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**eTables: 6**

Brain stimulation and other biological non-pharmacological interventions in mental disorders: an umbrella review

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**Introduction**

Nearly 228 million people worldwide suffer from serious mental illnesses, including major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia (SCZ), and many more from other psychiatric conditions (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018). Mental disorders are associated with disability, medical comorbidities, and a reduced life expectancy of >10 years (Correll, Solmi, et al., 2017; GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018).

Pharmacological treatments of mental disorders are not always effective and can have safety issues, whereas psychosocial interventions are not always effective, readily available or scalable (Bighelli et al., 2021; Howes et al., 2017; Papp et al., 2021). In fact, 30% of subjects with MDD do not achieve remission even after 4 medication trials (Gaynes et al., 2009); up to 30% of patients with schizophrenia are treatment-resistant, with 60% of those being clozapine-resistant (Chakos et al., 2001; Lally & Gaughran, 2019; Siskind et al., 2017). Consequently, the development of new therapeutic interventions is urgently needed.

Several biological non-pharmacological treatments have become progressively available (Brunoni et al., 2019). Treatments based on direct electro-/electromagnetic stimulation over targeted brain areas (neuromodulatory interventions) include invasive deep brain stimulation (DBS) and vagus nerve stimulation (VNS), and minimally invasive modalities, i.e. transcranial magnetic stimulation (TMS) and its variants, transcranial direct current stimulation (tDCS), electro-convulsive therapy (ECT), light therapy (LT), as well as miscellaneous interventions, such as sleep deprivation (Martin & Martin-Sanchez, 2012; Mutz et al., 2018; Ramirez-Mahaluf et al., 2020). These therapies have been used as stand-alone treatments or combined with medications in a wide range of psychiatric conditions, such as mood disorders, schizophrenia, substance use disorders, and others (Kennedy et al., 2018; Mutz et al., 2019; Razza, Afonso Dos Santos, et al., 2020; Trojak et al., 2017).

However, available primary studies or even systematic reviews of biological non-pharmacological treatments are limited to either specific interventions or disorders, with no systematic overview summarizing and appraising the overall and specific evidence of these interventions in mental disorders. Currently, clinical recommendations about the use of biological non-pharmacological treatments still lack consensus. In fact, only ECT in MDD finds a clear place in the therapeutic algorithms across international guidelines; in all other cases, some biological non-pharmacological interventions are considered, but less consistently recommended (American Psychiatric Association, 2010; Bauer et al., 2013; Cleare et al., 2015; Malhi et al., 2021; Milev et al., 2016; National Institute for Health and Care Excellence, 2009). A rigorous and comprehensive evidence synthesis can inform future clinical recommendations.

We aimed to quantitatively assess, through an umbrella review of available meta-analyses, the efficacy and safety of biological non-pharmacological treatments in patients with mental disorders, compared to inactive (i.e., placebo or sham interventions), treatment-as-usual (TAU), or other active treatments, to outline a comprehensive overview of their usefulness across psychiatric conditions. We only selected meta-analyses (MAs) of randomized-controlled trials (RCTs), which are considered the highest quality of evidence (Murad et al., 2016). We further supplemented our findings with an appraisal of the quality and certainty of evidence according to recommended guidelines (Page et al., 2021; Schünemann et al., 2013).

**Methods**

*Search and inclusion criteria*

This umbrella review followed a pre-registered protocol (PROSPERO CRD42020158827) and adhered to the PRISMA 2020 statement (interpreted for umbrella reviews) (Page et al., 2021).

We systematically searched PubMed, Cochrane Library, PsycINFO until July 4th, 2021 supplemented with manual searches (detailed search strategy available in eMethods).

Inclusion criteria were i) meta-analysis of RCTs, ii) reporting on efficacy and safety of biological treatments (i.e., DBS, ECT, LT, tDCS, TMS, VNS, see eBox 1) versus any control, ii) in psychiatric disorders according to DSM, ICD, validated scales with cut-off, or clinical records. Exclusion criteria were i) study designs other than MA of RCTs, ii) no psychiatric disorder, iii) primary neurological or physical diagnosis (e.g., depression in dementia), iv) interventions other than biological treatment, v) no safety or efficacy data to extract.

Screening of each article title/abstract and full text, as well as data extraction was done independently by two authors among a pool of five (MS, SR, RdF, EC, SP), and inconsistencies were resolved by consensus, or by a third author. Among overlapping meta-analyses (same Population/Intervention/Control/Outcome=PICO), we selected the one including more studies.

We extracted the following information from each included articles: doi, RCT identifier, author, year, k of RCTs, sample size, demographics, diagnostic group, intervention, control group, outcomes and their statistical estimates, information for quality and credibility assessment, and authors’ recommendations.

*Outcomes*

Co-primary outcomes were standardized mean difference (SMD) of total symptoms (in schizophrenia-spectrum disorders and neurodevelopmental disorders), disease-specific symptoms (in depressive episode of mood disorders, manic episode of bipolar disorder (BD), obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), substance use disorders (SUD), generalized anxiety disorder (GAD)), and risk ratio or odds ratio (RR/OR) of acceptability (considering retention rates between treatment and control group at endpoint, for all-cause discontinuation). Secondary outcomes were response, remission, and changes in symptoms in specific domains (i.e., cognition, SMD), occurrence of adverse events (AE).

*Data analysis and synthesis*

We re-ran meta-analyses with Comprehensive Meta-Analysis (Borenstein et al., 2013) i) calculating SMD if they reported mean differences, ii) using random-effects if fixed effect model was used and *I*2>50%, since this may suggest substantial heterogeneity (Deeks et al., 2022) iii) excluding non-RCTs. Co-primary outcomes were reported in forest plots using the software R 4.0.5, package “forestplot” (R Core Team, 2021).

*Quality and certainty of evidence assessment*

Quality of meta-analyses and their RCTs was assessed with AMSTAR-PLUS, for each PICO combination (Correll, Rubio, et al., 2017). Certainty of evidence was assessed with GRADE, using GRADEpro (details in eMethods) (GRADEpro GDT, 2020; Schünemann et al., 2013).

