TECHNOLOGY REVIEW (MINI-HTA)

TRANSCRANIAL DIRECT CURRENT STIMULATION (tDCS) FOR DEPRESSION AND SCHIZOPHRENIA

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
02/2024

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EVIDENCE INFORMED DELIBERATIVE PROCESS

This Technology Review underwent an evidence informed deliberative process during the Health Technology Assessment (HTA) Technical Advisory Committee meeting, chaired by the Director, Medical Development Division, MOH. Then it was endorsed in the HTA-CPG Council meeting chaired by the Director General of Health.

Published by:
Malaysian Health Technology Assessment Section (MaHTAS)
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62590, Putrajaya
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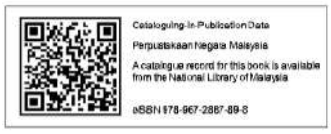
Available online via the official Ministry of Health Malaysia website:



e-ISBN: 978-967-2887-89-8

SUGGESTED CITATION: Nur Farhana M, Muhammad Ainuddin A, Roza S, and Izzuna MMG. Transcranial Direct Current Stimulation (tDCS) for Depression and Schizophrenia. Technology Review. Ministry of Health Malaysia: Malaysian Health Technology Assessment Section (MaHTAS); 2024. 86 p. Report No.: 02/2024

DISCLOSURE: The author of this report has no competing interest in this subject and the preparation of this report is entirely funded by the Ministry of Health Malaysia.

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EXECUTIVE SUMMARY

Background

Mental health disorders have emerged as a pressing global concern, with the World Health Organization (WHO) estimating that such conditions account for a substantial portion of the worldwide burden of disease. Mental disorders accounted for 654.8 million estimated cases in 1990 and 970.1 million cases in 2019, corresponding to an increase of 48.1% between 1990 and 2019 with mood disorders such as depression also contributing significantly to the overall disease burden.

In the context of Malaysia, mental health disorders have likewise gained increasing recognition and attention. According to the National Health and Morbidity Survey conducted in 2015, the prevalence of mental health disorders among Malaysian adults was estimated to be 29% which was a threefold increase in comparison with the 10% prevalence rate identified in 1996. A review of depression studies in Malaysia showed the prevalence of MDD in Malaysia to be between 8 to 12%. At the same time, for schizophrenia, the expected incidence rate was 100 cases/100,000 population/year and possible reasons for low reported incidence were delayed or underreporting and administrative reasons.

Although numerous advanced medications and psychotherapeutic interventions are available for the management of depression and schizophrenia, a significant proportion of patients either do not respond adequately or experience debilitating side effects. Treatment-resistant depression and schizophrenia remain significant challenges, highlighting the need for innovative treatment approaches. One such intervention that has garnered increasing interest is transcranial direct current stimulation (tDCS). This technique involves the application of a weak electrical current to specific regions of the brain, with the aim of modulating neural activity and potentially improving the symptoms associated with these mental health conditions.

Emerging evidence suggests that tDCS may offer a novel and effective adjunctive therapy for individuals struggling with treatment-resistant depression, potentially addressing a critical unmet need in the management of this debilitating condition. Similarly, research has also explored the potential of tDCS in the treatment of schizophrenia, with studies indicating that this non-invasive brain stimulation technique may have a positive impact on cognitive functioning, negative symptoms, and even auditory hallucinations in individuals living with this complex mental disorder.

Hence, this review was requested to assess the evidence on the use of tDCS as a therapeutic modality for patients with depression and schizophrenia focusing on its potential application in the Malaysian context before its introduction in health facilities in Ministry of Health.

Objective/ aim

The objective of this technology review was to assess the effectiveness, safety, and cost-effectiveness of transcranial direct current stimulation (tDCS) for depression and schizophrenia.

Methods

A systematic search was conducted on the following databases without any restriction on publication language and publication status. The Ovid interface: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to Dec 1st, 2023. Searches were also run in Cochrane Embase, PubMed, and INAHTA databases. Google was used to search for additional web-based materials and information. Additional articles were identified by reviewing the references of retrieved articles. The last search was conducted on 17th July 2024.

Results and conclusions

Search results

A total of **410** records were identified through the Ovid interface, Pubmed and other sources. After screening, 46 articles were assessed for eligibility and 344 records were excluded. After reading, appraising, and applying the inclusion and exclusion criteria to the full-text articles, 20 were included while the other 26 were excluded since the studies had irrelevant populations and few were narrative reviews. Twenty full-text articles finally selected for this review were one umbrella review, 12 systematic reviews and meta-analyses, five randomised controlled trials, one cross-sectional study, and one cost analysis.

Efficacy/ effectiveness

Transcranial direct current stimulation (TDCS) for depression

Multiple meta-analyses and systematic reviews demonstrated that transcranial direct current stimulation (tDCS) appeared as an effective treatment for major depressive disorder (MDD), showing significant improvements in depressive symptoms, with moderate evidence for improved response rates and, to a lesser extent, remission rates when compared to sham treatments. The effectiveness of tDCS appears to be enhanced when combined with medication, while evidence of its standalone efficacy remains limited. However, the quality of evidence is mixed, and the long-term effectiveness of tDCS is still uncertain.

Transcranial direct current stimulation (TDCS) for schizophrenia

Limited retrievable evidence suggests that tDCS has shown limited ability to reduce positive symptoms, improve executive function, working memory, attention, and auditory hallucinations. Some studies reported significant improvements in negative symptoms particularly with higher frequency stimulation, improvement in self-awareness, and psychological domain of life quality, however, the effects were short-term. The overall effectiveness of tDCS in treating schizophrenia appears inconsistent with mixed results across different studies.

Safety

Evidence consistently shows that transcranial direct current stimulation (tDCS) appears safe and well-tolerated intervention for both depression and schizophrenia. Multiple systematic reviews, meta-analyses, and randomized controlled trials report no significant differences in dropout rates or adverse events between active tDCS and sham groups. Common mild side effects include itching, tingling, and local discomfort, with no serious or irreversible adverse effects documented across numerous studies.

Economic implication

Limited retrievable evidence suggests that the cost of a tDCS treatment program for depression is around [redacted] per patient for a 15-session program. In Norway, tDCS treatment costs vary significantly between home-based and outpatient settings, with prices ranging from [redacted] depending on the setting. The estimated cost of tDCS devices ranges from a few hundred to several thousand dollars, depending on their features and research-grade capabilities.

Organisational Issues

Training

Training for tDCS focuses on proper device use and safety. Researchers and technicians must learn equipment setup, correct electrode placement, and dosage accuracy. Physicians should oversee higher-risk procedures, but no specific professional qualifications are required for operators. Training includes managing adverse effects like skin burns and cognitive changes, with competency assessments after instruction. Future certification for trainers may be required.

Guidelines

Clinical practice guidelines on transcranial direct current stimulation (tDCS) for depression and schizophrenia generally acknowledge its potential but fall short of making specific recommendations. For depression, some guidelines note the efficacy of tDCS, especially in non-drug-resistant cases, but no formal recommendation is provided. In schizophrenia, the evidence is mixed, with meta-analyses showing limited or no significant effects on symptoms, leading to a lack of endorsement for its use. Overall, while tDCS is recognized as a promising treatment, particularly for depression, more research is needed to support its broader clinical application, and its use should be carefully supervised by trained psychiatrists.

Ethical Issues

Ethical concerns in transcranial stimulation research focus on informed consent, risk-benefit analysis, and the fair distribution of outcomes. Using tDCS for neuroenhancement raises ethical issues, such as widening social inequalities and risks related to unknown long-term behavioral effects. An international survey among tDCS researchers found tDCS to be seen as partly effective in research and clinical contexts, but with greater ethical concerns for enhancement use. Most researchers opposed public availability due to safety risks, emphasizing the need for stricter regulations and more clinical trials. Woodham et al. (2021) also stressed the importance of regulation, particularly with the rise of DIY use, and highlighted concerns over maladaptive long-term neuroplastic changes, calling for professional oversight to ensure safety.

Conclusion

In conclusion, transcranial direct current stimulation (tDCS) shows potential as a treatment for depression, particularly in reducing depressive symptoms and improving response rates compared to sham treatments. While tDCS appears effective, its benefits may not surpass those of traditional antidepressants, and its effectiveness as a standalone treatment remains limited. The combination of tDCS with medication shows more significant improvements, suggesting that tDCS might be best used as an adjunctive therapy. However, its effectiveness for schizophrenia is less clear, with limited and inconclusive evidence regarding its impact on

negative and cognitive symptoms. In terms of safety, tDCS is generally well-tolerated, with a relatively low incidence of adverse effects. Economically, limited evidence suggests that the cost of a tDCS treatment program for depression is [redacted] per patient for a 15-session program. The use of tDCS for MDD is acknowledged though it is not specifically recommended in many guidelines.

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ABBREVIATION

AEs	Adverse Events
CASP	Critical Appraisal Skills Programme
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CI	Confidence Interval
DLPFC	Dorsolateral Prefrontal Cortex
FDA	Food and Drug Administration
g	Effect size
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HICs	High-Income Countries
HTA	Health Technology Assessment
INAHTA	International Network of Agencies for Health Technology Assessment
LMICs	Low and Middle-Income Countries
MaHTAS	Malaysian Health Technology Assessment Section
MD	Mean Difference
MeSH	Medical Subject Headings
MDD	Major Depressive Disorder
MICs	Middle-Income Countries
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-Analyses
OR	Odds Ratio
P3	Parietal lobe position 3
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized Controlled Trial
ROB2	Risk of Bias 2
ROBIS	Risk of Bias in Systematic Reviews
SR	Systematic Review
T3	Temporal lobe position 3
tDCS	Transcranial Direct Current Stimulation
UK	United Kingdom
USA	United States of America
WHO	World Health Organization

1.0 BACKGROUND

Mental health disorders have emerged as a pressing global concern, with the World Health Organization (WHO) estimating that such conditions account for a substantial portion of the worldwide burden of disease.[1] Specifically, mental disorders have been identified as the leading cause of years lived with disability, surpassing even cardiovascular and circulatory diseases.[1] Mental disorders accounted for 654·8 million estimated cases in 1990 and 970·1 million cases in 2019, corresponding to an increase of 48·1% between 1990 and 2019 with mood disorders such as depression also contributing significantly to the overall disease burden.[2] In 2019, 1 in every 8 people, or 970 million people around the world were living with a mental disorder, with anxiety and depressive disorders the most common.[1]

In the context of Malaysia, mental health disorders have likewise gained increasing recognition and attention. According to the National Health and Morbidity Survey conducted in 2015, the prevalence of mental health disorders among Malaysian adults was estimated to be 29% which was a threefold increase in comparison with the 10% prevalence rate identified in 1996.[3] Two of the most prevalent mental health conditions in the country are depression and schizophrenia which have significant impacts on individuals, families, and society as a whole. A recent study revealed that approximately 30% of Malaysian students aged 16 years and above experience mental health problems, with depression being a significant concern.[4]

Depression, characterized by persistent feelings of sadness, hopelessness, and loss of interest, is a debilitating condition that can severely impair an individual's ability to function.[5] Schizophrenia, on the other hand, is a chronic and complex mental disorder that often involves hallucinations, delusions, and cognitive impairments, profoundly affecting an individual's perception of reality and daily functioning.[6] A review of depression studies in Malaysia showed the prevalence of MDD in Malaysia to be between 8 to 12%.[7] At the same time, for schizophrenia, the expected incidence rate was 100 cases/100,000 population/year and possible reasons for low reported incidence were delayed or underreporting and administrative reasons.[8]

Although numerous advanced medications and psychotherapeutic interventions are available for the management of depression and schizophrenia, a significant proportion of patients either do not respond adequately or experience debilitating side effects. Treatment resistant depression and schizophrenia remain significant challenges, highlighting the need for innovative treatment approaches.[9] One such intervention that has garnered increasing interest is transcranial direct current stimulation (tDCS).[10] This non-invasive brain stimulation technique is claimed to have shown promising results in the treatment of both depression and schizophrenia.[10] This technique involves the application of a weak electrical current to specific regions of the brain, with the aim of modulating neural activity and potentially improving the symptoms associated with these mental health conditions.[10]

Emerging evidence suggests that tDCS may offer a novel and effective adjunctive therapy for individuals struggling with treatment-resistant depression, potentially addressing a critical unmet need in the management of this debilitating condition.[11] Similarly, research has also explored the potential of tDCS in the treatment of schizophrenia, with studies indicating that

this non-invasive brain stimulation technique may have a positive impact on cognitive functioning, negative symptoms, and even auditory hallucinations in individuals living with this complex mental disorder.[12]

Hence, this review was requested to assess the evidence on the use of tDCS as a therapeutic modality for patients with depression and schizophrenia focusing on its potential application in the Malaysian context before its introduction in health facilities in Ministry of Health.

2.0 OBJECTIVE / AIM

The objective of this technology review was to assess the effectiveness, safety, and cost-effectiveness of transcranial direct current stimulation (tDCS) for depression and schizophrenia.

3.0 TECHNICAL FEATURES

Transcranial Direct Current Stimulation (tDCS) is a non-invasive brain stimulation technique that modulates neuronal activity using a constant, low electric current. This method involves placing electrodes on the scalp to deliver direct current to specific brain regions. The primary aim of tDCS is to alter cortical excitability and promote neuroplasticity, which can lead to changes in brain function and behaviour.[13,14]

Transcranial Direct Current Stimulation (tDCS) operates by delivering a weak electrical current (typically 1-2 mA) through electrodes placed on the scalp. The current flows from the anodal electrode (positive) to the cathodal electrode (negative), modulating neuronal activity in the targeted brain regions. The effects of tDCS depend on the polarity of the electrodes. Anodal stimulation increases cortical excitability by depolarizing neurons, enhancing synaptic plasticity and promoting learning and memory. Cathodal stimulation decreases cortical excitability by hyperpolarizing neurons, reducing their likelihood of firing, and is used to inhibit overactive brain regions, such as in schizophrenia. While the exact mechanisms are still under research, tDCS is believed to affect neurotransmitter systems, synaptic plasticity, and neural network dynamics.[13,14]

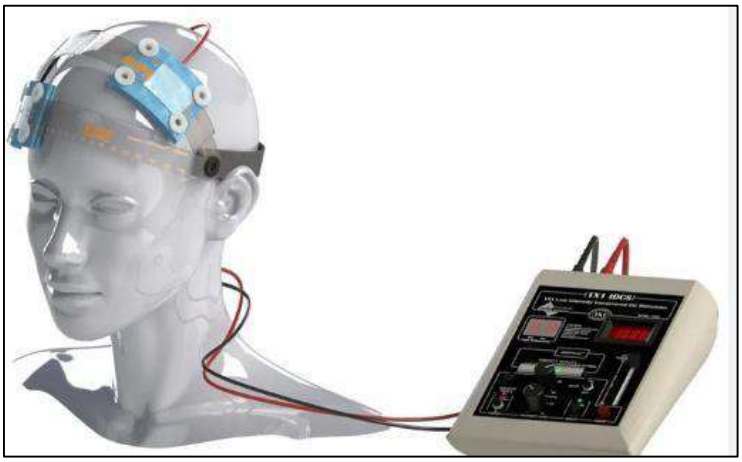

Figure 1: Transcranial Direct Current Stimulation (tDCS) device applied to a phantom head model, with the anode over F3 and the cathode over the right supraorbital area.

Transcranial Direct Current Stimulation (tDCS) devices primarily consist of four main components: electrodes (typically one anode and one cathode), a power supply (commonly 9V batteries), an amperemeter (to measure the current intensity), and a potentiometer (to adjust the electric current). One electrode is placed on the scalp over the targeted cortical area, while the other electrode can be positioned on the scalp or at an extra-cephalic site (such as the deltoid muscle), with the goal of restoring the left-to-right brain activity imbalance to a normal state.[13,14]

The typical electrode placement for tDCS in treating depression involves positioning the anode at F3 (according to the International 10-20 Electrode Placement System) over the left dorsolateral prefrontal cortex (DLPFC) and the cathode over the contralateral supraorbital area. For schizophrenia, the common setup places the anode over the right DLPFC at F4 and the cathode over the left temporoparietal junction (midway between T3 and P3). When tDCS is activated, a weak direct current (0.5–2 mA) flows from the anode (positive pole) to the cathode (negative pole), resulting in hypopolarization of brain areas near the anode and hyperpolarization of areas near the cathode.[14] Transcranial Direct Current Stimulation (tDCS) involves daily sessions lasting 20–40 minutes over a period of 5 to 15 days, requiring regular visits to the clinic, which can be inconvenient and may result in treatment being discontinued.

