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Is TMS Proven Effective for Depression?

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Transcranial magnetic stimulation (TMS) devices have stimulated the brains of tens of thousands of patients in the United States, often as a treatment for refractory depression. Refractory depression is defined as a depressive episode that has not responded to previous treatment efforts. TMS treatment (also called repetitive TMS or rTMS) typically costs $300 per session, usually 5 days/week for four to six weeks. And yet, there is no clear evidence that this very expensive treatment works or is more beneficial than the much less expensive and more convenient antidepressant medications. This report will examine how TMS became a frequently used treatment for depression in the United States despite what the research of the last decade shows about its very questionable effectiveness. Although the process was atypical in several ways, the pathway to widespread TMS use illustrates how FDA's willingness to ignore scientific evidence and their own scientific advisors can contribute to years of very expensive, questionable treatments for patients.

TMS and the Role of the FDA

TMS devices were cleared for market by the FDA in 2008 under the FDA review pathway known as the de novo process.[1] FDA's scientific advisory committee had recommended against the device when it was submitted through the 510(k) pathway, a review process that requires that the device be "substantially equivalent" to a medical device that is already on the market.[2] In the case of TMS, the company claimed that their device was substantially equivalent to electroconvulsive [shock] therapy (ECT), since both are for depression that is difficult to treat. Since the mechanism of action of ECT and TMS are very different, the substantial equivalence would need to be proven based on having a similar benefit to risk ratio.

Neuronetics, the manufacturer of the first TMS device NeuroStar TMS Therapy System, submitted one double-blind, randomized, controlled clinical trial and two uncontrolled, follow-up studies of the same patients for their 510(k) application. The agency also scheduled an FDA Advisory Committee to meet publicly to review the data.[3] Clinical trials and FDA Advisory Committee meetings are very rare for devices submitted through the 510(k) pathway.

The gold standard for clinical trials is the randomized, double-blind clinical trial; patients are randomly assigned to get treatment or a placebo, and neither the patient nor the person evaluating them knows which patients received the treatment being studied. An uncontrolled study, which is scientifically inferior for demonstrating safety or effectiveness, is when the patients are evaluated, but there is no comparison to patients getting a different treatment or a placebo.

In 2007, the FDA Advisory Committee rejected the TMS device for depression because of the failure to show benefit compared to a sham treatment.[3] A sham treatment is the device

equivalent of a placebo; it is designed to seem as similar to real treatment as possible, so that the study can be randomized and double-blind. That is very important for studies of treatments for depression, because depression tends to ebb and flow over time. Therefore, the comparison of a placebo or sham control makes it possible to determine if the treatment actually is beneficial and if it has unpleasant or unsafe side effects.

Treatments for depression are generally evaluated in terms of "responders" and remission. Responders are patients who show at least a 50% improvement in their scores on a depression severity scale such as the Hamilton Depression Scale (HAMD) or Montgomery-Åsberg Depression Rating Scale (MADRS). Remission is measured by a specified low score on that depression scales. HAMD and MADRS scales involve professionals rating the patient, whereas the also popular Beck Depression inventory relies on patients to report their own symptoms. However, when effectiveness is evaluated by a person paid to provide treatment, there is a financial conflict of interest that may interfere with the objectivity of the results.

The Advisory Committee concluded that TMS could not be considered substantially equivalent to ECT in terms of benefit to risk ratio because ECT has short-term benefits and the data indicated that TMS had no benefit.[3] With zero as the "benefit" the ratio of benefit to risk was mathematically zero, and therefore not equivalent to ECT.

The TMS study submitted by Neuronetics and reviewed by the Advisory Committee was of patients who had **one or more previous failure(s) with antidepressant medication**.[4] The results indicated no statistically significant difference between the patients receiving TMS treatment for five days/week for four weeks, compared to the sham control. For example 18% of TMS patients responded to treatment (defined as improving by at least 50% on the MADRS depression scale) compared to 11% of the sham patients. Remission rates were almost identical (7% vs. 6%).[2] For both the treatment and the sham control, the TMS device is applied to a patient's head; however, the TMS signal was blocked for the sham control group.

In medical research, it is required that researchers decide on their study design and protocol and analysis before the study is started. In this case, Neuronetics realized that TMS would seem more beneficial if they **excluded all patients with more than one previous failure**. They also excluded the approximately 50% of patients who dropped out of the study after 4 weeks, most because they had not benefitted from treatment (or from sham).[2,4] Changing the way the data are analyzed after the results are calculated is referred to as post-hoc analysis and is supposed to be used only to develop new hypotheses to test in future studies. The results indicated that TMS treatment was statistically significantly more beneficial than sham treatment (approximately 5-point greater reduction in symptoms on MADRS at four weeks and at 6 weeks).[5] Based on that post-hoc analysis, Neuronetics resubmitted their application as a de novo application, and the FDA cleared TMS for the impractical indication of patients who had previously **failed one (and only one) previous antidepressant medication**.[1,6] That indication was clearly based on the data but does not make sense from a treatment point of

view: It is common for depressed patients to try one antidepressant medication, and if the first one does not work doctors will prescribe at least one or two other antidepressant medications instead of or in addition to the first. Patients and physicians would not want to switch to a much more expensive and inconvenient treatment after only one medication failed to provide substantial improvement.

