1.08) (72) and −0.86 (95% CI = −1.54 to −0.19) (73). Although a prespecified sub-group analysis in meta-analysis with distinct types of chronic pain indicated that tDCS was superior to sham (ES = −0.59, 95% CI = −1.10 to −0.08) (30), a further meta-analysis failed to detect a superiority of tDCS over sham in reducing pain (74), possibly due to heterogeneity. The analgesic effect of tDCS combined with a technique of visual illusion induces a better effect regarding all pain subtypes, while the tDCS alone improves only in continuous and paroxysmal pain (75). Also, tDCS combined with visual illusion improves neuropathic pain in spinal cord injury, with a 50% mean decrease of symptoms (59). In episodic migraine without aura, anodal preventive treatment reduces migraine attack frequency, migraine days, attack duration and acute medication intake. This benefit persists on average 4.8 weeks after the end of treatment (76). In chronic migraine the anodal effect applied on a primary motor cortex induces a delayed response (57). Recent evidence also points to the potential of tDCS for the treatment of phantom limb pain (77, 78).

Although the findings on treating pain with tDCS have, thus, been varied, the effects with chronic pain are promising, and may justify the use of tDCS to treat pain in selected patient populations. For the most part, the studies of anodal stimulation have demonstrated at least a moderate size effect. Two excitability-enhancing (anodal) tDCS montages have resulted in analgesic effects, one montage with the anode over the primary motor cortex with mean ES of 9.59% (13, 15, 79, 80) and another montage with the anode over the DLPFC with a mean ES of 15.79% (81). Typically, the analgesic effects have been shown to be cumulative, with the majority of clinical trials providing stimulation on 5 consecutive days (with some extending over 10 days). Problems in this research have been (a) the heterogeneity of the studies that make specific comparisons difficult, (b) the lack of systematic intention to treat designs, and (c) the high dropout rates. Finally, new placebo-controlled studies of tDCS for the treatment of pain are required that include a systematic follow-up according to the recommendations of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (82).

tDCS has also been used to decrease craving associated with food, smoking, cocaine, and alcohol. A recent meta-analysis examined the use of frontal lobe tDCS (and rTMS) to reduce craving, considering both craving in substance dependence and craving for high palatable food (83). Both rTMS and tDCS over the DLPFC revealed a SE of 0.48 (95% CI = 0.316–0.636), with no significant difference between these treatments. In the application to manage tinnitus, anodal tDCS reduces the intensity of this symptoms with a SE of 0.77 (95% CI = 0.23–1.31) (84). Finally, anodal tDCS over the premotor areas also improves sleep and fatigue symptoms in patients with post-polio syndrome (85).

Current status on the use of TDCS

Table 1 summarizes the current regulatory status of tDCS in Australia, Brazil, France, Germany, India, Iran, Italy, Portugal, South Korea, Taiwan, and the US. These countries were chosen given some of the leading researchers of tDCS are from these countries.

Australia experience

In Australia, medicines and therapeutic medical devices are regulated by the Australian Therapeutic Goods Administration (TGA), which has a Register of approved medicines and devices. Currently, no tDCS machines are

Table 1. Current regulatory status of tDCS in Australia, Brazil, France, Germany, India, Iran, Italy, Portugal, South Korea, Taiwan and United States.