**Results**

***Search results***

From the initial 3,519 records, we retained 102 meta-analyses with 591 PICO combinations, including approximately 1,886 RCTs and 90,267 participants (Figure 1, Table 1, eTable 1). Meta-analyses focused on TMS (n=54), ECT (n=20), tDCS (n=18), LT (n=12), DBS (n=4), sleep deprivation (n=2), Magnetic Seizure Therapy (MST, n=1), and taVNS (n=1) administered in mood disorders (n=64), schizophrenia-spectrum disorders (SCZ, n=24), SUD (n=6), OCD (n=6), PTSD (n=2), anxiety disorders (n=1), attention-deficit/hyperactivity disorder (ADHD, n=1), autism-spectrum disorders (ASD, n=1), or combined conditions (n=1) (Table 1). The largest body of evidence was available for TMS (PICO=279), followed by ECT (PICO=206), tDCS (PICO=55), LT (PICO=36), DBS (PICO=12), MST (PICO=4), sleep deprivation (PICO=4), and VNS (PICO=1).

***Outcomes***

Results of the co-primary efficacy outcomes are reported in Figures 2-3, Table 2, and below. All efficacy and safety primary and secondary outcomes are displayed in eTable 2, and eResults. Certainty assessed with GRADE is reported in Figures 2-3, and in detail in eTable 3. Authors’ recommendations are displayed in eTable 4.

Below follows a synthesis of findings, presenting results within each disorder, by control intervention, and by outcome at the end of the acute treatment.

*Mood disorders: Primary outcomes*

1. *Any depressive disorder: depressive episode*

In any depressive episode (regardless if unipolar or bipolar), compared with inactive interventions, on primary outcome, the largest effect emerged for ECT (combining different protocols, SMD=0.91, 95%CI=0.54-1.27/GRADE=moderate), followed by rTMS (SMD=0.51, 95%CI=0.39-0.63/GRADE=moderate), tDCS (SMD=0.46, 95%CI=0.15-0.76/GRADE=low), DBS (SMD=0.42, 95%CI=0.12-0.72/GRADE=very low), and LT (SMD=0.41, 95%CI=0.18-0.64/GRADE=low) (Kedzior et al., 2014; Kisely et al., 2018; Mutz et al., 2019; Perera et al., 2016; UK ECT Review Group, 2003; R. Zhang et al., 2021).

Among different TMS protocols, a significant improvement was provided by theta-burst stimulation (TBS) (SMD=1.03, 95%CI=0.35-1.70/GRADE=low), low frequency (LF) right (R-) dorsolateral prefrontal cortex (DLPFC) rTMS (SMD=0.71, 95%CI=0.05-1.36/GRADE=low), high frequency (HF) left (L-)DLPFC rTMS (SMD=0.60, 95%CI=0.38-0.82/GRADE=low), and deep TMS (dTMS) (SMD=0.29, 95%CI=0.03-0.55/GRADE=moderate) (Berlim et al., 2017; Mutz et al., 2019). LF L-DLPFC rTMS (SMD=0.08, 95%CI-0.53-0.69/GRADE=moderate), B-DLPFC rTMS (SMD=0.14, 95%CI-0.10-0.39/GRADE=moderate), accelerated TMS (aTMS) (SMD=1.25, 95%CI-0.41-2.90/GRADE=very low), and synchronized TMS (sTMS) (SMD=0.55, 95%CI-0.02-1.13/GRADE=low) (Berlim et al., 2017; Chen et al., 2020; Mutz et al., 2019) did not bring a significant improvement.

Acceptability did not significantly differ from sham for any intervention (Berlim et al., 2017; Brunoni, Chaimani, et al., 2017; Chu et al., 2021; Mutz et al., 2018; Mutz et al., 2019; Razza, Palumbo, et al., 2020; UK ECT Review Group, 2003; R. Zhang et al., 2021).

Compared with TAU, DLPFC rTMS outperformed TAU in postpartum depression (SMD=1.02, 95%CI=0.66-1.37/GRADE=moderate) (Peng et al., 2020), adjunctive LT outperformed TAU pharmacotherapy in non-seasonal depression (SMD=0.55, 95%CI=0.39-0.73/GRADE=low) (Penders et al., 2016), while no difference emerged between adjunctive sleep deprivation vs TAU (SMD=0.13, 95%CI=-0.38–0.64/GRADE=very low) (Ioannou et al., 2021).

Regarding head-to-head comparisons, ECT outperformed antidepressants (ADs), mixed rTMS protocols, and HF L-DLPFC rTMS (SMD=0.80, 95%CI=0.29-1.29/GRADE=high; SMD=0.37, 95%CI=0.05-0.70/GRADE=low; SMD=0.94, 95%CI=0.26-1.61/GRADE=low) (Berlim, Van den Eynde, & Daskalakis, 2013; Ren et al., 2014; UK ECT Review Group, 2003). No difference emerged specifically between bitemporal (BT) ECT and HF L-DLPFC rTMS (SMD=0.78, 95%CI=-0.05-1.60/GRADE=very low) (Mutz et al., 2019). Among different ECT procedures, BT ECT outperformed right unilateral (RUL) ECT at low to moderate dose (LM) (SMD=0.88, 95%CI=0.49-1.28/GRADE=moderate) (Mutz et al., 2019). No significant difference was noticed for direct comparison of bifrontal (BF) ECT with BT ECT (SMD=0.10, 95%CI=-0.11-0.31/GRADE=low), BF ECT with high dose (H-)RUL ECT (SMD=-0.04, 95%CI=-0.39-0.32/GRADE=low), and BT ECT with H-RUL ECT (SMD=-0.03, 95%CI=-0.17-0.11/GRADE=low) (Dunne & McLoughlin, 2012; Kolshus et al., 2017; Mutz et al., 2019). Among different rTMS protocols, HF L-DLPFC outperformed LF R-DLPFC (SMD=0.48, 95%CI=0.15-0.81/GRADE=low), but no significant difference emerged for bilateral (B-) DLPFC rTMS versus HF L-DLPFC rTMS and for HF L-DLPFC rTMS versus LF L-DLPFC rTMS (SMD=0.09, 95%CI=-0.39-0.58/GRADE=low and SMD=0.37, 95%CI=-1.29-2.04/GRADE=low, respectively) (Mutz et al., 2019).