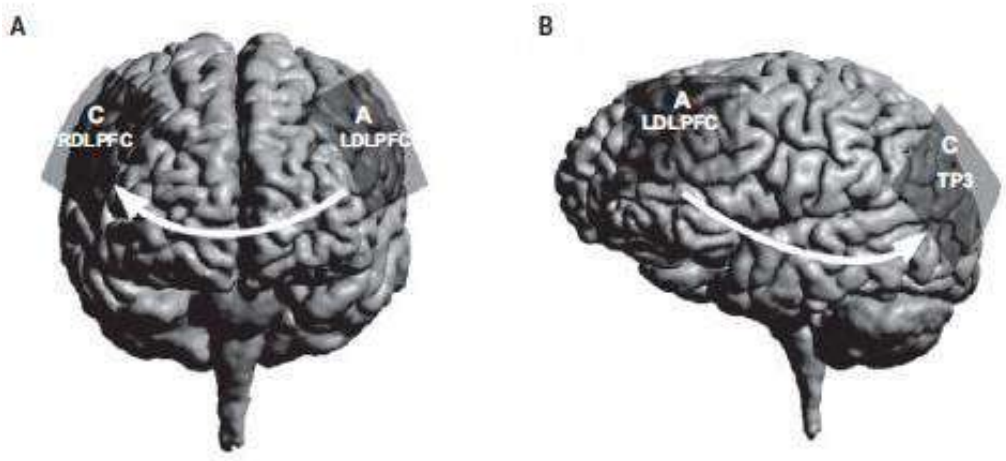

Figure 1: Transcranial direct current stimulation electrodes position and the current flow direction for each psychiatric disorder (A: Depression B: Schizophrenia)

Transcranial Direct Current Stimulation (tDCS) is claimed to be effective in treating depression and schizophrenia by modulating neuronal activity and promoting neuroplasticity. For depression, tDCS targets the dorsolateral prefrontal cortex (DLPFC) with anodal stimulation to enhance neuronal activity and is claimed to improve mood and cognitive function. In schizophrenia, tDCS is claimed to address symptoms like auditory hallucinations and cognitive deficits by using cathodal stimulation to inhibit overactive brain regions or anodal stimulation to activate underactive areas, helping to balance neuronal activity and reduce symptoms.

4.0 METHODS

A systematic review was conducted. Search strategy was developed by the two authors and an *Information Specialist*.

4.1 SEARCHING

The following electronic databases were searched through the Ovid interface:

- MEDLINE® All < 1946 to 17th July 2024>
- EBM Reviews - Health Technology Assessment 4th Quarter 2016
- EBM Reviews - Cochrane Database of Systematic Reviews 2005 to July 2024
- EBM Reviews - Cochrane Central Registered of Controlled Trials June 2024
- EBM Reviews - Database of Abstracts of Review of Effects 1st Quarter 2016
- EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2016

Other databases: PubMed, US FDA, INAHTA

General databases such as Google Scholar was used to search for additional web-based materials and information. Additional articles retrieved from reviewing the bibliographies of retrieved articles. The search was limited to articles on human. There was no language limitation in the search. **Appendix 1** showed the detailed search strategies. The last search was conducted on 17th July 2024.

4.2 SELECTION

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria. Relevant articles were then critically appraised depending on the type of the study design. Studies were graded according to *US/ Canadian Preventive Services Task Force* (**Appendix 2**). All data were extracted and summarised in evidence table as in **Appendix 3**.

The inclusion and exclusion criteria were:

Inclusion criteria:

a.	**Population**	Adult patients with depression and schizophrenia
b.	**Intervention**	Transcranial direct current stimulation (TDCS)

c.	**Comparator**	Sham tDCS, placebo, or other standard treatments (e.g., medication, psychotherapy)
d.	**Outcomes**	**Effectiveness:** Reduction in depressive symptoms (measured by standardized depression rating scales, e.g., Hamilton Depression Rating Scale) Reduction in schizophrenia symptoms (measured by standardized schizophrenia rating scales, e.g., Positive and Negative Syndrome Scale) Cognitive function improvements Quality of life **Safety:** Adverse events, complications **Economic implications:** cost, cost-analysis, cost-effectiveness analysis, cost-utility analysis, cost-benefit analysis, cost-minimisation, budget impact analysis
e.	**Study design**	HTA reports, systematic review with/out meta-analysis, randomised controlled trial (RCT), cohort, case-control, economic evaluation studies
f.	Full text articles published in English	

Exclusion criteria:

a.	**Study design**	Case report, case series, animal study, laboratory study, narrative review
b.	Non-English full text articles	

5.0 RESULTS

5.1 Search results

An overview of the search is illustrated in Figure 4. A total of 398 records were identified through the Ovid interface and PubMed while two were identified from references of retrieved articles. Twenty duplicate references were found; 390 potentially relevant titles were screened using the inclusion and exclusion criteria. Of these, 46 relevant abstracts were retrieved in full text. After reading, appraising, and applying the inclusion and exclusion criteria to the 46 full-text articles, 20 were included while the other 26 were excluded since the studies were included in the systematic reviews, had irrelevant populations and few were narrative reviews. All full-text articles finally selected for this review were one umbrella review, 12 systematic reviews and meta-analyses, five randomised controlled trials, one cross-sectional study, and one cost analysis.

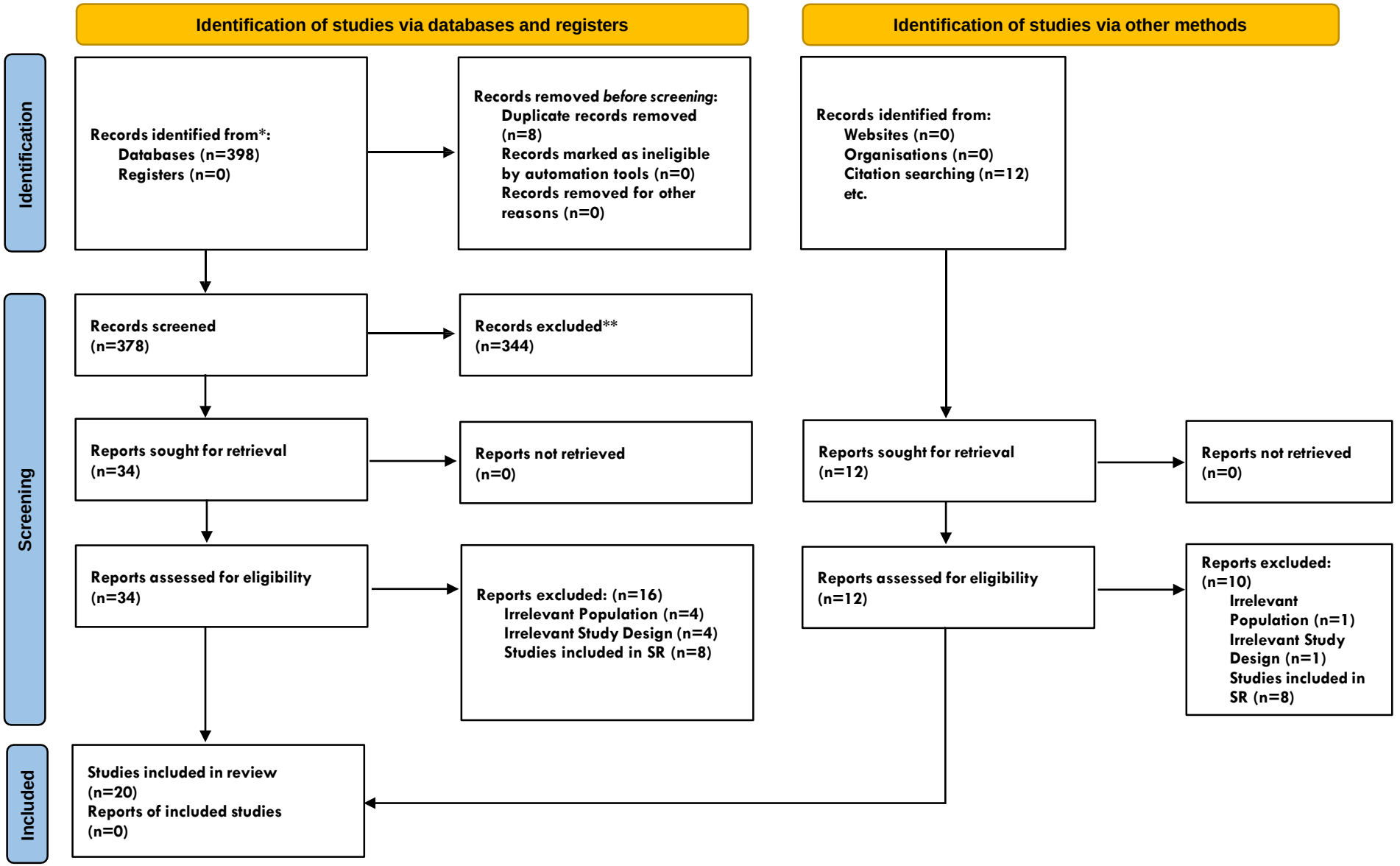

Figure 4: Flow chart of retrieval of articles used in the results

5.2 Quality assessment / risk of bias

Risk of bias was assessed using Risk of Bias in Systematic Reviews (ROBIS) for systematic review, Risk of Bias 2 (RoB2) for randomised control trial, and Critical Appraisal Skill Programme (CASP) checklist for non-RCTs and observational study. These assessments involved answering a pre-specified question of those criteria assessed and assigning a judgment relating to the risk of bias.

5.2.1 Risk of bias assessment for included systematic review.

The risk of bias in the included systematic reviews was assessed using the Risk of Bias in Systematic Reviews (ROBIS) tool. Most of the systematic reviews, whether they included meta-analyses (MA) or network meta-analyses (NMA), demonstrated a low risk of bias. This was primarily because the majority of the included studies were randomized controlled trials (RCTs) with a solid risk of bias profile. Only a few instances of "Unclear" risk were noted in the domain related to the identification and selection of studies, suggesting that the systematic reviews assessed are generally of high quality and have a low risk of bias.

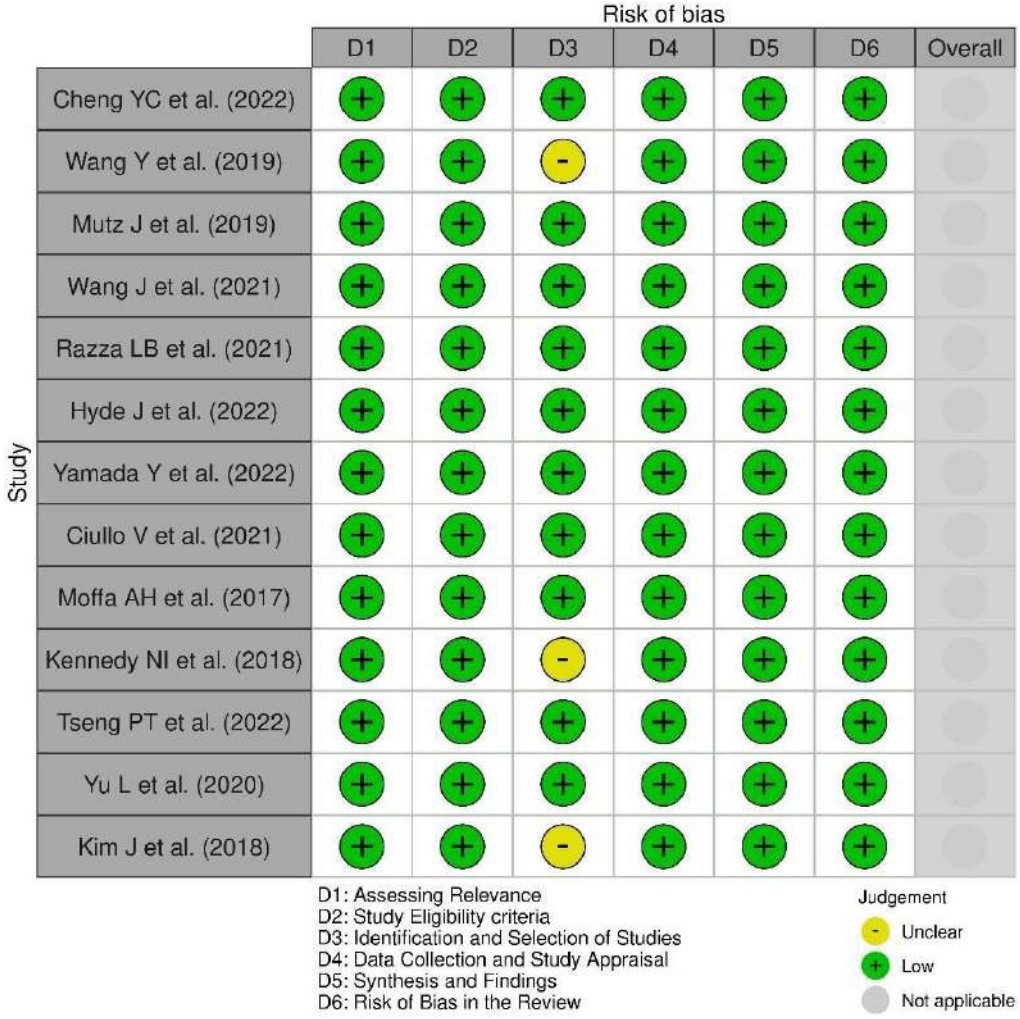

Figure 2: Summary of risk of bias assessment for systematic review using ROBIS

5.2.2 Risk of bias assessment for included RCT studies.

The risk of bias in the included randomized controlled trials (RCTs) was assessed using the Risk of Bias 2 (RoB2) tool. The overall assessment revealed a moderate to low risk of bias across the RCTs. However, there were notable issues in domain 1 (randomization process) in three RCTs. The randomization process and allocation concealment were not clearly defined, which is a critical aspect as it can significantly affect the internal validity of the trials.

The randomization process is crucial to ensure that the allocation of participants to different intervention groups is free from bias, thus maintaining the integrity of the comparison between groups. Inadequate reporting or implementation of randomization and allocation concealment can lead to selection bias, undermining the validity of the trial outcomes. Despite these concerns, the majority of the included RCTs adhered to rigorous methodological standards, suggesting that the findings from these studies are generally reliable, though some caution is warranted due to the identified biases in a few studies.

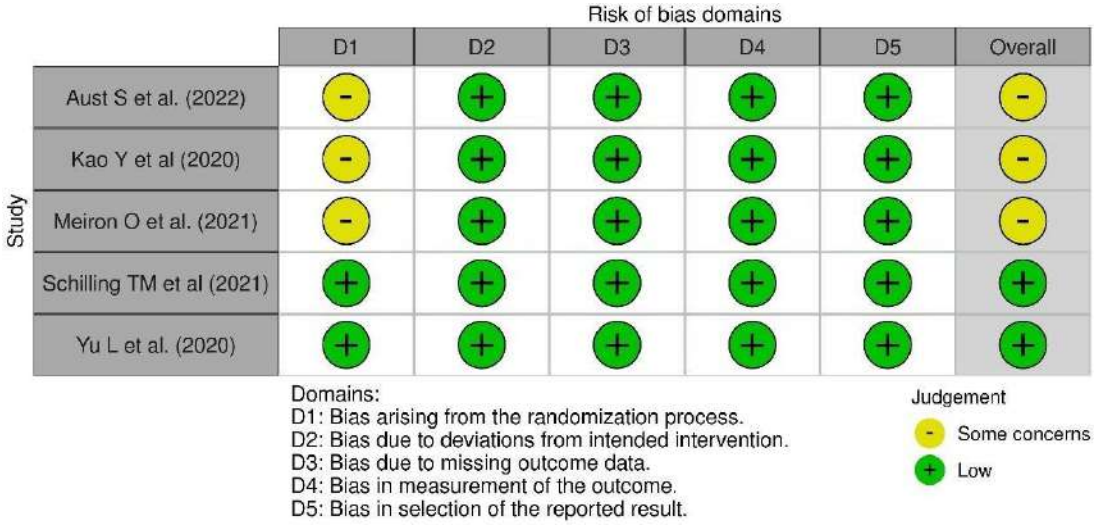

Figure 3: Summary of risk of bias assessment for RCT using ROB2

5.3 Characteristics of included studies

The systematic review included various studies focusing on the effectiveness of tDCS for treating depression and schizophrenia, published from 2017 to 2022. For depression, the review incorporated meta-analyses and systematic reviews from multiple countries including Brazil, Taiwan, China, and the United Kingdom. The number of patients in these studies ranged from 455 to 6,750. The primary intervention in all studies was tDCS, often compared against sham treatments. The outcomes assessed in these studies focused on depression improvement, response rates, remission rates, and primary and secondary outcomes. Depression improvement was measured by effect sizes (g) or mean differences (MD) in depression severity scores. Response rates were indicated by odds ratios (OR) showing the likelihood of patients responding to treatment, while remission rates were also measured by OR indicating the likelihood of patients achieving remission. Primary outcomes were typically depression scores on scales like the Montgomery-Åsberg Depression Rating Scale (MADRS) and Hamilton Depression Rating Scale (HDRS-17). Secondary outcomes included acceptability (dropout rates) and adverse events, providing a comprehensive view of tDCS's efficacy and safety in treating depression.

For schizophrenia, the review included meta-analyses and randomized controlled trials from various countries such as Taiwan, the United States, and Germany, with patient numbers ranging from 19 to 2,211. The primary intervention was tDCS, compared to sham treatments. The outcomes assessed in these studies included negative symptoms, positive symptoms, cognitive impairments, symptom reduction, self-appraisal of mental illness, medication adherence, and quality of life. Negative symptoms were measured by standardized mean differences (SMD) and Hedge’s g. Positive symptoms were evaluated for changes. Cognitive impairments were assessed through performance in working memory and other neuropsychological tests. Symptom reduction was measured using scales like the Positive and Negative Syndrome Scale (PANSS). Additional outcomes included self-appraisal of mental illness and medication adherence, evaluated through specific subscale scores, and quality of life, measured using domains of the World Health Organization Quality of Life (WHOQOL). Table 2 displays the characteristics of the included studies in this review.

