

Indications for Use approved for marketing, June 21, 2001

Approved Indications for Use for the *NTI Tension Suppression System (NTI-tss)*:

1. A device to be used in the prophylactic treatment of medically diagnosed migraine pain as well as migraine associated tension-type headaches, by reducing their signs and symptoms through reduction of trigeminally innervated muscular activity, and;
2. For the prevention of bruxism and TMJ syndrome through reduction of trigeminally innervated muscular activity

Background

Intraoral Devices: Disrupting Muscular Hyperactivity

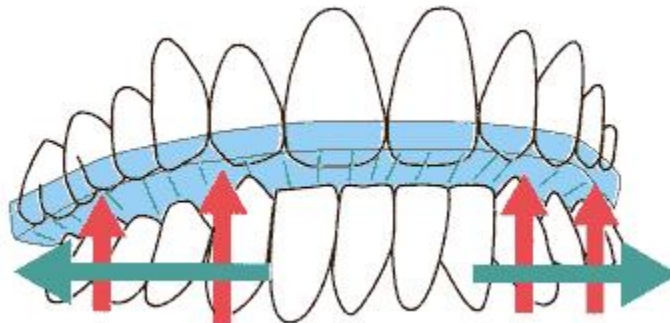
Dentistry has traditionally attempted to treat the signs and symptoms of masticatory muscular hyperactivity (one of which is pericranial tenderness) by reducing the muscular hyperactivity with an intraoral device. However, study results show that the presence of an occlusal coverage splint by itself does not guarantee a reduction in hyperactivity, but a disruption of the activity.

Percentage of patients with changes
in Masseter hyperactivity during full-coverage splint therapy(1)
Increase: 20% + Decrease: 52% = Observable change: 72%; No change: 28%

Percentage of patients with changes
in Temporalis hyperactivity during full-coverage splint therapy(2)
Increase: 12% + Decrease: 42% = Observable change: 54%; No change: 46%

Holmgren(3) showed that in 71% of patients, use of an occlusal splint resulted in significant but inconsistent changes in EMG activity levels during maximal clenching, which differed between patients and even, in some patients, between muscles.

The response of the masticatory musculature to the splint dictates the effects on the patient's symptoms. The Vissor(2) study (above) showed and concluded that patients with an increase of temporalis activity while using the splint also have an increase in pain, while those with a decrease in temporalis activity have a decrease in pain.



Traditional splints provide an ideal clenching surface (vertical arrows).
Some patient's muscular hyperactivity exploits the opportunity and increases muscular activity.

Pericranial tenderness and Temporalis hyperactivity in headache patients

Pericranial muscle tenderness in headache patients is a common complaint. Lous and Olesen reported the presence of pericranial muscle tenderness upon palpation in all headache groups (migraine, tension-type, and mixed migraine/tension-type) and absent in all controls(4) .

Suggesting a source of the pericranial tenderness, tension-type headache patients contract their temporalis muscles during sleep, on average, 14 times more intensely than asymptomatic controls(5).

	<u>Mean Temporalis EMG Levels</u>	
	Headache group	Asymptomatic Controls
Waking	6,642	5,136
Sleeping	13,392	943

Migraine Headache: A diagnosis of subjective report

The International Headache Society lists these criteria for making a diagnosis of migraine without aura:

- Headache pain lasts 4 to 72 hours
- Has at least two of the following characteristics: Unilateral (although bilateral is not uncommon); Pulsating quality; Moderate to severe intensity
- Is aggravated by normal routine physical activity
- Accompanying by at least one of the following: Nausea or vomiting (or both); Photophobia or phonophobia
- No evidence of related organic disease

Therefore, when a patient reports an intensity of headache can last at least 4 hours, is accompanied by either nausea, photophobia or phonophobia; their daily activity is limited; and all diagnostic tests are within normal limits, the diagnosis is migraine.

The American Migraine Study(6) estimated that 23 million persons older than 12 years of age have severe migraine headaches , however, this condition is undertreated and underdiagnosed world-wide(7,8). Not all headache sufferers seek medical attention, but those who do generally consult in this order of preference: family practitioners, internists or pediatricians, ophthalmologists, and finally, neurologists(9). The social and economic effects of migraine are staggering: reportedly between \$2 to \$17.2 billion are lost in productivity per year(9). The treatment of migraine has not only medical but also serious economic and social implications (an implementation of Merck’s migraine disease management program at Intermountain Health Care cut medical costs by one-third in a pilot study). Thus, primary health care providers should be well versed in the diagnosis and treatment of migraine.

The understanding of the mechanisms underlying migraine has evolved historically from demonic influences to psychogenic factors to abnormally constricting or dilating blood vessels to dysfunctional neuronal receptors, and it continues to evolve. The belief that migraine is a primary vascular phenomenon is no longer tenable(10). In fact, most theories of migraine etiology now include a trigeminal pathway, and recognize the common pericranial muscular tenderness in migraineurs(11).

The lack of objective evidence of a causative element for migraine pain has kept the health care industry from isolating an acceptable means of prevention. The medications currently accepted for prophylactic treatment rarely have a better than 55% efficacy(12). Some sufferers are not able to tolerate the side-effects of the “preventive” medications and due to the potential teratogenic effect of the prophylactic agents, women of childbearing age should be using a reliable type of birth control(13). The commonly chosen migraine

prophylactic agents (propranolol, amitriptyline, verapamil) have not been shown irrefutably to prevent migraine. Furthermore, their benefit, if any, does not exceed 50% over placebo(14).