Acceptability was significantly higher for ECT compared to AD (OR=2.94, 95%CI=1.12-16.39), and for B-DLPFC rTMS compared to LF R-DLPFC rTMS (OR=2.43, 95%CI=1.11-5.30) (Brunoni, Chaimani, et al., 2017; UK ECT Review Group, 2003). No other difference in acceptability was found comparing ECT with rTMS (Chen et al., 2017; Ren et al., 2014), among different protocols of ECT (Mutz et al., 2019), and of rTMS (Brunoni, Chaimani, et al., 2017; Chen et al., 2014; Mutz et al., 2019).

1. *Bipolar disorder: depressive episode*

In bipolar depressive episode, compared with inactive interventions, on primary outcome, the largest effect emerged for LT (SMD=0.43, 95%CI=0.04-0.82/GRADE=low) (Lam et al., 2020), followed by rTMS (SMD=0.30, 95%CI=0.06-0.55/GRADE=low) (Tee & Au, 2020).

No difference in acceptability between LT and inactive treatment was found (Lam et al., 2020).

Compared with TAU, adjunctive sleep deprivation had no significant effect (SMD=0.45, 95%CI=-0.09-0.99/GRADE=very low) (Ramirez-Mahaluf et al., 2020).

1. *Bipolar disorder: manic episode*

In bipolar disorder I, adjunctive ECT showed a larger decrease in manic symptoms in the manic phase compared to TAU (SMD=3.50, 95%CI=2.44-4.57/GRADE=moderate) (J. Zhang et al., 2021).

1. *Unipolar depression: depressive episode*

In unipolar depressive episode, on primary outcome, transcutaneous auricular (ta)VNS and tDCS (SMD=0.55, 95%CI=0.02-1.09/GRADE=very low; SMD=0.37, 95%CI=0,04-0,70/GRADE=low) (Zhang et al., 2016), but not TBS (SMD=2.46, 95%CI=-0.51-0.10/GRADE=very low) (Voigt et al., 2021) outperformed inactive interventions.

No difference in acceptability was found between tDCS and inactive treatment (OR=1.39, 95%CI=0.74-2.60) (Aparicio et al., 2016).

1. *TRD: depressive episode*

In treatment-resistant depression, compared with inactive interventions, on primary outcome, the effect was the largest for DBS (SMD=0.75, 95%CI=0.36-1.13/GRADE=very low]) (Hitti et al., 2020), and rTMS followed (SMD=0.50, 95%CI=0.28-0.73/GRADE=low) (Lam et al., 2008). The improvement was greater for HF L-DLPFC (SMD=0.50, 95%CI=0.28-0.73/GRADE=low) than B-DLPFC stimulation (SMD=0.42, 95%CI=0.13-0.71/GRADE=low), while no difference was found for LF R-DLPFC rTMS (SMD=1.81, 95%CI=-2.16-5.78/GRADE=very low) (Li et al., 2021; Sehatzadeh et al., 2019). dTMS did not seem to be more effective than sham stimulation (SMD=0.76, 95%CI=-0.9-1.60/GRADE=very low) (Hung et al., 2020).

No difference in acceptability could be found for any interventions (Li et al., 2021; Liu et al., 2014).

No studies compared any intervention with TAU.

In head-to-head comparisons, no significant difference emerged between HF L-DLPFC rTMS and B-DLPFC rTMS or LF R-DLPFC rTMS (SMD=-0.17, 95%CI=-1.49-1.15/GRADE=very low; SMD=-0.05, 95%CI=-0.68-0.59/GRADE=very low) (Li et al., 2021), nor between MST and LM-RUL ECT (SMD=0.14, 95%CI=-0.37-0.64/GRADE=very low) (Li et al., 2021).

For the same comparisons, no difference in acceptability emerged (Li et al., 2021).

*Mood disorders: Secondary outcomes*

ECT had higher response rates compared to sham in depressive disorders (OR=4.77, 95%CI=1.30-6.17) (Pagnin et al., 2004), and compared to TAU in TRD (RR=1.82, 95%CI=1.55-2.14) (Song et al., 2015).

DBS had higher response rates compared to sham in depressive disorders (OR=5.50, 95%CI=2.79-10.85) (Kisely et al., 2018).

