

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of transcutaneous electrical stimulation of the trigeminal nerve for ADHD

Attention deficit hyperactivity disorder (ADHD) can cause restlessness, hyperactivity and difficulty focusing on tasks. In this procedure, which is done at home, a single-use electrode patch is stuck to the forehead at bedtime. Wires connect the patch to a stimulator that sends small electrical pulses through the skin (transcutaneous) during sleep. The pulses stimulate the trigeminal nerve, which connects to parts of the brain that are thought to control attention. Treatment usually lasts for about 4 weeks. The aim is to reduce ADHD symptoms.

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Abbreviations

Word or phrase	Abbreviation
Attention deficit hyperactivity disorder	ADHD
ADHD-IV Rating Scale	ADHD-RS
Affective Reactivity Index	ARI
Analysis of variance	ANOVA
Attention Network Test	ANT
Behavioural Rating Inventory of Executive Functioning	BRIEF
Child Behaviour Checklist	CBCL
Children's Depression Inventory	CDI
Children's Depression Rating Scale	CDRS
Clinical Global Impressions-Improvement	CGI-I
Clinical Global Impressions-Severity	CGI-S
Children's Sleep Habits Questionnaire	CSHQ
Columbia–Suicide Severity Rating Scale	C-SSRS
Electroencephalogram	EEG
Intelligence quotient	IQ
Multidimensional Anxiety Scale for Children	MASC
Number-needed-to-treat	NNT
Randomised controlled trial	RCT
Standard deviation	SD
Spatial Working Memory	SWM
Trigeminal nerve stimulation	TNS
Wechsler Intelligence Scale for Children	WISC-4
Wide Range Achievement Test	WRAT

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety

and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and professional opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in April 2022 and updated in August 2022.

Procedure name

- Transcutaneous electrical stimulation of the trigeminal nerve for ADHD

Professional societies

- Royal College of Psychiatrists
- British Psychological Society
- Royal College of Paediatrics and Child Health
- Association for Child and Adolescent Mental Health

Description of the procedure

Indications and current treatment

ADHD is a heterogeneous disorder characterised by the core symptoms of hyperactivity, impulsivity and inattention, which are judged excessive for the person's age or level of overall development. Symptoms are usually evident in childhood and may persist into adulthood.

Treatment for ADHD may be non-pharmacological, pharmacological, or a combination of both. Non-pharmacological treatment includes cognitive behavioural therapy and parent-training programmes (for parents of children and young people with ADHD). Pharmacological treatment includes central nervous system stimulants such as methylphenidate and amphetamines.

What the procedure involves

In this procedure, an external TNS device is worn on the clothes and attached by wires to a single-use adhesive patch which is worn overnight. The patch contains 2 electrodes placed over the left and right V1 branches of the trigeminal nerve on the forehead. The stimulator bilaterally stimulates the trigeminal nerve for approximately 8 hours. For children, parents or carers attach the device. Treatment duration may vary – a clinical response may take several weeks, and continued therapy may be needed.

The mechanism of action is not completely understood. The trigeminal nerve connects to regions of the brain that may be associated with selective maintenance of attention, and it is thought that its stimulation improves the symptoms of ADHD.

Outcome measures

ADHD-specific symptom and behavioural measures

ADHD-RS

The ADHD-RS is an 18-item questionnaire that measures the severity of ADHD symptoms. The scale consists of 2 subscales: inattention (9 items) and hyperactivity-impulsivity (9 items). Higher scores indicate worse symptoms.

Conners Global Index

The Conners Global Index is a 10-item questionnaire that assesses the severity of common ADHD symptoms.

Other symptom and behavioural measures

ARI

The ARI is a 7-item questionnaire that assesses irritability across 3 aspects: threshold for an angry reaction; frequency of angry feelings/behaviours; and duration of such feelings/behaviours.

BRIEF

The BRIEF is an 86-item questionnaire that assesses impairment of executive function. The BRIEF includes items on behavioural regulation ('inhibit' – control impulses, 'shift' – move from 1 activity to another, and 'emotional control') and metacognition ('initiate' – begin activity, 'working memory', 'planning and organisation', and 'monitor' – assess own performance).

CBCL

The CBCL is a questionnaire used to assess emotional, behavioural, and social problems. The CBCL contains items across 8 categories: anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behaviour, and aggressive behaviour.

CDI

The CDI is a 27-item questionnaire that assesses the presence and severity of depression. Each item consists of 3 statements graded in order of increasing severity from 0 to 2. A higher CDI score means a higher depressive state.

CDRS

The CDRS is a 17-item scale that assesses the severity of depression and change in depressive symptoms. Items range from 1 to 5 or 1 to 7. A score of 40 or more is indicative of depression, whereas a score of 28 or less is often used to define remission.

CGI**CGI-I**

The CGI-I is a 1-item questionnaire that allows clinicians to compare the patient's overall clinical condition to baseline. The rating ranges from 1: 'very much improved since the initiation of treatment', to 7: 'very much worse since the initiation of treatment'.

CGI-S

The CGI-S is a 1-item questionnaire that allows clinicians to rate the severity of illness. The rating ranges from 1: 'normal' to 7: 'Extremely ill'.

CSHQ

The CSHQ is a 45-item questionnaire that assesses sleep behaviour in children. The CSHQ contains 8 subscales: Bedtime Resistance, Sleep Onset Delay, Sleep Duration, Sleep Anxiety, Night Wakings, Parasomnias, Sleep-Disordered Breathing, Daytime Sleepiness.

C-SSRS

The C-SSRS is a questionnaire that assesses the severity of suicidal ideation and suicidal behaviour. The C-SSRS contains items across the following domains: severity of ideation, intensity of ideation, behaviour, and lethality.

MASC

The MASC is a 39-item questionnaire that assesses the presence of symptoms related to anxiety disorders. The MASC consists of 4 subscales: physical symptoms, social anxiety, harm avoidance, and separation anxiety.

Cognitive functioning measures

ANT

The ANT is a task designed to test 3 attentional networks: alerting, orienting, and executive control.

Flanker test

The Flanker test is a test of interference inhibition that assesses ability to suppress incorrect responses in a particular context.