The original study design included patients with **at least one previous failure, rather than only one failure** – a much more logical treatment plan. It is unlikely that many depressed patients would have chosen to try TMS after failing to improve after trying just one antidepressant medication.

In 2008, the Affordable Care Act (ACA) had not yet become law, and it would be several years before the ACA required equitable coverage for mental illness. It was therefore especially unlikely that patients would be willing to undergo such an expensive, inconvenient treatment before trying at least two or probably more than two different antidepressant drugs.

Despite the initial findings that TMS only benefitted patients who had failed only one antidepressant medication, TMS would likely have been administered primarily to patients who had failed two or more antidepressant medications for the reasons given above. Although physicians were free to prescribe TMS for patients with numerous drug treatment failures, or even with no previous drug failures or adverse reactions, such uses were initially considered "off label." That refers to the fact that they were different from the intended use that FDA cleared – which specified one medication failure.

The indication for one prior medication failure was still on a NeuroStar TMS device application cleared by FDA in 2013.[7] It was not until 2014 that FDA changed the intended use after evidence from a new clinical trial that demonstrated an improvement over sham for patients who had failed at least one antidepressant medication.[8]

In contrast to the NeuroStar TMS Therapy System, Brainsway Deep TMS System was cleared for market in 2013 with the broader indication of treatment for patients "who failed to achieve satisfactory improvement from previous anti-depressant medication treatment in the current episode."[9]

FDA's Questionable Process

As noted previously in this report, after the FDA Advisory Committee members decided that the NeuroStar TMS device was not proven effective and should not be considered substantially equivalent to ECT in its risk-to-benefit ratio, the FDA cleared the TMS device through the de novo process. This was a very uncommon decision since de novo was the pathway to market of only 3 out of 3,116 devices (0.1%) that year.[10] [11] [12] [13]

The FDA requires that companies determine the types of patients to be studied and the type of statistical analyses to be conducted in a clinical trial before the data are analyzed: This is referred to as hypothesis testing. It is required in order to avoid a "fishing expedition" where researchers analyze patient data in many different ways until they finally find one that could support FDA approval. Since statistical significance is based on the assumption of a limited number of analyses, post-hoc analyses would enable the researcher to inappropriately lower the standards of evidence. For example, a "p value" of less than 0.05 means that there is less than a 5% chance that a statistically significant difference between TMS and placebo happened by chance. But if 5 comparisons (such as patients who had failed at 1) only 1 antidepressant, 2) only 2 antidepressants, 3) only 3 antidepressants, etc) were made instead of just one comparison (1 or more antidepressants), the likelihood of it happening by chance increases to the number of comparisons multiplied by 0.05 = 25%.

When the FDA cleared the TMS device on the basis of a post-hoc subgroup analysis, the agency essentially gave its seal of approval for a new type of device that was not scientifically proven to work. The FDA Advisory Committee's comments about the lack of effectiveness data were ignored when the FDA review process was changed in an unusual way. The FDA accepted scientifically unsound data that suggested that the product was effective for a type of depressed patient that depression experts knew did not make any sense.

Once the first Neuronetics TMS Therapy System was on the market, 21 other TMS 510(k) applications followed, including 5 changes to the Neuronetics TMS device.[10] TMS devices made by other 6 other companies have been cleared as "substantially equivalent" to the Neuronetics TMS device and only two of the 21 510(k)s provided new clinical trial data to prove safety or effectiveness. These two 510(k)s each provided a new double-blind, randomized, sham-controlled clinical trial. One, mentioned earlier, expanded the intended use of the NeuroStar TMS device.[8] The other was for the Brainsway Deep TMS System and provided evidence for a new type of TMS – deep TMS, which stimulates a larger area of the brain.[9] A third 510(k) provided a literature review of multiple TMS devices to evaluate a change in the pattern of pulses for the NeuroStar TMS System.[14]

Is TMS Effective?

In the 10 years since a TMS device was first cleared for market in the U.S., researchers have sought to improve the effectiveness. Treatment is consistently given 5 days/week but, studies have been conducted to evaluate the following changes to TMS to determine which are most effective:

- Frequency, length of treatment, intensity, and pattern of the pulses;

- Treating different areas of the frontal cortex (left/right/both dorsolateral prefrontal cortex and the anterior cingulate cortex);
- Number of treatments per day;
- Number of weeks of treatment;
- Types of patients appropriate for treatment; and
- Maintenance schedule for patients who respond well to treatment.

Even today there is no established effective treatment. For example, in a 2018 *JAMA* editorial commenting on a new TMS study of patients at Veterans Affairs medical centers, psychiatrist Charles Nemeroff concluded that the lack of efficacy compared to placebo "*are puzzling for several reasons. What might explain these findings? First, this population is largely male, in clear contrast to most depression clinical trials, which typically are about two-thirds female. Second, one cannot underestimate the psychological benefits of participation in clinical trials. The repeated engagement of the subjects by the treatment team is not a neutral experience but tantamount to at least supportive psychotherapy, if not more…. This is an important negative study, but it does not fully answer the question of what the appropriate role for rTMS is in the treatment of TRD [treatment resistant depression] in veterans.*"[15]

