Current Neurostimulation Targets And Techniques For The Management of Treatment Resistant Depression

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Introduction

Major depression is common and associated with significant disease burden. Up to a third of individuals suffer from treatment resistant depression (TRD.

These individuals are often referred for neurostimulatory interventions such as electroconvulsive therapy (ECT).

Media perception and adverse effects of ECT have contributed to the need for alternative options.

Alternatives forms of neurostimulation include:

- Transcranial magnetic stimulation (TMS) – Repetitive TMS (rTMS), Deep TMS (dTMS) and Intermittent theta burst stimulation (iTBS)
- Transcranial direct current stimulation (tDCS)
- Deep brain stimulation (DBS)

These techniques all show significant promise in their efficacy in the treatment of TRD.

Methods

- Searched EMBASE and Medline databases.
- Preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines used to select studies which utilised TMS, tDCS or DBS in participants with TRD.
- Study outcome used: change in level of depression after neurostimulation, assessed using a validated clinical tool.
- Participants needed to be adults with a primary diagnosis of treatment resistant depression.
- Reviewed only studies available in English language. Systematic reviews and meta analyses were excluded

Search Results

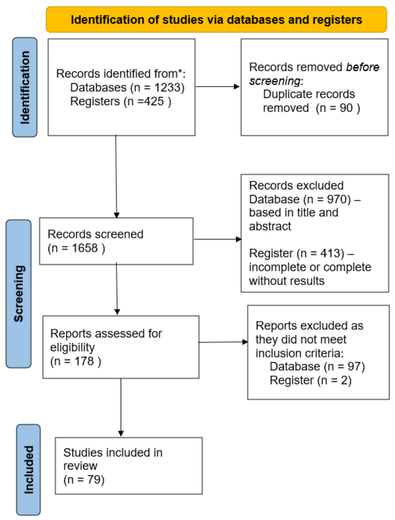

Figure 1: Schematic representation of the process used to screen and select studies for the review

Most studies used the Hamilton depression scale or Montgomery and Asberg depression rating scale (MADRS) assessments to measure outcome.

Response rate was classified as 50% improvement from baseline depression score after neurostimulation and remission was a score below 10 on assessment or a sustained reduction (50% improvement) over 4 weeks

Transcranial Direct Current Stimulation (tDCS)

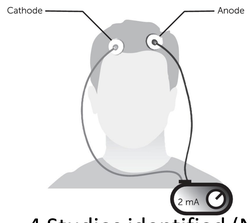

Figure 2: diagram of anode and cathode placement in tDCS (Zandvakili *et al.,* 2019)

4 Studies identified (N=74 participants)

Average response rates after tDCS in TRD: 43.2% (Range: 25–73%)

NICE allow use in TRD with special governance and consent. Advantage of being a portable device which can be used for neurostimulation delivery at home.

Transcranial Magnetic Stimulation (TMS)

TMS uses a magnetic field to generate an electrical current to stimulate targets in the brain. TMS techniques vary according to coil type and frequency of pulsations.

rTMS magnetic pulsations are at specific frequencies resembling long-term depression (LTD) or long-term potentiation (LTP).

Average response rates to rTMS in participants with TRD:

Location	N	Response rate (Range) (%)
Left DLPFC	789	42.8 (7.5-100)
Right DLPFC	296	47.8 (33-56.3)
Bilateral DLPFC	278	34 (20-57)

Responsiveness to right or left stimulation may be related to symptomatology. Whilst both magnetic field strength (measured using RMT) and frequency impact rTMS efficacy.

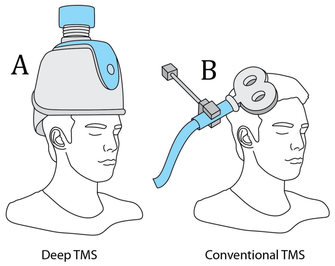

Figure 3: A: diagram of dTMS B: diagram of TMS(used for rTMS and TBS) coil positioning (Ekhtiari *et al.,* 2019)

Other TMS techniques efficacious in TRD include:

dTMS: TMS using a specialised coil, the H coil, which targets deeper structures within prefrontal cortex.
Average response rates: 47% (15-73%; N=265)

iTBS: TMS at intermittent high (theta) frequency
Average response rates: 48% (28-86%; N=150)

iTBS has been shown to be as efficacious as rTMS but more efficient in required delivery time 7 vs 20 days.
Limitation: Sham Stimulation as control.

Deep Brain Stimulation (DBS)

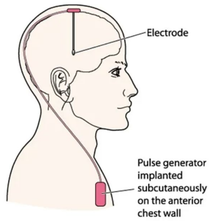

Figure 4: diagram showing principle of DBS with electrode neurosurgically implanted into target area with implanted control device containing battery

(**Image Credit:** Blamb / Shutterstock.com)

DBS is approved by the FDA and the NICE for neuropsychiatric conditions including Parkinson's disease but not TRD. Various target areas identified where DBS is efficacious in the treatment of TRD.

Average response rates after 12 months of DBS in TRD:

Location	N	Response rate (Range) (%)
Subcallosal gyrus (SCG)	123	45.6 (30-62.5)
Medial forebrain bundle (MFB)	21	78.7 (75-86)
Ventral lateral internal capsule (VLIC)	45	33 (20-40)
Nucleus accumbens (NAc)	17	47.5 (45-50)

A limitation of DBS studies includes ethics of using a pure control group. Adverse effects include infection (general post- surgical risk), stimulation related ocular muscle twitching (MFB) and increased suicidal ideation (NAc and SCG)

Conclusions and the Future

Neurostimulation has evolved significantly over the past 30yrs from ECT. rTMS appears to be clinically effective with iTBS and DBS showing great promise. In the near future closed loop DBS, which integrates neural sensing with neurostimulation, has been demonstrated by Scangos *et al.,* 2021 and shows significant potential, whilst wireless minimally invasive multifocal stimulation platforms such as the ENGINI (Empowering Next Generation Implantable Neural Interfaces) system are in development.