SWM

The SWM assesses retention and manipulation of visuospatial memory.

WISC-4

The WISC-4 is an IQ test for children. Subtests include the Digit Span subtest, in which children are asked to repeat increasingly long strings of numbers forward and backwards in the same order as presented aloud by an examiner.

WRAT

The WRAT assesses reading, comprehension, spelling, and mathematics abilities.

Efficacy summary

ADHD-specific symptom and behavioural measures

ADHD-RS

In an RCT of 62 children (32 who had active treatment and 30 who had sham treatment), total ADHD-RS scores decreased from 32.1 (SD 6.3) at baseline to 23.39 (SD 7.88) at week 4 in the active treatment group. In the sham group, ADHD-RS total scores decreased from 32.8 (SD 6.2) at baseline to 27.50 (SD 8.08) at week 4. There was a statistically significant group-by-time interaction, indicating a differential treatment effect between the groups ($F=8.12$, $df=1/228$, $p=0.005$). Estimated Cohen's d at week 4 was 0.50, suggesting a medium treatment effect. After treatment discontinuation for 1 week, week 5 ADHD-RS total scores were 25.52 (SD 7.84) and 29.11 (SD 7.79; McGough, 2019).

In a secondary analysis of data from McGough (2019), 51 participants were divided into responders ($n=25$) and non-responders ($n=26$). Twenty people randomised to sham crossed over after the initial 4-week treatment period and

were included in this analysis (Loo, 2021). Responders were those with a 25% or greater reduction in ADHD-RS total score from baseline to end of treatment. Responders and non-responders were then compared to determine if any measures were predictive of treatment response. The following measures were statistically significant predictors of end of treatment ADHD-RS total score:

- CBCL sluggish cognitive tempo ($\beta=-0.40$, 95% CI -0.68 to -0.14, $p=0.004$)
- BRIEF working memory ($\beta=-0.40$, 95% CI -0.70 to -0.14, $p=0.004$), planning ($\beta=-0.36$, 95% CI -0.51 to -0.08, $p=0.01$) and metacognition ($\beta=-0.32$, 95% CI -0.57 to -0.04, $p=0.02$)
- EEG right-frontal theta ($\beta=0.43$, 95% CI 0.2 to 1.1, $p=0.005$) and alpha band power ($\beta=0.45$, 95% CI 0.3 to 1.2, $p=0.003$).

Statistically significant group-by-time interactions indicated that TNS responders showed treatment-related improvement in BRIEF scores that were not observed in non-responders:

- metacognition ($F[1,45]=38.6$, $p<0.001$, partial eta squared=0.47: large effect size)
- working memory ($F[1,45]=41.1$, $p<0.001$, partial eta squared=0.48: large effect size)
- initiate ($F[1,45]=18.3$, $p<0.001$, partial eta squared=0.29: large effect size)
- planning ($F[1,45]=36.7$, $p=0.001$, partial eta squared=0.51: large effect size)
- organisation ($F[1,45]=19$, $p=0.001$, partial eta squared=0.30: large effect size).

Treatment-related changes in these BRIEF variables and ADHD-RS total scores were very strongly correlated, with Pearson r 's ranging from 0.65 (planning, $p=6.5E-7$) to 0.79 (working memory, $p=3.0E-11$).

In an open-label trial of 22 children, there was a statistically significant decrease in ADHD-RS scores from baseline to week 8 ($F=42.5$, $df=2/40$, $p<0.0001$; McGough, 2015).

Conners Global Index

In the RCT of 62 children, there were no statistically significant group-by-time interactions observed for Conners Global Index scores (McGough, 2019).

Other symptom and behavioural measures

BRIEF

In the RCT of 62 children, there were no statistically significant group-by-time interactions observed for BRIEF scores (McGough, 2019).

In the open-label trial of 22 children, there were statistically significant improvements in 7 of 11 BRIEF subscales, including inhibit ($p=0.004$), BRI index ($p=0.03$), working memory, ($p=0.0004$), plan/organise ($p=0.004$), monitor ($p=0.003$), MI index ($p=0.0008$), and global exec composite ($p=0.002$). There were no statistically significant improvements in 4 of 11 BRIEF subscales: shift, emotional control, initiate and organisation materials (all $p>0.05$; McGough, 2015).

CGI-I

In the RCT of 62 children, there was a statistically significantly greater improvement in CGI-I score with active treatment compared with sham treatment ($X^2=8.75$, $df=1/168$, $p=0.003$). Improvement rates for active compared with sham treatment were 25% versus 13%, 34% versus 15%, 47% versus 12%, and 52% versus 14%, respectively, based on raw CGI-I at weeks 1, 2, 3, and 4, respectively. The number needed to treat based on CGI-I at week 4 was 3 (McGough, 2019).

In the open-label trial of 22 children, there was a statistically significant decrease in CGI-I scores from baseline to week 8 ($F=6.89$, $df=8/140$, $p<0.0001$). A total of 64% children met the response criteria (improved or very much improved) at week 4, and 71% met these criteria at week 8 (McGough, 2015).

CSHQ

In the RCT of 62 children, there were no statistically significant group-by-time interactions observed for CSHQ scores (McGough, 2019).

In the open-label trial of 22 children, there were statistically significant improvements in CSHQ scores for sleep anxiety ($p=0.03$), total bedtime problems ($p<0.0001$), and total sleep problems ($p<0.0001$) from baseline to 8-week follow up. There were no statistically significant improvements in CSHQ scores for bedtime resistance, sleep onset delay, sleep duration, night wakings, parasomnias, disordered breathing, daytime sleepiness, total sleep behaviour problems, and total problems daytime sleepiness (all $p\geq 0.05$; McGough, 2015).

ARI

In the RCT of 62 children, there were no statistically significant group-by-time interactions observed for ARI scores (McGough, 2019).

Anxiety and depression

In the RCT of 62 children, there were no statistically significant group-by-time interactions observed for MASC or CDRS scores (McGough, 2019).

In the open-label trial of 22 children, there were statistically significant improvements in dimensional CDI scores ($F=3.40$, $df=2/38$, $p=0.04$), but no statistically significant changes in self-reported MASC scores ($p=0.82$). (McGough, 2015).