Over the years, concerns about TMS efficacy have been expressed even by those who strongly support it. For example, Dr. Philip Janicak, a consultant to Neuronetics who has written numerous articles that support its use, wrote in 2015, *"In summary, TMS is a promising, novel antidepressant treatment still relatively early in its development."*[16] In a 2015 review of TMS research for depression, Dr. Paul Holtzheimer from Dartmouth Medical School, who also supports the use of TMS, admitted in 2015 that there are many unanswered questions about how to ensure effectiveness of the treatment, stating *"the stimulation parameters required to optimize efficacy are not known and administration of repetitive TMS is thus not standardized......The number of treatments necessary for patients with acute major depression is not clear."*[17]

In 2016, the Canadian health agency, Health Quality Ontario, conducted a meta-analysis on the effectiveness of TMS. "*We calculated changes in depression scores measured by Hamilton Rating Scale for Depression from baseline to the end of treatment and conducted a meta-analysis on the mean changes in scores of the two groups of rTMS-treated and sham-treated patients. The weighted mean difference was 2.31 points [which is] below the mean value deemed a priori to be clinically important [at least 3.5 points]… On average, rTMS reduced depression scores by about two points more than sham rTMS.*"[18]

Examining Key Research on TMS

It is challenging to measure the impact of treatment for depression, because depression can get better or worse depending on life events, hormonal cycles, and other factors that may be impossible to measure. Major depression (MDD) is a long-term disease that tends to ebb and flow over time. Patients tend to seek a new treatment or even a clinical trial when they are feeling very depressed. With or without treatment, many depressed patients will tend to get better over a period of weeks and months. Studies that compare treatments over a period of 6-8 weeks tend to find improvement for treatment but also for patients on placebo. Frequently, the differences between depression treatment and placebo are small.

The first TMS device was cleared by the FDA based on 4-6 weeks of treatment for 5 days/week, and that is the duration of treatment that is still common.[19] Unfortunately, most early TMS studies were designed to be 2-3 weeks, with either 3 weeks of additional treatment as needed or a tapering off if the patient is in remission. In fact, numerous researchers admitted that it was difficult to keep patients in treatment for 4-6 weeks, whether TMS or sham, which suggested that TMS treatments that were evaluated in the first 5-8 years were not effective enough to persuade patients to continue.

Research on TMS is often funded by TMS device makers or conducted by psychiatrists who use TMS devices. In addition, many TMS studies are "open-label," which means that the patient and the person rating the patients' depression both know what treatment, if any, that the patient is getting. Open-label TMS studies often do not contain a control group, such as patients who would receive another treatment, a placebo, a sham treatment, or no treatment at all. That can introduce bias, which is even greater because the HAMD and the MADRS are both administered and scored by a clinician, who may also being paid for treating the patient. Such uncontrolled or open-label studies are likely to conclude that a treatment is effective. The patients want the treatment to work and usually at least some patients will seem to benefit when there is no control group to compare it to. There are many published studies of TMS that are uncontrolled or open label studies, and most conclude that TMS is effective, but uncontrolled and open-label studies are not considered scientifically sound evidence of effectiveness.

Since open-label, uncontrolled studies cannot provide persuasive evidence of effectiveness, this report focuses on randomized, sham-controlled, double-blind studies of TMS.

As noted earlier in this report, randomized, double-blind clinical trials are the gold standard for medical treatment research. These are especially important for TMS because depressed patients who are told that they are receiving a treatment, whether the treatment is effective or not, real or placebo, often get better. That is why depression treatment research is referred to as having a very strong "placebo response rate."[15]

In fact, studies of antidepressant drugs have found that the patients getting placebo do amazingly well. The percent of patients that respond well – defined as more than 50% improvement on the MADRS or HAMD depression scale – is usually only slightly lower for patients getting placebo than for patients getting the antidepressant drug being studied.

For example, a study of the antidepressant agomelatine compared it to placebo and to a popular SSRI antidepressant (Paxil).[20] Patients improved whether they were taking either of the drugs or placebo; patients taking placebo improved on HAMD 86% as much those taking the new drug. In other antidepressant studies, an average of 30% of patients taking placebo were "responders."[21] Some of those patients had never taken an antidepressant before, but others had previously failed to respond to a different antidepressant. The latter are the types of patients that FDA says TMS is intended to treat.

Early Sham-Controlled Studies of TMS

A TMS study by O'Reardon *et al.* that was funded by Neuronetics was the basis of FDA clearing the device for market.[2][22] After 4 weeks of TMS or sham, **21%** of 155 TMS treated patients responded compared to **12%** of 146 sham treated patients, but only **7%** of the TMS patients were in remission, compared to **6%** of sham patients. The results were only slightly better after 6 weeks of TMS (**25%** vs. **14%** responders and **16%** vs. **9%** in remission). The 6-week data are not scientifically sound because approximately half the patients dropped out of the randomized study (and therefore not be counted) after only 4 weeks. Most who dropped out did so because they had not improved. This obviously biased the 6-week results in favor of patients who had stayed in the study because they benefitted. However, even based on these questionable analyses, the differences in remission rates were not statistically significant at 4 weeks or 6 weeks, when the analysis controlled for multiple comparisons. It was only statistically significant when the researchers did not control for multiple comparisons or when they used their post hoc analysis of only those patients who tried TMS after failing only one antidepressant medication.