Divalproex sodium, for example (Depakote, Abbott) an anticonvulsant agent, has been approved for use in migraine prevention. In clinical trials, 13% of those taking divalproex chose to drop out of the study before an assessment could be made regarding migraine reduction due to intolerance of side-effects (the most frequently reported were nausea, asthenia, dyspepsia, dizziness, somnolence, and diarrhea). 48% who could tolerate the side-effects (if any) had a 50% or greater reduction in migraine(15,16). In clinical practice, compliance and acceptance of the preventive medications is poor, due to the required tolerance of side-effects and to the vast selection of the "rescue" medications, such as sumatriptan (Imitrex, Glaxo-Wellcome. Imitrex sales in 1999 approached 1.5 billion). Migraineurs are more willing to endure the same number of migraines with shorter duration (by using a rescue medication), than to take preventive medications and have less migraines, while enduring the adverse effects. Migraine prophylaxis is an unsatisfied treatment market. The use of sumatriptan does have its costs and risks as well. A typical migraineur may require four or more doses of sumatriptan per month at approximately \$50 per dose, or over \$2,000 per year. Although migraine itself is benign, treatment with sumatriptan can create considerable complications and health risks (the "Indications/Contraindications-/Warnings/Precautions/Adverse reactions" provided by Glaxo-Wellcome for Imitrex use includes admissions of reported fatalities).

The acknowledgment of nocturnal pericranial muscular hyperactivity and resultant tenderness in migraine and tension-type headache has prompted development of methods which specifically attempt to directly reduce pericranial muscular hyperactivity.

Recently, the use of botulinum toxin type A (BOTOX; Allergan, Inc.) has gained steady acceptance as a treatment to reduce the muscular hyperfunction pain associated with conditions such as cervical dystonia, achalasia, rectal fissures, myofascial pain syndrome(17), and now most recently, migraine and TMD.

In a double-blind, vehicle-controlled study of 123 subjects with a history of two to eight moderate-to-severe migraine attacks per month, pericranial injection of botulinum toxin type A, 25 U, was found to be a safe treatment that significantly reduced migraine frequency, migraine severity, acute medication usage, and associated vomiting(17).

BOTOX administered in a similar manner as above for TMD patients, specifically into the temporalis and masseter muscles, produces significant improvements in function and significant reductions in pain and tenderness(18).

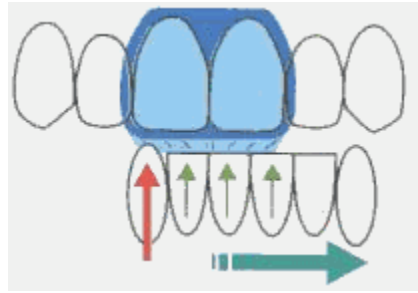
Full occlusal coverage splints reduce migraine frequency as well as the preventive medications

The premise that nocturnal muscular hyperactivity may be a precursor to migraine, and that an intraoral device (872.5410 orthodontic appliance and accessories. The non-commercially available and 510(k) exempt full coverage occlusal splint) may reduce the intensity of the hyperactivity, thereby reducing migraine frequency, has been observed.

When compared to a placebo (palatal acrylic), an occlusal coverage appliance reduced the number of attacks on average to about 40% of that normally experienced. The improvement was most marked in those who had frequent attacks of migraine, ie, two attacks per week on a regular basis. When using a soft full-coverage splint, 63% of migraineurs had an average 50% decrease in migraine frequency(20). The rate of migraine reduction using a full coverage splint is comparable to the commercially available preventive medications, but without the side-effects(12). These results may follow Visser's observation that the reduction of temporalis hyperactivity when using a full-coverage splint corresponds to reduction of symptoms (and perhaps conversely, an increase of temporalis hyperactivity leads to an increase of symptoms)(2).

Intraoral device design to specifically reduce muscular tension

Full-coverage splints allow muscular hyperactivity to perpetuate or intensify for at least 50% of patients (1,2) by providing the canine and posterior contacts required to provide the necessary resistance to the contractions. An intraoral device, which allows only reciprocating contacts on the central and lateral incisors, suppresses maximal pericranial muscular contraction (most notably, the temporalis) to 1/3 of maximum(21). Commonly referred to as a “muscle deprogrammer”, this type of device is frequently fabricated by dentists to “relax” pericranial masticatory musculature, thereby allowing an optimal condylar orientation within the fossa. However, the design of the deprogrammer only allows it to be used in a clinical setting, and not for therapeutic use.



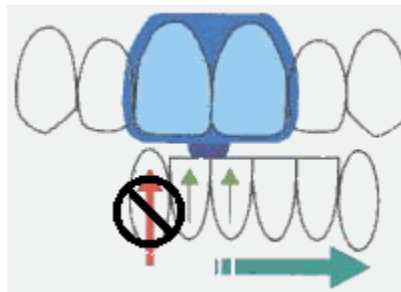
A typical “muscle deprogrammer” allows canine contact during excursive movement (vertical arrow), thereby allowing near-maximum clenching intensity

The width of the device, which covers both upper centrals and a percentage the laterals, provides a clenching surface for the lower canine teeth following natural excursive movement of the mandible. Canine contact on an intraoral appliance of any kind allows for near-maximal temporalis contraction intensity(22), which would make the typical deprogrammer contraindicated for therapeutic use.

Modification of the Muscle Deprogrammer: NTI Tension Suppression

In July of 1998, the FDA granted a marketing allowance for the “NTI Clenching Suppression System” (now NTI-tss), a pre-fabricated matrix which a dentist retro-fits to the patient. The NTI-tss differs from the muscle deprogrammer in that it is modified to reduce the possibility of canine contact, in addition to eliminating posterior contact. Used only during times of possible parafunction (never while eating, thereby eliminating potential for functional adaptation of the teeth), the NTI-tss significantly reduces or eliminates the tooth contacts necessary to generate the muscle contraction intensity that creates joint strain and perpetuates myogenous symptoms.