Cognitive measures

ANT

In the open-label trial of 22 children, there was a statistically significant decrease in ANT incongruent reaction time from baseline to 8-week follow up ($p=0.006$). There were no statistically significant changes in ANT neutral reaction time, neutral accuracy, congruent reaction time, congruent accuracy or incongruent accuracy (all $p>0.05$; McGough, 2015).

SWM

In the open-label trial of 22 children, there were no statistically significant changes in SWM subscales from baseline to 8-week follow up (McGough, 2015).

Safety summary

Cognitive functioning

Speech

In the open-label trial of 24 children, there were 2 (8%) cases of difficulty finding words and 2 (8%) cases of slurred speech (McGough, 2015).

Diminished mental acuity/sharpness

In the open-label trial of 24 children, there were 3 (13%) cases of diminished mental acuity/sharpness (McGough, 2015).

Poor memory

In the open-label trial of 24 children, there were 11 (46%) cases of poor memory. The authors note that this is a symptom of ADHD (McGough, 2015).

Trouble concentrating

In the open-label trial of 24 children, there were 22 (92%) cases of trouble concentrating and 17 (71%) cases of poor concentration. The authors note that these are symptoms of ADHD (McGough, 2015).

Slurred speech

In the open-label trial of 24 children, there were 2 (8%) cases of slurred speech (McGough, 2015).

Sleep**Trouble sleeping**

In the RCT of 62 children, there were 6 (19%) cases of trouble sleeping in the active arm and 5 (17%) cases in the sham arm (McGough, 2019).

In the open-label trial of 24 children, there were 7 (29%) cases of trouble sleeping (McGough, 2015).

Nightmares

In the RCT of 62 children, there were 2 (6%) cases of nightmares in the active arm and 1 (3%) case in the sham arm (McGough, 2019).

In the open-label trial of 24 children, there were 5 (21%) cases of nightmares (McGough, 2015).

Emotional**Apathy**

In the RCT of 62 children, there were 2 (6%) cases of apathy in the active arm and 2 (7%) cases in the sham arm (McGough, 2019).

In the open-label trial of 24 children, there were 3 (13%) cases of apathy (McGough, 2015).

Feeling drowsy

In the RCT of 62 children, there were 7 (22%) cases of drowsiness in the active arm and 4 (13%) cases in the sham arm (McGough, 2019).

In the open-label trial of 24 children, there were 5 (21%) cases of drowsiness (McGough, 2015).

Feeling nervous

In the open-label trial of 24 children, there were 14 (58%) cases of feeling nervous (McGough, 2015).

Feeling strange or unreal

In the open-label trial of 24 children, there were 2 (8%) cases of feeling strange or unreal (McGough, 2015).

Other symptoms**Lightheaded**

In the RCT of 62 children, there was 1 (3%) case of lightheadedness in the active arm and 0 cases in the sham arm (McGough, 2019).

Fatigue

In the RCT of 62 children, there were 4 (13%) cases of fatigue in the active arm and 1 (3%) case in the sham arm (McGough, 2019).

In the open-label trial of 24 children, there were 5 (21%) cases of weakness or fatigue (McGough, 2015).

Tingling

In the RCT of 62 children, there was 1 (3%) case of tingling in the active arm and 0 cases in the sham arm (McGough, 2019).

Headache

In the RCT of 62 children, there were 4 (13%) cases of headache in the active arm and 0 cases in the sham arm (McGough, 2019).

In the open-label trial of 24 children, there were 3 (13%) cases of headache (McGough, 2015).

Hyperactive

In the RCT of 62 children, there were 13 (41%) cases of hyperactivity in the active arm and 19 (63%) cases in the sham arm (McGough, 2019).

In the open-label trial of 24 children, there were 17 (71%) cases of trouble sitting still. The authors note that this is a symptom of ADHD (McGough, 2015).

Irritability

In the open-label trial of 24 children, there were 10 (42%) cases of irritability (McGough, 2015).

Stuffy nose

In the RCT of 62 children, there were 5 (16%) cases of stuffy nose in the active arm and 6 (20%) cases in the sham arm (McGough, 2019).

In the open-label trial of 24 children, there were 6 (24%) cases of stuffy nose (McGough, 2015).

Drooling

In the open-label trial of 24 children, there were 2 (8%) cases of drooling (McGough, 2015).

Muscle cramps

In the RCT of 62 children, there was 1 (3%) case of muscle cramps in the active arm and 1 (3%) case in the sham arm (McGough, 2019).

Muscle twitch

In the open-label trial of 24 children, there were 2 (8%) cases of muscle twitch (McGough, 2015).

Rapid heartbeat

In the RCT of 62 children, there was 1 (3%) case of rapid heartbeat in the active arm and 0 cases in the sham arm (McGough, 2019).

Out of breath

In the RCT of 62 children, there was 1 (3%) case of breathlessness in the active arm and 1 (3%) case in the sham arm (McGough, 2019).

Excess sweating

In the RCT of 62 children, there was 1 (3%) case of frequent sweating in the active arm and 1 (3%) case in the sham arm (McGough, 2019).

In the open-label trial of 24 children, there were 2 (8%) cases of excess sweating (McGough, 2015).

Itching

In the RCT of 62 children, there was 1 (3%) case of itching in the active arm and 0 cases in the sham arm (McGough, 2019).

Tooth pain

In the RCT of 62 children, there was 1 (3%) case of tooth pain in the active arm and 0 cases in the sham arm (McGough, 2019).

Clenching teeth

In the RCT of 62 children, there were 4 (13%) cases of clenching teeth in the active arm and 2 (7%) cases in the sham arm (McGough, 2019).

Skin whitening/discoloration

In the RCT of 62 children, there was 1 (3%) case of skin whitening/discoloration in the active arm and 1 (3%) case in the sham arm. This was attributed to removal of the electrodes (McGough, 2019).

Skin rash

In the RCT of 62 children, there were 3 (9%) cases of skin rash in the active arm and 0 cases in the sham arm (McGough, 2019).