	Basic tDCS research		Clinical tDCS research		tDCS device approved for clinical use		Off Label tDCS use		Compassionate tDCS Use	
Country	Yes/No	Comments	Yes/No	Comments	Yes/No	Comments	Yes/No	Comments	Yes/No	Comments
Australia	Yes	Requires Ethics Committee approval only.	Yes	Ethics Committee approval required plus Clinical Trial Notification form needs to be lodged with the TGA.	No	Registry required with the TGA.	Unclear	The use of tDCS outside the formal research protocol is in principle, possible on a patient-by-patient basis by using the TGA special scheme for unapproved medical devices.	Unclear	
Brazil	Yes	Requires Ethics Committee approval and in some cases CONEP.	Yes	Ethics Committee approval and ANVISA approval.	No	Requires ANVISA approval. Only registered device is the 'DC–STIMULADOR' from the company 'NEUROCONN GMBH'.	Yes	Although approved by the Brazilian Sanitary Agency (ANVISA) and by a professional society, off-label use is rare.	Yes	
France	Yes	Requires Ethics Committee and CPP approval	Yes	Ethics Committee approval required plus approval from the ANSM.	No	Requires CE mark.	Yes	Requires Ethics Committee approval.	Yes	
Germany	Yes	Requires Ethics Committee approval.	Yes	Ethics Committee approval required plus approval from the BfARM.			Yes	Not compensated by insur-ance. companies	Yes	
India	Yes	Requires Ethics Committee approval.	Yes	Requires mainly Ethics Committee approval although in 2013 national regulations were established.	No		Unclear		Unclear	
Iran	Yes	Requires Ethics Committee approval.	Yes	Requires Ethics Committee approval plus registry in the IRCT.	No	Currently two companies are developing their own devices.	Yes	Based on the IRIMC regulations.	Yes	
Italy	Yes	Requires Ethics Committee approval.	Yes	Requires Ethics Committee approval.	Yes	Requires CE mark.	Yes	In some Italian hospital and private medical centers, tDCS is offered as off-label treatment and is authorized as standard treatment, but it needs to undergo specific ethic committee approval.	Yes	Medical doctors can also prescribe tDCS free of charge for outpatients under the heading of electro-therapy but the structure where tDCS sessions will take place should be authorized for that prescription.

(*continued*)

Table 1. Continued

	Basic tDCS research		Clinical tDCS research		tDCS device approved for clinical use		Off Label tDCS use		Compassionate tDCS Use	
Country	Yes/No	Comments	Yes/No	Comments	Yes/No	Comments	Yes/No	Comments	Yes/No	Comments
Portugal	Yes	Requires Ethics Committee approval.	Yes	Requires Ethics Committee approval plus INFARMED approval	No		Unclear	Infarmed does not provide guidelines.	Yes	Requires Ethics Committee approval.
South Korea	Yes	Requires Ethics Committee approval.	Yes	Requires Ethics Committee approval plus MFDS approval.	No		No		No	
Taiwan	Yes	Requires Ethics Committee approval.			No	tDCS devices are not considered as medical devices.	Unclear		Unclear	
US	Yes	Requires Ethics Committee approval.	Yes	Requires IRB approval-IDE not often requested.	Yes	At the time of the writing of this article, the only companies having an IDE for tDCS devices from the FDA were Soterix Medical (tDCS and HD-tDCS) and, NeuroConn.	Yes	Subject to professional and ethical guidance. The adaptation of Iontophoresis devices—especially with outputs exceeding conventional tDCS protocols and with accessories not designed for the scalp—should be approached with caution since the dose and technology is different than devices designed for tDCS. Notably common Iontophoresis devices are not designed to be applied across the head as its electrodes and methods to control current may not be ideal for such purpose. We recommend that tDCS devices are strictly output-limited consistent with conventional tDCS protocols.	Yes	

ANSM, National French agency for medicines and health products safety; ANVISA, Brazilian Health Surveillance Agency; BfARM, German Federal Institute for pharmaceutical and medical products; CONEP, *Comitê Nacional de Pesquisa*; CPP, *Comité de Protection de Personnes*; IDE, Investigational Device Exception; INFARMED, Portuguese National Authority for Drugs and Medical Devices; IRB, Institutional Review Board; IRCT, Iranian Registry of Clinical Trails; IRIMC, Islamic Republic of Iran Medical Council; MFDS, Korean Ministry of Food and Drug Safety; TGA, Australian Therapeutic Goods Administration.

registered with the TGA. Thus, for each clinical trial in which tDCS is used, apart from obtaining approval from the institution's Research Ethics Committee for the trial protocol, a Clinical Trial Notification form needs to be lodged with the TGA, noting the trial protocol ID and providing specifications of the machine to be used. For use outside of a clinical trial (e.g. basic physiological research), the research protocol should be approved by the institution's Research Ethics Committee but does not need to be lodged with the TGA. Further, some professional societies may provide their own guidelines about the use of tDCS. For example, the Royal Australian and New Zealand College of Psychiatrists states