Another key TMS study, by George *et al.*, reported that after 3 weeks of TMS or sham, **14%** of the 92 TMS patients were in remission, compared to **5%** of the 98 sham patients. Similarly, **15%** of TMS patients were responders, compared to **5%** of sham patients. Both were statistically significant. Non-responders were moved into an open-label phase, after which 30% of 144 patients entered remission.[23]

Similar to the O'Reardon study, Triggs *et al.* found no significant differences between TMS treatments to the left or right side and similar sham treatments in their double-blind clinical trial at any time during treatment. However, the effectiveness of either treatment or sham on the left and right side differed significantly 1 month and 3 months <u>after</u> treatment.[24] After 2 weeks of treatment, **22**% of 18 patients receiving left-side TMS, **31%** of 16 patients

receiving right-side TMS, and **43**% of the 14 sham patients (left or right side combined) had responded to treatment with at least a 50% reduction in depression scores on HAMD. After 1 or 3 months, there were larger, significant differences in the number of responders between patients who had received treatment on a given side than between active and sham treatment.

Because many TMS studies are small and the differences between TMS and sham are inconsistent, researchers have combined the data in what is called a meta-analysis. Numerous meta-analyses conclude that TMS is effective compared to sham controls, but the differences are not due to the efficacy of TMS, but rather to the surprisingly poor outcome for sham patients, as was also shown in the O'Reardon and George studies. In their 2012 meta-analysis of 7 double-blind studies of <u>bilateral repetitive TMS</u>, Berlim *et al.* reported that **25%** of TMS patients were responders compared to only **7%** of the sham patients.[25] Those dropped to **19%** of TMS patients and **3%** of sham that were in remission. The patients averaged 12.6 treatment sessions, with study designs ranging from 10 to 25 sessions.

Similarly, in his 2014 meta-analysis of 29 double-blind studies of <u>high-frequency</u> repetitive TMS, Berlim *et al.* reported that **29%** of TMS patients were responders compared to only **10%** of sham patients.[26] Only **19%** of TMS patients went into remission, as did only **5%** of sham patients. The patients averaged 13 sessions, with study designs ranging from 10 to 30 sessions.

In his 2013 meta-analysis of 8 studies of <u>low-frequency TMS</u>, Berlim *et al*., **38%** of the TMS group were responders as were **15%** of the sham group.[27] Almost as many (**35%**) of TMS patients were in remission, as were **10%** of the sham patients. As was the case in his 2014 meta-analysis, the patients averaged a small number of sessions: just 12.9 with studies ranging from 10 to 20 sessions.

The poor outcome for sham patients raises questions about whether the sham groups in those studies were an effective control. As noted earlier in this report, in placebo-controlled studies of antidepressant medication, approximately 30% of patients receiving placebo are responders. If the sham control group suspect that that they are not receiving treatment, that could explain why their depression symptoms are not improving.

In summary, in these meta-analyses and the studies that they are based on, the benefit of TMS compared to sham controls is primarily due to the patients in the sham controls doing very poorly, not due to improvements among treated patients. Only 7-15% of sham patients "responded" with substantially improved depression scores and only 2-10% in remission.

Do Recent Studies Show Greater Benefits?

The most recent randomized, double-blind studies of TMS show a range of results. In a 2017 study of 20 sessions of high-frequency (HF)-TMS over 4-6 weeks, Carpenter *et al.* reported that there were no significant benefits for treatment compared to sham.[28] To improve their reported results, the researchers excluded the one site that had worse outcomes for the TMS group. Even then, there was not a statistically significant improvement in the response rate for the treatment group (**55%** of 37 patients receiving HF-TMS vs. **32%** of 38 patients receiving sham) or remission rate (**26%** HF-TMS vs. **19%** sham).

In a 2015 study of synchronized TMS (sTMS), Leuchter *et al.* evaluated a TMS frequency that was matched to the patient's own alpha waves.[29] After 6 weeks of treatment, the response rate was the same for active sTMS (**27%** of 103 patients) and sham (**27%** of 99 patients) on the HAMD.

Several recent studies indicated benefits for TMS patients but only for certain types of TMS treatment. Theta-burst stimulation is a type of TMS treatment that more closely mimics the activity pattern of the brain. A 2014 study by Li *et al.* of theta-burst stimulation (TBS) compared three variations of TBS to sham.[30] After 2 weeks of treatment, patients were statistically more likely to respond to treatment if they received either intermittent TBS (**40%** of 15 patients) or intermittent TBS plus continuous TBS (**67%** of 15 patients) compared to patients receiving continuous TBS (**25%** of 15 patients) or sham treatment (**13%** of 15 patients). However, there are too few patients in each of these treatments and sham to draw conclusions about effectiveness, and the low percentage of sham responders also raises questions about the results.

In a 2016 study, Blumberger *et al.* compared the more common (left side) high-frequency TMS to bilateral TMS (high-frequency left side and low-frequency right side) to sham.[31] If patients did not respond in the first 3 weeks, they received an additional 3 weeks of treatment or sham. Remission rates for bilateral treatment were significantly higher than sham (**20%** of 40 patients receiving bilateral treatment vs. **2%** of 41 patients receiving sham treatment), but not for treatment on just the left side (**8%** of 40 patients). Unilateral treatment was not significantly better than sham. Patients treated with bilateral TMS were also more likely to be responders than if they had sham treatment (**23%** vs. **5%**). However, patients with unilateral TMS treatment were not more likely to respond to treatment than patients in the sham group (**15%**). However, there was a higher percentage of patients with more severe depression randomized to the sham group compared to the other arms. This might account for the low response among the sham treatment patients.