Frequent urination

In the RCT of 62 children, there were 2 (6%) cases of frequent urination in the active arm and 0 cases in the sham arm (McGough, 2019).

Bronchitis

In the RCT of 62 children, there was 1 (3%) case of bronchitis in the active arm and 0 cases in the sham arm (McGough, 2019).

Upper respiratory infection

In the RCT of 62 children, there were 3 (9%) cases of upper respiratory infections in the active arm and 3 (10%) cases in the sham arm (McGough, 2019).

Rhinitis

In the RCT of 62 children, there were 2 (6%) cases of rhinitis in the active arm and 2 (6%) cases in the sham arm (McGough, 2019).

Vomiting

In the RCT of 62 children, there was 1 (3%) case of vomiting in the active arm and 0 cases in the sham arm (McGough, 2019).

Gastrointestinal**Nausea**

In the RCT of 62 children, there were 2 (6%) cases of nausea in the active arm and 0 cases in the sham arm (McGough, 2019).

Stomach ache

In the RCT of 62 children, there were 4 (12%) cases of stomach ache in the active arm and 2 (6%) cases in the sham arm (McGough, 2019).

In the open-label trial of 24 children, there were 2 (8%) cases of stomach discomfort (McGough, 2015).

Weight gain

In the open-label trial of 24 children, there were 2 (8%) cases of weight gain (McGough, 2015).

Constipation

In the RCT of 62 children, there were 3 (9%) cases of constipation in the active arm and 2 (7%) cases in the sham arm (McGough, 2019).

Decreased appetite

In the RCT of 62 children, there was 1 (3%) case of decreased appetite in the active arm and 1 (3%) case in the sham arm (McGough, 2019).

Poor appetite

In the RCT of 62 children, there was 1 (3%) case of poor appetite in the active arm and 0 cases in the sham arm (McGough, 2019).

Increased appetite

In the RCT of 62 children, there were 6 (19%) cases of increased appetite in the active arm and 2 (7%) cases in the sham arm (McGough, 2019).

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, professional experts are asked about anecdotal adverse events (events that they have heard about) and about theoretical adverse events (events that they think might possibly occur, even if they have never happened).

For this procedure, the professional experts did not list any anecdotal or theoretical adverse events.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to transcutaneous electrical stimulation of the trigeminal nerve for ADHD. The following databases were searched, covering the period from their start to 23 February 2022: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched. No language restriction was applied to the searches (see the [literature search strategy](#)). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The [inclusion criteria](#) were applied to the abstracts identified by the literature search. If selection criteria could not be determined from the abstracts the full paper was retrieved.

Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	<p>Clinical studies were included. Emphasis was placed on identifying good quality studies.</p> <p>Abstracts were excluded if no clinical outcomes were reported, or if the paper was a review, editorial, or a laboratory or animal study.</p> <p>Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.</p>
Patient	People with ADHD.
Intervention/test	Transcutaneous electrical stimulation of the trigeminal nerve.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 76 people from 1 RCT (with 1 secondary analysis) and 1 open-label trial.

Summary of key evidence on transcutaneous electrical stimulation of the trigeminal nerve for ADHD

Study 1 McGough JJ (2019)

Study details

Study type	RCT
Country	US
Recruitment period	Not reported
Study population and number	n=62 (32 active treatment; 30 sham) Children aged 8 to 12 with ADHD.
Age and sex	Active group: mean 10.3 years; 60% male
Patient selection criteria	<p>Inclusion criteria: Children aged 8 to 12 years with Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) ADHD, based on the Kiddie Schedule for Affective Disorders and Schizophrenia and clinical interview, minimum total of 24 on the clinician-administered parent ADHD-IV Rating Scale, baseline CGI-S Score of 4 or more, estimated full-scale IQ of 85 or more, and able to cooperate with electroencephalography and other study procedures.</p> <p>Exclusion criteria: current major depression or autism spectrum disorder, lifetime psychosis, mania, seizure disorder, or head injury with loss of consciousness, or baseline suicidality.</p>
Technique	<p>Trigeminal nerve stimulation (Monarch eTNS System, NeuroSigma) nightly during sleep for 4 weeks. Children were followed for an additional week without treatment to analyse whether the treatment effect persisted.</p> <p>Children were medicine free for at least 1 month prior to participation and remained so throughout the trial.</p> <p>Parents applied patches across their child's forehead to provide bilateral stimulation of V1 trigeminal branches for approximately 8 hours nightly. Patches were removed each morning. The active condition used a 120-Hz repetition frequency, with 250-μs pulse width, and a duty cycle of 30 seconds on/30 seconds off. Stimulator current settings between 2 and 4 milli-amperes (range: 0 to 10) were established at baseline by titration. Each night parents turned on the device, pressed the 'up' button until the stimulation was uncomfortable or until the device reached the maximum current, and then pressed 'down' to reduce it by one 0.1mA step.</p>
Follow up	5 weeks
Conflict of interest/source of funding	<p>Conflict of interest: One author had served as part of the management team of NeuroSigma, Inc. and has been allocated stock options.</p> <p>Source of funding: Supported by National Institute of Mental Health grant. Study devices and some materials were provided by NeuroSigma, Inc. in response to an investigator-initiated request.</p>

Analysis

Follow up issues: Outcomes were assessed weekly or at baseline and week 4 and 5. One person randomised to the sham group withdrew after 3 weeks. One additional participant in each group withdrew between weeks 4 and 5. qEEG data for 3 participants were excluded due to excessive movement artifact.

Study design issues: This RCT assessed the outcomes of TNS for children with ADHD. People were recruited through community advertisements and internet postings. Randomisation was 1:1, using random block lengths of 4 and 6, to active or sham TNS. Participants, parents, and staff were blinded (except for 1 staff member who managed the study devices). To maintain the blind, active and sham systems were identical in appearance and operation, and participants were informed via a scripted presentation that ‘pulses may come so fast or so slowly that the nerves in the forehead might or might not detect a sensation’. Outcomes included (see [Outcome measures](#) for full descriptions):

- Primary: ADHD-RS – clinician-completed, based on clinical information and parental interview.
- Secondary behavioural:
 - Clinician-completed: CGI-I, CDRS.
 - Parent-completed: BRIEF Scales, Conners Global Index, CSHQ, ARI, and MASC.
 - Teacher-completed: Conners Global Index.
- qEEG
- Safety: including adverse events, parent-completed Side Effects Rating Scales, and clinician-completed C-SSRS.