Transcranial Direct Current Stimulation (tDCS), another innovative brain stimulation treatment that does not involve seizure induction, has shown promise in recent trials for the treatment of depression. Until further data is available, it should only be given within approved research protocols. (Position Statement #79 on Repetitive Transcranial Magnetic Stimulation, revised October 2013)

There have been anecdotal reports of practitioners providing tDCS as a treatment to patients for depression outside formal research protocols and without TGA notification, i.e. practice that is outside regulatory approvals.

In Australia, tDCS research commenced in the mid-2000s with randomized controlled trials of tDCS in depression. Research interests have rapidly expanded and currently include the application of tDCS to the treatment of depression, schizophrenia, mild cognitive impairment and pain management. In addition, research groups have focused on cognitive effects of tDCS, and the use of neuroimaging and computer modeling to understand the effects of tDCS.

Brazil experience

Since 2005, Brazil has been involved with pioneering clinical trials testing tDCS for some clinical conditions such as stroke (86), pain (79), cognition (48), Parkinson's (87), tinnitus (88), and depression (89).

The use of tDCS in clinical research is regulated by the local ethics committee (Comitê de Ética em Pesquisa, CEP), which follows the statement of ethical principles from the World Medical Association-Declaration of Helsinki (90). In most cases, the CEP has enough autonomy to approve a clinical research proposal using tDCS. In some circumstances, particularly in centers where tDCS use is less common, the CEP consults the National Ethics Committee (Comitê Nacional de Pesquisa, CONEP) in order to approve clinical tDCS research.

The Health Related Products in Brazil needs to be approved by the Brazilian Health Surveillance Agency (ANVISA), which is a governmental regulatory agency characterized by its administrative independence and financial autonomy. To date, the only device registered by ANVISA (the health agency that regulates approval of medical devices and drugs in Brazil) to specific use as tDCS is the ''DC–STIMULADOR'' from the company ''NEUROCONN GMBH''. The approval from ANVISA would be similar for instance to the CE mark for devices used in Europe and also shares similarities with FDA approval for medical devices.

Besides ANVISA clearance, professional societies, in some cases, also make recommendations for use of medical devices and drugs. To date, the only professional society that has issued recommendations is the occupational therapist and physical therapy. In their resolution it says that tDCS can be used ''for treatment of individuals, when combined with physical therapy, with the aim of controlling pain, improving sensorimotor function and cognition'' (COFFITO–Resolution, 434, September 27, 2013). Although their resolution gives ON-label approval for a broad use of tDCS; additional details for each indication, taking into consideration the levels of scientific evidence for specifics situations, are necessary and thus need to be considered carefully by the clinician employing this technique.

Finally, it should be under-scored that the ''compassionate use'' of tDCS may be allowed in Brazil, in circumstances in which the patient is not eligible for a clinical trial and there are no satisfactory, alternative clinical therapies.

France experience

For now, French health authorities have not approved the use of tDCS for any condition clinically. The use of tDCS for clinical and research purposes in healthy participants and patients should be restricted to studies, predominantly clinical trials. The use of tDCS for clinical purpose should be restricted to hospital and labeled research units and should be delivered in a medical environment allowing an optimal management of adverse events. Serious adverse events occurring during protocols must be declared to ethical and health authorities within 24 h to warrant the safety survey of the device. tDCS is usually carried out by trained technicians, nurses, psychologists, or assistants under the supervision of a medically responsible licensed physician.

All protocols involving Humans receiving non-invasive brain stimulation have to obtain an approval by a regional ethical committee (i.e., CPP: Comité de protection de personnes) and by the national French agency for medicines and health products safety (ANSM). The benefit/risk ratio and the safety of the device must be clearly exposed for each novel protocol or indication. An independent scientific evaluation, a subscription to a specific insurance for the study, and a justification that the budget to complete the study was already obtained are usually recommended before the statement of the ethical committee. The device must have a CE mark for medical use.