Table 2: Characteristics of the included studies

Study	Study design	Number of patients	Intervention	Comparison	Key Outcomes
DEPRESSION					
1.Razza LB et al. (2021) Brazil	Umbrella review	7 meta-analyses 5,615 major depressive episodes patients	tDCS	Sham	**Depression improvement, response and remission** tDCS was superior to comparison groups across examined outcomes Depression improvement: (k = 25, g = 0.46, [95%CI]: 0.22-0.7) Response: (k = 18, OR = 2.28, 95%CI 1.52-3.42) Remission: (k = 18, OR = 2.12, 95%CI 1.42-3.16)
2.Cheng YC et al. (2022) Taiwan	SR and Meta-Analysis	65 studies, 2,686 MDD participants	tDCS	Sham	**Depressive symptoms** 0.544 (0.364‑0.725) Active tDCS group showed a significant effect on the response rate of depressive symptoms (OR = 1.959, p = 0.013) but not on the remission rate (OR = 1.500, p = 0.076)
3.Wang Y et al. (2019) China	SR and Meta-Analysis	9 studies, 623 MDD patients	tDCS	Sham	**Depressive symptoms (MADRS)** tDCS more effective than control group in reducing depression symptoms MD = -5.18, 95% CI: -7.13 to -3.23, p < 0.00001 **Depressive symptoms (HDRS-17)** tDCS more effective than control group in reducing depression symptoms MD =-3.95, 95% CI: -5.58 to -2.32, p < 0.00001

Study	Study design	Number of patients	Intervention	Comparison	Key Outcomes
4. Mutz J et al. (2019) United Kingdom	SR and Network Meta-Analysis	113 studies, 6,750 major depressive episodes patients	tDCS	Sham	**Response, remission, depression severity scores** Pairwise meta-analysis: tDCS more efficacious than sham therapy across all outcomes Network meta-analysis: -tDCS (OR 2.65, 95% CI: 1.55 to 4.55) were more efficacious than sham therapy
5. Wang J et al. (2021) China	SR and Meta-Analysis	12 studies, 455 MDD patients	tDCS tDCS + medication tDCS + psychotherapy	Sham	**Primary outcomes:** **Overall effects of tDCS for depression** Severity: Depression score of active group was significantly lower compared to sham group (z = 2.38, p = 0.017) Subgroup analysis: superiority of active treatment was only present in the tDCS + medication therapy group (g = − 0.855, 95% CI − 1.234 to − 0.475, z = 4.42, p < 0.001) not tDCS alone,or tDCS + psychotherapy, Acceptability: No significant difference in dropout rates **Secondary outcomes:** Response rate: Higher in active group but not statistically significant Remission: Higher in active group but not statistically significant
6. Razza L B et al. (2021) Brazil	SR and Meta-Analysis	11 studies, 311 MDE patients	tDCS	No TDCS	**Primary outcome** Follow-up depression improvement (*k* = 13, *g* = -0.81, 95% confidence interval [CI]: -1.28; -0.34, *I2* = 84.0%) **Secondary outcome:** -No predictor of response was associated with the outcome

Study	Study design	Number of patients	Intervention	Comparison	Key Outcomes
7. Aust S et al. (2022) Germany	RCT	148 MDD patients	CBT + tDCS	CBT	**Change in MADRS score:** No significant difference between groups
8. Hyde J et al. (2022) United Kingdom (UK)	Systematic Review and Meta-analysis	208 RCTs, (MDD) or bipolar disorder (n = 99), Schizophrenia or Schizoaffective Disorder (n = 59)	tDCS	Sham	tDCS active stimulation was significantly bettter than sham for symptoms of depression, SUD, total, negative symptoms and auditory hallucinations in schizophrenia Depression: −0.87 (−1.51 to −0.24) SUD: −0.73 (−1.00 to −0.46) Schizophrenia Total symptoms: −0.63 (−1.03 to −0.23) Negative symptoms: −0.54 (−0.95 to −0.14) Auditory hallucinations: −0.42 (−0.81 to −0.02)
9. Yamada Y et al. (2022) Japan	Systematic Review	5 studies, 132 patients	tDCS		tDCS had significant effects on emotion recognition in patients with schizophrenia or depression Among 3 tDCS studies, two of which found significant effects only in emotion recognition, one of which targeted depression and the other targeted schizophrenia
10. Ciullo V et al. (2021) Italy	Systematic Review	41 studies,	tDCS		tDCS has the potential to enhance processing speed, working memory, and executive functions in patients with mood and schizophrenia-spectrum disorders
11. Moffa AH et al. (2017)	Systematic Review and Meta-Analysis	6 RCTs, 289 MDD patients	tDCS	Sham	**Acceptability:** No significant difference in dropout rates between groups **Adverse events:** No significant difference in overall adverse effects rates between groups

Study	Study design	Number of patients	Intervention	Comparison	Key Outcomes
12. Sauvaget A et al. (2019)	Cost-analysis		tDCS		The hospital production cost of a tDCS depression treatment program for a single patient was estimated at € 1555.60: € 99 in equipment costs, € 1076.95 in staff costs, and € 379.65 in structural costs
SCHIZOPHRENIA					
1. Kennedy NI et al. (2018) United States	Systematic Review and Meta-Analysis	7 RCTs, 197 patients with Schizophrenia	tDCS	Sham	**Auditory Hallucinations:** Improved but no significant difference in symptom reduction **Positive psychotic symptoms:** Improved but no significant difference in symptom reduction **Negative symptoms:** Significant reduction in symptoms (Hedge's g = -0.63, p = 0.02).
2. Tseng PT et al. (2022) Taiwan	Systematic Review and Network Meta-Analysis	48 RCTs, 2,211 patients with Schizophrenia	tDCS	Sham	**Negative symptoms:** Significant alleviation of negative symptom severity in tDCS sham therapy group (SMD = 0.251 [95%CI, 0.022-0.480];P = 0.03) **Acceptability:** No significant difference **Positive symptoms:** No significant difference
3. Kao Y C et al. (2020) Taiwan	RCT	60 patients with Schizophrenia	tDCS	Sham	**Effects on clinical outcomes:** No significant group-by-time interaction for all dimensions of PANSS total modified, cognitive component and individual symptom dimension scores, global cognition as measured by MMSE, or psychosocial functioning as measured by PSP butshowed statistical significance for PANSS G12 item score [F(3,56) = 6.22, p = 0.001].

Study	Study design	Number of patients	Intervention	Comparison	Key Outcomes
					Effects on self-appraisal of mental illness: significant group-by-time interactions for SAIQ presence/outcome subscale score [F(2,55) = 7.64, p = 0.0012] **Effects on medication adherence:** significant group-by-time interactions for MARS total score [F(2,53) = 19.36, p < 0.001] and MARS subjective response to taking medication subscale score [F(2,53) = 20.10, p < 0.001] but not for medication adherence subscale score [F(2,53) = 4.07, p = 0.023]. **Effects on perceived quality of life:** significant group-by-time interaction for the WHOQOL psychological domain score [F(2,55) = 7.95, p < 0.001] but not for the global score of WHOQOL [F(2,55) = 4.23, p = 0.02] and social relationships [F(2,55) = 4.51, p = 0.015], physical [F(2,55) = 0.40,p = 0.67] and environmental [F(2,55) = 2.9, p = 0.064] domain scores.
4. Meiron O et al. (2021) Israel	RCT	19 patients with Schizophrenia	tDCS	Sham	**Positive and negative syndrome scale:** active tDCS condition patients' total PANSS scores significantly declined from baseline to post-tDCS intervention (p < 0.01) (from 76.2 [SD = 10.3] to 64.8 [SD = 14.2]) **Working memory performance:** WM-performance improved versus baseline in the active tDCS group, p < 0.01
5. Schilling TM et al. (2021) Germany	RCT	52 patients with Schizophrenia	tDCS	Sham	**Neuropsychological performance:** No significant difference

Study	Study design	Number of patients	Intervention	Comparison	Key Outcomes
6. Yu L et al. (2020) China	SR and Meta-Analysis	14 studies, 447 patients with Schizophrenia	tDCS	Sham	**Negative symptoms:** No significant difference between active and sham tDCS in ameliorating negative symptoms in schizophrenia patients (SMD: −0.14, 95% CI: −0.33– 0.05). **Cognitive impairments:** No significant difference in active tDCS vs sham stimulation in improving cognition (SMD:-0.21, 95%CI: -0.46– 0.04).
7. Kim J et al. (2018)	SR and Meta-Analysis	10 studies, 338 patients with Schizophrenia	tDCS	Sham	**Severity of auditory hallucinations:** No significant effect of tDCS on the severity of auditory hallucinations (7 studies, n=242) (SMD=0.50, 95% CI -0.09–1.09, p = 0.10), **Positive symptoms:** No significant effect of tDCS on the positive symptoms (9 studies, n=313) (SMD=0.03, 95% CI -0.24–0.31, *p*=0.81), **Negative symptoms:** No significant effect of tDCS on the negative symptoms (9 studies, n=313) (SMD=0.27, 95% CI - 0.09–0.62, *p*=0.14).
8. Wysokiński A. (2023)	Cross-sectional study	219 patients with Schizophrenia	tDCS		**Safety:** No serious adverse effects. All adverse effects were mild to moderate and transitory and the most frequent were: itching/tingling (81%), burning (53%) or heat sensation (48%) and skin reddening (35%).

5.1 EFFICACY/ EFFECTIVENESS

5.1.1 Transcranial direct current stimulation (TDCS) for depression

A Health Technology Assessment (HTA) was conducted by the Norwegian Institute of Public Health in 2022 that evaluated the efficacy, safety, and cost-effectiveness of transcranial direct current stimulation (tDCS) for depression. The assessment included systematic reviews and 25 trials comparing tDCS with sham treatments and antidepressants. The findings indicate that compared to sham-tDCS, tDCS increased response rates and probably improved depression scores and remission rates for patients with moderate to severe depression at 2-7 weeks follow-up. Small or no differences were found between patients given tDCS and patients given antidepressants. The HTA concluded that tDCS treatment probably reduces symptoms of depression in patients with moderate to severe depression. The effect of tDCS is probably not greater than antidepressant effects. Due to the full HTA being written in Norwegian, only the executive summary of this HTA is accessible in English.[37]

An umbrella review by Razza et al. (2021) was conducted aiming to summarise the therapeutic efficacy and safety of various brain stimulation techniques including tDCS for acute depressive episode that was associated with a diagnosis of major depressive disorder (MDD). A comprehensive search in PubMed/MEDLINE databases was performed, identifying seven meta-analyses that included 12 comparisons and 5,615 patients diagnosed with major depressive episodes. Data were extracted and assessed for quality using the A Measurement Tool to Assess Systematic Reviews (AMSTAR-2) tool, and the evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. The outcomes of interest assessed in the studies included depression improvement, response rates, remission rates, acceptability (dropout rates), and adverse events. The findings indicate that tDCS was superior to sham across examined outcomes for depression improvement ($k = 25$, $g = 0.46$, 95% CI: 0.22 to 0.7), response ($k = 18$, OR = 2.28, 95% CI: 1.52 to 3.42), and remission ($k = 18$, OR = 2.12, 95% CI: 1.42 to 3.16). According to AMSTAR-2, the overall methodological quality of this meta-analysis was high. Some specific findings include that active tDCS was more effective than sham in reducing depressive symptoms and improving response rates, but not all studies showed a significant difference in remission rates.[15]

Cheng YC et al. (2022) conducted a systematic review and meta-analysis which was aimed at evaluating the efficacy of non-invasive, non-convulsive electrical neuromodulation (NINCEN) techniques, including tDCS and cranial electrotherapy stimulation (CES), on depression, anxiety, and sleep disturbances. The analysis included 58 studies with 2,686 participants with MDD, with a mean age of 43.2 years and a median female proportion of 52.5%. The primary outcomes assessed were changes in depressive symptoms, before and after active and sham treatment using any clinically validated rating scale. Secondary outcomes included response and remission rates of depressive symptoms. The meta-analysis revealed significant effects of active tDCS on depressive symptoms (Hedges' $g = 0.544$, $p < 0.0001$) and response rates for depression (OR = 1.959, $p = 0.013$), but not on the remission rate (OR = 1.500, $p = 0.076$). For subgroup analysis of mild and moderate depression and of major depressive disorder, the active tDCS group was statistically superior to the sham group on depressive symptoms.

Subgroup analyses indicated that tDCS was effective across various depression severities and specific depression measurements, including the Hamilton Rating Scale for Depression (HAMD), Beck Depression Inventory (BDI), and Montgomery-Asberg Depression Rating Scale (MADRS).[16]

In another systematic review and meta-analysis by Wang Y et al. (2019) aimed to assess the efficacy of tDCS in treating MDD. Systematic search was performed in four databases including PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), China National Knowledge Infrastructure (CNKI), and Wanfang database for relevant articles published up to December 2018. The inclusion criteria were RCTs involving MDD patients who received either active tDCS alone or in combination with other treatments compared with sham tDCS, with outcomes measured using MADRS and HDRS-17. The meta-analysis included nine studies with a total of 623 participants, 331 of whom received active tDCS and 292 received sham tDCS. The results showed a significant improvement in depression severity for those treated with active tDCS compared to the control group, with a mean difference (MD) of -5.18 (95% CI: -7.13 to -3.23) on the MADRS and an MD of -3.95 (95% CI: -5.58 to -2.32) on the HDRS-17. The study concluded that tDCS is an effective and safe treatment for MDD, showing significant antidepressant effects and minimal adverse events.[17]

The study by Mutz J et al. (2019) systematically reviewed and conducted a network meta-analysis of non-surgical brain stimulation techniques for the acute treatment of major depressive episodes, including tDCS. Systematic search was done in databases like Embase, PubMed/Medline, and PsycINFO up to May 2018, and included 113 randomized clinical trials involving 6,750 patients. The primary outcomes were response (efficacy) and all-cause discontinuation (acceptability). Treatments analysed included tDCS, compared to sham therapy. The study found that tDCS was associated with a higher response rate compared to sham therapy. Transcranial direct current stimulation (tDCS) was found to be significantly more effective than sham therapy in treating major depressive episodes, with an odds ratio of 2.65 (95% CI: 1.55 to 4.55).The study concluded that these findings provide evidence for the consideration of non-surgical brain stimulation techniques as alternative or add-on treatments for adults with major depressive episodes.[18]

A systematic review and meta-analysis by Wang J et al. (2021) aimed to assess the effectiveness of tDCS as a monotherapy and in combination with medication, psychotherapy, and electroconvulsive therapy (ECT) for treating adult patients with major depressive disorder (MDD) and to identify the factors influencing treatment outcome measures. The review included 12 RCTs, focusing on four treatment strategies: tDCS alone, tDCS combined with medication, tDCS combined with psychotherapy, and tDCS combined with ECT. The different treatment strategies had different overall risks of bias. Of the tDCS monotherapy trials, two had a low risk of bias and two had an unclear risk. In tDCS + medication trials, two had low and one had unclear risk. For tDCS + psychotherapy trials, one had low, two had unclear, and one had a high risk of bias. The sole tDCS + ECT trial had a high risk of bias. Most studies used setups involving two electrodes (91.7%), 1 (16.7%) or 2 mA electric currents (66.7%), 20- (41.7%) or 30-min duration (58.3%), and 10 (50%) or > 10 (25%) sessions. The primary outcomes measured were depression severity, acceptability (dropout rates), response rates, and remission rates. The findings indicated that tDCS combined with medication significantly reduced depression scores and increased response rates compared to sham treatment, whereas tDCS alone, tDCS with psychotherapy, and tDCS with ECT did not show significant differences from sham treatment. The results showed that tDCS combined with medication

significantly reduced depression scores (SMD = -0.60, 95% CI: -0.92 to -0.28) and increased response rates (OR = 4.05, 95% CI: 1.60 to 10.27) compared to sham treatment, while tDCS alone did not show significant improvements in depression scores (SMD = -0.36, 95% CI: -0.79 to 0.06) or response rates (OR = 2.18, 95% CI: 0.86 to 5.54). Remission rates for tDCS combined with medication were not significantly different from sham (OR = 2.57, 95% CI: 0.93 to 7.14), and tDCS alone also did not significantly affect remission rates (OR = 2.28, 95% CI: 0.78 to 6.70). The active tDCS groups, in general, had a smaller depression score and a marginally higher response rate immediately post-treatment compared to sham groups, but the remission rates were not significantly different. Meta-regression analyses revealed that current intensity was significantly correlated with response rates (p = 0.008), suggesting that higher current intensities may enhance treatment efficacy. The study highlighted the limited effectiveness of tDCS alone, suggesting that the number of sessions in existing studies might be insufficient to demonstrate its antidepressant effects comprehensively. Meta-regression analyses showed that current intensity was significantly correlated with the response rate, whereas other factors such as the number of sessions or total charge did not show significant associations. Overall, the study highlighted the potential of tDCS as an adjunctive treatment to medication for MDD, while its effectiveness as a standalone treatment remains limited.[19]