A 2017 study by Theleritis *et al.* reported much higher levels of effectiveness than the other TMS studies. That study compared three weeks of <u>two</u> treatment sessions per day with high-frequency TMS (HF-TMS) to 1) a <u>single</u> session per day and to 2) one or two sessions of

sham treatment per day.[32] Two weeks after treatment was complete, **59%** of the 49 patients who received HF-TMS (either once or twice daily) responded to treatment (50% or better improvement) compared to only **3%** of the 40 patients responding to sham. In addition, **25%** of HF- TMS were in remission compared to **none** of those receiving sham. However, these findings are also suspect because only one person in the sham control group improved.

A response rate of only 1 patient out of 40 in the sham treatment group is so unusually low that it suggests that the sham was not an effective placebo, even though the authors state that there was no difference in patients' ability to correctly guess whether they received treatment or sham. As noted earlier, about 30% of patients in placebo groups in studies of antidepressant drugs are responders. In other words, it seems likely that many of the patients in the sham group suspected that they were not receiving the TMS treatment. That is the most logical explanation given what we know about very strong placebo effect for the treatment of depression.

We found a possible explanation for the differences in the sham control patients. The three studies that demonstrated a statistical difference between an active TMS treatment and sham (Li *et al.* 2014, Blumberger *et al.* 2016, Theleritis *et al.* 2017) all used a simpler version of the sham where the device was tilted perpendicular to the head instead of flat against it. This was done so that the signal would go over the brain instead of into it.[30 30 31] However, it also means that the clinicians treating the patients were not "blinded" because they could tell if the patient was getting sham or not. In contrast, Leuchter *et al.* (2015) found a response rate of 27% for patients receiving sham exactly at the same position as it would be for active treatment.[29] That sham would seem much more similar to the actual TMS treatment, so that during the study, the clinicians could be blinded to which treatment they were proving to each patient.

What is clear even in the most recent studies is that TMS is still an experimental treatment, with researchers testing variations of TMS to try to increase how well it works or how quickly a response occurs. And yet, patients are paying $300 per session for "treatment" that is often ineffective and in some cases clearly experimental.

Are There Long-Term Benefits of TMS?

If some types of TMS treatments reduce the symptoms of depression for some patients during the weeks during and just after treatment, it would not necessarily mean that TMS is a long-term solution to depression. As noted previously, depression often lasts for years or even decades. Although some studies have followed patients beyond the daily treatment period, most of the longer-term studies cannot scientifically evaluate long-term effectiveness because most are open-label or what are called "naturalist studies" that merely evaluate patients who

are undergoing treatment. Even patients who were initially randomized to treatment or sham were often switched to an open-label trial after the treatment period.[33] [34] An open-label trial is one where patients are aware they are getting treatment and there is no longer a sham control group.

In addition, antidepressants are often added or changed after the initial TMS treatment phase is completed, making it impossible to know the true benefit of the TMS treatment itself, rather than the impact of medication.

The often poor quality of the TMS studies is very different from the studies required for FDA drug approval. Many drug approval studies compared patients receiving a drug to patients receiving placebo or an alternative treatment for months or even years. This is especially important for depression studies, because depression ebbs and flows, but can last for years.

In one of the few studies that maintained the randomized, double-blind TMS treatment or sham for longer than 3 weeks, a 2015 study by Kreuzer *et al.* found that a new type of TMS called mediofrontal double cone coil stimulation was **more beneficial** than traditional TMS or sham after 3 weeks of treatment.[35] However, at the 12-week follow-up, scores on HAMD were **identical** to sham for both types of TMS. These results indicate that even for the minority of patients who apparently benefitted from TMS treatment, those benefits did not last. Despite these important findings, the published article focused on the good news about TMS – success at 3 weeks – rather than the bad news (no benefits compared to sham at 12 weeks).

Similarly, a 2018 study examined high-frequency TMS on veterans with treatment-resistant depression for 4-5 weeks.[36] At the end of treatment, **41%** of 73 patients receiving TMS were in remission compared to **37%** of 77 patients receiving sham, which was not significantly different. After the treatment period, the treatment was tapered off and patients were followed for 24 weeks. Again there was no statistically significant difference in the rate of patients in remission (**20%** of 60 patients who had received TMS vs. **16%** of 65 patients who had received sham).

Another study compared 4 weeks of treatment with TMS or sham while patients were treated with paroxetine (Paxil).[37] At the end of treatment, TMS treatment led to statistically better response and remission rates; these rates were much higher than other trials. Response rates were **96%** for 22 patients receiving TMS compared to **71%** of 21 patients receiving sham, and remission rates were **68%** for TMS compared to **38%** for sham. However, 4 weeks later, when patients were only receiving the antidepressant medication, the differences disappeared: **91%** of TMS vs. **86%** of sham were responders and **86%** of TMS vs. **76%** of sham were in remission. Nevertheless, the addition of Paxil seems to have greatly benefitted the patients in this study, regardless of whether they had TMS or sham.

Because depression often lasts for years, even 12 weeks or 24 weeks of follow-up is not long enough to determine the long-term effectiveness of TMS. In the rare studies that followed

patients for more than 6 months, the sham patients were usually given the opportunity to initiate TMS after just 2-3 weeks and, therefore, could no longer provide comparison data to the TMS treatment group. Moreover, as shown above, even when differences occur at the end of treatment, those differences may disappear within a few weeks or months after treatment ends.

