Original research

Decision-making for non-invasive neuromodulation prescription in the treatment of generalized anxiety disorder: a roadmap proposal

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ABSTRACT | INTRODUCTION: Non-invasive brain stimulation (NIBS) has been used in the treatment of generalized anxiety disorder (GAD). However, the diversity of protocols, indications, and target populations requires careful standardization to ensure safety, efficacy, and uniformity in clinical practice based on the best available evidence, professional experience, and patient preferences. **OBJECTIVE:** To develop a clinical decision-making tree to standardize approaches and facilitate prescriptions by healthcare professionals regarding the use of NIBS to treat GAD. **METHODOLOGY:** Clinical reasoning study based on a roadmap for developing a decision-making tree. After reviewing the best evidence on the topic, five systematic reviews with meta-analyses were selected, from which randomized clinical trials with the largest effect sizes were extracted. From these trials, specific protocols were chosen and presented to researchers and clinical specialists in the field who, by consensus, constructed the clinical decision-making tree. The tools used to assess GAD symptoms in the studies were evaluated, identifying the most suitable ones for the Brazilian population, with recommendations on the best assessment instruments. The tree was presented to other specialists who validated the protocol recommendations. **RESULTS:** Four protocols were selected as interventions that could be recommended in clinical practice. The protocol with the largest effect size was not chosen as the first option due to the number of pulses exceeding the established safety criteria and the report of a tonic-clonic seizure as an adverse effect of stimulation. Three repetitive magnetic stimulation protocols presented equivalent effect sizes, but continuous Theta Burst stimulation to the right dorsolateral prefrontal cortex was chosen as the first indication because, in addition to having the largest effect size, it is an accelerated protocol, reducing application time, which impacts cost-effectiveness. **CONCLUSION:** The clinical reasoning process identified three instruments for outcome assessment and four transcranial magnetic stimulation protocol options for the treatment of GAD.

KEYWORDS: Neurosciences. Non-Invasive Brain Stimulation. Generalized Anxiety Disorder. Clinical Reasoning. Decision Making.

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1. Introduction

Generalized anxiety disorder (GAD) affects approximately 300 million people, or 4.05% of the world population[1]. It is the most common mental disorder, affecting 12.9% of people diagnosed with some type of mental disorder[2]. A significant increase in GAD cases has been observed, especially in recent decades. The number of people diagnosed annually climbed from 31 million in 1990 to 46 million in 2019, a rise of 48.4%[3]. Moreover, in the period after the COVID-19 pandemic began, estimates indicate approximately 76.2 million new anxiety cases annually, representing a 25.6% increase from pre-pandemic levels[4]. This disorder carries a high individual and collective burden[5].

Only 27.6% of people with GAD receive some form of treatment. Among treated individuals, only 9.8% receive adequate treatment[6]. First-line treatments include psychotropic medications, mainly serotonin reuptake inhibitor antidepressants, and psychotherapy, primarily Cognitive Behavioral Therapy (CBT)[7]. However, 57% to 64% do not achieve remission with psychotropic medications, and 48.6% with psychotherapy[8]. Additionally, 46% of people treated with medications abandon treatment between three and seven months due to unwanted side effects[9].

This scenario sparks interest in alternative treatments. Non-invasive brain stimulation (NIBS) has emerged as a therapeutic modality that has demonstrated beneficial effects in controlling symptoms in GAD cases in recent decades[10,11]. Among NIBS modalities, the most commonly used for GAD are classical repetitive transcranial magnetic stimulation (rTMS), patterned transcranial magnetic stimulation - Theta Burst Stimulation (TBS), transcranial direct current stimulation (tDCS), and trans auricular vagus nerve stimulation (taVNS). However, the diversity of protocols, indications, and target populations requires careful standardization to ensure safety, efficacy, and uniformity in clinical practice based on the best available evidence, professional experience, and patient preferences. The objective of this study is to develop a clinical decision-making tree to standardize approaches and facilitate prescriptions by healthcare professionals regarding the use of non-invasive neuromodulation to treat generalized anxiety disorder.

2. Methodology

This is a clinical reasoning study based on a roadmap method for developing a decision-making tree for the assessment and treatment of generalized anxiety disorder with non-invasive neuromodulation. Following we present the **steps we followed for developing the decision tree**.

2.1. Step 1 - Data collection

2.1.1. Literature review

This step aimed to identify and select the best available evidence in the scientific literature to support clinical decisions. The search focused on studies with higher quality evidence, such as umbrella reviews and systematic reviews with meta-analyses, which provide reliable data on indications according to clinical dysfunctions, application sites for non-invasive neuromodulation techniques, and protocol parameters.