[\(protocol oversights which can allow joint strain\)](#)



A modified muscle deprogrammer, the NTI Tension Suppression System (NTI-tss), reduces the probability of canine contact during excursive mandibular movements, thereby reducing the opportunity for temporalis contraction intensity.

Data from clinical trials observing the effects of the NTI-tss vs. a full-coverage occlusal splint on medically diagnosed migraine and tension-type headache, submitted to the FDA.

(also submitted for journal publication, June 2001)

Lead Investigator: [Wesley Shankland, DDS, MS, Phd](#); Columbus, Ohio

Clinical investigators: Chris Brown, DDS, MS, Versailles, Indiana; Norm Bryan, DDS, Elkhart, Indiana; John Eriksmoen, DDS, Costa Mesa, CA.

Study Objective:

The primary objective of this study was to evaluate the safety and effectiveness of the intraoral Nociceptive Trigeminal Inhibition Tension Suppression System (NTI-tss) device for the reduction of frequency and severity of tension-type and migraine headaches, as compared to the known efficacy of the non-commercially available full-coverage occlusal splint.

Experimental Design:

A multi-centered, open labeled, two parallel-groups randomized clinical trial in randomized blocks was used to examine a differential response following an eight week use of the test device and a control device, preceded by a four week baseline observation assessment.

A Visual Analog Scale (VAS) reporting presence or intensity of head pain was recorded by patients three times per day (upon waking in the morning, mid-day, and at night before bedtime), and percentage of waking time with a headache during the previous 24 hours. Subjects also recorded: presence/absence of photophobia, nausea, phonophobia; analgesics taken and dosage; usage of rescue medication (sumatriptan); degree of compliance; and any adverse events.

Inclusion Criteria

Medically diagnosed Migraine

- Previously medically screened and diagnosed by a physician as having at least two migraine episodes per month
- Prescribed and were using sumatriptan as a rescue medication for their migraine attacks.

Pericranial tenderness

Palpation of the temporalis to confirm tenderness, compared to a control palpation of equal pressure at the mid-hairline on the forehead.

Dental evaluation:

Each subject's dental evaluation required:

- Presence of natural or fixed prosthetic upper and natural lower anterior incisors
- Overbite and overjet within normal limits (requiring no adaptation of the test device)
- Stable dentition: no current orthodontic treatment, teeth fully erupted (excluding third molars)
- No significant periodontal disease or signs and/or symptoms of temporomandibular joint disorder.

Baseline Data Collected:

Diagnostic opposing study models; measurement of tooth mobility and sensitivity (temperature, pressure, contact by explorer to CEJ); full periodontal charting; anterior periapical x-rays; tooth vitality.

Test Device (Non-significant risk):

Nociceptive Trigeminal Inhibition Tension Suppression System (NTI-tss) intraoral device, 510(k) product K981546, current approved indications for use: *For the prevention of chronic tension and temporal mandibular joint syndrome that is caused by chronic clenching of the posterior mandibular and maxillary teeth by the temporalis muscle. The device is custom made for the individual.*

The NTI-tss is a small intraoral device, which is fitted over the two maxillary central incisors and has a dome shaped protrusion, which extends lingually. The dome is customized by the provider, to act as single point contact at the incisal embrasure of the two mandibular central incisors, thereby preventing posterior or canine tooth contact. The device does not introduce any chemicals or substances into the patient's system. The only known direct effect of this device is the significant suppression of temporalis muscle contraction intensity.

There are no additional precautions or safety risks when using an NTI-tss to suppress muscle contraction intensity when the condition being treated is migraine and/or tension-type headache, over its current indication (suppression of clenching and TMJ syndrome).

Control Device:

A mandibular full-coverage occlusal splint.

(compared to a placebo (palatal acrylic) a full-coverage splint reduces migraine frequency by 40% (19))

Device Administration / Duration of Study:

Following a four week pretreatment baseline observation, patients were instructed to insert and wear their device during sleep, and as required during perceived stressful times during the day, for eight consecutive weeks. Dental Baseline Data was re-collected following the eighth week

94 patients, each diagnosed by a physician as having at least 2 migraine episodes per month and were prescribed Imitrex as a rescue medication and who also reported chronic tension-headache, were examined. A complete documentation of each patient's dentition (radiographic and complete periodontal charting, including mobility), occlusal relationship (plaster models) and pericranial tenderness was recorded (pericranial tenderness was present in every subject during baseline recordings).

Each patient kept a daily log for four weeks (creating baseline data), recording three times per day (upon waking, mid-day, evening):

- Presence (or absence) of headache and VAS to record intensity
- Presence (or absence) of migraine and VAS to record intensity
- Presence (or absence) of: nausea, photophobia, phonophobia
- Analgesics or rescue medications taken.

At random, 51 patients were fitted with a full-coverage occlusal splint, and 43 were fitted with an NTI-tss. Each was instructed to wear their device every night while asleep, and during stressful times throughout the day, for two consecutive months. Each patient's log was reviewed on a weekly basis. As with all migraine reduction protocols, a month of use was allowed to elapse before observing the actual effect of the method during the second month of treatment.

RESULTS

Safety

Following eighth week of NTI-tss use, there was **no** measurable evidence of:

- tooth movement;
- increased tooth sensitivity;
- extrusion;
- increased periodontal pocket depth;
- widening of the PDLs;
- new pain or discomfort.

There were no reports of dislodgment of the device. In five of the 43 NTI-tss patients, a slight degree of mobility (less than 1mm) was measured at the lower incisors.

