NEURONETICS

Depression Patient's Manual

for Transcranial Magnetic Stimulation with the NeuroStar TMS Therapy® System

This Depression Patient's Manual is a supplement to the NeuroStar TMS System User Manual. It does not take the place of consultation and advice from your physician. For a complete discussion of indications for use, contraindications, precautions, warnings, and potential side effects, talk to your doctor. Specifically, talk with your doctor about:

- How this device is used
- Who can be treated with this device
- Who should not be treated with this device
- Warnings
- Side effects

Your doctor's phone number: 803-329-1915

Introduction to NeuroStar TMS Therapy

Your doctor has prescribed NeuroStar TMS Therapy® to reduce the symptoms of your depression.

TMS stands for "Transcranial Magnetic Stimulation". In NeuroStar TMS Therapy, TMS is delivered by the NeuroStar TMS System as powerful magnetic field pulses. NeuroStar TMS Therapy has been shown to be safe and effective in the treatment of patients with depression who have failed to achieve satisfactory improvement from one prior antidepressant medication at or above the minimal effective dose and duration in the current episode. NeuroStar TMS Therapy has not been shown to be effective for the treatment of patients who have failed 2 or more antidepressant medications at or above the minimal effective dose and duration in the current episode or who have had no prior antidepressant treatment. Your physician will use a medication checklist to help determine whether or not your antidepressant medication history makes you a potential candidate for NeuroStar TMS Therapy. Further details on the medication checklist can be obtained from your provider.

NeuroStar TMS Therapy is performed in your doctor's office under his or her care. The treatment is non-invasive and non-systemic which means that it does not involve surgery and does not circulate in the blood stream throughout the body. Treatment with NeuroStar TMS Therapy does not involve anesthesia or sedation, and patients are awake and alert during the treatment session. A typical treatment course consists of 5 treatments per week over a 4-6 week period for a total of 20-30 separate treatment sessions. Each treatment session lasts approximately 40 minutes. You should discuss the number of treatments and treatment schedule with your doctor.

NeuroStar TMS Therapy is not an appropriate treatment for all patients with depression. You should review this patient manual and discuss the information with your doctor in order to determine if NeuroStar TMS Therapy is an appropriate treatment option for you.

How Does NeuroStar TMS Therapy Work?

During treatment with the NeuroStar TMS System, the NeuroStar treatment "coil" is positioned gently on the left front side of the head over a region of the brain called the Left Prefrontal Cortex. By sending short bursts of electricity through the treatment coil, the NeuroStar TMS System generates magnetic fields that turn on and off very rapidly. These magnetic fields are the same type and strength as those used in magnetic resonance imaging (MRI) machines.

The rapidly pulsing magnetic fields that are generated by the NeuroStar go directly through the hair, scalp and skull and create small electric currents in the area of the brain directly under the treatment "coil". The electric currents created in the brain make nerve cells in that region become active.

When Can NeuroStar TMS Therapy Be Used?

Indications for Use

NeuroStar TMS Therapy is indicated for the treatment of Major Depressive Disorder in adult patients who have failed to achieve satisfactory improvement from one prior antidepressant medication at or above the minimal effective dose and duration in the current episode.

When Should NeuroStar TMS Therapy Not Be Used?

NeuroStar TMS Therapy delivers a magnetic field that could cause any metal objects that are near the device to move or to get hot.

NeuroStar TMS Therapy should not be used in patients who have magnetic-sensitive metals implanted in their head or within 12 inches of the NeuroStar treatment coil.

NeuroStar TMS Therapy should not be used in patients who have an implanted device that may not properly function in the presence of the NeuroStar TMS System, even if the device is located outside this (12 inch) distance.

Your doctor will ask you to list any metal devices or objects in your head or body in order to determine if those devices could be affected by the NeuroStar TMS System. Use of NeuroStar TMS Therapy in the presence of these objects could result in serious injury or death.

Standard amalgam dental fillings are not affected by the magnetic field and are acceptable in patients being considered for treatment with NeuroStar TMS Therapy.

Effectiveness of NeuroStar TMS Therapy

The effectiveness of Neurostar TMS Therapy for the treatment of depressed patients - who failed to achieve satisfactory improvement from one prior antidepressant medication at or above the minimal effective dose and duration in the current episode - was demonstrated in a retrospective analysis of a 6 week clinical trial. In clinical trials, half of the patients had already received 4 or more antidepressant medication treatment attempts in their current episode of depression, but only one antidepressant medication had been given at a high enough dose for a long enough period of time that it would have been likely to be effective. A retrospective analysis was done for this population because the original study included patients who had failed to achieve satisfactory improvement from one to four antidepressants medications, and failed to show that the device was effective in the overall group.