For statistical analysis, a general linear mixed model was used with treatment group (active vs. sham), time (in weeks), and group-by-time interactions to test for differential treatment effects as primary predictors, along with subject level random intercepts. This accounts for repeated measures and for missing data. Categorical outcomes were assessed using chi square. Effect size differences between groups were estimated using Cohen’s *d* and NNT. For Cohen’s *d*, cut-off values for small, medium, and large effects were defined as 0.2, 0.5, and 0.8, respectively. For NNT, small, medium, and large effects were defined as 9, 4, and 2, respectively. ADHD-RS was identified as the primary outcome *a priori*. However, there was no hierarchical testing of endpoints or adjustment for multiple comparisons. $p < 0.05$ was considered statistically significant.

Study population issues: There were no statistically significant differences between the groups for age, sex, race/ethnicity, height, weight, vital signs, IQ, ADHD subtype, or baseline behavioural ratings.

Key efficacy findings

ADHD-RS

Number of people analysed: 32 active treatment; 30 sham

- In the active treatment group, ADHD-RS total scores decreased from 32.1 (SD 6.3) at baseline to 23.39 (7.88) at week 4. In the sham group, ADHD-RS total scores decreased from 32.8 (SD 6.2) at baseline to 27.50 (8.08) at week 4.
- Total ADHD-RS scores showed statistically significant group-by-time interaction, indicating a difference in the treatment groups ($F=8.12$, $df=1/228$, $p=0.005$).

- There was no statistically significant group-by-time² ('time²' represents the change in slope after the initial week) interaction, indicating an equal levelling-off of improvement following week 1.
- Estimated Cohen's *d* at week 4 was 0.50, suggesting a medium treatment effect.
- Week 4 scores in active vs. sham groups were 23.39 (7.88) and 27.50 (8.08) respectively. After discontinuation, week 5 scores were 25.52 (7.84) and 29.11 (7.79), respectively.
 - The time effect was statistically significant ($F=6.23$, $df=1/57$, $p=0.02$), with a non-statistically significant trend for group differences ($F=4.18$, $df=1/57$, $p=0.05$), but no statistically significant group-by-time interaction ($F=0.12$, $df=1/57$, $p=0.73$), suggesting both groups deteriorated at similar rates.
 - Cohen's *d* at Week 5 was 0.46, suggesting maintenance of a medium treatment effect 1 week after treatment cessation.

CGI-I

Number of people analysed: 32 active treatment; 30 sham

- There was a statistically significant greater improvement in CGI-I scores with active treatment compared to sham ($\chi^2=8.75$, $df=1/168$, $p=0.003$).
 - Improvement rates for active vs. sham were 25% vs. 13%, 34% vs. 15%, 47% vs. 12%, and 52% vs. 14% based on raw CGI-I at weeks 1, 2, 3, and 4.
- NNT based on CGI-I at week 4 was 3.
- After discontinuation, Week 5 CGI-I ratings showed 13% improved in active vs. 7% improved in sham groups compared to baseline ($\chi^2=0.53$, $df=1$, $p=0.46$).

Other outcome measures

Number of people analysed: 32 active treatment; 30 sham

- Statistically significant group-by-time interactions were not observed for the parent-completed Conners Global Index, MASC-Parent Report, MASC Child Report, CDRS, BRIEF, CSHQ, teacher-completed Conners Global Index, and ARI scales.

qEEG

Number of people analysed: 30 active treatment; 26 sham

- There were statistically significant group-by-time effects for frequency bands in the right frontal (F4 delta, theta, beta, gamma) and frontal midline (Fz gamma) channels.
- Week 4 changes in right frontal (F4 theta, beta bands) and frontal midline (Fz Gamma 1) regions were statistically significantly associated with changes in ADHD-RS total and hyperactive/impulsive scores (r 's range $-.34$ to $-.41$).

Key safety findings

Number of people analysed: 32 active treatment; 30 sham

There were no serious adverse events in either group and no participant withdrew for adverse events.

- C-SSRS showed no responses suggestive of suicidality.
- The following side effects were endorsed on the administered rating scale at some point during the study:

Side Effect	Participants Reporting (%)			
	Active (N=32)		Sham (N=30)	
	n	%	n	%
Trouble sleeping	6	19	5	17
Nightmares	2	6	0	0
Drowsy	7	22	4	13
Hyperactive	13	41	19	63
Fatigue	4	13	1	3
Feels strange	0	0	2	7
Tingling	1	3	0	0
Headache	4	13	0	0
Stuffy nose	5	16	6	20
Muscle cramps	1	3	1	3
Muscle twitch	0	0	2	7
Tremor	0	0	1	3
Slurred speech	0	0	1	3
Rapid heartbeat	1	3	0	0
Out of breath	1	3	1	3
Nausea	1	3	0	0
Stomach ache	2	6	1	3
Constipation	3	9	2	7
Frequent urination	2	6	0	0
Frequent sweating	1	3	1	3
Decreased appetite	1	3	1	3
Increased appetite	6	19	2	7
Skin rash	2	6	0	0
Finding words	0	0	2	7
Apathy	2	6	2	7
Clenching teeth	4	13	2	7

- The following adverse events were spontaneously reported:

Adverse Event	Participants Reporting, n (%)			
	Active (N=32)		Sham (N=30)	
	n	%	n	%
Anxiety	0	0	1	3
Bronchitis	1	3	0	0
Headache	3	9	1	3
Itching	1	3	0	0
Lightheaded	1	3	0	0
Mouth pain	0	0	1	3
Nausea	1	3	0	0
Nightmares	0	0	1	3
Poor appetite	1	3	0	0
Rash	1	3	0	0
Rhinitis	2	6	2	6

Skin whitening/ discoloration	1	3	1	3
Stomach ache	2	6	1	3
Tooth pain	1	3	0	0
Upper respiratory infection	3	9	3	10
Vomiting	1	3	0	0
Wrist sprain	0	0	1	3