Razza L B et al. (2021) conducted a systematic review and meta-analysis to evaluate the long-term effects of tDCS for treating major depressive episodes (MDEs). The aim was to assess the follow-up efficacy of tDCS, given its established short-term benefits. The study included 11 trials (13 datasets, n = 311) retrieved from databases like MEDLINE/PubMed, Scopus, and others, up to April 29, 2021. The trials incorporated both interventional and observational follow-up designs, with varying session regimens from one to eight sessions per month. Quality assessment using ROBINS-I tool revealed that 0%, 72.7%, 27.3% and 0% of the included studies presented low, moderate, serious and critical risk of biases, respectively. Primary outcomes were measured using standard depression scales, with a focus on depression score changes between the end of acute treatment and the follow-up phase. Results indicated a significant improvement in depression scores during follow-up (Hedges' g = -0.81, 95% CI: -1.28 to -0.34, I^2 = 84.0%), particularly driven by interventional studies (Hedges' g = -1.12, 95% CI: -1.84 to -0.40, I^2 = 87.1%), whereas observational studies showed no significant changes (Hedges' g = -0.47, 95% CI: -1.11 to 0.17, I^2 = 80.1%). No predictors of response were identified, and no publication bias was detected. The findings suggested that tDCS has sustained antidepressant effects beyond the acute intervention period, particularly with maintenance sessions.[20]

A randomised controlled trial (RCT) by Aust S et al. (2022) investigated whether the efficacy of CBT for major depressive disorder (MDD) could be enhanced by concurrent tDCS. The trial included 148 participants (89 women, 59 men; mean age 41.1 years) with MDD across six university hospitals in Germany. Participants were randomised into three groups: CBT alone (53 participants), CBT plus tDCS (48 participants), and CBT plus sham-tDCS (47 participants). Over six weeks, all participants attended 12 sessions of group CBT, with active tDCS involving a 2 mA current for 30 minutes per session. The primary outcome was the change in the Montgomery-Åsberg Depression Rating Scale (MADRS) score from baseline to posttreatment. The results showed that the mean reduction in MADRS scores was approximately 6.5 points in each group, with a Cohen's d effect size of -0.90, indicating a significant improvement over time. However, there was no significant difference between the groups, with no interaction effect of group and time, suggesting that the additive effects of tDCS were not statistically

significant. The study concluded that while CBT is effective for MDD, the addition of tDCS did not significantly enhance its efficacy.[21]

The study by Hyde J et al. (2022) aimed to assess the efficacy of neurostimulation techniques across various mental disorders through a systematic review and meta-analysis. The study design involved a comprehensive literature search and adherence to PRISMA guidelines, with the methodology including both qualitative and quantitative analyses of selected studies. Neurostimulation techniques evaluated included tDCS. The meta-analysis incorporated data from multiple studies, quantifying effect sizes using standardized mean differences (SMD) and assessing heterogeneity and publication bias. For depression, tDCS demonstrated a significant effect, with an effect size of -0.87 (95% CI: -1.51 to -0.24; p=0.007), indicating moderate efficacy but with high heterogeneity (I^2=88%). Regarding tDCS, active stimulation was significantly bettter than sham for symptoms of depression, substance use disorder (SUD), total, negative symptoms and auditory hallucinations in schizophrenia but not for symptoms of generalised anxiety disorder (GAD), obsessive compulsive disorder (OCD), and overall positive symptoms in schizophrenia. For depression, tDCS was found to have a modest effect on executive functioning (SMD = -0.19, 95% CI: -0.51 to 0.12, p = 0.231) and working memory (SMD = -0.11, 95% CI: -0.42 to 0.19, p = 0.465), with no significant improvement in processing speed (SMD = 0.05, 95% CI: -0.31 to 0.41, p = 0.771).[22]

The study by Yamada Y et al. (2022) employed a systematic review and meta-analysis design to evaluate the efficacy and safety of transcranial direct current stimulation (tDCS) for treating emotion recognition deficits in psychiatric disorders, specifically depression and schizophrenia. The review included three RCTs that utilized different tDCS configurations and intensities. Two studies focused on schizophrenia and one on depression, with sample sizes ranging from 12 to 37 participants. The tDCS parameters varied, with current intensities of 1.5 to 2 mA and session durations of 20 to 30 minutes. The studies mainly assessed emotion recognition using tasks like the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) and the Facial Emotion Identification Test (FEIT). The findings indicated significant improvements in emotion recognition in two studies (one targeting depression and one schizophrenia) with tDCS application, while the third study found no significant effects. These results suggest that tDCS, particularly targeting the left dorsolateral prefrontal cortex (DLPFC), may enhance emotion recognition in psychiatric patients, with implications for improving social cognitive deficits in these populations. The studies did not report significant adverse effects related to the use of tDCS in these settings.[23]

This systematic review by Ciullo et al. (2020) aimed to assess the efficacy and safety of transcranial direct current stimulation (tDCS) on cognitive deficits in mental disorders, including depression and schizophrenia. The study design involved a comprehensive literature search using PubMed, PsycNET, and Scopus databases up to January 2020. Eligible studies included peer-reviewed articles with at least 10 patients, diagnosing neuropsychiatric disorders using ICD or DSM criteria, and employing sham-controlled conditions. Data extraction focused on sample characteristics, stimulation protocols, clinical efficacy, and findings, while the quality of studies was assessed using the RoB 2 tool. The review included 41 studies, highlighting that most tDCS protocols targeted the dorsolateral prefrontal cortex (DLPFC) due to its involvement in cognitive functions and pathophysiology of depression and schizophrenia. The findings indicated that active tDCS compared to sham significantly improved working memory and processing speed in depression, with consistent benefits noted even after a single session. In

schizophrenia, tDCS showed potential in enhancing cognitive functions, though results varied.[24]

5.1.2 Transcranial direct current stimulation (TDCS) for Schizophrenia

Hyde J et al. (2022) reported in their systematic review and meta-analysis that for schizophrenia, the meta-analysis indicated that tDCS had a moderate effect on total symptoms of schizophrenia, with an SMD of -0.35 (95% CI: -0.62 to -0.09, p = 0.008). In terms of specific symptom domains, tDCS had a significant impact on negative symptoms, with an SMD of -0.40 (95% CI: -0.65 to -0.15, p = 0.002). For auditory hallucinations, the effect of tDCS was less pronounced, showing a small and non-significant effect with an SMD of -0.20 (95% CI: -0.45 to 0.06, p = 0.127). In schizophrenia, tDCS demonstrated a small but significant improvement in attention (SMD = -0.30, 95% CI: -0.55 to -0.05, p = 0.021) and working memory (SMD = - 0.38, 95% CI: -0.74 to -0.03, p = 0.032), though it did not significantly enhance executive functioning (SMD = -0.13, 95% CI: -0.37 to 0.12, p = 0.317) or processing speed (SMD = -0.38, 95% CI: -0.78 to -0.18, p = 0.061).[22]

A systematic review and meta-analysis by Kennedy et al. (2018) aimed to assess the efficacy and safety of transcranial direct current stimulation (tDCS) for treating schizophrenia, particularly focusing on positive and negative symptoms. The review included randomized controlled trials (RCTs) published until February 1st, 2017, involving a total of 105 participants from seven tDCS studies. The studies were analysed to quantify treatment efficacy and identify significant moderators related to patient characteristics and stimulation parameters. The main findings revealed that tDCS improved all symptom dimensions compared to sham treatment, but the effect was only statistically significant for negative symptoms (Hedge's g = -0.63, p = 0.02). The improvement in positive symptoms was associated with the cumulative tDCS stimulation, although this effect did not reach statistical significance. The study also explored various moderator variables, finding that greater cumulative stimulation significantly increased the efficacy of tDCS in reducing auditory hallucinations. However, no significant contributions were found from other moderators like montage and current amplitude. The study concluded that while tDCS shows promise in treating certain symptom dimensions of schizophrenia, particularly negative symptoms, further research is necessary to refine stimulation protocols and improve patient selection.[25]

Tseng P T et al. (2022) conducted a systematic review and network meta-analysis aimed at evaluating the effectiveness and safety of non-invasive brain stimulation (NIBS) techniques, including tDCS for treating negative symptoms in schizophrenia. This systematic review and network meta-analysis included 48 RCTs with a total of 2211 participants. The study design utilized a frequentist model network meta-analysis to assess various NIBS interventions, including tDCS, repetitive transcranial magnetic stimulation (rTMS), theta-burst stimulation, and others. The primary outcomes measured were changes in the severity of negative symptoms and treatment acceptability, defined as dropout rates for any reason. The findings indicated that excitatory NIBS strategies, such as high-definition transcranial random noise stimulation, intermittent theta-burst stimulation, anodal tDCS, high-frequency rTMS, and extreme high-frequency rTMS, were associated with significant reductions in negative symptoms compared to sham controls. The study reported a significant alleviation of negative symptom severity in patients with schizophrenia treated with tDCS compared to the sham therapy group (SMD = 0.251 [95%CI, 0.022 to 0.480]; P = 0.03). The study concluded that

excitatory NIBS protocols over the left DLPFC are associated with significant improvements in negative symptoms in schizophrenia, although the authors noted the need for further large-scale, well-designed RCTs to confirm these findings and better understand the mechanisms involved.[26]

A randomised controlled trial by Kao et al. aimed to investigate the impact of fronto-temporal tDCS on various aspects of schizophrenia, including self-appraisal of illness, medication adherence, life quality, and autonomic functioning. The study involved 60 schizophrenia patients who were randomly assigned to receive either active tDCS (2 mA, 20 minutes, twice daily for five days) or sham stimulation. The participants were assessed using the Self-Appraisal of Illness Questionnaire (SAIQ), Medication Adherence Rating Scale (MARS), and World Health Organization Quality of Life-BREF (WHOQOL-BREF), as well as heart rate variability (HRV) measures. The results showed significant improvements in the tDCS group compared to the sham group in terms of self-awareness of the presence and outcome of schizophrenia (Cohen's d = 0.465, p = 0.0011), subjective response to medication adherence (Cohen's d = 0.639, p < 0.001), and the psychological domain of life quality (Cohen's d = 0.459, p = 0.00114). Significant group-by-time interactions were observed in the SAIQ presence/outcome subscale [F(2,55) = 7.64, p = 0.0012], indicating improved self-awareness of the illness. Additionally, there were significant improvements in the MARS total score [F(2,53) = 19.36, p < 0.001] and the subjective response to taking medication subscale score [F(2,53) = 20.10, p < 0.001], suggesting enhanced medication adherence. In terms of quality of life, significant improvement was noted in the WHOQOL psychological domain score [F(2,55) = 7.95, p < 0.001], but not in the global score or the social relationships, physical, and environmental domain scores. These improvements were observed immediately after the intervention but were not sustained beyond one month. The study also noted that tDCS had no significant effect on clinician-rated psychosocial functioning or HRV indices. No significant group-by-time interaction found for the Positive and Negative Syndrome Scale (PANSS) total modified scores, cognitive components, individual symptom dimension scores, global cognition measured by MMSE, or psychosocial functioning measured by PSP. These findings suggest that fronto-temporal tDCS may offer short-term benefits in enhancing patients' insight into their illness and improving attitudes towards medication adherence and psychological well-being, but its effects on broader psychosocial functioning and autonomic regulation are limited.[27]

Meiron O et al. (2021) conducted a double-blind, randomized, sham-controlled trial to investigate the efficacy and safety of left prefrontal tDCS for alleviating symptoms and enhancing working memory (WM) in schizophrenia patients. Nineteen chronic schizophrenia patients, who met DSM-IV criteria, were randomly assigned to receive either active or sham tDCS. The active tDCS group received 10 sessions of 2-mA unilateral left prefrontal stimulation across five consecutive days, while the sham group received placebo treatment. Baseline and post-tDCS assessments were conducted at baseline, immediately after the intervention, and during follow-ups every four weeks for 12 weeks, including clinical evaluations using the Positive and Negative Syndrome Scale (PANSS) and WM tasks. The study found that active tDCS significantly reduced symptom severity compared to both baseline and the sham group, with improvements maintained for four weeks post-treatment. Significant reductions in PANSS scores were observed in the active tDCS group immediately post-intervention (mean reduction: 15.3 points; p < 0.01), sustained at one week (mean reduction: 13.2 points; p < 0.01) and four weeks (mean reduction: 12.4 points; p < 0.01) post-tDCS, compared to the sham group. Working memory (WM) performance in the active tDCS group improved significantly, with WM accuracy scores increasing from a mean of 65 (SD=23.9) to 80 (SD=22.9) immediately post-

intervention (t(10) = -5.3, p < 0.01), approaching the WM scores of healthy controls (HCs) (mean WM accuracy: 96.5, SD=14.7). There were no significant differences in baseline WM accuracy and RTs between the active and sham groups. The findings suggest that left prefrontal tDCS is a safe and effective intervention for reducing symptom severity and enhancing cognitive function in SZ patients, with sustained effects observed up to four weeks post-intervention.[28]

A randomised controlled trial by Schilling et al. (2021) aimed to investigate the acute effects of tDCS on executive functions in patients with schizophrenia. The sample consisted of 48 in-patients randomly assigned to receive either verum tDCS (2 mA for 20 minutes over the left dorsolateral prefrontal cortex) or sham stimulation. Methods included a comprehensive set of neuropsychological tests administered in two sessions to evaluate working memory, response inhibition, mental flexibility, and planning ability. The primary analysis employed mixed-model repeated-measures ANOVAs to assess changes in performance between sessions. The findings indicated no significant improvement in executive function for the verum group compared to the sham group across most measures. Additionally, an exploratory analysis revealed that response inhibition performance was worse in patients tested within 20 minutes after receiving the actual stimulation. The study concluded that the specific tDCS parameters used did not enhance cognitive performance in patients with schizophrenia and highlighted the need for further research with larger sample sizes and varied stimulation settings to determine optimal therapeutic efficacy.[29]

This systematic review and meta-analysis by Yu et al. aimed to evaluate the efficacy of tDCS in ameliorating negative symptoms and cognitive impairments in patients with schizophrenia. The study included a literature search conducted across multiple databases, resulting in 14 studies that met the inclusion criteria of having randomized controlled trials comparing active tDCS to sham stimulation in patients diagnosed with schizophrenia, schizoaffective disorder, or psychosis. The meta-analysis included 12 studies focused on negative symptoms and 7 studies on cognitive impairments. The results for negative symptoms showed no significant difference between active and sham tDCS overall (Standard Mean Difference (SMD): −0.14, 95% Confidence Interval (CI): −0.33 to 0.05). However, a subgroup analysis of studies that applied high-frequency stimulation (twice daily) indicated a significant improvement in negative symptoms with active tDCS compared to sham (SMD: −0.31, 95% CI: −0.58 to −0.05). For cognitive impairments, there was a trend suggesting potential benefits of active tDCS, but the overall meta-analysis did not achieve statistical significance (SMD: −0.21, 95% CI: −0.46 to 0.04). The findings highlight that while tDCS might be a promising approach for addressing negative symptoms in schizophrenia, particularly with higher frequency stimulation, its efficacy in improving cognitive impairments remains inconclusive.[30]

Kim J et al. (2018) conducted a systematic review and meta-analysis to evaluate the efficacy of transcranial direct current stimulation (tDCS) on positive symptoms, particularly auditory hallucinations, and negative symptoms in patients with schizophrenia. The study also aimed to investigate whether the number of stimulation sessions and frequency of stimulation influence the therapeutic outcomes. This meta-analysis followed PRISMA guidelines and included studies from 1950 to October 2018, identified through the OVID database, encompassing Embase, Medline, and PsycINFO. Studies were included if they involved at least five participants, included a sham control group, and provided sufficient data to calculate standardized mean differences (SMDs) for changes in symptom severity. The study included 10 eligible studies with a total of 338 participants, focusing on those with schizophrenia or

schizoaffective disorder. The primary outcomes measured were the severity of auditory hallucinations, positive symptoms, and negative symptoms, using standardized rating scales like the Auditory Hallucinations Rating Scale (AHRS), the Positive and Negative Syndrome Scale (PANSS), and the Scale for the Assessment of Negative Symptoms (SANS). The overall analyses showed no significant effect of tDCS on the severity of auditory hallucinations (7 studies, n=242) (SMD=0.50, 95% CI -0.09 to 1.09, p = 0.10), positive symptoms (9 studies, n=313) (SMD=0.03, 95% CI -0.24 to 0.31, *p*=0.81), or negative symptoms (9 studies, n=313) (SMD=0.27, 95% CI - 0.09 to 0.62, *p*=0.14). Subgroup analyses showed that studies applying twice-daily stimulation showed a significant reduction in the severity of auditory hallucinations (4 studies, n=138, SMD=1.04, 95% CI 0.20 to 1.89, p=0.02). In addition, studies with 10 or more stimulation sessions demonstrated reductions in both auditory hallucinations (5 studies, n=186, SMD=0.86, p=0.009) and negative symptoms severity (7 studies, n=257, SMD=0.41, p=0.04). The analyses indicated that older mean age was associated with smaller treatment effects on auditory hallucinations and negative symptoms. Conversely, higher baseline severity of negative symptoms correlated with greater improvements following tDCS.[31]