This trial had one group treated with the NeuroStar TMS device, while another group received an inactive treatment. One hundred sixty-four patients were assigned in a random fashion to one of these two groups and received 6 weeks of treatment

The primary endpoint was the change from baseline (i.e., the starting score before treatment) in a standard scale for measuring depression symptoms, known as the (Montgomery-Asberg Depression Rating Scale (MADRS). The average baseline score in the patient group assigned to treatment with the NeuroStar TMS device was 32 points, and in the group assigned to treatment with the inactive device was 33 points.

At the end of 4 weeks, the group treated with the NeuroStar TMS device improved an average of 7.1 points (an average reduction in score of 22.1%), while the group treated with the inactive device improved an average of 2.1 points (an average reduction in score of 9%). This difference was statistically significant.

Between weeks 4 and 6, patients could leave the study if they were not responding. The overall discontinuation rate through week 4 across both treatment groups was 19 of 164 patients or 11.6%. For each treatment group, the discontinuation rate through week 4 was 11 of 88 patients, or 12.5%, in the active TMS treatment group, and 8 of 76 patients, or 10.5%, in the inactive treatment group. At 4 weeks, patients who did not respond to TMS therapy were allowed to exit the study. Twenty-three of 88 (26.1%) patients in the active TMS group and 32 of 76 (42.1%) patients in the inactive treatment group exited the study after week 4 due to lack of efficacy. An additional 7 patients exited the study after week 4 across both treatment groups for reasons unrelated to efficacy. Therefore, the cumulative overall discontinuation rate through week 6 across both treatment groups was 81 of 164 patients or 49.4%.

Following completion of this therapy all patients received ongoing treatment with an antidepressant medication. Relapse into depression is likely without follow-up treatment. You should discuss long-term treatment planning with your doctor.

Further details on the study can be obtained from your treating provider.

Limitations of NeuroStar TMS Therapy

NeuroStar TMS Therapy has been shown to be safe and effective in the indicated patient population only. Care should be taken to ensure that NeuroStar TMS Therapy is the right treatment for you.

Most patients who benefit from NeuroStar TMS Therapy experience results by the fourth week of treatment. Some patients may experience results in less time. NeuroStar TMS Therapy was administered for six weeks so it is unknown whether longer treatment would be effective for your depression.

As with any antidepressant, there is a risk of worsening of your depression during treatment with NeuroStar TMS Therapy. Contact your doctor immediately if symptoms persist or worsen.

The device was shown to be safe and effective in patients who had been able to stop taking their antidepressant medications. If you feel that your depression worsens when you stop your antidepressant medications, contact your doctor immediately.

This therapy has not been demonstrated to be safe and effective for patients who have a suicide plan.

NeuroStar TMS Therapy Safety Information

The safety of NeuroStar TMS Therapy was determined in clinical trials of 323 patients with moderate to severe Major Depressive Disorder who ranged in age from 18 to 70 years, and who had failed to achieve satisfactory improvement from prior antidepressant treatment.

- Less than 5% of all patients dropped out of the clinical trial because of side effects from the treatment.
- There were no deaths or seizures in patients who took part in the clinical trial.
- Systemic side effects such as weight gain, sexual problems, stomach problems, sleepiness, and dry mouth were not observed.
- Tests of memory function during treatment showed no change during the clinical trial.

This section provides information about adverse events observed with the use of the NeuroStar TMS System in clinical trials.

Warnings and precautions to be considered prior to receiving NeuroStar TMS Therapy are also provided and should be discussed with your doctor to determine what, if any, precautions should be taken during your treatment with NeuroStar TMS Therapy.

Worsening Depression or Suicidality

Depression is a serious medical illness. Not all patients treated with an antidepressant will get better with treatment. Because of this, some patients may experience worsening of their depression before they begin to see improvement of their symptoms. NeuroStar TMS Therapy may require up to 4-6 weeks of treatment before symptom improvement occurs and has not been studied in patients who need rapid improvement in their depression symptoms.

You should inform your doctor if your symptoms do not improve, or if they get worse. If you have thoughts of death or suicide you should immediately discuss this with your doctor. Your doctor will determine whether NeuroStar TMS Therapy should be discontinued and, if so, what other treatment options are available. You should be carefully monitored for worsening symptoms, signs or symptoms of suicidal behavior and/or unusual behavior. Families and caregivers should also be aware of the need to observe the patient and notify the treatment provider if symptoms worsen.

Risk of Ineffective Therapy

NeuroStar TMS Therapy is indicated for patients who have failed to receive satisfactory improvement from one prior antidepressant medication given at a high enough dose for a long enough period of time to be effective. In clinical trials, patients had also received additional antidepressant medication attempts in their current episode of depression, but only one antidepressant had been given at the adequate dose and duration for it to be effective.

The clinical trial included patients who had failed to achieve satisfactory improvement from one to four antidepressant medications. The device was not demonstrated to be effective for patients who had failed to benefit from two or more antidepressant medications. Therefore, it is important that your prior antidepressant medication history is carefully evaluated by your doctor to determine if NeuroStar TMS Therapy is right for you.