Efficacy

As is customary when observing the effect of a prophylaxis method of reducing migraine and tension-type headache, at least a month of use is allowed to lapse before an effect (if any) can be realistically observed. Following the eighth week of use:

82% of NTI-tss users had a 77% average reduction in migraine events.

Percentage *reductions* of listed symptoms (23)

Description	<u>Control</u>	<u>NTI-tss</u>	<u>P-value</u>
Migraine episodes	38.1	61.9	<.05
Phonophobia	-1.6	68.4	<.002
Nausea	40.4	78.0	<.01
Photophobia	22.8	65.6	<.01
Tension-type headache episodes	15.0	37.3	<.05
All headpain episodes	25.1	46.9	<.01
Imitrex use	17.6	46.8	<.01
% of day with headpain	14.6	35.3	<.01
Intensity of head pain	23.7	36.9	<.06

Other Observations

16% of NTI-tss users reported an 85-100% reduction of migraine events.

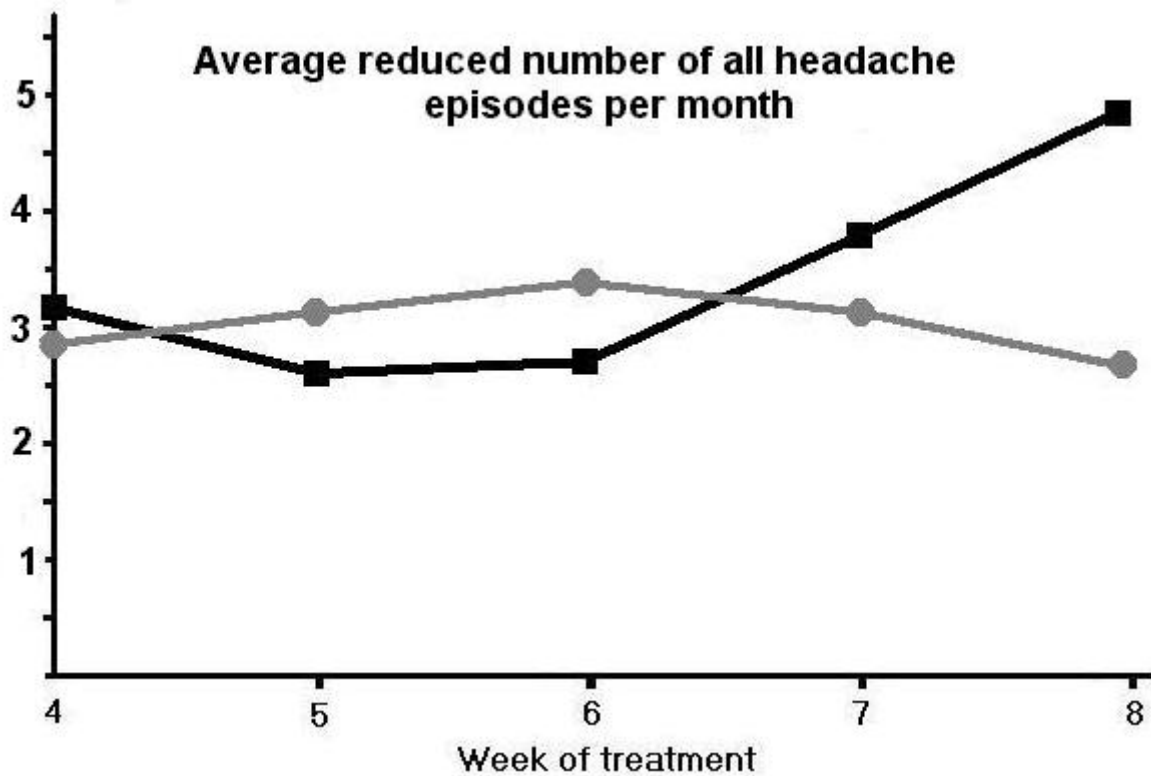
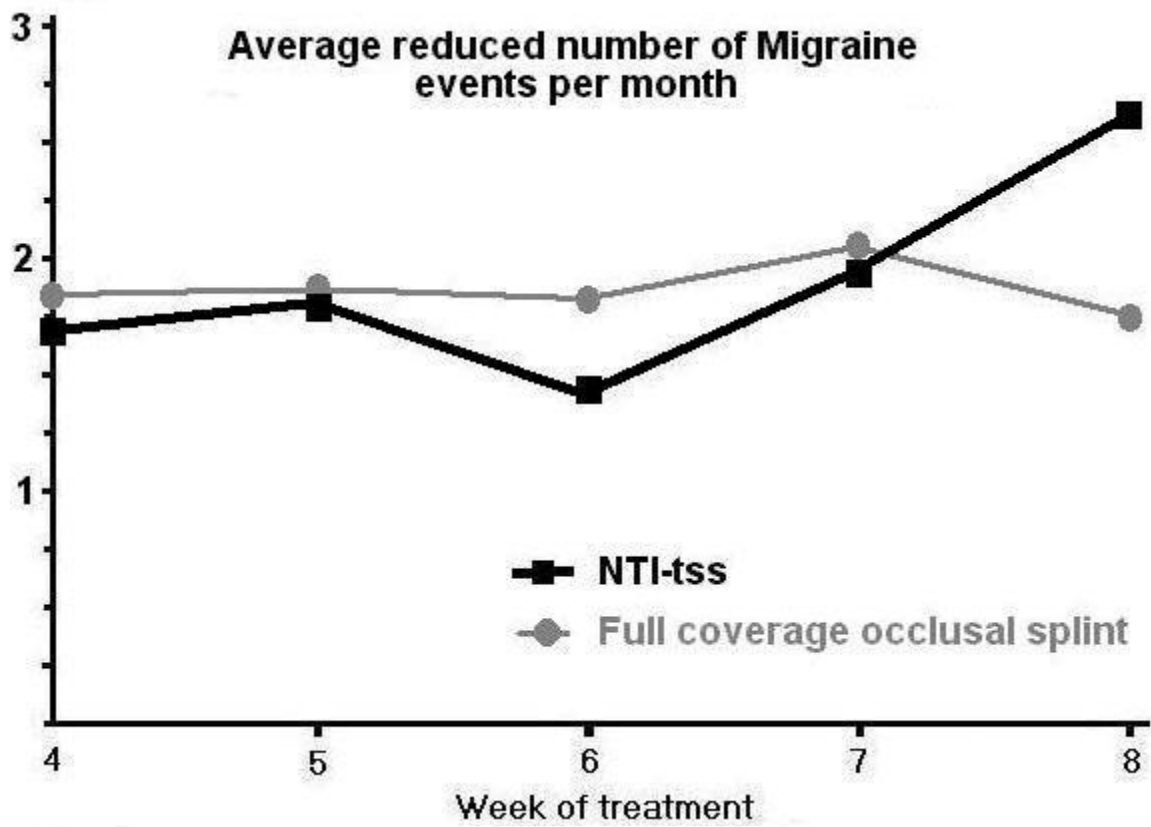
7% of Full-Coverage Splint users reported an 85-100% reduction of migraine events.