''Off-labele'' (off-label) applications such as patients suffering from resistant disabling symptoms can be envisaged with the approval of an ethical committee. In this case, the benefit/risk ratio must be clearly in favor of therapeutic benefits for the patient. In all cases, patients must be clearly informed and must give their written informed consent. The cost is not paid for by national or private health insurances.

tDCS is used in France by several teams for clinical and research purposes. Clinical uses are mainly for neuropsychiatric conditions (e.g. chronic pain, stroke, depression, schizophrenia, addiction). Groups of professionals aim to establish guidelines; for instance, French users of tDCS for psychiatric purposes have developed a national association organizing annual training courses and scientific meetings to warrant

optimal and safe use of tDCS in accordance with recent international literature (STEP section from French Association for biological psychiatry and neuropsychopharmacology).

Germany experience

The regulatory situation for application of tDCS in Germany is complex. With regard to application of tDCS in research, it has to be discerned between clinical trials, and non-clinical studies. Clinical trials are defined by the aim to explore clinical, physiological, and side-effects of a drug or device, in the context of establishing or improving a clinical treatment tool, which is usually not certified for clinical use (91). These studies, which are in most cases initiated by the producer of the device, have to be approved not only by the local ethics committee, but also by the respective federal organization, the BfARM (Federal Institute for pharmaceutical and medical products). For all other studies, which do not fulfill these criteria, which is the case for most tDCS protocols, approval by the local ethics committee is sufficient. In the past, however, there has often been confusion about this regulation, because the wording of the respective laws and regulations suffers from some fuzziness. With regard to approval by the ethics committee, no formal criteria, such as about ''minimal risk'' do exist, which gives the committees some freedom of decision to evaluate risk-benefit relations. No major difficulties have been experienced however to receive ethics approval to perform respective studies in the past, although, especially when the committee has not been confronted with this specific research field before, it might be necessary to deliver very detailed information about protocol, and safety aspects.

For clinical application of tDCS beyond studies, off-label treatment (in terms of compassionate use) is principally possible, but will in most cases not be compensated for by the health insurances. In these cases, informed consent of the patient, detailed documentation, and clarification that the individual treatment, and not scientific interest, is the main cause for the therapeutic decision, are critical.

India experience

Research studies on tDCS from India have been on the increase in the recent past (92). Most of these research reports are based on IRB approved protocols that have followed stringent guidelines with respect to the safety of tDCS administration that match contemporary international standards (93). Significant bulk of these publications has illustrated the clinical utility of tDCS in schizophrenia as a monotherapy, add-on treatment in acute phase of psychosis resulting in quicker amelioration of symptoms (92) insight facilitation into illness (93). In addition, studies from India have reported certain important leads towards the understanding of possible neurobiological basis for beneficial effects of tDCS in schizophrenia (94). However, all these studies are of open-label nature; currently, controlled studies with stringent research design are in progress to ascertain the potential leads obtained in earlier reports.

With regards to the regulation of tDCS usage in India, it is noteworthy that, until the recent past, the application of medical devices in India has remained largely unregulated. In 2013, the Government of India has introduced the Drugs and Cosmetics (Amendment) Bill to establish several quality control measures with regards to the regulation of medical devices application; the implementation of this bill into an act is still in progress. Meanwhile, the contemporary use of tDCS in India is primarily regulated by stringent review of study protocols by the IRB of respective institutes. Similar review of protocols by IRB's is expected for targeted tDCS application using arrays of small electrodes termed as HD-tDCS. In India, currently, systematic applications of tDCS are predominantly restricted to research studies to understand the neurobiological mechanisms and to facilitate its implementation for treating various neuropsychiatric disorders like schizophrenia.