Other Risks

Seizures (sometimes called convulsions or fits) have been reported with the use of TMS devices. No seizures were observed with use of the NeuroStar TMS System in clinical trials that included over 10,000 treatment sessions. Since the introduction of the NeuroStar TMS System into clinical practice, seizures have been rarely reported. The estimated risk of seizure under ordinary clinical use is approximately 1 in 30,000 treatments (0.003% of treatments) or 1 in 1000 patients (0.1% of patients). You should discuss with your doctor if you have had a seizure, or if you have a medical condition that you have been told may put you at increased risk of having a seizure. Your doctor will decide if it is appropriate for you to receive NeuroStar TMS Therapy.

The safety and effectiveness of NeuroStar TMS Therapy has not been established in the following patient populations or clinical conditions through a controlled clinical trial.

- Patients who have failed to receive benefit from 2 or more antidepressant medications given at or above minimal effective dose and duration in the current episode or patients who have had no prior antidepressant medication.
- Patients who can not tolerate withdrawal of antidepressant medications.
- Patients who have a suicide plan or have recently attempted suicide
- Patients with seasonal affective disorder
- Patients younger than 22 years of age or older than 70 years of age
- Patients with history of substance abuse, obsessive compulsive disorder or post-traumatic stress disorder. Patients with a psychotic disorder, including schizoaffective disorder, bipolar disease, or major depression with psychotic features.
- Patients with neurological conditions that include a history of seizure, cerebrovascular disease, dementia, increased intracranial pressure, movement disorders, having a history of repetitive or severe head trauma, or with primary or secondary tumors in the CNS.
- Patients with metal in or around the head, including metal plates, aneurysm coils, cochlear implants, occular implants, deep brain stimualtion devices and stents.
- Patients with implants controlled by physiological signals, including pacemakers, implantable cardioverter defibrillators, and vagus nerve stimulators.
- Patients with major depressive disorder who have failed to receive clinical benefit from ECT or VNS.
- Patients who are pregnant or nursing

The NeuroStar TMS System produces a loud click with each magnetic pulse, patients treated with the NeuroStar TMS System must always wear earplugs or similar hearing protection devices with a rating of 30dB or higher of noise reduction during treatment. In clinical trials, NeuroStar TMS Therapy had no effect on hearing when earplugs were used.

The long term effectiveness of NeuroStar TMS Therapy for treating depression has not been evaluated. In clinical studies, NeuroStar TMS Therapy was safely tolerated in patients for periods up to 12 continuous weeks, and no negative effects of treatment were seen during a 24-week follow-up period. However, effectiveness has not been established for treatment beyond a single six week course.

Longer term effects of exposure to the NeuroStar TMS System magnetic field are not known. However, exposure to other devices (such as MRI scanners) with the same type and strength of magnetic fields produced by the NeuroStar TMS System coil are not associated with significant short-term or long-term safety concerns.

Adverse Events

Temporary pain or discomfort at the area of the head where the treatment coil was placed was reported in about a third of patients who were treated with the NeuroStar TMS System, while this occurred in less than 5% of patients treated with sham (placebo), suggesting that this is a direct effect of NeuroStar TMS Therapy.

Inform your doctor if you experience discomfort during treatment. Your doctor can decrease the NeuroStar TMS dose or move the NeuroStar TMS coil slightly to ease or eliminate the discomfort. Treatment site discomfort went away rapidly with time, usually getting better within the first week of treatment.

Headaches were reported by about half of the patients who took part in the clinical trial regardless of whether they were treated with real TMS or with the sham (placebo) treatment. In general, the headaches got better over time, and could be relieved by using common over-the-counter pain medications such as acetaminophen.

The following table presents a summary of adverse events that occurred in the clinical trial in ≥5% or more of the patients treated with NeuroStar TMS Therapy and at least twice as often as was seen in patients treated with sham (placebo) treatment. Safety information is provided from all patients who had been treated in the clinical study

Table 1. Adverse Events Reported with NeuroStar TMS Therapy:
(Study 101, Incidence with Active TMS > 5% and at Least Twice the Rate with Sham Treatment)

Event Type	Active TMS (N=165 Patients) N%	Sham TMS (N=158 Patients) N%
Eye pain	10 (6.1)	3 (1.9)
Toothache	12 (7.3)	1 (0.6)
Application site discomfort	18 (10.9)	2 (1.3)
Application site pain	59 (35.8)	6 (3.8)
Facial pain	11 (6.7)	5 (3.2)
Muscle twitching	34 (20.6)	5 (3.2)
Pain of skin	14 (8.5)	1 (0.6)

For more information on TMS, visit the Neuronetics Web site:
http://www.NeuroStarTMS.com