2.1.2. Definition of search terms and strategies

Initially, the authors gathered to define the terms used in the search (Table 1). The terms consisted of descriptors extracted from MeSH and other free terms (synonyms, other related terms, acronyms, or terms not represented).

Table 1. Terms extracted from MeSH and related free terms

MeSH	Keyword
Generalized Anxiety Disorder	Generalized Anxiety Disorder GAD
Magnetic, transcranial stimulation	Repetitive magnetic transcranial stimulation rTMS TMS Non-invasive magnetic brain stimulation
Transcranial Direct Current Stimulation	Transcranial Direct Current Stimulation tDCS Non-invasive brain electrical stimulation
Theta Burst Stimulation	Theta Burst Theta Burst Stimulation TBS
Vagus Nerve Stimulation	Vagus Nerve Stimulation Trans Auricular Vagus Nerve Stimulation taVNS Vagus Nerve Neuromodulation
Hamilton Anxiety Scale	Hamilton Anxiety Scale HAS Hamilton Anxiety Rating Scale HARS
Beck Anxiety Inventory	Beck Anxiety Inventory BAI
Depression, Anxiety, and Stress Disorders	Depression, Anxiety, and Stress Disorders DASS-21
Hospital Anxiety and Depression Scale	Hospital Anxiety and Depression Scale HAD HADS

Source: the authors (2025).

Search strategies were then standardized to ensure efficient retrieval of the best available evidence. The formulation followed the PICO structure, using the components: P (Population) and I (Intervention), connected by the Boolean operator AND. The table below presents the population, interventions, and macro-outcomes defined by the guideline organizers. All possible combinations with the terms in Table 1 were used for the search as presented in Table 2.

Table 2. Search Strategies

Example of an search strategy
(Generalized Anxiety Disorder) AND (magnetic, transcranial stimulation)
(Generalized Anxiety Disorder) AND (transcranial direct current stimulation)
(Generalized Anxiety Disorder) AND (vagus nerve stimulation)

Source: the authors (2025).

2.1.3. Data search

After defining the terms and search strategies, the article search was conducted exclusively in the Medline database (via PubMed) by two researchers independently. The objective was to select between 3 and 5 systematic reviews with meta-analyses that show high quality and up to date data. Thus, it included only studies that met the following criteria:

- Reviews published in the last five years (from 2021 to 2025);
- Reviews in which the study selection, risk of bias analysis, and data extraction steps were performed by two independent authors;
- Use of appropriate statistical methods: use of standardized mean difference when outcome measures included in the meta-analyses were different;
- Reviews that evaluated the selected clinical trials using standardized tools, such as the Cochrane Risk of Bias Tool or PEDro - Risk of Bias Assessment;
- Reviews that present effect size data on the use of neuromodulation on anxiety symptoms for each selected clinical trial, either in a forest plot, table, or described in the text;
- Articles from predatory journals were not selected.

From the selected systematic reviews with meta-analysis, clinical trials presenting protocols that could be indicated and prescribed in clinical practice were selected. The selection of clinical trials followed these criteria:

- Randomized, sham-controlled clinical trials;
- Clinical trials that demonstrated efficacy, whose confidence interval in the forest plot did not touch the null line;
- Clinical trials with the largest effect size (furthest from the null line) and lowest sample heterogeneity (narrowest confidence interval);
- Clinical trials with larger samples (larger square in the forest plot line);
- Articles from predatory journals were not selected.

2.1.4. Data extraction

Data extraction was divided into two parts:

- **Data extraction from reviews:** Outcomes, outcome measures, and type of stimulation were extracted. These reviews were then used to identify the randomized clinical trials (RCTs) reporting the largest effect sizes, in order to subsequently analyze the most effective protocols.
- **Data extraction from randomized clinical trials:** Information on protocol characteristics, application site, and outcome measure effect sizes was extracted.

2.2. Step 2 - Infographic construction

This step aimed to organize the information collected in the literature review step into a clear, logical, and practical flowchart. The objective was to structure evaluative and therapeutic alternatives in a visual and accessible way, highlighting the most effective intervention options based on effect sizes found in the literature to facilitate clinicians' decision-making in selecting treatment protocols with neuromodulatory techniques for generalized anxiety disorder. From the clinical trials, the most commonly used outcome measures were extracted, along with the parameters of the intervention protocols, with the respective percentage of improvement expected by the clinician and patient with the proposed intervention. Also in this infographic construction stage, a critical assessment of the GAD evaluation instruments used in the clinical trials was conducted, as well as research on the best instruments for the same purpose was validated and adapted for the Brazilian population.