5.2 SAFETY

The HTA by the Norwegian Institute of Public Health in 2022 reported that the evidence showed that tDCS probably resulted in small or no differences in the proportion of drop-out and serious adverse effects, but mild and transient side effects such as skin redness, tingling, and itching under the electrodes were reported in most of the included trials.[37] The umbrella review conducted by Razza et al. (2021) reported that the results for acceptability showed no significant difference in dropout rates between active tDCS and sham groups. Similarly, there was no significant difference in overall adverse event rates between active and sham tDCS groups.[15] In addition, Mutz J et al. (2019) reported in their systematic review and meta-analysis that tDCS was at least as acceptable as sham therapy, with comparable discontinuation rates, suggesting good tolerability.[18] Wang J et al. (2021) also reported that acceptability was similar between tDCS and sham treatments, indicating good tolerability. Subgroup analysis indicated that the dropout rates were similar in both groups for all treatment strategies: tDCS alone, OR = 0.656, 95% CI 0.164 to 2.949, z = 0.55, p = 0.583; tDCS + medication, OR = 0.688, 95% CI 0.167 to 2.835, z = 0.52, p = 0.604; tDCS + psychotherapy therapy, OR = 0.302, 95% CI 0.080 to 1.134, z = 1.77, p = 0.076; tDCS + ECT therapy, OR = 1.000, 95% CI 0.053 to 18.915, z = 0.00, p = 1.000.[19]

In the RCT by Aust S et al. (2022), it is reported that there were no severe adverse events identified and the incidence of self-reported adverse effects was similar across the tDCS and sham-tDCS groups. A total of 25 adverse events affecting 16.2% of all randomized patients were reported. Five events (20%) were considered potentially related or related (active tDCS: three events [local pain at stimulation site], sham-tDCS: 2 events [local pain at stimulation site and dizziness]), but all were limited to previously described adverse reactions typical for tDCS.[21] Ciullo et al. (2020) also reported that regarding safety, tDCS was generally well-tolerated with few adverse effects reported.[24]

A systematic review and meta-analysis by Moffa AH et al. (2017) analysed the safety and acceptability of transcranial direct current stimulation (tDCS) in treating major depressive disorder (MDD) involving patient data from six randomized clinical trials. The review involved a

detailed search of electronic databases and consultation with primary study authors to obtain comprehensive datasets. Data extraction focused on demographic information, treatment parameters, and reported adverse events. Statistical analyses included logistic regression and mixed-effects models to compare safety (adverse event rates) and acceptability (dropout rates) between active and sham tDCS groups. The findings showed no significant difference in dropout rates between active (8.8%) and sham (12%) groups (OR=0.7, p=0.38) and no significant difference in adverse event rates between active (73.5%) and sham (68.3%) groups (OR=1.4, p=0.23). Notably, higher current densities correlated with lower adverse event rates. The study concluded that active tDCS is as safe and acceptable as sham tDCS for MDD patients.[32]

Another systematic review and meta-analysis by Kennedy et al. (2018) found that the safety profile of tDCS was favorable, with the most commonly reported adverse event being itchiness under the electrode, and no significant differences in dropout rates or side-effect rates between active and sham conditions.[25] Tseng P T et al. (2022) reported that the safety and acceptability of tDCS were comparable to sham treatments, suggesting that it is a well-tolerated intervention.[26]

According to an expert panel review by Fregni F et al. (2015), tDCS is a relatively safe technique, associated with mild side effects such as itching, tingling, headache, burn sensation, and discomfort. tDCS is easy to administer and its use within standard parameters has been associated with minimal risk of serious adverse effects.[13] Bikson M et al. (2016) mentioned in their evidence update that the use of conventional tDCS protocols in human trials ($\leqslant$40min, $\leqslant$ 4 mA, $\leqslant$7.2 Coulombs) has not produced any reports of a serious adverse effect or irreversible injury across over 33,200 sessions and 1,000 subjects with repeated sessions. This includes a wide variety of subjects, including persons from potentially vulnerable populations.[14]

Wysokiński A.(2023) conducted a cross-sectional study in Poland to assess the safety and tolerability of transcranial direct current stimulation (tDCS) in schizophrenia patients. The study involved analysis of 219 tDCS sessions conducted on patients with paranoid and catatonic schizophrenia. Using a 2.0 mA current and monitoring adverse effects, the study found that there were no serious side effects, with most adverse events being mild or moderate and transitory, such as itching, burning, and heat sensations. The study concluded that tDCS is a safe and well-tolerated treatment method for schizophrenia, with most side effects resolving quickly and without major distress.[41]

As of this date, the FDA “MedWatch” database search returns no reports for “tDCS” or “transcranial Direct Current Stimulation.” According to the expert panel review by Fregni F et al. (2015), tDCS can potentially be used as an off-label treatment in Iran, Germany, US, Italy, Brazil and France.[13] 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. 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.[13] In Malaysia, there is one device currently registered in Medical Device Authority (MDA) Malaysia. It is designed for non-invasive neuromodulation, delivering low-intensity direct current to targeted brain areas to treat conditions like pain, post-stroke rehabilitation, addiction, depression, and cognitive deficits. The

device, operated by trained professionals, allows for customizable treatment settings and ensures proper electrode attachment. Its registration is valid from March 14, 2024, to March 13, 2029.

5.3 ECONOMIC IMPLICATION

The study conducted by Sauvaget et al. (2019) in France aimed to evaluate the hospital production cost of tDCS for the treatment of MDD. The research was conducted under realistic conditions in a hospital setting and sought to provide an economic evaluation of tDCS. The methodology involved calculating the direct costs associated with a 15-session tDCS treatment program, including equipment, staff, and structural costs. The equipment costs for a single session and a 15-session program were minimal, with total equipment costs amounting to 99 euros for the entire treatment course. Staff costs were significant, with the combined costs for nurses and doctors totaling 538.17 euros for nurses and 538.78 euros for doctors over the 15 sessions. Structural costs added another 379.65 euros to the total. The overall cost for a 15-session tDCS program was calculated to be 1,555.60 euros. The study also conducted a sensitivity analysis to account for variables such as annual volume of sessions, staff qualifications, and potential technological advancements. This analysis indicated that increasing the number of annual sessions could reduce the cost per session, highlighting the cost-efficiency potential of scaling up tDCS treatment in a hospital setting. The findings suggest that tDCS is a cost-effective treatment option for MDD, with lower production costs compared to other non-invasive brain stimulation techniques like repetitive transcranial magnetic stimulation (rTMS).[33]

In Norway, a 4-week tDCS treatment for depression costs about [redacted] in an outpatient setting.[37] The cost of tDCS devices can vary from hundreds for a basic tDCS devices to thousands of dollars for “research-grade” tDCS systems. There is a broad range of features and capabilities across different devices.

5.4 ORGANISATIONAL ISSUES

5.4.1 Training

Training for tDCS involves two key aspects: proper device usage and safety management. Researchers, technicians, and even subjects (in home-use cases) must be trained on equipment setup, correct electrode placement, and ensuring the prescribed dose of stimulation. Physicians should oversee procedures with more than minimal risk, but there are no specific professional requirements for operators. Training includes recognizing and handling adverse effects, such as skin burns, and dealing with potential cognitive or emotional changes. After instruction, individuals should be assessed to ensure competency, and in the future, certification for trainers may be necessary.[38]

5.4.2 Guidelines

Clinical Practice Guidelines (CPG) on Management of Major Depressive Disorder (2019)
The guidelines mentioned evidence on tDCS for depression including two meta-analyses demonstrated that tDCS was significantly more effective in treating moderate to severe MDD than sham. However, those with history of treatment resistance had poorer response to tDCS. No specific recommendation was made on tDCS for MDD in this guideline.[7]

Clinical Practice Guidelines (CPG) on Management of Schizophrenia (2021)
The guidelines stated evidence on tDCS for schizophrenia including meta-analysis of 10 RCTs which found no effect of transcranial direct current stimulation compared with sham treatment on auditory hallucinations, positive symptoms or negative symptoms in schizophrenia or schizoaffective disorder. No recommendation was made on the use of tDCS for schizophrenia in this guideline.[8]

European Psychiatric Association (EPA) guidance on treatment of negative symptoms in schizophrenia 2022
No recommendation was formulated on the use of tDCS for the treatment of negative symptoms in schizophrenia in this guidance. The EPA mentioned although overall, meta-analyses suggest that a moderate effect on negative symptoms in comparison with sham tDCS but the effect is not always significant. The number of available studies and included patients were small and studies have rarely targeted negative symptoms as a primary outcome. Therefore, the available meta-analyses do not allow formulating any recommendations at this point.[34]

Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS) by the European Chapter of the International Federation of Clinical Neurophysiology (2017)
Level B recommendation (probable efficacy) is proposed for: anodal tDCS of the left dorsolateral prefrontal cortex (DLPFC) (with right orbitofrontal cathode) in major depressive episode without drug resistance. No recommendation was made for the use of tDCS for schizophrenia.[35]

Clinical Memorandum of Transcranial direct current stimulation (tDCS) by The Royal Australian and New Zealand College of Psychiatrists (RANZCP), July 2022
The Royal Australian and New Zealand College of Psychiatrists (RANZCP) has developed this memorandum to inform psychiatrists who are interested in using transcranial direct current stimulation (tDCS) as a treatment for psychiatric disorders.[36]

Key messages of the memorandum:

1) tDCS is a brain stimulation technique that uses constant, low intensity, unidirectional current delivered through electrodes placed on the scalp to subtly modify brain activity.
2) tDCS for the treatment of psychiatric disorders should only be administered after careful evaluation by, and under the supervision of, a psychiatrist with training and expertise in tDCS.
3) There is evidence for the use of tDCS in the treatment of depression, emerging evidence of efficacy in treating symptoms of schizophrenia and insufficient evidence for treatment of other psychiatric disorders. There is also no definitive evidence that it is useful for cognitive enhancement.

4) Further ongoing research into the use of tDCS in the treatment of neuropsychiatric disorders to develop a more substantial body of evidence to identify and support its clinical efficacy is encouraged.

5.5 ETHICAL ISSUES

Ethical concerns in transcranial stimulation research revolve around informed consent, risk-benefit analysis, and equitable distribution of research outcomes. There are debates about the ethical implications of using stimulation for neuroenhancement, which could exacerbate social inequalities by giving advantages to those who can access such treatments. Additionally, there are risks related to the unknown long-term effects on behaviour, such as impulsivity or decision-making. Researchers must follow strict ethical protocols, report any deviations, and assess risks carefully, especially in high-risk studies.[38]

Riggall K et al. (2015) conducted an international survey to gather researchers' perspectives on the effectiveness, ethical concerns, and public availability of tDCS. The researchers conducted an international online survey with 265 participants, targeting those involved in tDCS research. The survey covered topics such as the efficacy of tDCS in research, clinical, and enhancement contexts, as well as ethical considerations. Findings indicated that while researchers viewed tDCS as "partly" or "mostly effective" in research and clinical settings, there were greater ethical concerns regarding its use for enhancement in healthy individuals. Most researchers were cautious about public availability due to safety and regulatory concerns, particularly regarding non-expert use. Ethical concerns were more pronounced for enhancement use, particularly around safety, the limited risk-benefit ratio, and the lack of long-term data. Researchers emphasized the need for larger clinical trials, better communication of research findings, and more stringent safety protocols. Regarding public availability, 71% of researchers were against making tDCS readily available to the public, citing concerns over misuse by non-experts and insufficient understanding of its effects. However, a small group supported public access if proper regulations were in place. Overall, the study concluded that while tDCS holds potential in clinical and research settings, there is a critical need for more research on its long-term safety and efficacy, better interdisciplinary communication between researchers and bioethicists, and stronger regulations to prevent misuse.[39] Woodham R et al. (2021) highlighted ethical concerns regarding tDCS, focusing on who will administer the treatment and how it will be delivered. They emphasized the need for regulation, especially with the rise of the ‘do-it-yourself’ community, which currently lacks regulatory oversight. There is also concern about the potential for maladaptive long-term neuroplastic changes. To address these concerns, clear regulatory standards and professional oversight are necessary to ensure the safe and ethical use of tDCS.[40]

5.5 LIMITATIONS

This systematic review has several limitations that should be considered when interpreting the results. Although there was no language restriction during the search, only full-text articles published in English and peer-reviewed journals were included, potentially excluding relevant studies in other languages and thereby limiting the scope of the review. Additionally, the

included studies varied in design, sample size, and outcome measures, which may contribute to heterogeneity in the findings and complicate direct comparisons across studies. The number of studies and patients included in the meta-analyses for both depression and schizophrenia were relatively small, which may reduce the statistical power to detect significant effects and limit the generalizability of the results. Many studies had relatively short follow-up periods, which limits the understanding of the long-term efficacy and safety of tDCS. Long-term effects and sustainability of treatment benefits remain unclear. The evidence on the cost-effectiveness and economic implications of tDCS is limited, making it difficult to draw definitive conclusions about its financial impact on healthcare systems.

6.0 CONCLUSION

In conclusion, transcranial direct current stimulation (tDCS) shows potential as a treatment for depression, particularly in reducing depressive symptoms and improving response rates compared to sham treatments. While tDCS appears effective, its benefits may not surpass those of traditional antidepressants, and its effectiveness as a standalone treatment remains limited. The combination of tDCS with medication shows more significant improvements, suggesting that tDCS might be best used as an adjunctive therapy. However, its effectiveness for schizophrenia is less clear, with limited and inconclusive evidence regarding its impact on negative and cognitive symptoms. In terms of safety, tDCS is generally well-tolerated, with a relatively low incidence of adverse effects. Economically, limited evidence suggests that the cost of a tDCS treatment program for depression is [redacted] per patient for a 15-session program. In terms of clinical practice guidelines, the use of tDCS for MDD is acknowledged but not specifically recommended in many guidelines.

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APPENDIX 1: LITERATURE SEARCH STRATEGY

1 MENTAL DISORDERS/
2 (psychiatric adj1 (diagnosis or disease or disorder or illness*)).tw.
3 (mental adj1 (disorder* or illness*)).tw.
4 (severe adj2 mental disorder*).tw.
5 behaviour disorder*.tw.
6 MENTAL DISORDERS or (psychiatric adj1 (diagnosis or disease* or disorder* or illness*)).tw. or (mental adj1 (disorder* or illness*)).tw. or (severe adj2 mental disorder*).tw. or behaviour disorder*.tw.
7 DEPRESSION/
8 depression.tw.
9 (depressive adj1 symptom*).tw.
10 (emotional adj1 depression).tw.
11 DEPRESSION or depression.tw. or (depressive adj1 symptom*).tw. or (emotional adj1 depression).tw.
12 DEPRESSIVE DISORDER/
13 (depression adj1 (endogenous or neurotic or unipolar or disorder* or neuros* or syndrome*)).tw.
14 DEPRESSIVE DISORDER or (depression adj1 (endogenous or neurotic or unipolar or disorder* or neuros* or syndrome*)).tw.
15 SCHIZOPHRENIA/
16 (schizophrenic adj1 disorder*).tw.
17 Schizophrenia*.tw.
18 SCHIZOPHRENIA or (schizophrenic adj1 disorder*).tw. or Schizophrenia*.tw.
19 MENTAL DISORDERS or DEPRESSION or DEPRESSIVE DISORDER or SCHIZOPHRENIA
20 TRANSCRANIAL DIRECT CURRENT STIMULATION/
21 (transcranial adj2 electrical stimulation*).tw.
22 (cathodal adj2 stimulation tdcs*).tw.
23 (anodal adj2 stimulation tdcs*).tw.
24 ((anodal or cathodal) adj 5 stimulation transcranial direct current stimulation).tw.
25 repetitive transcranial electrical stimulation.tw.
26 transcranial random noise stimulation.tw.
27 Tdc*.tw.
28 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29 19 and 28

Other Databases		
PubMed		Same MeSH and keywords as per MEDLINE search
INAHTA		
US FDA		

APPENDIX 2: HIERARCHY OF EVIDENCE FOR EFFECTIVENESS

DESIGNATION OF LEVELS OF EVIDENCE

I	Evidence obtained from at least one properly designed randomized controlled trial.
II-I	Evidence obtained from well-designed controlled trials without randomization.
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

APPENDIX 3: EVIDENCE TABLE

Evidence Table : Effectiveness/ safety/ organisational/ economic implication
Question : What is the effectiveness, safety, and cost-effectiveness of transcranial direct current stimulation (tDCS) for Major Depressive Disorder?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up	Outcome Measures/ Effect Size	General Comments
1. Razza LB, Afonso Dos Santos L, Borrione L et al. Appraising the effectiveness of electrical and magnetic brain stimulation techniques in acute major depressive episodes: an umbrella review of meta-analyses of randomized controlled trials. Braz J Psychiatry. 2021;43(5):514-524. **Brazil**	**Umbrella review of meta-analysis** **Aim:** To summarise evidence on the therapeutic efficacy of brain stimulation techniques treat depression through an umbrella review **Methods:** Systematic review based on an electronic database search according to PRISMA and Cochrane Group guidelines was performed. Inclusion criteria: 1. meta-analyses of pairwise, network, or individual patient data with the largest number of RCTs for each technique 2. Only meta-analyses in English that evaluated the effects of any brain stimulation technique vs. sham for the treatment of depression	I	A total of seven meta-analyses (two network and five pairwise meta-analyses) providing information on 12 direct comparisons between active brain stimulation techniques and their respective sham counterparts in a total of 5,615 patients.	tDCS	Sham therapy	-	**Results:** **Depression improvement, response and remission** tDCS was superior to comparison groups across examined outcomes per random-effect (k = 25, g = 0.46, 95% confidence interval [95%CI] 0.22-0.7) and OR calculation for response and remission (k = 18, OR = 2.28, 95%CI 1.52-3.42, and k = 18, OR = 2.12, 95%CI 1.42-3.16, respectively).	