Study 2 Loo SK (2021)

Study details

Study type	Secondary analysis of McGough, 2019 (Study 1)
Country	US
Recruitment period	Not reported
Study population and number	n=51 (25 responders and 26 non-responders) Children aged 8 to 12 with ADHD.
Age and sex	Responders: mean 10.5 years, 44% male; non-responders: mean 10.1 years; 88% male
Patient selection criteria	As described in McGough, 2019 (Study 1). After the 1-week discontinuation period, participants assigned to sham were given the option to crossover into 4 weeks of open-label active treatment. The sample for this study was then comprised of the people originally randomised to active treatment, and the people randomised to sham who chose to crossover.
Technique	As described in McGough, 2019 (Study 1).
Follow up	Up to 9 weeks
Conflict of interest/source of funding	Conflict of interest: One author reported expert witness testimony for 2 pharmaceutical companies and honoraria from another company. Source of funding: Supported by National Institute of Mental Health grant. Study devices and some materials were provided by NeuroSigma, Inc. in response to an investigator-initiated request.

Analysis

Follow up issues: Data was available for 51 total people (31 active treatment; 20 sham crossover).

Study design issues: This secondary analysis of McGough (2019) evaluated whether baseline cognitive or EEG characteristics were predictors of positive response and associated with ADHD symptom reduction within the original RCT sample. The sample was divided into responders and non-responders. Responders were those with a 25% or greater reduction in ADHD-RS score from baseline and the end of active treatment (week 4 for people randomised to active treatment and week 9 for the people randomised to sham who chose to crossover). Non-responders were those with a less than 25% reduction in ADHD-RS score. Outcome measures (in addition to those described in McGough, 2019) included (see [Outcome measures](#) for full descriptions):

- CBCL, WISC-4 and Digit Span subtest, WRAT, SWM, Flanker Task, and resting state EEG.

Analysis of variance (ANOVA) was used to identify baseline differences between responders and non-responders. Two analyses were used to then predict response status: linear regression analyses for prediction of post-treatment ADHD-RS Total scores and receiver operating characteristics curve analysis to determine area under the curve for prediction of responder status. Significant baseline predictors of ADHD symptoms were then tested for TNS treatment-related change by responder status and time (pre-/post-TNS) using repeated measures ANOVAs.

Pearson correlations between baseline predictors and ADHD symptoms were used to characterize degree of change occurring in both variables with TNS treatment. Partial eta squared was used as the measure of effect size and was interpreted as follows: small: 0.01, medium: 0.06, large: 0.14. Two procedures were used to control for multiple comparisons: only variables that were significant at $p < 0.05$ in the baseline profile were

further tested for prediction of treatment outcomes and treatment related change; and a p-value of $p < 0.01$ was used as the threshold for statistical significance in subsequent analyses.

Study population issues: Responders and non-responders did not differ on any demographic or baseline clinical variables, including age, gender, IQ, or socioeconomic status.

Key efficacy findings

Responder baseline profile

Number of people analysed: 51

- Responders had statistically significantly lower scores on baseline Wide Range Achievement Test (WRAT) Spelling ($F(1,49)=4.6$, $p=0.04$) and Math ($F(1,49)=4.1$, $p=0.05$).
- Responders had statistically significantly worse cognitive functioning relative to non-responders on:
 - CBCL Sluggish Cognitive Tempo index ($F(1, 49)=7.3$, $p=0.009$)
 - BRIEF:
 - Initiate ($F(1, 49)=7.2$, $p=0.01$)
 - Working Memory ($F(1, 49)=20.7$, $p < 0.001$)
 - Planning ($F(1,49)=17.8$, $p < 0.001$)
 - Organisation ($F(1, 49)=5.9$, $p=0.02$)
 - Metacognition ($F(1, 49)=14.9$, $p < 0.001$)
 - General Executive Composite (GEC; [$F(1,49)=5.8$, $p=0.02$]).
- Responders had statistically significantly lower right frontal spectral power in the theta (4-7 Hz [$F(1,45)=9.2$, $p=0.004$]) and alpha (8-12 Hz; [$F(1,45)=9.2$, $p=0.004$]) bands.

Prediction of treatment response

Number of people analysed: 51

- The measures that differed significantly at baseline were then tested for whether the baseline score was predictive of end of treatment ADHD-RS Total Score.
- The following measures were statistically significant predictors of end of treatment ADHD-RS Total score:
 - CBCL Sluggish Cognitive Tempo ($\beta=-0.40$, 95% CI -0.68 to -0.14, $p=0.004$)
 - BRIEF Working Memory ($\beta=-0.40$, 95% CI -0.70 to -0.14, $p=0.004$), Planning ($\beta=-0.36$, 95% CI -0.51 to -0.08, $p=0.01$) and Metacognition ($\beta=-0.32$, 95% CI -0.57 to -0.04, $p=0.02$)
 - EEG right-frontal theta ($\beta=0.43$, 95% CI 0.2 to 1.1, $p=0.005$) and alpha band power ($\beta=0.45$, 95% CI 0.3 to 1.2], $p=0.003$).

TNS treatment-related change in cognitive function and EEG power

Number of people analysed: 28 (EEG); 51 (BRIEF scores)

- Among responders, TNS treatment resulted in right frontal theta- and alpha-band power increase that was not seen in the non-responders (F4 theta: $F(1, 25)=4.4$, $p=0.05$, F4 alpha: $F(1, 25)=4.1$, $p=0.06$, partial eta squared=0.18: large effect size).
 - Treatment-related change in F4 theta was moderately correlated with ADHD symptom change but this was not statistically significant ($r=0.3$, $p=0.14$).
- Statistically significant group-by-time interactions indicated that TNS responders showed treatment related improvement in BRIEF that were not observed in non-responders:
 - Metacognition ($F(1,45)=38.6$, $p<0.001$, partial eta squared=0.47: large effect size)
 - Working Memory ($F(1,45)=41.1$, $p<0.001$, partial eta squared=0.48: large effect size)
 - Initiate ($F(1,45)=18.3$, $p<0.001$, partial eta squared=0.29: large effect size)
 - Planning ($F(1,45)=36.7$, $p=0.001$, partial eta squared=0.51: large effect size)
 - Organisation ($F(1,45)=19$, $p=0.001$, partial eta squared=0.30: large effect size)
 - Treatment-related change in these BRIEF variables and ADHD-RS Total scores were very strongly correlated, with Pearson r 's ranging from 0.65 (Planning, $p=6.5E-7$) to 0.79 (Working memory, $p=3.0E-11$).
- BRIEF Working Memory score was the strongest predictor ($AUC=0.83$, $p=0.003$).