2.3. Step 3 - Clinical validation

This step aimed to evaluate the decision tree created through third-party specialists (psychiatric physicians and psychologists) who did not participate in the research and development stage. A group of specialists was asked to provide their opinion on the decision-making tree, identifying possible flaws or points for improvement in the infographic. This phase allowed for adjustments that increase the clinical applicability and accuracy of the tree before application in a clinical environment.

2.4. Step 4 - Complementary analysis

To guide clinicians in the pre- and post-intervention evaluation of their clients, we compiled information on the assessment scales commonly used to measure GAD symptoms and systematically reviewed their psychometric properties within Brazilian populations. Based on this analysis, we established a recommended hierarchy of scales according to the strength of their psychometric evidence.

3. Results

From the reviewed studies, eight meta-analyses were identified with the pre-defined search strategies. After analysis of methodological quality, four meta-analyses were excluded[12–15], and four were chosen to represent the highest level of evidence (Table 3), from which the four randomized clinical trials with the largest effect sizes were analyzed and selected (Table 4), from which the protocols were extracted.

Based on these findings, the researchers met to develop the infographic of the decision-making tree for assessment and treatment prescription applying non-invasive neuromodulation in the treatment of generalized anxiety disorder (Figure 1). In this stage, the authors decided to adopt the following criteria to hierarchize the protocols and choose a prescription order: effect size of the intervention on anxiety symptoms, cost-effectiveness, replication of data by other studies, adherence to safety criteria, and reported side effects.

The developed tree was sent to five clinical research specialists to provide their considerations on the recommendation.

Table 3. Characteristics of systematic reviews with meta-analyses included in the first level of evidence used for constructing the infographic

	Population	Intervention	Outcomes	Selection by two independent researchers	Adequate Statistical Analysis	Adequate Risk of Bias Analysis
Cox et al., 2022[16]	GAD and PD	rTMS	HAM-A, GAD-7	yes	yes	yes
Parikh et al., 2022[17]	GAD	rTMS	HAM-A	no	yes	no
Qi et al., 2024[11]	GAD	rTMS, TBS, and tDCS	HAM-A	no	yes	yes
Hyde et al., 2022[18]	GAD	rTMS and tDCS	Anxiety Disorder Scale	yes	yes	yes