Iran experience

Iran should be considered as a good sample among developing countries with no or limited exposure to tDCS. tDCS as a low-cost and easy to use technology provides both researchers and clinicians in Iran and other developing countries with new opportunities for clinical, cognitive, brain mapping, and computational modeling studies and finally clinical services. There are limited but growing numbers of publications from Iranian institutes using tDCS for stroke, pain, and drug addiction patients since 2011. In 2014, one private company and one university affiliated research group have received funds for ''Research and Development'' studies to produce different range of tDCS devices ''to be used in research settings but not for clinical use'' with options for alternating and random noise currents and high definition stimulations. However, they are obligated to receive governmental approval to be able to sell their devices in the official market to the Labs with ''tDCS labels''. In Iran, tDCS devices are under the control of medical technologies office of Food and Drug Organization at Ministry of Health and, to our best knowledge, no Iranian company has received any approval from this office yet to sell tDCS devices produced in Iran (June 2014), but an international company is registered there to sell tDCS devices in Iran.

Ethical committees in Iranian universities are the main approval reference for tDCS studies as ''non or minimally invasive interventions''. All clinical trials using tDCS must be registered in Iranian Registry of Clinical Trails (IRCT). First approvals from ethical committees for tDCS studies were time consuming regarding the lack of knowledge for tDCS among committee members, but now it could be done in less than 3 months in most of the universities. The major challenge for getting an ethical approval for tDCS studies in Iran is for children subjects (under age 18).

Basically, there is no official approval for ''on-label'' use of tDCS as a clinical service in Iran. However, there are growing numbers of clinical centers using tDCS as an ''off-label'' intervention for a wide range of disorders including tinnitus, stroke (mainly aphasia and dysphagia), depression, auditory hallucination, drug addiction, etc., based on their professional and ethical regulations as a member of the Islamic Republic of Iran Medical Council (IRIMC). Insurance companies do not cover any costs related to tDCS interventions. There was an expert panel in the Islamic Republic of

Iran Psychology and Counseling Council (IRIPC), as the main regulatory body for the psychological interventions in the country in May 2014, discussing applying technologies such as neurofeedback, biofeedback, tDCS, and TMS, by registered psychologists. This expert panel concluded that psychologists should abandon any electric or magnetic stimulatory intervention without presence and supervision of an in-charge medical doctor. Based on Iranian experiences with recent exposure to tDCS as a new medical technology with potential benefits for clinical populations, we would recommend other developing countries with no or limited experience with tDCS to put a wide range of educational programs at their first priority. Policy-makers, granting agencies, regulating bodies, researchers, clinicians, and even public audiences should be targeted with educational programs regarding potentials, threads, challenges, hopes, abuse potentials, and regulations for clinical use of tDCS.

Italy experience

tDCS, first applied in Italy several years ago for the non-invasive modulation of cortical excitability (95) in more recent years, has increasingly gained attention as one of the most innovative approaches under investigation as a therapeutic tool for neurological diseases. In particular, the primary area of application is the rehabilitation of cognitive impairments in patients with Alzheimer's disease and the treatment of motor and language disorders in stroke patients (18, 62, 63, 96). Noteworthy, the IV Italian Report on stroke published in 2014, which focuses to innovations in the field of stroke prevention and rehabilitation, has a section dedicated to tDCS (97). More recently, it has been proposed for the treatment of neuropathic pain and hemicrania and, in neuropsychiatry, for depression and psychosis (3, 98). In stroke rehabilitation, tDCS is largely used as add-on intervention to standard physical/cognitive therapies, generally administered in the chronic stage of illness (99). The treatment protocols generally include randomized designs with at least 10 tDCS sessions on consecutive weekdays (20 min, 2 mA). Although being considered as minimal risk, therapeutic applications of tDCS follow the same recommendations for the use and safety of transcranial magnetic stimulation.