Any rTMS compared to sham had higher response rates (RR=2.35, 95% 1.70-3.25) and remission rates (RR=2.24, 95%CI=1.53-3.27) in TRD (Leggett et al., 2015). Among protocols, HF L-DLPFC rTMS was superior to sham in response (OR=3.23, 95%CI=2.33-4.55) (Brunoni, Chaimani, et al., 2017) and remission (OR=2.56, 95%CI=1.73-3.78) (Mutz et al., 2019) in depressive disorders, in response (OR=2.57, 95%CI=1.17-5.66) (Nguyen et al., 2021) in bipolar depression, and in response (RR=2.41, 95%CI=1.40-4.16) (Li et al., 2021) and remission (RR=2.33, 95%CI=1.52-3.58) (Sehatzadeh et al., 2019) in TRD. LF R-DLPFC was superior to sham in response (OR=3.35, 95%CI=1.40-8.02) (Berlim, Van den Eynde, & Jeff Daskalakis, 2013) and in remission (OR=2.50, 95%CI=1.03-5.88) (Brunoni, Chaimani, et al., 2017) in depressive disorders, but not in response in bipolar depression (OR=5.21, 95%CI=0.96-28.13) (Nguyen et al., 2021) or in response in TRD (RR=2.01, 95%CI=0.80-5.02) (Li et al., 2021). B-DLPFC rTMS had higher response rates in depressive disorders (OR=3.33, 95%CI=1.92-5.88) (Brunoni, Chaimani, et al., 2017) and response rates in TRD (RR=3.85, 95%CI=2.00-7.43) (Li et al., 2021), but not higher response rates in bipolar depression (OR=2.05, 95%CI=0.50-8.41) (Nguyen et al., 2021). TBS was superior to sham in response and remission rates in depressive disorders (respectively, OR=3.64, 95%CI=1.61-8.23 and OR=2.45, 95%CI=1.11-5.42) (Chu et al., 2021), and in response rates in unipolar depression (RR=2.40, 95%CI=1.27-4.55) (Voigt et al., 2021). dTMS compared to sham had higher response and remission rates in depressive disorders (OR=1.69, 95%CI=1.00-2.85; OR=2.24, 95%CI=1.24-4.06) (Mutz et al., 2019), and in TRD (OR=1.37, 95%CI=1.02-1.84; OR=1.60, 95%CI=1.15-2.23) (Hung et al., 2020). LF L-DLPFC rTMS, aTMS, and sTMS did not increase response or remission rates compared to sham when tested in mood disorders (Mutz et al., 2018; Mutz et al., 2019; Sonmez et al., 2019).

tDCS compared to sham increased response and remission rates in unipolar depression (OR=1.63, 95%CI=1.26-2.12; OR=2.50, 95%CI=1.26-4.50) (Shiozawa et al., 2014), but not in any depressive disorder (OR=1.75, 95%CI=0.85-3.58; OR=1.29, 95%CI=0.59-2.83) (R. Zhang et al., 2021).

Light therapy, compared to sham treatment, had higher response (OR=2.90, 95%CI=1.60-5.40) (Golden et al., 2005) and remission rates (RR=1.42, 95%CI=1.08-1.85) (Pjrek et al., 2020) in seasonal affective disorder; in bipolar depression, it increased response (OR=2.32, 95%CI=1.12-4.81) but not remission rates (OR=3.21, , 95%CI=0.83-12.40) (Lam et al., 2020).

Other efficacy/safety secondary outcomes can be found in detail in the supplementary material.

*Schizophrenia: Primary outcomes*

1. *Schizophrenia-spectrum disorders*

In schizophrenia-spectrum disorders, compared with inactive interventions, on primary outcome, ECT had the strongest efficacy (SMD=0.88, 95%CI=0.31-1.45/GRADE=moderate) (Tharyan & Adams, 2005), followed by tDCS (SMD=0.45, 95%CI=0.06-0.84/GRADE=very low) (Fregni et al., 2020), TBS on prefrontal cortex (PFC) (SMD=0.58, 95%CI=0.20-0.97/GRADE=low) and rTMS on L- temporoparietal cortex (TPC) (SMD=0.42, 95%CI=0.06-0.78/GRADE=low) (Dougall et al., 2015; Kennedy et al., 2018). Lumping any TMS protocol yielded no significant difference (SMD=0.29, *p*=0.06/GRADE=very low).

Acceptability did not significantly differ from sham for ECT, rTMS, and tDCS (Dougall et al., 2015; Osoegawa et al., 2018; Tharyan & Adams, 2005).

1. *Treatment-resistant schizophrenia*

In treatment-resistant and clozapine-resistant schizophrenia (TRS, CRS), no meta-analytic comparison with inactive interventions was found.

Adjunctive ECT outperformed TAU (SMD=0.64, 95%CI=0.22-1.06/GRADE=low), non-clozapine antipsychotics (SMD=0.67, 95%CI=0.39-0.95/GRADE=low), and clozapine (SMD=0.88, 95%CI=0.44-1.33/GRADE=low) (Sinclair et al., 2019; Zheng et al., 2016; Zheng et al., 2018).

Acceptability did not differ when comparing adjunctive ECT and TAU in TRS, and when comparing adjunctive ECT and clozapine in CRS (Sinclair et al., 2019; Wang et al., 2018).

Considering head-to-head comparisons, ECT outperformed antipsychotics alone (SMD=0.76, 95%CI=0.19-1.04/GRADE=very low) (Gu et al., 2017).

*Schizophrenia: Secondary outcomes*

Adjunctive ECT, compared to TAU, increased response and remission rates in TRS (RR=1.48, 95%=1.24-1.77; RR=2.18, 95%CI=1.45-3.28) (Zheng et al., 2016) and in CRS (RR=1.94, 95%=1.59-2.36; RR=3.28, 95%CI=1.80-5.99) (Wang et al., 2018).

Positive symptoms were improved by adjunctive ECT compared to clozapine (SMD=0.45, 95%CI=0.22-0.68) (Wang et al., 2018) in CRS and TPC-rTMS compared to sham (SMD=0.46, 95%CI=0.23-0.68) (Dougall et al., 2015) in schizophrenia, but not by other protocols of rTMS or by tDCS compared to sham (Cheng et al., 2020; Dougall et al., 2015) in schizophrenia spectrum disorders.

Negative symptoms were improved by tDCS (SMD=0.43, 95%CI=0.11-0.75) (Cheng et al., 2020), rTMS (SMD=0.19, 95%CI=0.07-0.32) (Osoegawa et al., 2018), and specifically the protocols DLPFC rTMS (SMD=0.64, 95%CI=0.32-0.96) (Aleman et al., 2018) and PFC TBS (SMD=0.60, 95%CI=0.21-0.99) (Dougall et al., 2015), but not TPC rTMS (SMD=0.07, 95%CI=-0.24-0.38) (Dougall et al., 2015), compared to sham in schizophrenia spectrum disorders. Adjunctive ECT did not improve negative symptoms compared to TAU in TRS (SMD=-0.07, 95%CI=-0.33-0.19) (Sinclair et al., 2019) and CRS (SMD=0.24, 95%CI=-0.01-0.49) (Wang et al., 2018).