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up	Outcome Measures/ Effect Size	General Comments
	Quality of the studies assessed using A Measurement Tool to Assess Systematic Reviews (AMSTAR)-2. GRADE evidence profile and Summary of Findings tables were adopted. The AMSTAR-2 scores for high-, moderate-, and low-quality meta-analyses were 42.9, 42.9, and 14.2%, respectively. No meta-analysis was considered to have critically low methodological quality. **Outcomes:** dichotomous (response and remission) and/or continuous (improvement in depression scales) outcomes							

Evidence Table : Effectiveness/ safety/ organisational/ economic implication
Question : What is the effectiveness, safety, and cost-effectiveness of transcranial direct current stimulation (tDCS) for Major Depressive Disorder?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up	Outcome Measures/ Effect Size	General Comments
2. Cheng YC, Kuo PH, Su MI et al. The efficacy of non-invasive, non-convulsive electrical neuromodulation on depression, anxiety and sleep disturbance: a systematic review and meta-analysis. Psychol Med. 2022;52(5):801-812. **Taiwan**	**Systematic Review and meta-analysis** **Aim:** To analyse the effects of tDCS and CES on depression,anxiety and sleep disturbance and to investigate the effects of all types of NINCEN on these psychiatric problems; and to estimate the influence of demographic data and treatment parameters on the analytical results using meta-regression **Methods:** PubMed, Embase, PsycInfo, PsycArticles and CINAHL were searched for articles before March 2021 and included published randomized clinical trials of all types of NINCEN for symptoms of depression, anxiety and sleep in clinical and non-clinical populations. Inclusion criteria: 1. human randomized clinical trials used various types of NINCEN and intended to measure the mean changes of mood and sleep symptoms at baseline and at the	I	65 studies met the inclusion criteria for systematic review and 58 studies were entered for quantitative analysis. A total of 2686 participants were included. Mean age of the participants was 43.23 years (range 12–71.94 years) Median female proportion was 52.53% (range 0–100%). Sample size ranged from 16 to 256. Mean number of treatment sessions with NINCEN was 17.4 (range 5–180).	tDCS	Sham		**Results:** **Depressive symptoms** active tDCS group showed a significant effect on depressive symptoms (Hedges' g = 0.544, p < 0.0001) 0.544 (0.364–0.725) **Secondary study outcomes** active tDCS group showed a significant effect on anxiety (Hedges' g = 0.667, p < 0.0001) active tDCS group showed a significant effect on the response rate of depressive symptoms (OR = 1.959, p = 0.013) but not on the remission rate (OR = 1.500, p = 0.076) **For subgroup analysis of mild and moderate depression and of major depressive disorder:** active tDCS group was statistically superior to the sham group on depressive symptoms. **For subgroup analysis of specific depression measurements:** active tDCS group was superior to the sham group on the Hamilton Rating Scale for Depression (HAMD), the Beck Depression Inventory (BDI) and the Montgomery-Asberg Depression Rating Scale (MADRS).	

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	end of the intervention; 2. active NINCEN and sham stimulation were conducted in two parallel groups; 3. sufficient data were provided for obtaining the mean and standard deviation (S.D.). Methodological quality of eligible trials was assessed using the Cochrane Collaboration assessment tool to assess the risk of bias. Any discrepancies were resolved by consensus with a third investigator Data were pooled using a random-effects model. **Primary outcome:** 1. change in depressive symptoms before and after active and sham treatment using any clinically validated rating scale. **Secondary outcomes:** 1. anxiety (measured by the mean change of anxiety scale), 2. sleep (measured by the mean change of						**For subgroup analysis of different current intensities and treatment sessions:** active tDCS group showed a superior effect compared to the sham group. When separating different positions of electrodes, only F3–F4 revealed a significantly higher effect in the tDCS group than in the sham group. **Authors' conclusion:** tDCS has significant effects on both depression and anxiety and that these effects are robust for different populations and treatment parameters.	

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	sleep measurement), 3. a response rate of depressive symptoms (estimated as the proportion of patients who achieved a reduction of 50% or more in the depression rating score) 4. depression remission rate (measured by the proportion of patients who had a depression score under the remission cut-off).							

Evidence Table : Effectiveness/ safety/ organisational/ economic implication
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Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow-up (if applicable)	Outcome Measures/ Effect Size	General Comments
3. Wang Y. Transcranial direct current stimulation for the treatment of major depressive disorder: A meta-analysis of randomized controlled trials. Psychiatry Res. 2019;276:186-190. **China**	**Systematic Review and Meta-analysis** **Aim:** To evaluate the effects of tDCS applied for the treatment of MDD **Methods:** Databases including PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), China National Knowledge Infrastructure (CNKI) and Wanfang database were searched for articles published from inception to December 2018. **Inclusion Criteria:** 1. Study design: randomized controlled trial(RCT). 2. Subjects were required to have a diagnosis of MDD, or the participants had a major depressive episode. 3. tDCS alone or in combination with other treatments compared with placebo tDCS or sham tDCS.	I	9 qualified studies were included in the meta-analysis Involving 623 patients. 331 patients of them received tDCS and 292 patients received sham tDCS Number of participants in each study included in the meta-analysis ranged from 16 to 149. Three studies utilized the HDRS-17, and the MADRS was observed in seven studies.	tDCS	Sham		**Results:** **Primary outcome (MADRS)** Significant difference between tDCS compared with the control group was found in this analysis ($p < 0.00001$, MD = -5.18, 95% CI: -7.13 to -3.23;heterogeneity test: Tau2 = 1.61, Chi2 = 9.77, p = 0.28, I2 = 18%). **Secondary outcome (HDRS-17)** Significant statistical difference between tDCS and the control group ($p < 0.00001$, MD =-3.95, 95% CI: -5.58 to -2.32; heterogeneity test: Tau2 = 0.00, Chi2 = 0.03, p =0.99, I2 = 0%). **Author's Conclusion:** The intervention of active tDCS was superior to the use of sham tDCS in improving MDD.	

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	4. Outcomes related to MDD were reported. 5. Results were reported in the form of mean and standard deviation or necessary data could be obtained after calculation. **Primary outcome:** Montgomery-Asberg depression rating scale (MADRS). **Secondary outcome:** Hamilton Depression Rating Scale, 17-items (HDRS-17). Risk of bias of RCTs was evaluated using the Cochrane Handbook for Systematic Reviews of Interventions							

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4. Mutz J, Vipulananthan V, Carter B et al. Comparative efficacy and acceptability of non-surgical brain stimulation for the acute treatment of major depressive episodes in adults: systematic review and network meta-analysis. BMJ. 2019;364:l1079. **United Kingdom**	**Systematic Review and Network Meta-analysis** **Aim:** To estimate the comparative clinical efficacy and acceptability of non-surgical brain stimulation for the acute treatment of major depressive episodes in adults. **Methods:** Systematic search was performed in Electronic search of Embase, PubMed/Medline, and PsycINFO up to 8 May 2018, supplemented by manual searches of bibliographies of several reviews (published between 2009 and 2018) and included trials. **Inclusion criteria:** 1. -Clinical trials with random allocation to electroconvulsive therapy (ECT), transcranial magnetic stimulation (repetitive (rTMS), accelerated, priming, deep, and	I	113 trials (262 treatment arms) that randomised 6750 patients (mean age 47.9 years; 59% women) with major depressive disorder or bipolar depression. Most studied treatment comparisons were high frequency left rTMS and tDCS versus sham therapy, Most trials (81%) recruited only patients with treatment resistant depression, typically defined as a minimum of two failed drug treatments, 13% recruited patients with treatment resistant depression and nontreatment resistant depression, and the remaining 6% recruited patients with non-treatment resistant	tDCS	Sham		**Results:** **Pairwise meta-analysis:** tDCS more efficacious than sham therapy across all outcomes **Network meta-analysis:** -tDCS (2.65, 1.55 to 4.55) were more efficacious than sham therapy **Conclusion:** These findings provide evidence for the consideration of non-surgical brain stimulation techniques as alternative or add-on treatments for adults with major depressive episodes.	

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	synchronised), theta burst stimulation, magnetic seizure therapy, transcranial direct current stimulation (tDCS), or sham therapy. **Primary Outcomes:** 1. Response (efficacy) and all cause discontinuation (discontinuation of treatment for any reason) (acceptability) 2. Remission 3. Continuous depression severity scores after treatment Cochrane tool was used for assessing risk of bias in randomised trials to evaluate each study		depression. Quality of the evidence was typically of low or unclear risk of bias (94 out of 113 trials, 83%)					

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5. Wang J, Luo H, Schülke R et al. Is transcranial direct current stimulation, alone or in combination with antidepressant medications or psychotherapies, effective in treating major depressive disorder? A systematic review and meta-analysis. BMC Med. 2021;19(1):319. **China**	**Systematic Review and Meta-analysis** **Aim:** To evaluate the clinical efficacy of tDCS as a monotherapy and in combination with medication, psychotherapy, and ECT for treating adult patients with major depressive disorder (MDD) and identified the factors influencing treatment outcome measures (i.e. depression score, dropout, response, and remission rates). **Methods:** Systematic search was performed in PubMed/Medline, EMBASE, PsycINFO, Web of Sciences, and OpenGrey. **Inclusion Criteria:** 1. adult participants aged > 18 years with a diagnosis of MDD; 2. studies that examined tDCS as a treatment for depression;	I	Twelve randomised, sham-controlled trials (active group: N = 251, sham group: N =204) were included. A total of 455 patients (mean age = 45.7 years, 58.2% female) of whom n = 251 were randomised to active and n = 204 to sham treatments. No significant difference in the number of participants and age between the two groups, but significantly more males were included in the active group. The baseline depression scores were 24.36 ± 5.74 (mean ± SD) and 25.36 ± 5.13 (mean ± SD) for the active and	tDCS	Sham		**Results:** **Primary outcomes:** **Overall effects of tDCS for depression** Depression score of active group was significantly lower compared to the sham group (z = 2.38, p = 0.017), the overall effect size of combing all therapies was small (Hedges' g = − 0.442, 95% CI − 0.805 to − 0.079), while heterogeneity was moderate (I2 = 67.7%, Q = 37.18, p <0.001). **Dropout rates** Overall dropout rates of the active and sham groups were 7.17% (18/251) and 11.8% (24/204), respectively. No statistically significant difference between the two groups. **Secondary outcomes:** Overall response rate in the active group (41.95%, 99/236) was higher than that in the sham group (29.73%, 50/185). Difference in the response rate between the two groups was marginally significant (z = 1.85, p = 0.065), The remission rate in the active group (22.46%, 53/236) was also	

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	3. randomised, sham-controlled trials, where the sham was either sham of tDCS or sham of tDCS + other therapies; 4. stimulation targeting the dorsolateral prefrontal cortex; 5. tDCS protocols with at least five tDCS stimulation sessions on consecutive days; 6. inclusion of a clinician-administered depression rating scale, i.e. the Hamilton Depression Rating Scale (HDRS) of any version or the Montgomery–Åsberg Depression Rating Scale (MADRS) at baseline and posttreatment; 7. articles written in English The Cochrane tool was used to evaluate the risk of bias in included RCTs.		sham groups, respectively				higher than that in the sham group (16.22%, 30/185). No significant difference found (z = 0.72, p = 0.470), with a positive overall effect size OR = 1.265 (95% CI 0.669–2.395) and low heterogeneity (I2 = 15.2%, Q = 11.79, p =0.299). Further analysis showed that only tDCS + medication achieved a significant lower score (g = − 0.855, p < 0.001). This combination achieved a significantly higher response rate than sham intervention (OR = 2.7, p = 0.006), while the response rate remained unchanged for the other three therapies. Dropout and remission rates were similar in the active and sham groups for each therapy and also for the overall intervention. Meta-regression results showed that current intensity is the only predictor for the response rate. **Authors' conclusion:** The effect size of tDCS treatment was obviously larger in depression score compared with sham stimulation. The tDCS combined selective serotonin re-uptake inhibitors is the optimized therapy that is effective on depression score and response rate. tDCS monotherapy and combined psychotherapy have no significant effects. The most important	

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	Primary outcomes: standardized mean difference (SMD) for continuous depression scores after treatment and odds ratio (OR) dropout rate; **Secondary outcomes:** included ORs for response and remission rates. The overall effect of tDCS was investigated by meta-analysis. Sources of heterogeneity were explored via subgroup analyses, meta-regression, sensitivity analyses, and assessment of publication bias.						parameter for optimization in future trials is treatment strategy.	

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6. Razza LB, De Smet S, Moffa A et al. Follow-up effects of transcranial direct current stimulation (tDCS) for the major depressive episode: A systematic review and meta-analysis. Psychiatry Res. 2021;302:114024. **Brazil**	**Systematic Review and Meta-analysis** **Aim:** To investigate the evidence regarding the follow-up effects of tDCS and explore its potential moderators. **Methods:** MEDLINE/PubMed, Scopus (EMBASE), Web of Science, Cochrane Library and additional sources were searched from inception to April 29, 2021. **Inclusion criteria:** 1. Studies that followed up adults treated with tDCS during an MDE - using (*interventional*) and/or not using (*observational*) tDCS in the follow-up period were included. 2. studies written in English, 3. primary clinical outcomes measured by	I	11 trials (13 datasets, *n* = 311) were included, most presenting moderate bias. Quality assessment using ROBINS-I tool revealed that 0%, 72.7%, 27.3% and 0% of the included studies presented low, moderate, serious and critical risk of biases, respectively	tDCS	No tDCS	4 to 24 weeks	**Results:** **Primary outcome** Follow-up depression improvement (*k* = 13, *g* = -0.81, 95% confidence interval [CI]: -1.28; -0.34, *I2* = 84.0%) **Secondary outcome:** -No predictor of response was associated with the outcome. No risk of publication bias was found. **Authors' Conclusion:** tDCS produces effects beyond the intervention period during major depressive episode (MDE)	

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	standard depression scales Methodological quality was assessed using the Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tool. **Primary Outcome:** Evaluate depression changes between the last acute treatment evaluation and the last evaluation of the follow-up. (the Hedges' *g* for the follow-up depression scores). **Secondary Outcome:** Response moderators via meta-regressions.							

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7.Aust S, Brakemeier EL, Spies J et al. Efficacy of Augmentation of Cognitive Behavioral Therapy With Transcranial Direct Current Stimulation for Depression: A Randomized Clinical Trial. JAMA Psychiatry. 2022;79(6):528-537. **Germany**	**RCT** **Aim:** To investigate whether the efficacy of cognitive behavioral therapy (CBT) for the treatment of MDD can be enhanced by concurrent transcranial direct current stimulation (tDCS). **Methods:** Double-blind, placebo-controlled randomized clinical trial was conducted at 6 university hospitals across Germany. Enrollment between June 2, 2016, and March 10, 2020; follow-up was completed August 27, 2020. 1. Adults aged 20 to 65 years with a single or recurrent depressive episode were eligible. 2. either not receiving medication or were receiving a stable regimen of antidepressant medication (selective serotonin reuptake inhibitor	II	A total of 148 women and men underwent randomization: 53 individuals were assigned to CBT alone (group 0), 48 to CBT plus tDCS (group 1), and 47 to CBT plus sham-tDCS (group 2). Of these, 126 patients (mean [SD] age, 41.5 [14.0] years; MADRS score at baseline, 23.0 [6.3]) completed the study	CBT plus tDCS	CBT		**Results:** **Primary Outcome** In the ITT analysis, the intervention was able to reduce MADRS scores by a mean of 6.5 points (95%CI, 3.82-9.14 points) on average. The Cohen *d* value was –0.90 (95% CI, –1.43 to –0.50), indicating a significant effect over time. No significant effect of group and no significant interaction of group × time. **Safety:** No severe adverse events throughout the whole trial, and there were no significant differences of self-reported adverse effects during and after stimulation between groups 1 and 2 **Authors' Conclusion:** Based on MADRS score changes, this trial did not indicate superior efficacy of tDCS-enhanced CBT compared with 2 CBT control conditions.	

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	and/or mirtazapine). 3. Participants attended a 6-week group intervention comprising 12 sessions of CBT. If assigned, tDCS was applied simultaneously. Active tDCS included stimulation with an intensity of 2mA for 30 minutes **Primary Outcome:** Change in Montgomery Asberg Depression Rating Scale (MADRS) score from baseline to posttreatment in the intention-to-treat sample. Scores of 0 to 6 indicate no depression; 7 to 19, mild depression; 20 to 34, moderate depression; and 34 and higher, severe depression.							

