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Deep TMS: A comprehensive summary of adverse events from five multicenter trials

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Dear Editors,

Deep repetitive transcranial magnetic stimulation, commonly known as Deep TMS, is a noninvasive neuromodulation tool which is now actively used throughout the world for the treatment of a variety of psychiatric diseases. Through electromagnetic induction Deep TMS coils lead to neural depolarization in a network of neural regions that are modulated by the specific conformation of the coil. Currently, there are three Deep TMS coils cleared for use in the United States by the Food and Drug Administration (FDA)- the H1, H4, and H7 coils. These coils have been studied in 5 multicenter double-blind, randomized, controlled studies [1–5], 4 of which were sham controlled [1,3–5].

The H1 coil is indicated for major depression and anxious depression, the H7 is indicated for obsessive compulsive disorder, major depression, and anxious depression, and the H4 coil is indicated for short-term smoking cessation. Each coil has a distinct geometric configuration. While these unique configurations are important for modulating different neural networks, the unique coil configurations may also have unique adverse event profiles. Although the FDA labeling requires reporting only on adverse events that occur in $\geq$5% of subjects, to be even more transparent and comprehensive events present in at last 2% of the aggregate population are included.

This Letter describes the aggregate adverse event frequency across five multicenter clinical trials utilizing the H1, H4, H7 and sham coils for the treatment of major depressive disorder, smoking addiction, obsessive compulsive disorder and post-traumatic stress disorder.

Data Sources. Adverse event data was compiled from 884 individuals that participated in one of five multicenter, double-blind, randomized, sham-controlled clinical trials of Deep TMS, published from 2011 to 2023 (Supplementary Table 1). Adverse event reporting terminology was standardized using MedDRA coding. The relationship to the study device was determined by the site investigator. **Data analysis.** The data were analyzed using Pearson's chi-squared test on multiple factorial proportions followed by Z-test to compare between two proportions. A significance level (α) of $p < 0.05$ was set for all statistical analyses. The adverse event data associated with a given coil data was combined from all the multicenter studies that used that coil.

Adverse event frequency. The adverse events reported by more than 2% of subjects are listed in Fig. 1. The most common events associated with active TMS were headache (35.43%), treatment site discomfort (29.92%), muscle spasm (5.91%), jaw pain (5.71%), neck pain (4.53%), mastication (2.76%), dental pain (2.56%), and general discomfort (2.56%) (Fig. 1A). These were all transient but significantly more common following active TMS. Of these 8 symptoms, there was a significant difference in the distribution of the events across the coils as a whole ($X = 61.05$, df:30, $P = 0.0007$) with the H4 coil having lower rates of headache ($X = 17.99$, $P < 0.0001$), treatment site discomfort ($X = 19.92$, $P < 0.0001$), and jaw pain ($X = 6.336$, $P = 0.0421$), but higher rates of general discomfort ($X = 8.013$, $p = 0.0182$)(Fig. 1B). **Secondary analysis by population**. It is possible that adverse event sensitivity may vary based on the underlying disease state. While it is not possible to directly test that hypothesis with these data, an exploratory posthoc analysis for the H7 revealed no differnece in headache or treatment site discomfort among MDD, OCD, and PTSD patients (supplemental data). It is also possible that the likelihood of some of these adverse events is proportional to the absolute dose of TMS delivered (e.g. measured by machine output). While that level of detail is not current available to us for these studies, a future investigation in a large sample is warranted.

Summary and recommendations. Initially cleared for the treatment of depression in 2013, there have now been five FDA-pivotal trials of various Deep TMS coils. Our analysis demonstrates that the most frequent adverse events were headaches and treatment site discomfort – observations which are consistent with decades of work in the TMS field. Perhaps more interesting is the comparatively low adverse event profile of the H4 coil relative to the H1 and H7 coil. The lower proportion of adverse events with the H4 coil may be related to the treatment position. It could also be related to the treatment population (tobacco cigarette smokers). From a practical perspective, most of the adverse events were transient and resolved within days and their severity was mild to moderate. No hearing loss cases were reported and hearing protection was used. Since the most common adverse event is application site discomfort or pain and headache, we recommend telling patients to premedicate for the first several days of TMS treatment with a non-steroidal anti-inflammatory or acetaminophen.