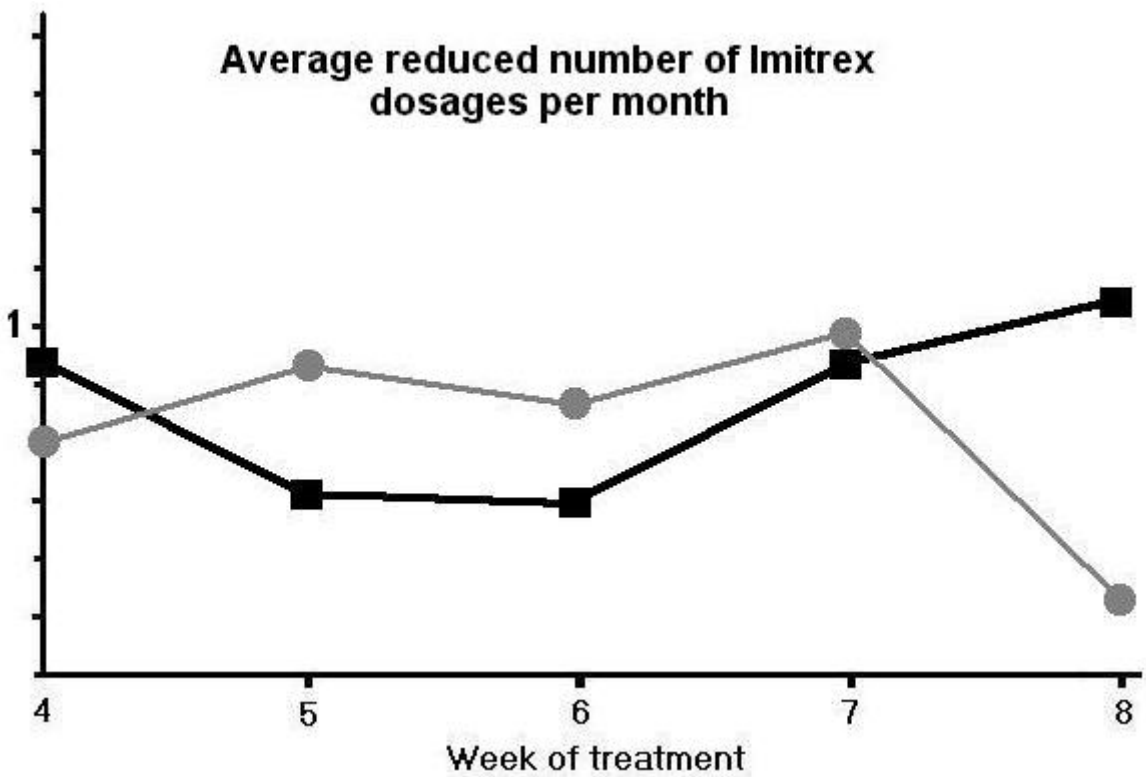
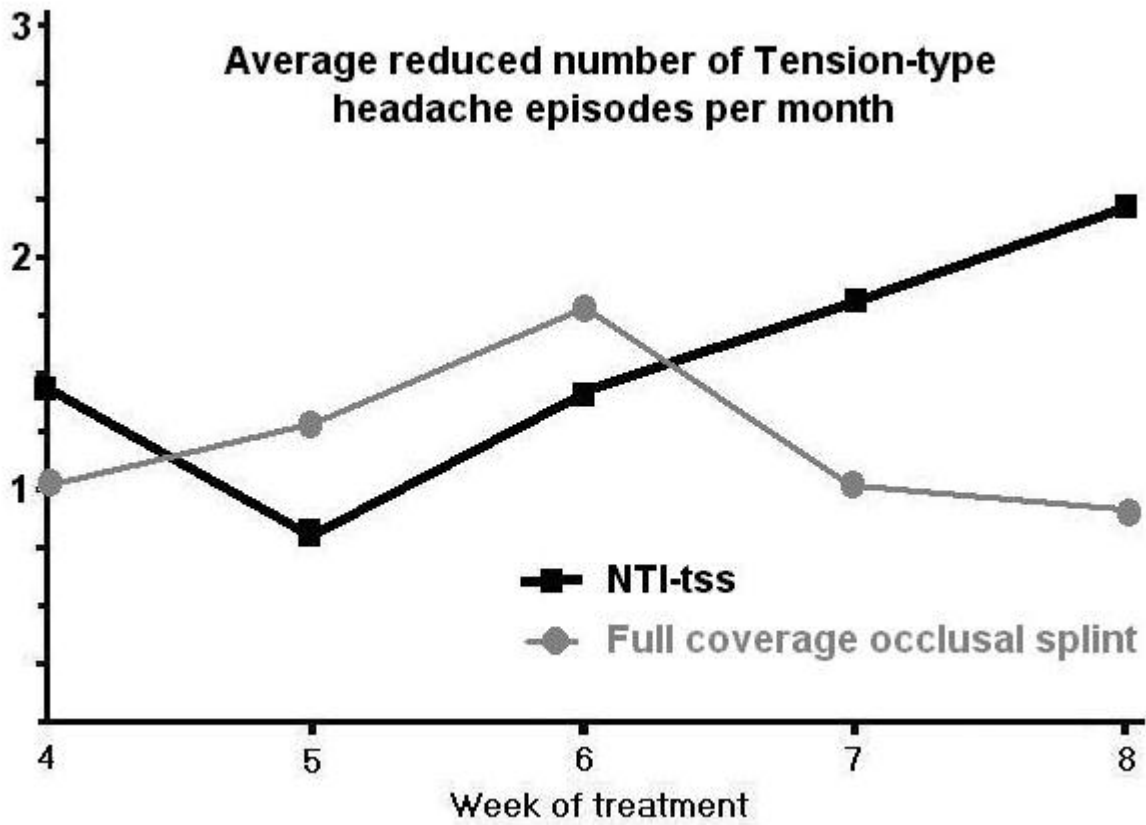
11% of NTI-tss users reported an average 12% increase in migraine events following the second month, which was one-half of their reported increase in the first month. Their migraine frequency was *decreasing*.