General psychopathology symptoms improved more with PFC TBS (SMD=0.54, 95%CI=0.15-0.92) (Dougall et al., 2015) but not with TPC rTMS (SMD=0.36, 95%CI=-0.06-0.79) (Dougall et al., 2015) compared to sham in schizophrenia, and not with adjunctive ECT compared to TAU in TRS (SMD=0.31, 95%CI=-0.24-0.86) (Sinclair et al., 2019) or in CRS (SMD=0.12, 95%CI=-0.53-0.77) (Wang et al., 2018).

Other efficacy/safety secondary outcomes can be found in detail in the supplementary material.

*Substance-related disorders: Primary outcomes*

In substance-related disorders, compared with inactive interventions, on primary outcome, the largest effect emerged for HF B-DLPFC/insula dTMS (SMD=1.16, 95%CI=0.69-1.64/GRADE=moderate) and HF L-DLPFC rTMS (SMD=0.77, 95%CI=0.02-1.53/GRADE=low) (Zhang et al., 2019), followed by tDCS (in alcohol use disorder) (SMD=0.19, 95%CI=0.01-0.38/GRADE=low) (Kim & Kang, 2021).

Acceptability in any substance dependence did not differ between tDCS and sham (OR=0.63, 95%CI=0.15-2.62) (Aparicio et al., 2016)

No meta-analytic evidence comparing biological non-pharmacological treatments and TAU or other active treatment was found for this diagnostic spectrum.

*Substance-related disorders: Secondary outcomes*

Compared to sham treatment, tDCS mitigated significantly more craving in alcohol use disorder (SMD=0.33, 95%CI=0.08-0.58) (Kim & Kang, 2021), and mixed protocols of rTMS in nicotine use disorder (SMD=1.00, 95%CI=0.48-1.51) (Maiti et al., 2017). rTMS did not improve significantly craving in alcohol use disorder compared to sham or TAU (SMD=-0.06, 95%CI=-0.89-0.77) (Maiti et al., 2017), and protocols of rTMS other than HF L-DLPFC (SMD=0.62, 95%CI=0.35-0.89) did not improve craving in substance dependance compared to sham (Zhang et al., 2019).

*Post-traumatic stress disorders: Primary outcomes*

rTMS was effective on PTSD symptoms compared to inactive interventions (SMD=0.43, 95%CI=0.19-0.68/GRADE=moderate) (McGirr et al., 2020). Among TMS protocols, the only effective one was LF R-DLPFC rTMS (SMD=0.54, 95%CI=0.23-0.85/GRADE=low) (McGirr et al., 2020). HF L-DLPFC rTMS and HF R-DLPFC rTMS did not yield significant improvement (SMD=0.05, 95%CI=-0.95-1.06/GRADE=low; SMD=1.18, 95%CI=-0.03-2.37/GRADE=low) (McGirr et al., 2020).

Acceptability did not differ between rTMS and sham stimulation (McGirr et al., 2020).

No meta-analytic evidence was found versus TAU, or head-to-head comparisons.

*Post-traumatic stress disorders: Secondary outcomes*

In PTSD, rTMS improved self-reported PTSD symptoms (SMD=2.38, 95%CI=1.45-3.30) and anxiety symptoms (SMD=0.89, 95%CI=0.29-1.50) compared to sham, but not depressive symptoms (SMD=0.07, 95%CI=-0.29-0.43) (Yan et al., 2017).

*Obsessive-compulsive disorder: Primary outcomes*

In OCD, compared with inactive interventions, on primary outcome, DBS had the largest effect (SMD=0.89, 95%CI=0.48-1.30/GRADE=moderate) (Martinho et al., 2020), followed by rTMS (SMD=0.64, 95%CI=0.39-0.89/GRADE=very low) (Perera et al., 2021). Among TMS protocols, the largest effect emerged for B-DLPFC rTMS (SMD=0.65, 95%CI=0.38-0.92/GRADE=low) (Zhou et al., 2017), followed by HF rTMS over the anterior cingulate cortex/middle prefrontal cortex (SMD=0.52, 95%CI=0.16-0.87/GRADE=low) (Liang et al., 2021), LF rTMS over the bitemporal-supplementary motor area (SMD=0.32, 95%CI=0.03-0.61/GRADE=low) (Perera et al., 2021), while LF rTMS over the orbitofrontal cortex was not have a significantly superior to inactive interventions (SMD=0.56, 95%CI=-0.06-1.18/GRADE=very low) (Zhou et al., 2017).

Acceptability of rTMS did not significantly differ from inactive treatment for any of the protocols (Berlim, Neufeld, et al., 2013; Liang et al., 2021).

No meta-analytic evidence was found versus TAU, or head-to-head comparisons.

*Obsessive-compulsive disorder: Secondary outcomes*

In OCD, DBS compared to sham more effective in achieving response (RR=2.40, 95%CI=1.30-4.30), but not remission (RR=1.30, 95%CI=0.20-10.55) (Martinho et al., 2020).

*Generalized anxiety disorder: Primary outcomes*

In GAD, compared with inactive interventions, on primary outcome, the largest effect emerged for any rTMS (SMD=0.68, 95%CI=0.46-0.89/GRADE=low) (Cui et al., 2019).

Acceptability did not seem to differ between actual and sham rTMS application (RR=1.14, 95%CI=0.72-1.82) (Cui et al., 2019).

No meta-analytic evidence was found versus TAU, or head-to-head comparisons.

*Attention-deficit/hyperactivity disorder: Primary outcomes*

In ADHD, compared with inactive interventions, on primary outcome, only tDCS was significantly more effective (SMD=0.23, 95%CI=0.05-0.41/GRADE=moderate) (Brauer et al., 2021).

No meta-analytic evidence was found versus TAU, or head-to-head comparisons.