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8. Moffa AH, Brunoni AR, Fregni F et al. Safety and acceptability of transcranial direct current stimulation for the acute treatment of major depressive episodes: Analysis of individual patient data. J Affect Disord. 2017;221:1-5.	**Systematic Review and Meta-analysis** **Aim:** (1) to perform an individual patient data (IPD) analysis regarding safety and acceptability in patients with MDD treated with tDCS; and (2) to explore whether clinical, demographic and treatment characteristics were associated with these outcomes. **Methods:** Individual patient data from 6 randomized clinical trials that had been previously identified in a systematic review and meta-analysis were collected. **Primary outcomes:** 1. Safety (rate of adverse events) 2. acceptability (rate of dropouts). **Secondary outcomes:** clinical, demographic and treatment predictors of the primary outcomes.	I	6 RCTs were included All trials presented low risk of bias per the Cochrane risk of bias tool Data from 289 patients were analyzed. Mean age was 47.2 years with standard deviation (SD) of 13.4 and 62.3% were female; 55.4% presented severe depression; 42.6% had anxiety as a comorbidity; 51.6% presented a treatment-resistant depression, with a mean of 2.3 (SD = 2.4) previous antidepressant failed trials.	tDCS	sham		**Results:** **<u>Acceptability</u>** The dropout rates between active (13 out of 147, 8.84%) and sham (17 out of 142, 11.97%) groups were not significantly different (OR =0.70, 95% CI 0.32– 1.54; p=0.379) **<u>Adverse events:</u>** The overall adverse effects rates for any reason (most commonly tingling, itching, redness, headache and discomfort) between active (108 out of 147, 73.47%) and sham (97 out of 142, 68.31%) groups in all 6 RCTs were not significantly different (OR = 1.44, 95% CI 0.80–2.61; p= 0.228). **Authors' Conclusion:** Active tDCS was as acceptable and tolerable as sham tDCS for MDD treatment, since those interventions presented similar rates of acceptability and tolerability,	

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9. Sauvaget A, Tostivint A, Etcheverrigaray F et al. Hospital production cost of transcranial direct current stimulation (tDCS) in the treatment of depression. Neurophysiol Clin. 2019;49(1):11-18.	Cost-analysis study **Aim:** To evaluate the production cost of tDCS for the treatment of depression in hospitals, under realistic conditions. **Methods:** **C**ost accounting method was adapted and was developed by a multidisciplinary working group of clinicians, public health physicians, pharmacists, administrative and financial managers, and health economists **I**ncludes equipment, staff, and structural costs Cost of producing a tDCS session was estimated based on annual activity objective, and then estimated the cost of a 15-session treatment program. This was followed up with a sensitivity analysis applying appropriate parameters.			tDCS			**Results:** The hospital production cost of a tDCS depression treatment program for a single patient was estimated at € 1555.60 euros: € 99 in equipment costs, € 1076.95 in staff costs,and € 379.65 in structural costs	

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10. Hyde J, Carr H, Kelley N et al. Efficacy of neurostimulation across mental disorders: systematic review and meta-analysis of 208 randomized controlled trials. Mol Psychiatry. 2022;27(6):2709-2719.	**Systematic Review and Meta-Analysis** **Aim:** To assess the efficacy of non-invasive brain stimulation **(**NIBS), compared to sham, for core symptoms and cognitive functioning within a broad range of mental conditions. **Methods:** PubMed, OVID, and Web of Knowledge databases were systematically searched, from inception until April 26th 2021, **Inclusion criteria:** 1. randomized, sham-controlled trials using TMS and/or tDCS, 2. including children and/or adults with a primary diagnosis of a mental health condition using standardized diagnostic criteria (DSM-III/IV/5, ICD-9/10/11 or based on other	I	208 RCTs identified in a systematic review (MDD) or bipolar disorder (n = 99), Schizophrenia or Schizoaffective Disorder (n = 59), Obsessive Compulsive Disorder (OCD, n = 27), Substance Use Disorder (SUD, n = 10), Posttraumatic Stress Disorder (PTSD, n = 8), Generalized Anxiety Disorder (GAD, n = 5), Attention-deficit/hyperactivity disorder (ADHD, n = 2), and tourettes/tic disorders (n = 2). 23% RCTs were considered overall high risk of bias, most commonly due to inappropriate	tDCS	sham		**Results:** **Meta-analyses results-efficacy on core symptoms-continuous outcomes** tDCS active stimulation was significantly bettter than sham for symptoms of depression, SUD, total, negative symptoms and auditory hallucinations in schizophrenia but not for symptoms of GAD, OCD, and overall positive symptoms in schizophrenia Depression: −0.87 (−1.51 to −0.24) SUD: −0.73 (−1.00 to −0.46) Schizophrenia Total symptoms: −0.63 (−1.03 to −0.23) Negative symptoms: −0.54 (−0.95 to −0.14) Auditory hallucinations: −0.42 (−0.81 to −0.02) **Meta-analyses results-efficacy on cognitive functioning** tDCS significantly enhanced attention and working memory in patients with schizophrenia. **Authors' conclusion:** tDCS can benefit individuals with a variety of mental conditions, significantly improving clinical	

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	standardized diagnostic tools) 3. using standardized scales assessing core symptom severity and/or tasks measuring cognitive functioning (executive function, attention/vigilance, processing speed, and working memory). **Primary outcomes:** Change in core symptom severity in each mental disorder **Secondary outcomes:** -Secondary outcomes were score changes in standard cognitive functioning tasks.		analysis (15%) and/or reporting of missing data (16%). Overall, the risk of bias was typically of some concerns (69%), or low (10%;				dimensions, including cognitive deficits in schizophrenia which are poorly responsive to pharmacotherapy.	

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11. Yamada Y, Inagawa T, Hirabayashi N et al. Emotion Recognition Deficits in Psychiatric Disorders as a Target of Non-invasive Neuromodulation: A Systematic Review. Clin EEG Neurosci. 2022;53(6):506-512.	**Systematic Review** **Aim:** To investigate the impact of tDCS on social cognitive dysfunction psychiatric disorders, specifically in the domains of emotion recognition, social perception, theory of mind (ToM), and attributional bias. **Methods:** Literature search was performed using PubMed, PsycINFO, and Web of Science databases to identify eligible studies. **Inclusion criteria**: 1. Randomized Controlled Trials (RCTs), 2. targeting patients with psychiatric disorders 3. evaluating the effect of tDCS or rTMS, 4. reporting at least one standardized social cognition test.	I	Five papers (3 articles on tDCS and 2 articles on rTMS) met the inclusion criteria which deal with schizophrenia or depression. -Three studies included in the systematic review used tDCS. -Two studies included patients with schizophrenia, while one included depression.	tDCS			**Results:** **Effects of tDCS for social cognitive deficits** The results of the included studies showed that tDCS had significant effects on emotion recognition in patients with schizophrenia or depression Among 3 tDCS studies, two of which found significant effects only in emotion recognition, one of which targeted depression and the other targeted schizophrenia **Authors' conclusion:** tDCS may enhance some domains of social cognition in patients with psychiatric disorders. Further research is warranted to identify optimal parameters to maximize the cognitive benefits of this neuromodulation method.	

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	Risk of bias in individual studies was assessed using the Cochrane Collaboration's risk of bias tool. **Outcome measures:** Our domains of social cognition, ie, emotion recognition, social perception, ToM, and attributional bias.							

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12. Ciullo V, Spalletta G, Caltagirone C et al. Transcranial Direct Current Stimulation and Cognition in Neuropsychiatric Disorders: Systematic Review of the Evidence and Future Directions. Neuroscientist. 2021;27(3):285-309. Italy	**Systematic Review** **Aim:** To evaluate the effects of tDCS on cognitive functions in patients with mood disorders, schizophrenia-spectrum disorders, Alzheimer's disease (AD), and mild cognitive impairment (MCI), and to discuss future directions for standardized stimulation protocols and effective clinical practice. **Methods:** Extensive literature search using various databases was conducted and included studies that met specific criteria, 1. Published in English, 2. peer-reviewed, 3. and including patients diagnosed with neuropsychiatric disorders. Quality of the included studies was evaluated using the RoB 2 tool.	I	Data from 41 studies, comprising patients with diagnosis of mood disorders, schizophrenia-spectrum disorders, Alzheimer's disease (AD), and mild cognitive impairment (MCI), were included.	tDCS			**Results:** tDCS has the potential to enhance processing speed, working memory, and executive functions in patients with mood and schizophrenia-spectrum disorders. The evidence for a positive effect on general cognitive functioning and memory was inconclusive in AD and weak in MCI. The review also highlighted the heterogeneity in stimulation parameters, cognitive measures, and evaluation procedures as a major source of variability in tDCS efficacy. **Authors' conclusion:** Transcranial direct current stimulation (tDCS) has the potential to improve cognitive dysfunctions in mood disorders and schizophrenia-spectrum disorders, particularly in the domains of working memory, processing speed, and executive functions. However, the evidence for its effectiveness in Alzheimer's disease (AD) and mild cognitive impairment (MCI) is inconclusive or weak. The reviews highlight the need for standardized stimulation protocols, larger cohorts, and further research to establish the optimal parameters and protocols for tDCS and to determine its long-term effects on cognitive functioning. Additionally, stratifying target populations based on	

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							disease severity and medication status may help maximize the effectiveness of tDCS across different neuropsychiatric disorders.	

Evidence Table : Efficacy/ safety/ organisational (TCDS – SCHIZOPRENIA)
Question : What is the efficacy, safety, and organisational issue related to the use of transcranial direct stimulation for **schizophrenia**?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow up (if applicable)	Outcome Measures/ Effect Size	General Comments
1. Kennedy NI, Lee WH, Frangou S. Efficacy of non-invasive brain stimulation on the symptom dimensions of schizophrenia: a meta-analysis of randomized controlled trials. European Psychiatry. 2018 ;49:69-77. **United States**	**SR and meta-analysis of randomised controlled trials.** **Aim:** to evaluate the efficacy of rTMS and tDCS on the positive, negative and general symptoms of schizophrenia. Second, to quantified the moderator effects relating to patient-related characteristic and stimulation parameters. **Data sources and searches:** Systematic search of the major electronic databases was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria to identify studies published between January 1st 1996 till February 1st 2017. Selection criteria include: (a) Peer-reviewed, original studies of patients with schizophrenia and related psychoses diagnosed according to	I	7 RCTs investigating tDCS vs sham included in meta-analysis. tDCS group (n=97,), sham group (n=100). No descriptive analysis of the participants given.	tDCS	sham		**<u>Auditory Hallucinations.</u>** Active tDCS was associated with symptom reduction, the effect was not significant (Hedge's g = -0.28, p = 0.38) with evidence of substantial heterogeneity (I^2 = 77.11%). The efficacy of active tDCS increased significantly with greater cumulative stimulation (coefficient =- 0.02, p = 0.01). **<u>Positive psychotic symptoms.</u>** There was a non-significant reduction in symptoms (Hedge's g =- 0.10, p = 0.59) which was linearly associated with cumulative stimulation but this effect was also not significant (p = 0.13). **<u>Negative symptoms.</u>** Active tDCS showed a significant effect of treatment (Hedge's g = -0.63, p = 0.02). However, there was evidence of significant heterogeneity (I2 = 69.70%). The contribution of cumulative stimulation was minimal and not significant (p = 0.97). **<u>Overall symptoms severity.</u>** There was no significant effect of treatment (Hedge's g = -0.48, p = 0.12). **<u>Safety and tolerability.</u>** The most commonly reported adverse event was itchiness under the	

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	standardized criteria (b) Double-blind randomized sham-controlled design (c) Symptoms rating using the Auditory Hallucination Rating Scale (AHRS) and/or the Positive and Negative Syndrome Scale (PANSS) (d) Sufficient data to calculate effect size using Hedge's g (e) Available information about study drop-outs/withdrawals. **Quality assessment:** **NOT MENTIONED** **Data synthesis and analysis:** All analyses were conducted using the Comprehensive Meta-Analysis (CMA) v3.3.070 software. Main outcome were: (a) Reduction in auditory hallucinations as measured by composite score derived from the						electrode and there were no dropouts and no effect of treatment condition on the rates of reported side-effects.	

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	AHRS and the PANSS auditory hallucination subscale (b) Reduction in positive symptoms as measured by the positive symptoms subscale of the PANSS (c) Reduction in negative symptoms as measured by the negative symptoms subscale of the PANSS (d) Reduction in overall symptoms severity as measured by the PANSS total score (e) Number of dropouts (f) Type and number of side effects For each outcome, weighted standardized mean difference (Hedges'g) between active and sham conditions were calculated using a DerSimonian and Laird's random effect model. Studies were weighted by sample size as calculated							

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	by the Mantel-Haenszel method.							

Evidence Table : Efficacy/ safety/ organisational (TDCS – SCHIZOPRENIA)
Question : What is the efficacy, safety, and organisational issue related to the use of transcranial direct stimulation for **schizophrenia**?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow up (if applicable)	Outcome Measures/ Effect Size	General Comments
2.Tseng PT, Zeng BS, Hung CM, et al. Assessment of noninvasive brain stimulation interventions for negative symptoms of schizophrenia: a systematic review and network meta-analysis. JAMA psychiatry. 2022 ;79(8):770-9. **Taiwan**	**A systematic review and network meta-analysis.** **Aim:** to compare the efficacy and acceptability of different NBS interventions for treating negative symptoms. **Data sources and searches:** Author searched and screened ClinicalKey, Cochrane CENTRAL, Embase, ProQuest, PubMed, ScienceDirect, Web of Science, and ClnicalTrials.gov. Inclusion criteria: (1) RCT (2) Application of NIBS intervention (3) Participant with schizophrenia (4) Studies comparing the efficacy of different NIBS strategies to manage participant's negative symptoms. **Quality assessment:** Cochrane risk of bias tool.	I	48 RCTs included in the network meta-analyses with a total of 2211 participants. Most included studies investigate efficacy of various NIBS compared to sham. The mean (range) age was 38.7 (24.0-57.0) and the mean (range) proportion of female participants was 2.8 (1-12) weeks.	a-tDCS-F3Fp1 + c-tDCS-F4Fp2 / a-tDCS-F3 + c-tDCS-Fp2 / a-tDCS-F3 + c-tDCS-TP3 / hd-a-tDCS-F3 + c-tDCS-AF3F7FC5FC1 / a-tDCS-F3Fp1 + c-tDCS-TP3 / a-tDCS-F3 + c-tDCS-F4 / a-tDCS-TP3 + c-tDCS-F3Fp1.	Sham	The mean (range) treatment duration was 2.8 (1-12) weeks. The mean (range) overall study duration (ie, treatment + follow-up duration) was 9 (1-32) weeks.	**Negative symptoms.** There was significant alleviation of negative symptom severity in tDCS sham therapy group (SMD = 0.251 [95%CI, 0.022-0.480];P = .03) However, there was no significant differences between group was detected between rTMS-theta-burst stimulation and tDCS sham therapy group. According to the SUCRA, hd-tRNS-AF3AF4F2F6FC4 was ranked the highest probability of being the best, followed by iTBSF3 and a-tDCS-F3Fp1 + c-tDCS-F4Fp2 (SUCRA = 3.0, 12.4, and 16.2, respectively.) **Acceptability.** None of the investigated NIBS modalities were associated with significantly different acceptability rates relative to sham. **Positive Symptoms.** None of the investigated NIBS approaches was associated with significantly different changes in positive symptom severity compared with sham control groups **Depressive symptoms.** a-tDCS-F3Fp1 + c-tDCS-F4Fp2 (SMD = -0.79 [95% CI, -1.43 to -0.15]) was associated with significant alleviation of depressive symptom.	