To date many Italian research institutions have set up ad-hoc neuromodulation laboratories, accessible to both in- and out-patients, dedicated to basic and clinical research with tDCS. Clinical trials are typically conducted by a multidisciplinary team of professionals with expertise in various areas, such as neuropsychology, neurophysiology, and neurology, and they are carried out by trained technicians, usually a psychologist or a medical assistant under the supervision of a neurologist. A licensed physician serves as a medically responsible clinician, closely supervising the tDCS application and medical conditions of the patients. In some Italian hospital and private medical centers, tDCS is offered as off-label treatment and is authorized as standard treatment, but it needs to undergo specific ethic committee approval. Medical doctors can also prescribe tDCS free of charge for outpatients under the heading of electrotherapy, but the structure where tDCS sessions will take place should be authorized for that prescription.

Portugal experience

In Portugal, as with many other countries, it is necessary to make the distinction in research studies between clinical trials and non-clinical trials.

Non-clinical trials only require approval from the local ethics committee (23, 24) following the general guidelines established in the declaration of Helsinki (90), even if they pose more than minimal risk.

Clinical trials require also initial approval from the local ethics committee, and then a formal approval from the National Authority for Drugs and Health Products (*infarmed - Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.*). There is also a mandatory online registration in the national database of clinical trials (PNEC – *Portal Nacional de Ensaios Clínicos*) that will also be available through the European Clinical Trials Portal–EU Clinical Trials Register. There are also additional steps if the medical device is not CE marked.

To the best of our knowledge there are currently no *infarmed* approved tDCS devices. In order to approve one, the manufacturer or its representative in the European Union (EU) needs to apply for a validation of the device, providing all the required information. After that, the medical device needs to be classified based on the potential risk for humans. Device and accessories are assessed independently based on a set of criteria (e.g. invasiveness), and the device receives an overall classification based on the element, which can potentially pose more risk.

Compassionate treatments are possible after approval from the local ethics committee. Off label treatments are not regulated by the *infarmed*. Lastly, the use of medical devices will also be based on the internal regulations of professional societies based on the empirical evidence, which will determine what constitutes the ''clinical procedure'', the required training to perform it, and who is certified to administer it.

South Korea experience

A medical device that potentially poses safety hazards to the intended user should first be approved by the Korean Ministry of Food and Drug Safety (MFDS) before it can be legally marketed and sold. According to personal communications with the MFDS, the MFDS regards tDCS as having a risk profile equivalent to Class II, which is an even higher risk category than transcranial magnetic stimulation (Class III). Currently, there is no government approved tDCS device for brain stimulation on the market in Korea. Therefore, the application for product approval of tDCS should be undertaken for any clinical use. In order to secure product approval, technical documents, along with clinical study reports, have to be submitted and reviewed by the MFDS. Regarding the evidence of clinical study reports, pre-existing clinical data from studies conducted outside Korea can be submitted. However, if the MFDS judges that the data are not sufficient to establish the clinical efficacy of the medical device, a formal clinical trial for product approval should be conducted in Korea.

A scientific clinical trial can be conducted regardless of product approval considerations. MFDS and the local

institutional review board (IRB) should approve the study protocol. A protocol submitted to the MFDS should not only contain the detailed clinical study protocol, but also detailed technical information about the device; this requirement may be onerous and require significant administrative work by the clinical researcher for submission. This process should be repeated for every research study using tDCS; tDCS devices explicitly used for clinical trial should be destroyed afterwards. The approval criteria for study protocols using tDCS are inconsistent among local IRBs: Some IRBs initially offer conditional approval requiring further approval by MFDS; however, other IRBs may offer a full approval of the study protocol without any review by MFDS, probably due to lack of knowledge regarding MFDS's strict regulation. This is an important concern given that some protocols may not follow all regulatory needs in Korea according to the Korean Medical Appliances Act.

A search using the keywords ''tDCS'' or ''transcranial direct current stimulation'', along with ''Korea'', on the PubMed search engine between 2008–2014 resulted in a total of 29 articles. Approval of study protocol by a local IRB was described in 26 articles; there were no available descriptions of IRB approval in the other three articles—which may indicate either lack of reporting or research without necessary IRB approval.