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A) Adverse event rate in 5 multisite clinical trials

	Active Deep TMS	
	Total^	Percent
Headache	180	35.43%
Treatment Site Discomfort	152	29.92%
Muscle Spasm	30	5.91%
Pain In Jaw	29	5.71%
Neck Pain	23	4.53%
Mastication	14	2.76%
Dental Pain	13	2.56%
General Discomfort	13	2.56%

^Number of patients that reported having this AE at least once
*All of these items were significantly greater in the Active (n=508) versus Sham TMS groups (N=376; Chi Square p<0.005). See Supplementary material for detail.

B) Adverse events by coil type

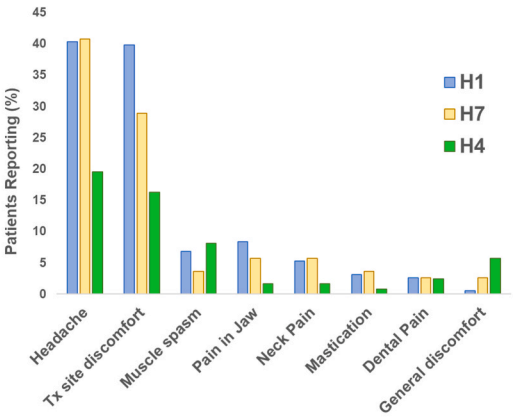

Fig. 1. Summary of the adverse events reported across 5 multisite clinical trials of Deep TMS. (A) The data are shown as a list of all adverse event reported by more than 2% of the patients. (B) Distribution of adverse events associated with Active TMS, sorted by coil type. There is a significant difference in the overall frequency of events across the coils ($X = 61.05$, df:30, $P = 0.0007$) with the H4 coil having lower rates of headache ($X = 17.99$, $P < 0.0001$), treatment site discomfort ($X = 19.92$, $P < 0.0001$), and jaw pain ($X = 6.336$, $P = 0.0421$), but higher rates of general discomfort ($X = 8.013$, $p = 0.0182$). All adverse events were transient.

Mastication symptoms or jaw pain may be caused by stimulation of the motor and sensory roots of the trigeminal nerve. Placing foam between the temple and the coil often improves tolerability with minimal effects on the total amplitude of the TMS dose [6]. Neck pain can be ameliorated with a good chair, supporting neck cushion, patient posture, and proper TMS positioning techniques. Once the Deep TMS coils are placed, and the chin strap secured, the coil should be relatively weightless.

The primary limitation for generalizing the result of this analysis to real-world patients is that data analysis was limited to prospective randomized trials, which often have lower efficacy rates than real-world practice. Additionally, the likelihood of the events was more common in the active versus sham groups when data from these 884 individuals are assessed in aggregate. While this is important to note for future development, it is it does not preclude the fact that the adverse event rate in the sham group was still sufficient in each of the multicenter studies to maintain the blinding based on the "forced choice" question subjects answered after the first treatment. There was also not sufficient power in the sample to assess for rare adverse events such as seizure ($n = 1$; active) [7], syncope ($n = 2$; both sham) [8], or hearing loss ($n = 0$) [9] (See supplement for full list of reported adverse events). In summary, this paper presents the most comprehensive analysis of adverse events associated Deep TMS coils (relative to sham). We intend for this to be a resource to the TMS community at large.

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BrainsWay.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Aron Tendler has a financial interest in BrainsWay, the manufacturer of deep TMS systems, and is the BrainsWay consultant chief medical officer. He also has a financial interest in the Clinical TMS society, Liva Nova, Alpha Tau Medical, Biohaven, and a commercial clinical and research psychiatry office with TMS services. Roman Gersner and Tal Harmelech were employed by BrainsWay. Yiftach Roth is the chief scientist, founding physicist, and has a financial interest in BrainsWay. Ahava Stein is a consultant for BrainsWay and has a financial interest in BrainsWay. Colleen A Hanlon is employed by BrainsWay and has a financial interest in the company.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2023.07.048.

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