*Attention-deficit/hyperactivity disorder: Secondary outcomes*

Compared with inactive interventions, tDCS was significantly more effective in reducing inattention (SMD=0.47, 95%CI=0.08-0.85) and impulsivity (SMD=0.27, 95%CI=0.06-0.46), but not hyperactivity (SMD=0.40, 95%CI=-0.08-0.86) in patients with ADHD (Brauer et al., 2021).

*Autism-Spectrum Disorders: Primary outcomes*

In ASD,compared with inactive interventions, on primary outcome, only tDCS was significantly more effective (SMD=0.97, 95%CI=0.36-1.58/GRADE=very low) (García-González et al., 2021).

No meta-analytic evidence was found versus TAU, or head-to-head comparisons.

*Autism-Spectrum Disorders: Secondary outcomes*

In ASD, tDCS compared to sham improved the social (SMD=0.68, 95%CI=0.32-1.05) and behavioral domains (SMD=0.66, 95%CI=0.30-1.02), but not the language (SMD=0.05, 95%CI=-0.30-0.40) or sensory/cognitive awareness domains (SMD=0.34, 95%CI=-0.09-0.76) (García-González et al., 2021).

**Quality and certainty of the evidence**

The median AMSTAR score was 8 (IQR 2), corresponding to a high quality in the methodological conduct of the meta-analyses. The median AMSTAR Content score was 2 (IQR=2), suggesting overall low quality for the included RCTs. The median total AMSTAR score was 10 (IQR=3) (details in eTable 2).

The certainty of evidence based on GRADE was high only for 4/109 of the selected primary outcomes, in 22% moderate, 48% low, and in 26% very low. The lowering of the rating was largely driven by the risk of bias of the included trials, but also other factors, such as low sample size and high heterogeneity (details in eTable 3).

**Discussion**

To our knowledge, this is the first comprehensive umbrella review exploring efficacy and safety of biological non-pharmacological treatments across a broad array of psychiatric disorders, based on MAs of RCTs.

The largest body of evidence was found for mood disorders as a diagnostic spectrum, and for rTMS as the biological non-pharmacological treatment. The certainty of evidence was low or very low for 74% of the meta-analyzed outcomes.

Regarding efficacy, ECT was the intervention with the largest effect size in mood and in schizophrenia-spectrum disorders. In both cases, its efficacy was tested against inactive treatment, in add-on to TAU, and alone versus oral medications, showing consistent superiority (Gu et al., 2017; Pagnin et al., 2004; Sinclair et al., 2019; UK ECT Review Group, 2003; Wang et al., 2018; Zheng et al., 2016)*.* The efficacy of ECT is well established in depressive disorders, with several international guidelines including ECT as a therapeutic option (American Psychiatric Association, 2010; Bauer et al., 2013; Cleare et al., 2015; Malhi et al., 2021; Milev et al., 2016; National Institute for Health and Care Excellence, 2009). Comparing head-to-head different ECT protocols, the only placement proven to be inferior to others was the RUL when applied at low to moderate dose, with a large effect size and a moderate certainty of evidence (Dunne & McLoughlin, 2012; Kolshus et al., 2017; Mutz et al., 2019). Despite the non-significant difference in efficacy, all other protocols (BT, BF, H-RUL) have unique differences including rapidity of action and side effects, that need to be taken into account when tailoring an ECT course to the individual (Kellner et al., 2010). ECT was also the only treatment for which we could find meta-analytical evidence of efficacy in manic episodes of bipolar disorder, with a moderate certainty of evidence and a very large effect size(J. Zhang et al., 2021). This was consistent with a recent review considering both RCTs and retrospective studies on the same primary outcome for the same treatment (Elias et al., 2021). ECT is still not clearly recommended for patients with schizophrenia (American Psychiatric Association, 2020; Galletly et al., 2016; Hasan et al., 2012; National Institute for Health and Care Excellence, 2014; Remington et al., 2017) , and its use may vary from a country to another. Only few guidelines consider this treatment for selected cases, such as clozapine resistance, clozapine intolerance, catatonic features, or as add-on treatment when a rapid clinical response is urgently needed (Galletly et al., 2016; Hasan et al., 2012). Despite the limited certainty given by the GRADE score, our results support the use of ECT as an augmentation strategy in forms of refractory schizophrenia, having shown a synergistic effect with antipsychotic medications, and as an adjunct to TAU even being superior to clozapine (Sinclair et al., 2019; Wang et al., 2018; Zheng et al., 2016). Our findings are consistent with previous literature reviews exploring the same topic (Ali et al., 2019; Grover et al., 2019).

Extensive clinical research has been conducted on rTMS as an intervention in several psychiatric conditions, such as depressive disorders, schizophrenia, OCD, PTSD, GAD, and substance-related disorders, showing in all of them some degree of efficacy depending on the protocols applied. In mood disorders, HF-L DLPFC rTMS improved depressive symptoms consistently and with the largest body of evidence, although with a low certainty both in any depressive disorder and in TRD (Mutz et al., 2019; Sehatzadeh et al., 2019). Evidence of efficacy was also found for less commonly used protocols, like LF R-, B-DLPFC rTMS, dTMS, and TBS, but with variable results depending on the target population (Berlim et al., 2017; Hung et al., 2020; Li et al., 2021; Mutz et al., 2019; Sehatzadeh et al., 2019). No significant advantage over sham treatment emerged for aTMS, sTMS, or LF L-DLPFC rTMS (Chen et al., 2020; Mutz et al., 2019). In schizophrenia-spectrum disorders, different protocols improved different symptom clusters. PFC rTMS and TBS were useful for negative symptoms, while TPC rTMS, usually applied at low frequencies, was effective for positive symptoms, including auditory hallucinations. PFC TBS and TPC rTMS also lowered total symptoms. In GAD, rTMS significantly improved anxiety symptoms versus inactive treatment, with an overall medium effect size and low certainty of evidence (Cui et al., 2019). These promising results are particularly relevant since anxiety disorders are the most prevalent psychiatric condition worldwide (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018). Current meta-analytic evidence still fails to identify the best combination of coil placement and frequency of application for rTMS in GAD. Limited evidence was available for substance-related disorders. For these conditions, HF B-DLPFC dTMS and HF L-DLPFC rTMS were effective for the primary outcome with, respectively, a large and medium effect size, and a moderate to very low certainty (Zhang et al., 2019). The versatility of rTMS comes from the possibility to target specific brain areas in combination with the desired stimulation parameters and coil type, together with limited safety concerns as discussed below. International guidelines are increasingly considering rTMS as a therapeutic option, especially in depressive disorders where a large number of trials and patients treated support its efficacy. For instance, the Canadian guidelines consider rTMS after just one failed medication trial in MDD, while other associations are more cautious with their recommendation (American Psychiatric Association, 2010; Bauer et al., 2013; Malhi et al., 2021; Milev et al., 2016; National Institute for Health and Care Excellence, 2009). Meta-analytic results from trials directly comparing ECT and rTMS in mood disorders were conflicting. ECT with mixed protocols seemed superior to pooled rTMS with a small effect size, but when comparing ECT with HF L-DLPFC rTMS the efficacy seemed comparable, despite low to very low certainty (Mutz et al., 2019; Ren et al., 2014). The discrepancies may be due to the limited evidence regarding direct comparison of ECT versus rTMS. Moreover, these results need to be interpreted with caution given that subjects included in trials might not be fully representative of patients addressed to these treatments in a real-world clinical setting.