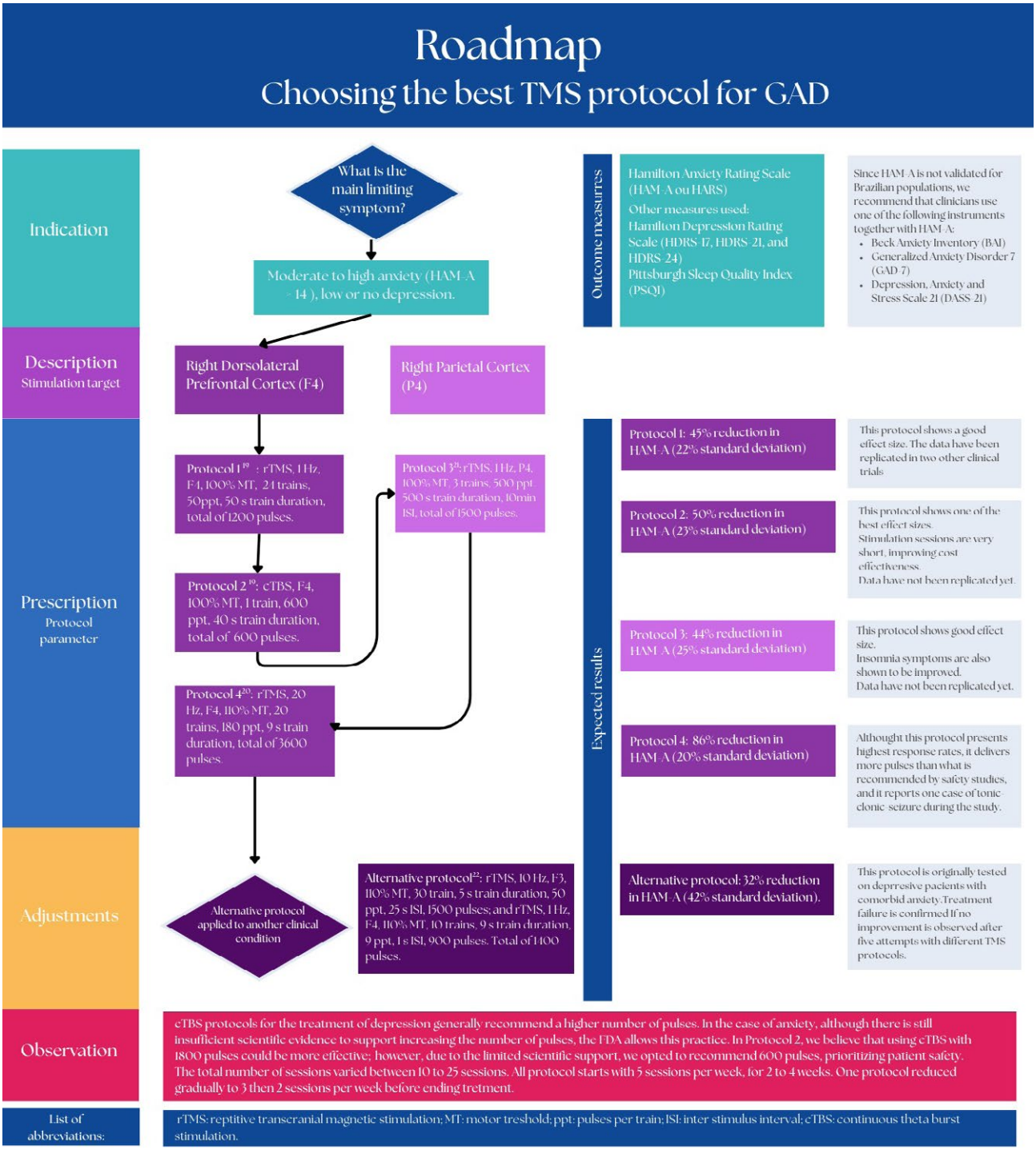
Source: the authors (2025).
GAD: Generalized Anxiety Disorder; PD: Panic Disorder; rTMS: repetitive transcranial magnetic stimulation; TBS: theta burst stimulation; tDCS: transcranial direct current stimulation; HAM-A: Hamilton Anxiety Scale; GAD-7: 7-item Generalized Anxiety Disorder Scale.

Table 4. Characteristics of non-invasive stimulation protocols for the treatment of generalized anxiety disorder

	NIBS	Target	Coil	Frequency	Pulses	Trains	Total	Interval	Intensity	Outcome	% Improvement
Li et al. 2022[19]	rTMS	F4	8	1 Hz	50	24	1,200	1 s	100% MT	HAM-A	- 44.7 (22%)
Li et al., 2022[19]	cTBS	F4	8	50Hz triplets modulated at 5Hz	600	3	600	0 s	100% MT	HAM-A	-50% (23,3%)
Dilkov et al 2017[20]	rTMS	F4	8	20 Hz	180	20	3,600	51 s	110% MT	HAM-A	-86% (20,7%)
Huang et al., 2018[21]	rTMS	F4	8	1 Hz	500	3	1,500	600 s	90% MT	HAM-A	43,8% (25,3%)

Source: the authors (2025).
cTBS: Continuous Theta Burst Stimulation; HAM-A: Hamilton Anxiety Scale; NIBS: non-invasive brain stimulation; MT: motor threshold; rTMS: repetitive Transcranial Magnetic Stimulation; s: second.

Figure 1. Roadmap presenting a decision tree to help choosing which transcranial magnetic stimulation protocol to use when treating generalized anxiety disorder and other relevant information for assessment and intervention



Source: the authors (2025).

4. Discussion

Based on a literature review of the best available evidence for decision-making in the assessment and treatment of GAD using NIBS, and following a roadmap model, this study proposes a clinical reasoning framework for healthcare professionals regarding protocol prescription. A hierarchical proposal was developed based on combining the results of studies demonstrating the largest effect sizes with the opinions of the experts who constructed and revised the decision tree.