TMS has also been studied to see if it can be used again to delay a relapse; this referred to as maintenance TMS treatment. Most clinical trials that evaluate maintenance TMS and include a comparison group are open-label and only compare TMS to patients prescribed an antidepressant or with no treatment at all. However, in both cases, patients that receive TMS meet with clinicians much more frequently than the control group. This increased interaction can be very supportive to patients and could cause any differences seen in these trials.

A 2015 study of deep-TMS (dTMS) by Levkovitz *et al.* examined daily treatment for 4 weeks followed by 12 weeks with maintenance treatments twice a week.[38] One week after completion of daily treatments, statistically more patients receiving dTMS were responders or in remission compared to those in the sham group. Of the 101 patients receiving dTMS, **37%** were responders compared to **28%** of 111 patients receiving sham; **30%** of dTMS patients were in remission compared to **16%** of sham patients. After 16 weeks, patients receiving dTMS also had statistically higher response rates than patients receiving sham (**41%** dTMS vs. **26%** sham), but they did not have statistically significantly higher rates of remission (**29%** dTMS vs. **22%** sham). A large percentage of patients dropped out during the study; only 43 dTMS patients and 28 sham patients completed the study, which may have affected the results. It also raises questions about the effectiveness when most patients drop out.

High-frequency TMS was evaluated as a maintenance treatment in a 2017 study by Benadhira *et al.*[39] All patients were initially treated with daily HF-TMS for 4 weeks. Responders were randomized to TMS or sham for 11 months; during this phase patients and those evaluating them were blinded to treatment. The two groups of patients was small (only 10 patients in the active group and 7 in the sham group) and the dropout rate was high (only 3 HF-TMS patients and 2 sham patients completed the study), making it impossible to draw conclusions. However, it is important that there were no statistical differences in the change in HDRS scores for treated patients compared to controls when they are adjusted for multiple comparisons.

TMS Compared to ECT

Electroconvulsive Therapy (ECT) is used for severe depression that has not responded to numerous medications or in cases where the patient is catatonic or seems to be a danger to himself or herself, because they are suicidal or unresponsive. Unlike antidepressant medication, which can take weeks to provide benefit, if ECT works, it works immediately.

Dr. Mark George, a researcher who conducted a key, early study of TMS for Neuronetics, as noted earlier in this report, studied whether TMS might be effective at preventing suicides. In his 2014 study of suicidal inpatients, TMS was given to each patient 3 times a day for 3 days and suicidal thoughts were measured by the Beck Scale of Suicidal Ideation (SSI).[40] The study showed **no benefit for TMS**; changes in scores on that scale were virtually identical to sham (15 point improvement in TMS and sham). In their published article, the authors emphasized the safety of the use of TMS, rather than the lack of effectiveness.

Numerous studies have compared the effectiveness of ECT and TMS. The studies have been small, with inconsistent results. However, a meta-analysis published in 2016 found ECT to be significantly more effective than high-frequency TMS.[20] ECT has more serious side effects, however, because it can cause permanent memory loss and related cognitive impairment. Like TMS, the long-term benefits of ECT are not established.

TMS Compared to Antidepressants

Only a few studies have compared TMS to antidepressant medications in randomized, double-blind, sham-controlled, and placebo-controlled trials.

In a 2005 study, Chistyakov *et al.* compared clomipramine with low-frequency left-side TMS, low-frequency right-side TMS, high-frequency left-side TMS, and high-frequency right-side TMS.[41] Clomipramine is a 50-year old drug that is more often used for obsessive compulsive disorder rather than depression. For each TMS arm, patients were given a placebo instead of clomipramine, and patients treated with clomipramine were given sham TMS. At the end of only 2 weeks of treatment, **55%** of 11 left LF-TMS patients had improved at least 50% on the HDRS, which was statistically more responders than the other patients (**17%** of 6 left HF-TMS patients, **17%** of 12 right LF-TMS, **33%** of 6 right HF-TMS, **13%** of 15 clomipramine patients). Interpretation of the results are complicated because early HF-TMS was much more uncomfortable than it is now and resulted in a high dropout rate from those arms.

A 2009 study by Bares *et al.* compared low-frequency TMS paired with placebo to sham paired with venlafaxine ER (Effexor ER).[42] At the end of 4 weeks of treatment, there was no statistically significant difference in the number of responders (**33%** of 27 TMS patients and **39%** of 31 venlafaxine ER patients). Similarly, there was no difference in the number of patients in remission (**19%** TMS treated patients and **23%** venlafaxine ER treated patients).

Brunelin *et al.* conducted a large multicenter trial comparing TMS with venlafaxine (Effexor) that was published in 2014.[43] Patients received either TMS and placebo, sham and venlafaxine, or TMS and venlafaxine. Treatment with TMS or sham occurred for 2-6 weeks, stopping if patients achieved remission. After 6 weeks, there was no difference in the number

of patients in remission: **41%** of 54 TMS treated patients, **43%** of 51 venlafaxine treated patients, and **28%** of 50 patients receiving both.

The Placebo Effect for Antidepressants

In order to understand the TMS studies, it is helpful to review studies of patients who try a second antidepressant medication when a first medication is not effective. Studies of the drug Abilify provide an excellent comparison, because like TMS, Abilify is not used as a first line of treatment for depression, rather it is used only after at least one antidepressant medication has not worked well.[44] A typical double-blind randomized Abilify study will evaluate patients who are already taking an SSRI and who are given either Abilify or a placebo the clinical trial.