MST, a convulsive therapy developed as an alternative to ECT, has still very limited evidence and has been applied mainly in depressive disorders. No meta-analysis of sham-controlled trials was available for MST. Its efficacy was comparable to that of LM-RUL ECT, the only ECT protocol established to be inferior to others currently used in clinical practice (Jiang et al., 2021; Li et al., 2021). Despite an initial interest in a possible mitigation of cognitive effects by MST, no significant advantage has yet been identified to recommend its use (Jiang et al., 2021).

tDCS is a non-invasive neuromodulation treatment with growing evidence of applicability in different psychiatric disorders (Fregni et al., 2020). tDCS had a small magnitude of improvement on primary outcomes in depressive disorders, schizophrenia-spectrum disorders, alcohol use disorders, albeit with a low to very low certainty of evidence (Fregni et al., 2020; Kim & Kang, 2021; Razza, Palumbo, et al., 2020; Shiozawa et al., 2014). A novel research field is the application of neuromodulation in developmental disorders. tDCS proved to reduce overall severity and core symptoms both in ADHD and in autism-spectrum disorders, respectively with a moderate and a very low certainty of evidence (Brauer et al., 2021; García-González et al., 2021). Despite these promising findings, the limited certainty of evidence especially in autism calls for further high-quality trials (National Institute for Health and Care Excellence, 2015).

Surgical biological treatments include DBS and VNS. Of these, DBS seemed effective in reducing depressive symptoms in TRD with a moderate effect size and a very low certainty of evidence (Hitti et al., 2020). As an invasive and long-term treatment, RCTs to test efficacy of DBS for depression are few, mostly designed as cross-over trials and with few participants (Kisely et al., 2018). Efficacy was sound, however, in different meta-analyses, and these initial results have been corroborated by open-label studies (Hitti et al., 2020; Kisely et al., 2018; Wu et al., 2021). DBS also improved OCD symptoms with a large effect size, and with a moderate certainty of evidence (Martinho et al., 2020). Despite multiple trials investigating efficacy and safety of surgical VNS in depressive disorders starting from 2005, we could not find any meta-analytic evidence meeting our eligibility criteria (Bottomley et al., 2019). We included a meta-analysis of two RCTs of the non-invasive taVNS, which suggested a possible positive effect for depressive symptoms in MDD (Zhang et al., 2016). The certainty of evidence for taVNS, however, remains very low.

LT was not only effective in seasonal affective disorder, the condition it was originally designed for, but also in other mood disorders, such as non-seasonal depression and bipolar disorder, with a low to moderate magnitude of improvement (Lam et al., 2020; Pjrek et al., 2020; Tao et al., 2020). LT was compared both to sham treatment and in add-on to TAU, with consistent results (Penders et al., 2016). Compared to antidepressant treatment (fluoxetine), response and remission rates were similar in patients with seasonal affective disorder (Thaler et al., 2011).

Finally, sleep deprivation, despite possible superiority regarding depression to TAU during the first week, was not superior anymore at follow-up, and the certainty of evidence was very low. The little body of evidence may reflect its scarce application in current practice. The Canadian guidelines consider sleep deprivation as a third-line intervention in moderate to severe depression among therapeutic options, classifying sleep deprivation in the “Complementary and alternative medicine treatments” (Ravindran et al., 2018).

Regarding safety, all-cause discontinuation rates overlapped between biological non-pharmacological treatments and control interventions for all psychiatric disorders. Nevertheless, specific adverse events were more common in the treatment arms compared to controls.

For ECT, the need of repeated induction of anesthesia and the delivery of an electrical current above the seizure threshold still rises the concern of serious adverse events. ECT-related mortality, independently from the underlying disease, was not estimable from RCTs, given that death is an extremely rare event associated with ECT. Mortality data come from the analysis of large registers, retrospective studies and surveys, and it is estimated to be around 2.1 cases every 100.000 treatments (Torring et al., 2017). No increase in serious adverse event rates was found in the studies we included. Adverse events more frequent with ECT versus controls were headache and memory impairment reported during the acute treatment (Gu et al., 2017; Wang et al., 2018; Wang et al., 2015; Zheng et al., 2018). Indeed, for ECT the main safety concern involves cognitive side effects. Most studies evaluated this outcome as self-report AE or with a global cognition assessment at the end of an acute ECT course, while fewer studies investigated specific cognitive domains/tasks (Wang et al., 2018; Wang et al., 2015; Zheng et al., 2018). Cognitive function assessments and the timing of a possible interference of ECT are complex. When assessed as an AE, memory was more impaired in subjects with schizophrenia-spectrum disorders after ECT than after AP exposure only, but this difference disappeared within 2 weeks (Wang et al., 2015; Zheng et al., 2018). Moreover, the whole memory quotient did not differ between treatment arms (Wang et al., 2018). The durability of differences revealed in selected cognitive tasks after ECT treatment is still unknown (Zheng et al., 2018). In mood disorders, few investigations were conducted on cognitive functions comparing ECT (alone or as add on) with other treatments, namely AD and rTMS, while trials mainly compared different ECT protocols to establish the stimulation parameters with minimized cognitive side effects. These studies identified some advantage in H-RUL ECT over BT ECT, and with the adjustment of other stimulation parameters, such as pulse width (Kolshus et al., 2017; Tor et al., 2015).