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	Data synthesis and analysis: The network meta-analysis used mvmeta command in Stata version 16.0 (StataCorp). All analysis were conducted using random-effects and frequentist models. Main primary outcome: (1) Changes of negative symptoms after NIBS (2) Acceptability (i.e dropout)						According to the SUCRA, a-tDCS-F3+c-tDCS Fp2 was associated with the most alleviation but did not achieve statistical significance (SMD = -0.93 [95%CI, -1.94 to 0.07]), followed by a-tDCS-F3Fp1 + c-tDCS-F4Fp2 (SUCRA value: 10.1 and 10.1, respectively)	

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Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow up (if applicable)	Outcome Measures/ Effect Size	General Comments
3. Kao YC, Tzeng NS, Chao CY et al. Modulation of self-appraisal of illness, medication adherence, life quality and autonomic functioning by transcranial direct current stimulation in schizophrenia patients. Clinical Neurophysiology. 2020 **Taiwan**	**Randomized Controlled Trial** **Aim:** to examine the effects of fronto-temporal tDCS on self-appraisal of illness, beliefs about medication compliance, subjective QoL, psychosocial functioning and cardiac autonomic functioning. **Study Design:** Randomized double-blind sham-controlled clinical trial. The description of procedure of randomization and blinding, definition of medication-refractory AVHs and dropout, and the list of medications participants were taken provided in the supplementary information. (*however no access to supplemental*) Study Period: Primary Outcome: 1. Clinician administered assessment 2. Self-appraisal of mental illness	I	60 patients were randomly allocated to active, n=30 and sham, n=30. The mean age in active group were 46.40 ± 10.29 compared to 42.17 ± 10.29 in sham. The differences between the active and sham groups in sociodemographic and cardiovascular characteristic were not statistically significant. (Table 1) Only significant difference between group at baselinewere longer duration of illness and higher depression scores of PANSS in the active tDCS.	TDCS An Eldith DC stimulator (Neuroconn DC Stimula Tor Plus, GmbH, Ilmenau, Germany) Stimulation was applied at an intensity of 2 mA (current density = 0.57 A/m2) for 20 min, twice-daily, separated by 3 hours, on 5 consecutive weekdays (total charge density = 1368C/m2).	Sham stimulation, after 30 s of 2 mA stimulation, only a small current pulse occurred every 550 ms (110 lA over 15 ms) instead of the real stimulation throughout the remainder of the 20-min period.		**<u>Clinician administered assessment.</u>** There was no significant group-by-time interaction for all dimensions of PANSS total modified, cognitive component and individual symptom dimension scores, global cognition as measured by MMSE, or psychosocial functioning as measured by PSP when outcomes were adjusted for illness duration and baseline depression. **<u>Self-appraisal of mental illness.</u>** After adjusted to illness duration and baseline depression severity, there is significant group-by-time interventions for SAIQ presence/outcome subscale score [F(2,55) = 7.64, p = 0.0012], trends toward significance for SAIQ total [F (2,55) = 5.31, p = 0.0078] and the need for treatment subscale [F (2,55) = 6.62, p = 0.0027], and non-significance for worry subscale [F(2,55) = 3.26, p = 0.046] scores. Immediately after tDCS the SAIQ presence/outcome subscale and the need for treatment subscale scores were significantly increased from baseline in the active tDCS group relative to sham and the significance reduce to trend-level at 1-month follow-up.	

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	3. Medication adherence 4. Subjective life quality 5. Measurement of heart rate variability (HRV) Secondary Outcome: 1. Correlation between changes in medication adherence and self-appraisal of mental illness. 2. Safety of TDCS						**Medication adherence.** There is significant group-by-time interactions for MARS total score [F(2,53) = 19.36, p < 0.001] and MARS subjective response to taking medication subscale score [F (2,53) = 20.10, p < 0.001] but not for medication adherence subscale score [F(2,53) = 4.07, p = 0.023]. Immediately after tDCS the MARS total score and MARS subjective response to taking medication subscale score were significantly increased from baseline in the active tDCS group relative to sham but the between-group differences did not attain significance at 1-month follow-up. **Subjective life quality.** Significant group-by-time interaction for the WHOQOL psychological domain score [F(2,55) = 7.95, p < 0.001]. However, not significant in global score of WHOQOL [F(2,55) = 4.23, p = 0.02] and social relationships [F(2,55) = 4.51, p = 0.015], physical [F(2,55) = 0.40,p = 0.67] and environmental [F(2,55) = 2.9, p = 0.064] domain scores. Post-hoc analyses showed that between group difference in percent change of the psychosocial domain score was significant immediately after tDCS (small effect size, 0.459) but became non-significant at 1-month follow up.	

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							Measurement of heart rate variability (HRV). No significant group-by-time interaction for mean RR intervals [F(2,43) = 2.97, p = 0.06], variance [F(2,43) = 2.42, p = 0.10], LF [F(2,43) = 3.04, p = 0.06], HF [F(2,43) = 3.86, p = 0.029] or ratio [F (2,57) = 1.00, p = 0.38].* Secondary outcome: **Correlations between the changes in medication adherence and self-appraisal of mental illness.** All 6 correlation that were tested in the active TDCS group were all not significant. (between the changes in MARS total score and subjective response to taking medication subscale score, SAIQ presence/outcome of illness subscale and the need for treatment subscale scores, and PANSS total modified score from baseline to immediately after tDCS assessment.) **Safety.** The side effect profiles were reported in the Supplementary Information and there were no major adverse events in the present study.	

Evidence Table : Efficacy/ safety/ organisational (TDCS – SCHIZOPRENIA)
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Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow up (if applicable)	Outcome Measures/ Effect Size	General Comments
4. Meiron O, David J, Yaniv A. Left prefrontal transcranial direct-current stimulation reduces symptom-severity and acutely enhances working memory in schizophrenia. Neuroscience Letters. 2021;755:135912. Israel	**Randomized Controlled Trial** **Aim:** to examine the effects of repetitive active tDCS (versus sham tDCS) on patients' symptoms and verbal WM performance. **Study Design:** Double blind randomized sham-controlled clinical trial. 19 patients were randomized to either active or sham conditions using a random number generation computerized system). **Inclusion Criteria:** Diagnosis according to DSM-IV criteria for schizophrenia or schizoaffective disorder, right handed, under stable doses of antipsychotic medication criteria, ages 18–75, willing/capacity to provide informed consent, and normal vision. **Exclusion Criteria:** Concurrent or past history of substance dependence or abuse, history of seizures, other current axis I disorders, intracranial	I	A total of 19 SZ patients and 12 HC's took part in this study, the majority were men (84.2 %) and the age ranged from 20 to 65 (M = 38.48, SD = 14.1) with no significant differences in age between SZ = = and HC groups (t (29) = 0.05, p> 0.05). In the SZ group, 11 patients were randomly assigned to the active tDCS group and eight to the sham tDCS group.	A total of 10 consecutive 20-minute tDCS sessions of active 2-mA unilateral left prefrontal tDCS	Unilateral left prefrontal sham stimulation.		**<u>The positive and negative syndrome scale.</u>** The tDCS group showed a mean reduction of 15 % in their total PANSS scores (from 76.2 [SD = 10.3] to 64.8 [SD =14.2]) (p<0.01), whereas the sham group had a mean reduction of 0.69 % in their total PANSS scores (from 72.1 [SD = 16.2] to 71.667 [SD = 24]) In the active tDCS group, total PANSS scores were reduced by 15.3 % at 1 week (N=10) and by 16 % at four weeks after termination of tDCS (N = 10) where as in sham, PANSS scores were reduced by 4% at 1 week post sham intervention (N=8) and were worse than baseline-scores at 4-weeks post intervention. A significant interaction between group and time (F3), 45) = 3.18, p < 0.05). **<u>Working memory performance.</u>** ***WM was not analyzed in sham group in view of low numbers of participant complete the assessment.* Active tDCS (N= 11) acutely improved WM-performance reflecting significantly higher WM-accuracy scores immediately after tDCS intervention (t (10) = -5.3, p< 0.01) versus baseline WM scores. The active group showed a mean improvement of 18.7% in WM	

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	metal implants, pregnancy, history of adverse reaction to neuromodulation, frequent persistent migraines, current significant laboratory abnormality, participation in a clinical trial in the past 6 weeks before study onset. Study Period: Primary Outcome: 3. The positive and negative syndrome scale 4. Working memory performance						accuracy scores (from 65 [SD = 23.9] to 80 [SD= 22.9]). Patients' post-tDCS WM accuracy scores (M = 80.18, SD = 22.9) and reaction times (M = 673.7, SD = 127.5) were apparently "normalized" immediately after tDCS intervention, and statistically comparable to HC WM scores, ($t(21) = 2.0$, $p > 0.05$), and ($t(21) = 1.2$, $p > 0.05$), respectively. Secondary outcome: **Safety.** Patients did not experience side effects, and most of them reported mild tingling or itching sensation under electrodes during the tDCS intervention. In some patients skin-redness was observed after tDCS sessions, which disappeared after two to five minutes.	

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5.Schilling TM, Bossert M, König M et al. Acute effects of a single dose of 2 mA of anodal transcranial direct current stimulation over the left dorsolateral prefrontal cortex on executive functions in patients with schizophrenia—A randomized controlled trial. Plos one. 2021;16(7):e0254695. **Germany**	**Randomized Controlled Trial** **Aim:** to examine the impact of tDCS on performance in several executive functions in patients with schizophrenia, schizoaffective disorder or acute transient psychotic disorder. **Study Design:** Double blind randomized sham-controlled clinical trial. Participants were randomly assigned to one of two groups A and B following randomization sequence in block of four positions. The performing experimenters knew the allocation of participants to group A or B, but blinded to whether group A or B coded for tDCS or sham. Clinical sample was recruited from the Department of Psychiatry and Psychotherapy at the SRH Clinic Karlsbad-Langensteinbach, Germany	I	In total 52 patients were included in the study. 3 discontinued intervention and 1 were lost to follow up, due to reported adverse side effect of stimulation and technical issue respectively. Final sample size N=48 were divided equally in both group (n=24). Only participant completed the protocol were analysed. 14 patients (7 in both groups) were diagnosed with one or more comorbid psychiatric disorders. Patients of both groups did not differ in age, sex, duration of disease, handedness, current intake of antipsychotic medication, smoking, self-reported	tCDS stimulator with stimulation of 2mA for 20 minutes (8s fade in, 1200s tDCS 2mA, 8s fade out; total duration 1216s) DC-Stimulator Mobile Transcranial direct current stimulation was applied with the (Neuro-Conn, Ilmenau, Germany)	A true stimulation was simulated in the beginning before the device reduced the applied current after 40 seconds (8s fade in, 40s tDCS 2mA, 8s µA; fade out, 1120s sinus 85 Hz 50 total duration 1216s).		**<u>Neuropsychological performance</u>** Neuropsychological performance in all three performance measures improved from session 1 to session 2, however, stronger improvement from session 1 to session 2 in the sham compared to the verum group. “online” stimulation received, did not influence performance in the neuropsychological tests. (p>0.05) a stronger improvement from session 1 to session 2 in the sham compared to the verum group in participants who had performed the neuropsychological response inhibition task within 20 minutes after the end of the stimulation. (“offline”) <u>Secondary outcome:</u> **<u>Rating of perceived stimulation.</u>** Generally, rating of pain were comparatively low (verum group M = 17.17, SD = 22.69, sham group M = 11.83, SD = 16.35, VAS from 0 to 100). Other reported side effects were burning, tingling or itching sensations on the skin, optical effects, a feeling of heat, disturbed concentration or	

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	Inclusion Criteria: Patients (age range = 18–65) with an ICD-10 diagnosis of schizophrenia (ICD-10: F20), schizoaffective disorder (ICD-10: F25) or acute transient psychotic disorder (ICD-10: F23) **Exclusion Criteria:** Patients were excluded if they were minors, were of legal age but were unable to give their informed consent, had an impaired intelligence (i.e. IQ < 85), had used drugs in the last 8 weeks, were suffering from any central nervous system disorder, had an history of skull or heart surgery, fragments of metal in the skull or skin irritations at the forehead Study Period: May 2018 and July 2019		depression or estimated premorbid verbal intelligence. No baseline differences were observed for any performance measures of any neuropsychological test (all p >.5)				tiredness. However, groups did not differ on their reported side effects The stimulation was generally well tolerated and participants were not able to discern verum from sham stimulation.	

Evidence Table : Efficacy/ safety/ organisational (TCDS – SCHIZOPRENIA)
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6.Yu L, Fang X, Chen Y, Wang Y, et al. Efficacy of transcranial direct current stimulation in ameliorating negative symptoms and cognitive impairments in schizophrenia: a systematic review and meta-analysis. Schizophrenia research. 2020 ;224:2-10. **China**	**Systematic Review and Meta Analysis.** **Aim:** to systematically evaluate the efficacy of transcranial direct current stimulation (tDCS) in ameliorating negative symptoms and cognitive impairments in schizophrenia patients **Data sources and searches:** Systematically searched in the PubMed, Embase, PsycINFO and Cochrane Library databases through March 23, 2020, using the following terms: (transcranial direct current stimulation or tDCS) and (schizophrenia or schizoaffective or psychosis). This procedure was based on the preferred reporting items for systematic reviews and meta-analysis (PRISMA) 2009 flow diagram. Inclusion Criteria:	I	14 studies that met the inclusion criteria were selected for the meta-analysis, of which 12 studies were included for negative symptoms and 7 studies were eligible for cognitive deficit. Negative symptoms: A total of 447 patients with schizophrenia or schizoaffective disorder – 225 in the active tDCS group and 222 in the sham stimulation. Cognitive impairments: A total of 256 patients – 135 in the active tDCS group and 121 in the sham stimulation group.	tDCS	Sham		**Negative symptoms.** The difference between active and sham tDCS on negative symptoms in schizophrenia failed to reach the significance level in the overall analysis (SMD: -0.14, 95% CI: -0.33 – 0.05) When subgroup analysis was done, only studies with the higher stimulation frequency of twice a day revealed a significant difference in therapeutic effects between active tDCS and sham stimulation (SMD:-0.31, 95%CI: -0.58 to -0.05) **Cognitive impairments.** The overall result showed that there was no significant difference in active tDCS vs sham stimulation in improving cognition (SMD:-0.21, 95%CI: -0.46–0.04).	

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow up (if applicable)	Outcome Measures/ Effect Size	General Comments
	1. Subjects were exclusively patients with schizophrenia, schizoaffective disorder or psychosis. 2. Active tDCS and shamestimulation were conducted in two parallel groups. 3. Sufficient data was provided for obtaining the mean and standard deviation (SD) for negative symptoms or cognitive deficit severity levels. 4. The study design was based on a randomized controlled trial. <u>Exclusion Criteria:</u> 1. They were not original research studies. 2. Participants received nonpharmacological treatments in addition to tDCS. 3. Insufficient information was provided for extraction, 4. The subjects were animals 5. They were published in languages other than English. **Quality assessment:** Two independent authors conducted the assessment procedure in dependently							

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	according to the Cochrane Handbook for Systematic Reviews of Interventions, where seven item of bias described. **Data synthesis and analysis:** Meta-analysis was conducted using Review Manager Version 5.3 and Stata15 (Stat Corp., College Station, Texas,USA). <u>Data extraction:</u> name of the first author, publication year, demographic and clinical characteristics of participants (age, sex, diagnosis and diagnostic criteria),medica tion status, tDCS parameters and the extracted outcome measures. Standardized mean difference (SMD) was chosen as the summary statistic whenever data from different scales / scores were mixed. Egger's test was used to conduct quantified assessment of publication bias risk.							

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7. Kim J, Iwata Y, Plitman E, et al. A meta-analysis of transcranial direct current stimulation for schizophrenia: "Is more better?" J Psychiatr Res. 2019 Mar;110 117-126.	**Systematic Review and Meta Analysis.** **Aim:** To evaluate the efficacy of transcranial direct current stimulation (tDCS) on positive symptoms, particularly auditory hallucinations, and negative symptoms in patients with schizophrenia **Data sources and searches:** Systematically searched for English language publications from 1950 to October 2018 were searched for using OVID database (Embase, Medline®, and PsycINFO using following terms (transcranial direct current stimulation or tDCS) and (schizophreni* or psychosis). The reference sections of review articles were gleaned for relevant publications overlooked by the search strategy. Meta-analysis was conducted in accordance	I	10 eligible studies with a total of 338 participants, focusing on those with schizophrenia or schizoaffective disorder.	tDCS	Sham		Results: No significant effect of tDCS on the severity of **auditory hallucinations** (7 studies, n=242) (SMD=0.50, 95% CI -0.09–1.09, p = 0.10), **positive symptoms** (9 studies, n=313) (SMD=0.03, 95% CI -0.24–0.31, p=0.81), **or negative symptoms** (9 studies, n=313) (SMD=0.27, 95% CI -0.09–0.62, p=0.14). Subgroup analyses showed that studies applying twice-daily stimulation showed a significant reduction in the severity of auditory hallucinations (4 studies, n=138, SMD=1.04, 95% CI 0.20-1.89, p=0.02). Studies with 10 or more stimulation sessions demonstrated reductions in both auditory hallucinations (5 studies, n=186, SMD=0.86, p=0.009) and negative symptoms severity (7 studies, n=257, SMD=0.41, p=0.04).	

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	with the guidelines outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) group. Two individuals (JK and PG) performed the search (last search: October 9, 2018), assessed eligibility, and extracted the data. <u>Inclusion Criteria:</u> (1) they consisted of at least 5 participants with schizophrenia or schizoaffective disorder, (2) they included a sham group, and (3) data were sufficient to obtain the standardized mean difference (SMD) for the change in severity of the primary outcomes. <u>Exclusion Criteria:</u> -Studies that only reported on the frequency of symptoms were excluded. -Studies that combined tDCS with other intervention strategies other than antipsychotic medication (e.g., psychoeducation or cognitive training) were also excluded **Quality assessment:** conducted the assessment using risk of bias tool							

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow up (if applicable)	Outcome Measures/ Effect Size	General Comments
	Publication bias was assessed using Egger's regression test Primary outcomes measured: severity of auditory hallucinations, positive symptoms, and negative symptoms, using standardized rating scales like the Auditory Hallucinations Rating Scale (AHRS), the Positive and Negative Syndrome Scale (PANSS), and the Scale for the Assessment of Negative Symptoms (SANS).							

TECHNOLOGY REVIEW (MINI HTA) TRANSCRANIAL DIRECT CURRENT STIMULATION (tDCS)FOR DEPRESSION AND SCHIZOPHRENIA

e ISBN 978-967-2887-89-8

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