For example, in a 2008 study, **32%** of patients taking an antidepressant (usually an SSRI) plus Abilify were responders, which means they improved their MADRS scores by at least 50%, compared with only **17%** of patients taking a placebo with their SSRI/antidepressant. Remission rates also were greater with Abilify (**25%**) than placebo (**15%**).[45] Although Abilify was more effective than placebo, the relatively small difference indicates that most of the benefit for Abilify patients was from the placebo effect. In a similar randomized double-blind study of 349 resistant depressed patients published in 2009, **47%** of Abilify patients were responders compared to **27%** for the placebo group, and **37%** of Abilify patients went into remission compared to **19%** who took placebo.[46] Again, when you compare the statistics you can see that more than half of the benefit apparently came from the placebo effect. This is typical for depression medications because the placebo effect is powerful.

Similarly, for the two studies that led to Abilify's approval for treatment-resistant depression, MADRS mean scores were reduced by almost **34%** for patients who were given Abilify in addition to the antidepressant they were already taking. The depression scores were reduced by **21-22**% for the antidepressant plus placebo group.[44] In other words, the placebo provided almost exactly two-thirds of the benefit as Abilify provided in patients who had previously failed to benefit from an antidepressant.

Why is the "Placebo Effect" Weaker for TMS?

A "placebo" in a clinical trial for medication is typically a "sugar pill" with no active ingredients that provide treatment. When medical devices are compared to a "non-active control" it is called a "sham treatment," but the impact is still called a "placebo effect." The placebo effect should be similar in the antidepressant studies as in the TMS studies, if the

patients and researchers are unaware of which patients are getting treatment and which are not.

Therefore, the sham treatments in the TMS trials should result in improved symptoms for 15-27% of patients, as was the case in the double-blind antidepressant medication trials. In the TMS trials, the sham group was exposed to a TMS device that was applied to patient's head but intentionally modified so that it did not provide treatment.

Some of the studies indicate that the sham is effective. For example, Herwig *et al.* found no difference between TMS and sham in their double-blind study: **31%** of all patients' symptoms improved whether they were treated by TMS or sham.[47] Those researchers were very careful to make sure the sham experience was realistic, which may explain the impressive placebo improvement. However, Herwig's study was not included in the meta-analyses that have been conducted because he did not specify whether he required all patients to have failed at least one medication prior to receiving TMS. His only information about treatment failures was that approximately 20% of the patients (in both TMS and sham) had failed at least three different medical treatments.

One possible explanation for the poor outcome for patients in many of the sham control groups compared to placebo groups in medication trials is that patients in the sham group were not truly "blind" because they suspected that they were not getting real treatment. It is also possible that the professionals who rate the patients' depression scores are not truly "blind." For example, although they express strong support for TMS in their articles, in 2013 Berlim *et al.* admitted that the quality of the sham control was "*clearly not optim*al" and that studies in their meta-analyses did not discuss the "integrity of the blinding."[27]

When blinding is effective in TMS studies, there is evidence that TMS and sham have similar benefits. For example, in a study where blinding was found to be very effective because patients and rating physicians could not accurately guess which group the patients were in, Kreuzer *et al.* (2015) found that the final scores on a depression scale were **identical** for TMS and sham at the end of the study.[35] In contrast, another study that evaluated the blinding by asking patients to guess whether they were getting TMS or not, Mogg *et al.* (2008) found that 69% of their guesses were correct.[48] The authors discuss the difficulty of maintaining the blind for patients and those rating them, admitting that "*Blinding was difficult to maintain for both patients and raters*." In their small study of less than 60 patients, Mogg *et al.* concluded that TMS was effective, because **32%** of TMS-treated patients responded to treatment compared to **10%** of sham-treated patients, and **25%** of TMS patients were in remission compared to **10%** for sham. Those comparisons are similar to several other TMS studies. If the studies were not truly double-blind, those results are not credible; however, blinding seems to have become more effective in TMS studies in the last few years.

The 2018 Yesavage *et al.* study and the 2010 Triggs *et al.* study are two of the small percentage of TMS studies where sham patients responded well.[24][36] In both cases, the

researchers reported that their study provided a very supportive social environment to the veterans in their study; for example, in the Triggs study the clinic coordinator spent an average of 15 hours with patients, whether they underwent TMS or sham. This supportive environment could explain why their TMS patients and sham patients did so much better than in many other TMS studies.

If many of the TMS studies that were described as double-blind were not double-blind, then their results would be as meaningless as the open-label studies. A closer look at the effectiveness data shows that **when TMS was significantly more effective than sham, it was usually because the patients in the sham group did poorly compared to typical placebo groups, not because TMS was particularly beneficial**. In fact, in the studies published prior to 2016, the percentage of patients who responded well (**15-38%**) to <u>**TMS treatment**</u> or were in remission (**7-35%**) were **similar to the percentage of <u>placebo patients</u>** who responded (**17-27%**) or were in remission (**15-19%**) **in the Abilify studies**! This suggests that for most of the years that TMS has been used to treat depression, it has offered so little benefit that patients would have been just as well served receiving a placebo in a double-blind clinical trial for medication.