Key safety findings

Safety findings were reported in McGough, 2019 (Study 1).

Study 3 McGough JJ (2015)

Study details

Study type	Single arm, open-label trial
Country	US
Recruitment period	Not reported.
Study population and number	n=24 Children aged 7 to 14 with ADHD.
Age and sex	Mean 10.3 years; 92% male
Patient selection criteria	Inclusion criteria: Children aged 7 to 14 years with DSM-IV ADHD as assessed with the Kiddie Schedule for Affective Disorders and Schizophrenia; minimum baseline scores of 12 on both the inattentive and hyperactive/impulsive subscales of the investigator-completed Parent ADHD-RS; baseline CGI-S rating 4 or more; no current use of medicine with central nervous system effects; and a parent able and willing to complete all required ratings and monitor proper use of the TNS device. Exclusion criteria: levels of ADHD-related impairment that required immediate medication management; current diagnoses of pervasive developmental or depressive disorders; current suicidality; and lifetime histories of psychosis, mania, or seizure disorder.
Technique	Trigeminal nerve stimulation (EMS7500 Stimulator, TENS Products, Inc. Granby, CO) nightly during sleep for 8 weeks. Parents applied patches across their child's forehead to provide bilateral stimulation of V1 trigeminal branches for 7 to 9 hours nightly. Patches were removed each morning. The active condition used a 120-Hz repetition frequency, with 250- μ s pulse width, and a duty cycle of 30 seconds on/30 seconds off. Stimulator current settings between 2 and 4 milli-amperes (range: 0 to 10) were established at baseline by titration.
Follow up	8 weeks
Conflict of interest/source of funding	Conflict of interest: Not reported. Source of funding: This study was funded in part by an investigator-initiated research grant from NeuroSigma, Inc., the manufacturers of the Monarch eTNS device.

Analysis

Follow up issues: Two participants were lost to follow up prior to Visit 4 outcome assessments, one each at Visits 2 and 3. One further participant was lost to follow up after Visit 6.

Study design issues: This single arm, open-label trial was a pilot study of the use of TNS for ADHD. Children were recruited and followed prospectively. The primary behavioural outcome was the investigator-completed Parent ADHD-RS. Other outcomes included investigator-completed CGI-I, parent-completed Conners Global Index, CSHQ, computer-based ANT and SWM, parent-completed BRIEF, MASC, and participant-completed CDI.

Potential side effects and adverse events were assessed with weekly parent-completed Side Effect Ratings Scales and open-ended Adverse Event Inquiries with parents conducted by study investigators.

The safety population included all participants with at least 1 night's exposure to TNS. The treatment population included all participants with outcomes data at week 4, the first post-baseline point at which primary behavioural and cognitive outcomes were obtained. Behavioural and cognitive measures were assessed for

change over time with the general linear mixed model. $p < 0.05$ was considered statistically significant. No adjustments for multiple comparisons were made.

Key efficacy findings

ADHD-RS

Number of people analysed: 22

- There was a statistically significant decrease in ADHD-RS scores from baseline to week 8 follow up ($F=42.5$, $df=2/40$, $p < 0.0001$).

CGI-I

Number of people analysed: 22

- There was a statistically significant decrease in CGI-I scores from baseline to week 8 follow up ($F=6.89$, $df=8/140$, $p < 0.0001$).
- 64% met response criteria (improved or very much improved) at week 4, and 71% met these criteria at week 8.

BRIEF

- There were statistically significant improvements in 7 of 11 BRIEF subscales, including Inhibit ($p=0.004$), BRI Index ($p=0.03$), Working memory, ($p=0.0004$), Plan/organise ($p=0.004$), Monitor ($p=0.003$), MI index ($p=0.0008$), and Global exec composite ($p=0.002$).
- There were no statistically significant improvements in 4 of 11 BRIEF subscales, including Shift, Emotional control, Initiate, and Organisation materials (all $p > 0.05$).

Anxiety and depression

Number of people analysed: 22

- There were statistically significant improvements in dimensional CDI scores ($F=3.40$, $df=2/38$, $p=0.04$).
- There were no statistically significant changes in self-reported MASC scores ($p=0.82$).

Cognitive functioning

Number of people analysed: 22

- ANT:
 - There was a statistically significant decrease in ANT incongruent reaction time from baseline to 8-week follow up ($p=0.006$)
 - There were no statistically significant changes in ANT neutral reaction time, neutral accuracy, congruent reaction time, congruent accuracy, and incongruent accuracy (all $p > 0.05$).
- SWM:
 - There were no statistically significant changes in SWM subscales from baseline to 8-week follow up.

CSHQ

Number of people analysed: 22

- There were statistically significant improvements in CSHQ scores for Sleep Anxiety ($p=0.03$), Total Bedtime Problems ($p<0.0001$), and Total Sleep Problems ($p<0.0001$) from baseline to 8-week follow up.
- There were no statistically significant improvements in CSHQ scores for Bedtime resistance Sleep onset delay, Sleep duration, Night wakings, Parasomnias, Disordered breathing, Daytime sleepiness, Total sleep behaviour problems, and Total problems daytime sleepiness (all $p\geq0.05$).