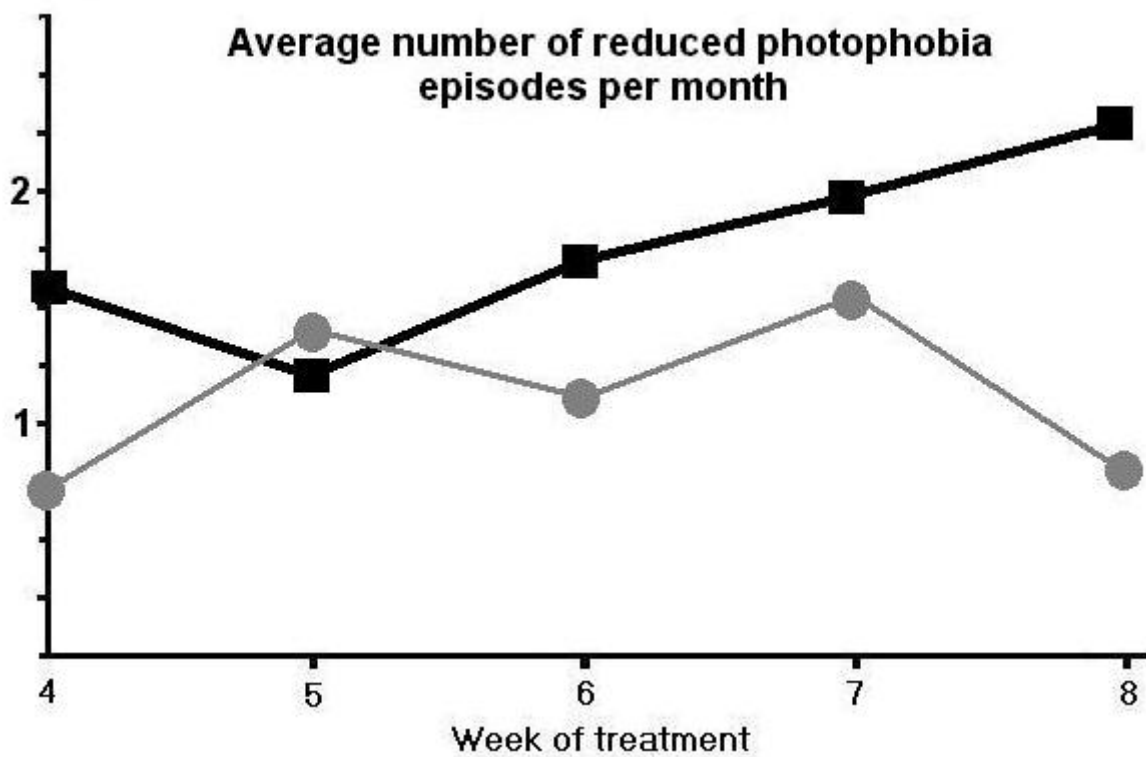
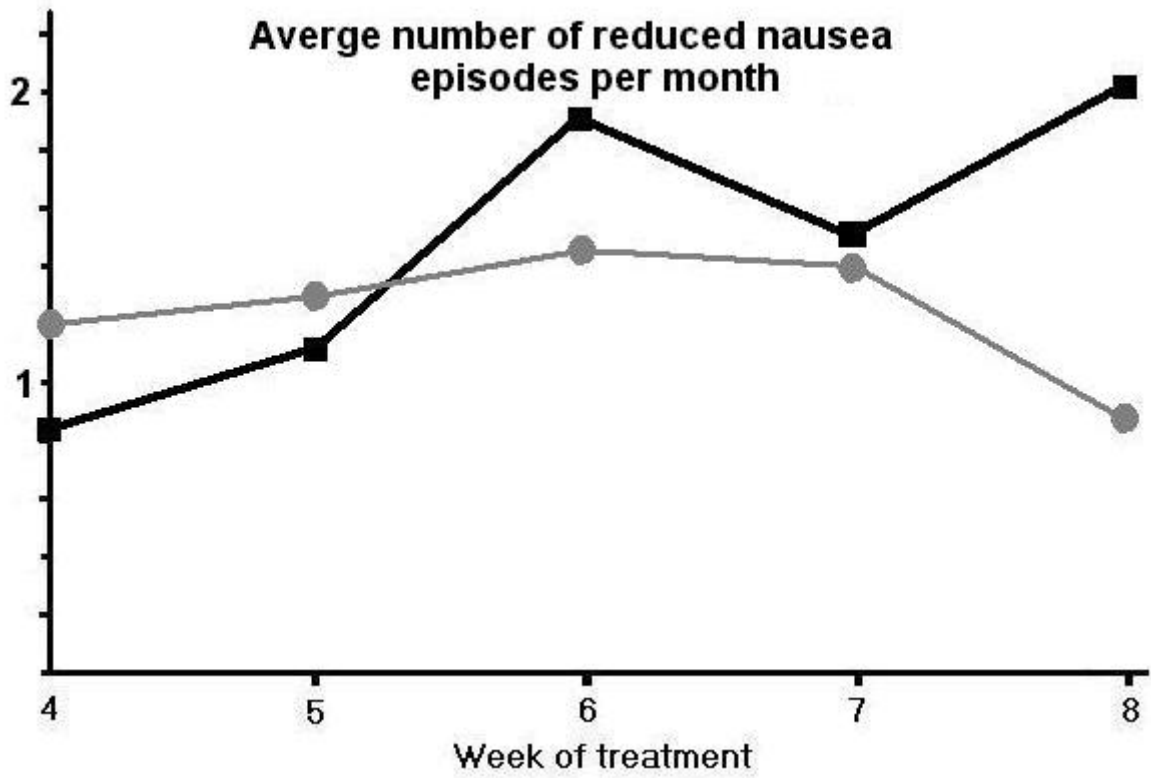
27% of Full-Coverage Splint users reported an average 46% increase in migraine events following the second month of use, which was twice their reported increase in the first month. Their migraine frequency was