Taiwan experience

The current regulatory situation of tDCS in Taiwan is quite similar to that of Germany. As of now the tDCS (including HD-tDCS) device is not considered as a medical device in Taiwan, and thus non-clinical research only requires the approval of the local ethics committee, without the need to obtain approval from the Food and Drug Administration (FDA) of Taiwan. Clinicians can also apply for minimal risk or regular IRB applications to the ethics committee in hospitals. However, since tDCS is still a novel research tool in Taiwan, the IRB process can be different from time to time, depending on the reviewers'' degree of familiarity towards brain stimulation. In the absence of a set of clearly-defined clinical protocols for tDCS, in our experience it is useful to provide details of tDCS effect and possible risk or side-effects based on reports from the literature or international safety guidelines (100) to the IRB committee. Note that, as of now, researchers in Taiwan may sometimes encounter difficulties when trying to import tDCS devices due to different interpretations among officials on whether tDCS should go through the clearance process of a medical device. In our view, it is important for researchers and clinicians to engage in crosstalk with regulation agencies to facilitate the establishment of a more comprehensive regulation and protocols for the safe use of tDCS in research contexts.

US experience

In the US, medical devices, such as tDCS, are regulated by the FDA. As noted above, the FDA definition for a medical device would include any brain stimulation device, including tDCS and, thus, tDCS in the US can be regulated as a medical device regardless of indications for use. Clinical trials using tDCS are regulated under the ''Investigational Device Exception'' (IDE) that allows for human research pending controls, documentation, and monitoring by both the manufacturer and investigator. Every clinical trial with tDCS requires an IDE approval by the FDA except for defined exceptions. These exceptions include those clinical trials which are determined by the (local) institutional IRB to be ''non-significant-risk'' (NSR)—such trials are provided a de-facto ''expedited IDE'' by the FDA and are subject to be reduced by specific regulatory burden by the manufacturer and investigator.

To our knowledge, in the US, IRBs ubiquitously (at a minimum overwhelmingly) designate tDCS trials NSR (see adverse event discussion above), thus not requiring a formal IDE application to the FDA. At investigator/IRB discretion, the FDA may be directly asked to provide a risk-designation for a trial. To our knowledge, in response to such requests that are trial-specific, the FDA generally considers tDCS trials as NSR (101–103). Even if a trial is considered significant-risk, it may be ethically approved by the IRB/FDA (or funding agency such as NIH) if the benefits offset risk and/or appropriate measures are taken to control risk.

Based on FDA statutes and other device precedents, we are aware of no legal basis for tDCS, for any application and any use, to be excluded from medical device regulations the US. The production and distribution of medical devices in the US is subject to strict regulations including FDA Quality Systems. We recommended that the devices and protocols not reproducing clinical tDCS in regards to device/electrode design and protocols (including strict dose control, include/exclusion, professional monitoring) not be conflated with tDCS in regards to safety or efficacy.

The granting of an (expedited) IDE is not indicative of clearance by the FDA to market devices for uses other than ''investigational'' ones or plans to approve tDCS for the treatment of a disease—but only the sanctioning of a clinical trial. The US FDA clears devices only in response to specific manufacturers request to review products, not spontaneously or in general based on a body of medical research. In the absence of such a manufacturer application, tDCS has not been cleared by the US FDA for the treatment of any medical indication. At the time of the writing of this article, the only companies having an IDE for tDCS devices from the FDA were Soterix Medical (tDCS and HD-tDCS) and NeuroConn. However, many IRB-sanctioned studies have been able to gain NSR approval using off-label devices or devices available from commercial sources not having an IDE.

In the US, physicians may prescribe treatment to patients that are ''off-label'' subject to professional and ethical guidance. Off-label conventionally implies using a therapy considered safe and without changing dose, applying it for an indication or intended use other than that which has been cleared by the FDA. In this sense, the adaptation of Iontophoresis devices—especially with outputs exceeding conventional tDCS protocols and with accessories not designed for the scalp—should be approached with caution since the dose and technology is different than devices designed for tDCS. Notably common Iontophoresis devices are not designed to be applied across the head as its electrodes and methods to control current may not be ideal for such purpose. We recommend that tDCS devices are

strictly output-limited consistent with conventional tDCS protocols.