The main studies evaluated during the development process of the decision tree utilized three different versions of the Hamilton Anxiety Rating Scale (HAM-A) for assessing anxiety symptoms (versions with 17, 21 and 24 items). These scales are indeed one of the most popular in international clinical studies and demonstrate good internal consistency ($\alpha = 0.74$)[20]. However, no validation and cross-cultural adaptation studies for the Brazilian population were identified. A noteworthy point encountered during the research for this study was the difficulty in finding validation and adaptation studies for assessment instruments. When utilizing an assessment instrument, several aspects must be considered, including cultural differences between the instrument's country of origin and the target population, among other factors. In our decision tree, we recommend the use of the Beck Anxiety Inventory (BAI)[21], the 7-item Generalized Anxiety Disorder scale (GAD-7)[22], and the Depression, Anxiety, and Stress Scales (DASS-21)[23]. All three instruments have been validated and adapted for the Brazilian population and exhibit excellent reliability, sensitivity, and specificity indices[24-26]. In practice, few clinicians routinely use standardized tools to assess and monitor patient progress, as these are more commonly employed in research settings. Nevertheless, the use of validated instruments is highly recommended - both for patients and professionals - as they enable objective quantification of outcomes following applied protocols.

The evidence searches and evaluation conducted in this study identified four selected protocols as potential interventions recommended for clinical practice. The protocol with the largest effect size (protocol 4) was not selected as the first-line option because it applies several pulses exceeding the limit established by safety guidelines[27] and reported a case of tonic-clonic seizure as an adverse effect of the stimulation[18]. Thus, we decided to place it in the last option of the 4 recommended protocols. The remaining three protocols showed practically equivalent effect sizes, demonstrating a reduction percentage in the clinical outcome between 44% and 50%. Protocol 1 was chosen as the primary recommendation because its stimulation parameters were applied to other studies and consistent outcomes were observed. Protocol 2 shows the numerically largest effect size, it is an accelerated protocol utilizing continuous Theta Burst stimulation (cTBS) allowing for significantly shorter session times, saving time for both the clinician and the patient, and offering greater benefits from a cost-effectiveness standpoint. Yet, its lack of replicated data led us to the decision of not recommending it first. Protocol 3 remained as the third option because it shows the numerically smaller effect size and numerically bigger standard deviation out of the three protocols that did not report relevant side effects.

In this study, we presented evidence pertaining only to the use of repetitive Transcranial Magnetic Stimulation (rTMS) and Theta Burst Stimulation (TBS). Recently, other non-invasive brain stimulation (NIBS) modalities have been explored, such as transcranial direct current stimulation (tDCS)[28] and transcranial alternating current stimulation (tACS)[29], as well as other application sites, such as cerebellar magnetic stimulation[28]. However, the limited evidence does not yet permit their broad recommendation, reinforcing the need for developing new, well-designed clinical trials with more robust sample sizes to advance the science in this field.

The main limitations of the present study include searching only one database, the lack of a critical assessment of methodological quality using more robust tools such as AMSTAR 2 and AMSTAR Rank, and the absence of results from the clinical application of the proposed decision tree, which was not presented due to the requirement for prior review by a research ethics committee. A second limitation, directly related to the clinical applicability of our roadmap, lies in the patient populations in the trials that underpin our recommendations. While being of high quality, the selected RCTs tended to exclude patients with significant psychiatric comorbidities, such as major depressive disorder or substance use disorders. Consequently, our roadmap is most applicable to patients with a 'purer' GAD diagnosis and does not, at present, allow for differentiated recommendations for clinical subgroups. This is a limitation not only of our method, but of the current state of the literature. Future studies are urgently needed to investigate the differential efficacy of these protocols in more heterogeneous and clinically representative patient populations, which would allow for the creation of more personalized roadmaps. Furthermore, the construction of a complete roadmap should ideally include a final step that was not performed in this study. In this step, the roadmap would be used to guide a clinical case, followed by the presentation of a brief case report and an evaluation of the roadmap's practical application.

It can be concluded that clinical reasoning based on the best available evidence and expert evaluation allowed for the identification of three instruments for outcome assessment and four protocol options for the treatment of generalized anxiety disorder (GAD). The Beck Anxiety Inventory (BAI), the 7-item Generalized Anxiety Disorder scale (GAD-7), and/or the Depression, Anxiety, and Stress Scales (DASS-21) are recommended for application before and after interventions. The primary recommended treatment option was the use of continuous Theta Burst stimulation (cTBS) over the right dorsolateral prefrontal cortex (r-DLPFC), owing to both its effect size and cost-effectiveness ratio; this is followed by three options of repetitive transcranial magnetic stimulation (rTMS) protocols, with different parameters, applied to the same cortical region.

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Authors contributions

The authors declared that they have made substantial contributions to the work in terms of the conception or design of the research; the acquisition, analysis or interpretation of data for the work; and the writing or critical review for relevant intellectual content. All authors approved the final version to be published and agreed to take public responsibility for all aspects of the study.

Competing interests

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