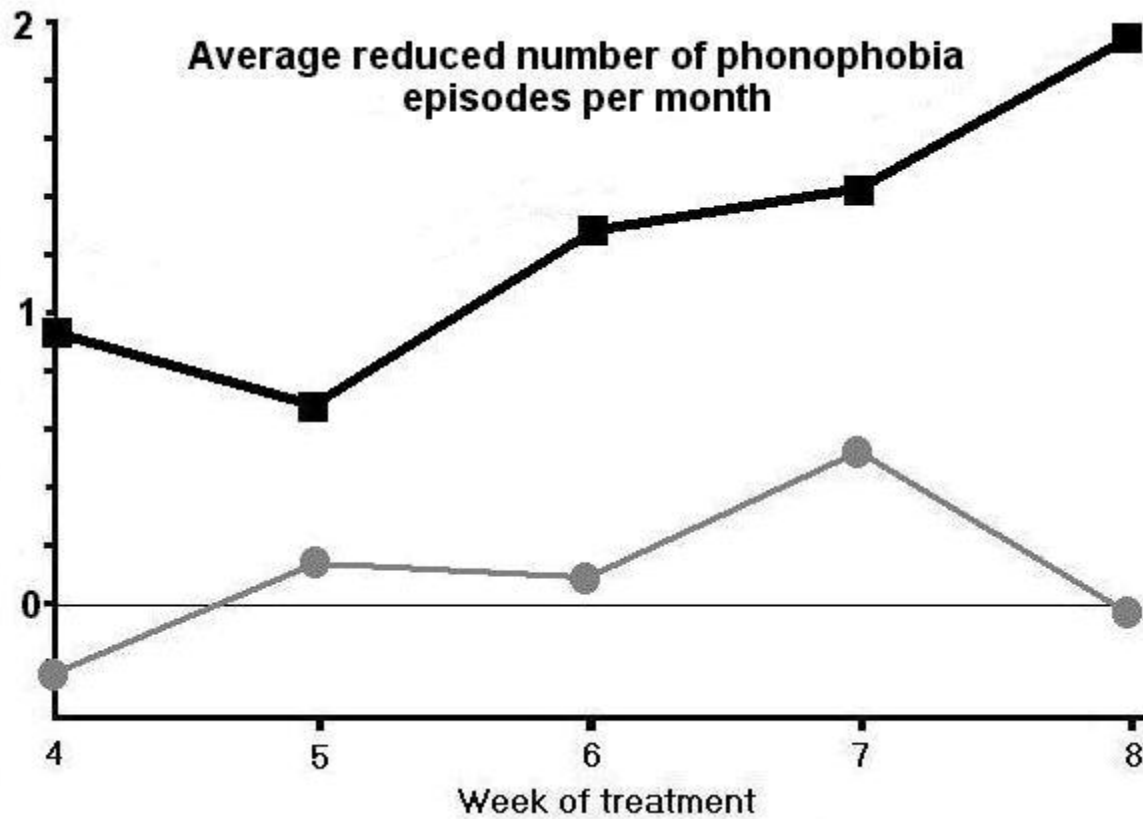
increasing.

Note: In the line graphs below, **positive values are represented as a reductions of signs or symptoms**. For example, the upward slope in the graph below shows a decrease in number of migraines.