For rTMS, a major safety concern regards the potential induction of seizures, which were described in medical literature (Taylor et al., 2021). However, seizure rates were not estimable from RCTs, given the rarity of such events. Data from a large survey indicate an overall seizure rate of 0.31 events per 10.000 sessions, with a slightly higher rate when using the H-coil (Taylor et al., 2021). Moreover, research efforts in the last years aimed to further minimize seizure risk (Rossi et al., 2021). Treatment-related adverse events included headache, muscle twitching, and local pain, not leading to an increase in drop-out rates (Dougall et al., 2015; Zhang et al., 2013; Zis et al., 2019).

For tDCS, treatment-emergent mania was a potential AE concern, but meta-analytic evidence was discordant. Treatment-emergent mania risk seemed slightly increased in a meta-analysis including patients with unipolar depression but was not different in another meta-analysis that pooled together different depressive disorders (Berlow et al., 2019; Brunoni, Moffa, et al., 2017). However, the total number of suspected cases to date remains small, with little over 10 events reported in the medical literature (Antal et al., 2017). No increased risk of serious adverse events for tDCS was reported in the meta-analyses we included, similar to a previous systematic review (Antal et al., 2017).

For LT, the main concern are possible iatrogenic mood switches; with a higher risk of hypomania but not mania having been reported in a 2004 meta-analysis of LT studies in depression, but without an increased risk in a 2020 review of LT studies in bipolar disorder (Lam et al., 2020; Tuunainen et al., 2004). No other potential harm was reported (Tuunainen et al., 2004).

Using our eligibility criteria, evidence of specific AEs was lacking for other biological non-pharmacological interventions. It would be of interest to define the incidence of specific AEs following DBS, including complications of surgery, such as infections (Kantzanou et al., 2021).

The present results should be considered in light of several limitations. First, despite the satisfactory methodological conduct of the MAs, leading to an average good AMSTAR quality score, the overall quality of the included RCTs was low, affecting not only the AMSTAR content score, but also the final certainty of the evidence. Second, different protocols of the same techniques and of control interventions were sometimes pooled together, not allowing for a precise identification of the best treatment (e.g., the application of LF or HF rTMS over the same area could theoretically lead to opposite effects) and making it difficult to rule out a placebo effect (especially for LT, where inactive and no intervention were often together in the control arms). Third, in some cases, conflicting evidence emerged (e.g., relative efficacy of ECT versus rTMS in mood disorders; superior response rate but not continuous depression symptom outcome of LF R-DLPFC rTMS versus control), highlighting the need of further investigations. Fourth, most outcomes were assessed at treatment end, while evidence for both risks and benefits beyond the active treatment, such as durability of the improvement and the persistence of side effects over time, was limited. Fifth, the meta-analyses we selected included some RCTs conducted with methodological and clinical standards that may have shifted over the years (eg, older ECT protocols compared to nowadays applications), and that are difficult to replicate or update due to ethical issues and limited sponsor appeal. Sixth, the little number of trials for some interventions, such as newer protocols of TMS (aTMS, sTMS, and TBS), could also lead to underestimate their efficacy due to less data availability. Lastly, in the comparison of such different therapies we stratified results by the main diagnoses but did not have sufficient information to stratify trials and results by baseline severity, presence of treatment-resistance, and other specific information for special populations such as women in their peripartum period or the elderly. These clinically relevant aspects could have had an impact for higher heterogeneity, and their analyses could have yielded even greater differences in the results.

Nevertheless, despite these limitations, to our knowledge, this is the largest and most comprehensive umbrella review of biological non-pharmacological treatments versus any control condition or active intervention for any mental disorder. Beyond informing clinicians and guideline developers alike about the relative efficacy, effectiveness and safety of biological non-pharmacological treatments, this umbrella review also points to gaps and next steps. For example, given the wide array of available biological non-pharmacological treatments and increasing number of studies supporting their action in psychiatric disorders, it seems crucial to better define the subjects who could benefit the most from one intervention compared to another. Individual-patient data network meta-analyses could inform on this matter, together with further clinical research reporting a clear-cut definition of treatment-resistance across severe mental illnesses and a precise description of the baseline characteristics of subjects, including previous unsuccessful pharmacological trials (Fornaro et al., 2020; Fornaro & Giosuè, 2010). Moreover, dose-response (network) meta-analyses are being conducted in the field of pharmacology, but are currently lacking regarding brain stimulation techniques. Future studies are also needed to clarify when to use biological non-pharmacological interventions in the treatment algorithm in relationship to psychosocial and/or pharmacological interventions. Finally, another future direction in the field of neuromodulation is the combination of these interventions with each other, which is already being evaluated, for example, for tDCS and rTMS, and in combination with cognitive therapies, which have already produced very interesting findings (Donse et al., 2018; Loo et al., 2009).

In conclusion, neuromodulation treatments provide clinicians a broad set of treatment options beyond standard care. A large body of evidence is available for non-pharmacological biological treatments in mental disorders regarding efficacy and safety. Evidence suggests they can be a valid therapeutic option for specific outcomes of specific diseases. Their acceptability is overlapping with that of inactive treatments, but the possibility of treatment-related adverse events needs to be considered.

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