The size of the placebo effect has increased over the years, so that in more recent studies there tends to be more improvement for both patients treated with TMS and those in the sham control group compared to earlier studies.[49] This is likely due to improvements in the use of the TMS devices and improvements to the sham control that make it a more convincing placebo. The results may also be affected by changes in patients' expectations.

The implications of these data for TMS effectiveness are clear: only a minority of patients are benefitting from TMS according to most of the best designed studies. Although TMS treatments and sham controls may be improving, there are many studies that indicate that TMS is not more effective than placebo.

Do Meta-Analysis Data Provide an Accurate Summary of TMS Studies?

As shown previously in this report, the percentage of TMS patients responding well or in remission in the meta-analyses is higher than in the largest, most credible double-blind TMS studies – even though those same studies were included in the meta-analyses. One concern expressed in previous TMS reports, such as the one prepared for the U.S. Agency for Healthcare Research and Quality, is that the meta-analyses included studies that were not necessarily well-designed, with problems with double-blinding.[50] Another problem with meta-analyses is publication bias: studies showing TMS is effective are more likely to be published than those that show it is not effective. There are several reasons for this:

1. Clinicians who have invested in the TMS device for treating their patients have a financial incentive to publish articles indicating that TMS is effective.
2. Researchers who receive consulting fees or other funding from companies that make or use TMS devices have an incentive to publish articles favorable to those companies.
3. Medical journals are more likely to publish articles that indicate a new treatment is effective than to publish articles indicating it is not effective.

Publication bias is well-established in research on depression. For example, a study by Turner *et al.* examined all antidepressant studies that were known to the FDA.[51] They found that the results of more than one-third of the studies were never published. All but one of the studies showing the benefit of the antidepressant was published. In contrast, studies that found that the antidepressant was not safe and effective or had questionable results were, with three exceptions, either not published (22 studies) or published in a way that conveyed a positive outcome (11 studies). As a result, 94% of the trials that were published showed the benefits of antidepressants, whereas the FDA analysis showed that only 51% of the studies actually showed that the antidepressants were beneficial.

Meta-analyses are based only published studies, so publication bias will skew the results toward showing effectiveness of the product being studied. Although Berlim and other researchers stated that they made an effort to consider publication bias, it is often impossible to eliminate, because studies that are not published tend to disappear and their findings cannot be considered.

Bottom Line: How Effective is TMS Compared to Other Treatments or Placebos?

As shown above, most data demonstrating benefit for TMS over to sham treatment are questionable. The data suggest that some of the newer types of TMS treatment may possibly be more effective than sham in the first weeks of treatment, but the evidence of longer-term benefits is lacking. As this report shows, there are few studies that compare TMS to other antidepressant medications, and there is little information about how effective TMS is for treatment-resistant patients compared to other alternative treatments, such as cognitive behavioral therapy.

One could argue that although it is not more effective than antidepressant medication, TMS has a safety advantage because it has fewer side effects than antidepressants. However, in many of the TMS studies, the patients undergoing TMS were also taking antidepressants, either during the weeks of treatment or immediately after TMS therapy was completed. Because TMS often does not replace medications, it does not eliminate those safety concerns.

It is, therefore, reasonable to look at the effectiveness of TMS for treatment-resistant patients compared to medications for treatment-resistant patients.

As noted above, previous studies indicate that **32-47%** of Abilify patient had at least a 50% reduction in their depression scores and **25-37%** went into remission, when they added Abilify to an ineffective antidepressant. These relatively impressive results are not unique to Abilify, however. In fact, they are similar to other "second string" antidepressant drugs that are taken when the first drug has a small impact on depression. In the STAR*D trial of antibiotic medications: "in the [second] phase of the trial, patients who did not achieve remission [with Celexa] were assigned or randomized to alternative treatments," either replacing Celexa with a different antidepressant (such as an SSRI or tricyclic) or having patients take a second antidepressant in addition to Celexa.[52] They report that the overall remission rate for "level 2 treatments" was **31%**. Even those who failed the second new medication had some benefit if they kept trying, with remission rates of 14% at the third try and 13% at the forth try.

Conclusions

For this report, we focused on the best designed trials of TMS, which were randomized, double-blind studies. While authors of dozen of TMS studies and meta-analyses have concluded that TMS is an effective treatment for depression, careful scrutiny of the study designs and results indicates that:

➢ There are various types of TMS treatment and the different protocols are still being evaluated because of uncertainty about which (if any) might be beneficial;

➢ Research efforts are still underway to determine how to make the treatment as effective and convenient as other treatment options, but there is no evidence that TMS is more effective than trying another antidepressant;

➢ Most TMS patients do not benefit in the short-term and even fewer in the months after daily TMS;

➢ While TMS may seem effective when it is not compared to other types of treatment or to an ineffective sham, it is not shown to be beneficial compared to typical placebo effects; and

➢ The long-term benefits of TMS in general and in terms of specific types of TMS treatment regimens need further study but are not impressive thus far.

Research to date has been biased by short-term studies and by many researchers who are studying their own patients and therefore have financial incentives to support the use of TMS. Although potentially safer than antidepressant medication, TMS often does not take the place of antidepressant medication, thus limiting any safety benefits.[53] Overall, the research suggests that TMS is generally no more effective than antidepressant medications for refractory depression, and often not significantly more effective than taking placebo in an antidepressant study.

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