The FDA has developed various guidance documents for expedited regulation of non-invasive electrical stimulation devices (with indications ranging from esthetic to clinical) with either prescription of over-the-counter access; although pending these provide a basis for considering ''Limited Output'' tDCS. tDCS should not be confused with FDA designated Cranial Electrotherapy Stimulation (CES) that is not a comparable dose (not Direct Current) (104).

Conclusion

tDCS is a relatively safe technique, associated with mild side-effects such as itching, tingling, headache, burn sensation, and discomfort (22, 35). tDCS is easy to administer and its use within *standard parameters* (as defined above) has been associated with minimal risk of serious adverse effects.

There is now promising clinical evidence about the effects of tDCS in several clinical conditions such as depression, stroke, chronic pain, tinnitus, schizophrenia, amongst others (15, 18, 21, 77, 79, 89), especially when applied with other therapies (105, 106). There is also available data for phase II/III clinical trials combining tDCS with other interventions for major depression (105). However, large trials are still needed to confirm the effects of tDCS when testing in a more heterogeneous sample, taking into account more its clinical and functional outcomes.

According to our review, tDCS can potentially be used as an off-label treatment in Iran, Germany, the US, Italy, Brazil, and France. The regulations for off-label treatment vary according to the country''s internal policies, and in most of the cases there is not a clear policy in place for the off-label use of tDCS. In some cases off-label use requires IRB//Ethical Committee and/or medical executive approval. The device needs also to be approved for clinical use. Presently, only Iran, US, Europe, and Brazil have such approved devices. However, for instance, in some cases, such as the US, the only approved devices are Iontophoresis, which may not be the optimal ones, namely because of the type of electrodes and the parameters that typically exceed the *standard parameters* defined above. Off-label treatment should then be conducted with caution, as presently there is insufficient data about the long-term use of such treatments.

Another option is to use it as ''compassionate treatment''. According to the FDA, the use of a medical device in patients which do not meet the inclusion criteria for clinical research, is possible if the physician believes that such use could benefit the treatment of that disease or condition. In that sense, based on the severity of the disease or condition, and in the absence of other treatment alternatives, tDCS can been used as a compassionate treatment option. This seems to be the case in most countries, with the exception of South Korea, where such an option seems not to be possible.

In terms of research, in most countries, only IRB/Ethical Committee approval is required, and usually the studies using tDCS are considered to be of minimum risk. France and South Korea require an additional approval from their National Health Agency. However, it seems that most IRB approve the protocol based on the promising data already available, without major concerns or obstacles.

Nonetheless, clear guidelines about the standard tDCS application protocols, which include parameters such as duration, intensity, standardized adverse effects assessment, and reporting, amongst others, are still needed. Then IRBs/Ethics Committees and national agencies can have at their disposal guidelines that can be useful for a harmonization of the regulatory requirements that seems to be impairing the development of tDCS in some countries. In the event that the results from brain stimulation studies is confirmed on larger samples of subjects and the optimal parameters to use during stimulation (i.e. intensity, duration, areas to stimulate) will be determined, tDCS may be a good tool for the treatment of different neurological and neuropsychiatric disorders as additional treatment option. Indeed this technique requires portable devices and may represent an additional economical and practical treatment for the rehabilitation of patients at home. Moreover, because tDCS electrodes are simply secured to the scalp and leave the patient free to move, it can be easily delivered during rehabilitation (online stimulation). Our international review with some of the most productive and leading researchers in this area has shown that tDCS has been considered safe for research protocols at a global level and given its initial effect and safety profile, there has been increasing pressure for the clinical use of this device as seen by its off-label and compassionate use in many of the countries surveyed in this review. It is, therefore, imperative that a global or local effort is organized to pursue definite evidence to either approve or abandon the use of tDCS in the clinical practice on the basis of adequate randomized controlled treatment trials and also as to regulate its safe clinical use. Although tDCS seems to be an easy tool to use, it is also easy to misuse it, in turn with lack of efficacy or even inducing worse, adverse effects.

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