Key safety findings

Number of people analysed: 24

- The following adverse events were spontaneously reported and considered related or potentially related to treatment:
 - Eye twitch, $n=1$
 - Headache, $n=2$
- The following adverse events were rated 'moderate' or 'severe' on the Side Effects Rating Scale and reported at least once by at least 5% of participants:

Side effect	Number reporting	%
Trouble sleeping	7	29
Nightmares	5	21
Feeling drowsy	5	21
Feeling nervous	14	58
Weakness or fatigue	5	21
Irritable	10	42
Poor memory*	11	46
Trouble concentrating*	22	92
Feeling strange or unreal	2	8
Headache	3	13
Stuffy nose	6	24
Drooling	2	8
Muscle twitch	2	8
Trouble sitting still*	17	71
Poor concentration*	17	71
Slurred speech	2	8
Stomach discomfort	2	8
Excess sweating	2	8
Weight gain	2	8
Diminished mental acuity/sharpness	3	13
Difficulty finding words	2	8
Apathy/emotional indifference	3	13

*ADHD symptom.

Validity and generalisability of the studies

- The patient populations were highly similar in the 2 studies (Loo, 2021 was a secondary analysis of McGough, 2019). No studies were identified that included people older than 14.
- The technique used was highly similar in both studies. As this intervention is parent-applied, there may have been some variability in its application.
- Both studies had small sample sizes and were conducted by the same group of investigators.
- One study (McGough, 2019) was an RCT. The blinding in this study appeared adequate.
- The other study (McGough, 2015) was an open-label trial. Open-label studies may overestimate the treatment effect as participants, parents, and investigators are aware of treatment allocation.
- Neither study conducted an adjustment for multiple comparisons during statistical analysis. Testing many hypotheses without adjustment for multiple comparisons increases the likelihood of a Type 1 error (false positive).
- The maximum follow up was 8 weeks.

Existing assessments of this procedure

In 2019, the Food and Drug Administration (FDA) approved the Monarch eTNS device to treat ADHD in children aged 7 to 12 years old who are not currently taking prescription ADHD medicine ([FDA press release](#)). This approval was based on the findings of McGough, 2019 (Study 1 in this overview) and McGough, 2015 (Study 3 in this overview).

Related NICE guidance

NICE guidelines

- [Attention deficit hyperactivity disorder: diagnosis and management](#). NICE guideline [NG87] Published: 14 March 2018 Last updated: 13 September 2019.
- [Antisocial behaviour and conduct disorders in children and young people: recognition and management](#). Clinical guideline [CG158] Published: 27 March 2013 Last updated: 19 April 2017

Additional information considered by IPAC

Professional experts' opinions

Expert advice was sought from consultants who have been nominated or ratified by their professional Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by professional experts, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, when comments are considered voluminous, or publication would be unlawful or inappropriate.

Two professional expert questionnaires for transcutaneous electrical stimulation of the trigeminal nerve for ADHD were submitted and can be found on the [NICE website](#).

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Company engagement

A structured information request was sent to 1 company who manufactures a potentially relevant device for use in this procedure. NICE received 0 completed submissions.

Issues for consideration by IPAC

- All evidence was in children and young people. As the CE mark permits use in adults, the indication for this assessment was expanded to all ages. However, no evidence in adults was identified.

References

1. McGough JJ, Sturm A, Cowen J et al. (2019) Double-Blind, Sham-Controlled, Pilot Study of Trigeminal Nerve Stimulation for Attention-Deficit/Hyperactivity Disorder. *Journal of the American Academy of Child and Adolescent Psychiatry* 58(4):403-11e3.
2. Loo SK, Salgari GC, Ellis A et al. (2021) Trigeminal Nerve Stimulation for Attention-Deficit/Hyperactivity Disorder: Cognitive and Electroencephalographic Predictors of Treatment Response. *Journal of the American Academy of Child and Adolescent Psychiatry* 60(7):856-64e1.
3. McGough JJ, Loo SK, Sturm A et al. (2015) An eight-week, open-trial, pilot feasibility study of trigeminal nerve stimulation in youth with attention-deficit/hyperactivity disorder. *Brain stimulation* 8(2):299-304.

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	23/02/2022	Issue 2 of 12, February 2022
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	23/02/2022	Issue 2 of 12, February 2022
International HTA database	23/02/2022	-
MEDLINE (Ovid)	23/02/2022	1946 to February 22, 2022
MEDLINE In-Process (Ovid) & MEDLINE ePubs ahead of print (Ovid)	23/02/2022	1946 to February 22, 2022
EMBASE (Ovid)	23/02/2022	1974 to 2022 February 22
Embase Conference (Ovid)	23/02/2022	1974 to 2022 February 22

Trial sources searched April 2021

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- General internet search

MEDLINE search strategy

The MEDLINE search strategy was translated for use in the other sources.

Strategy used:

- 1 Transcutaneous Electric Nerve Stimulation/
- 2 Electric Stimulation Therapy/
- 3 Electric Stimulation/
- 4 ((transcutaneous or neuromodulat* or analgesic or transdermal or percutaneous) adj4 electr* adj4 (stimulat* or therap*)).tw.
- 5 electroanalges*.tw.
- 6 (NMES or TENS or FES or eTENS or TNS).tw.
- 7 Electrostimul*.tw.
- 8 Electrotherap*.tw.

IP overview: Transcutaneous electrical stimulation of the trigeminal nerve for ADHD

9 ((trigemin* or cran*) adj4 nerv* adj4 (stimulat* or therap*)).tw.
 10 or/1-9
 11 exp Attention Deficit Disorder with Hyperactivity/
 12 "attention deficit and disruptive behavior disorders"/
 13 ((attenti* or disrupt*) adj4 disorder*).tw.
 14 (adhd or addh or ad hd or ad??hd).tw.
 15 hkd.tw.
 16 (hyperactiv* or inattent* or hyperkin* or hyper-kin*).tw.
 17 Child Development Disorders, Pervasive/
 18 Child* development disorder*.tw.
 19 neurodevelopmental disorders/
 20 (neurodevelop* adj4 disorder*).tw.
 21 or/11-20
 22 eMonarch.tw.
 23 monarch eTNS system.tw.
 24 Monarch eTNS.tw.
 25 external Trigeminal Nerve Stimulation.tw.
 26 or/22-25
 27 10 and 21
 28 26 or 27
 29 animals/ not Humans/
 30 28 not 29
 31 limit 30 to english language

Appendix

There were no additional papers identified.