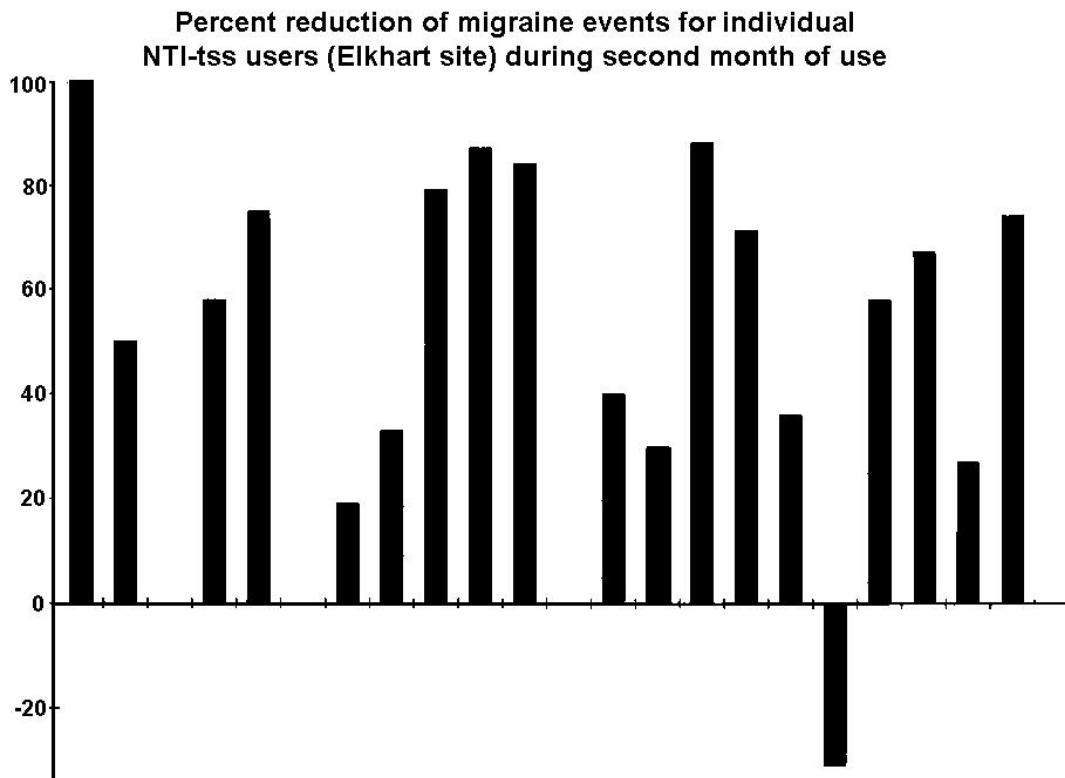




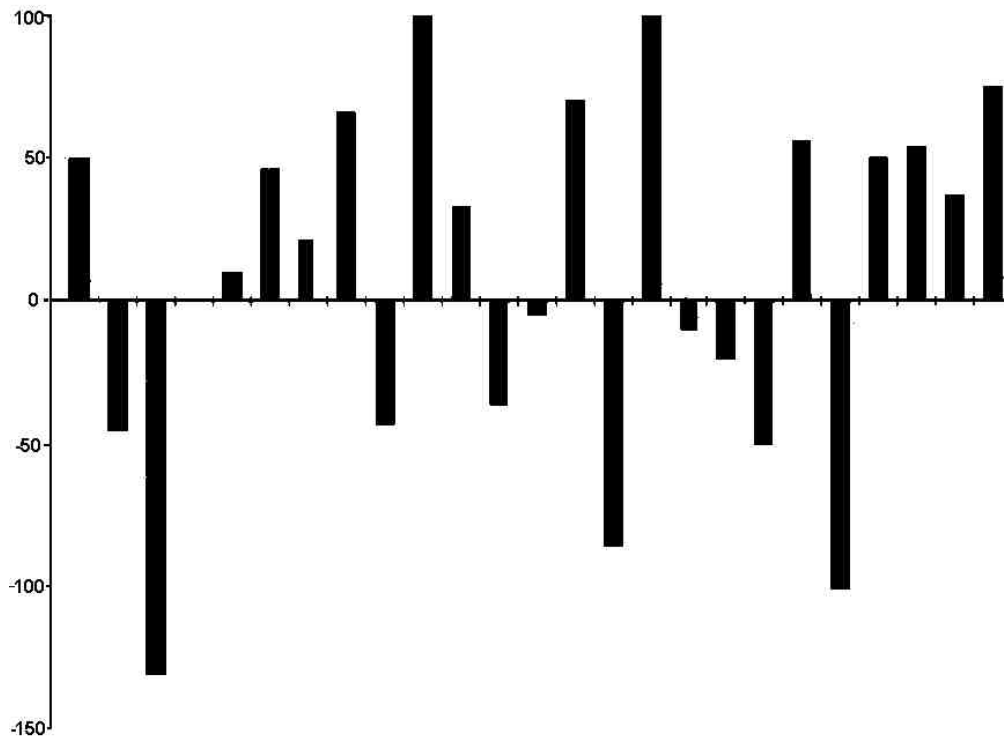




In the graphs below, each bar represents an individual patient. The positive values represent the percentage reduction in migraine episodes, while a negative value represents a "negative reduction", that is, an increase in migraine episodes.



Percent reduction of migraine events for individual full-coverage splint users (Elkhart site) during second month of use



Holmgren(3) also observed that: "...the number of patients who had an identical level of EMG activity during maximal clenching in the intercuspal position and on the occlusal splint tended to increase". This tends to support the observations of some of the full-coverage control device patients whose headache frequencies increased.

Conclusion

The NTI-tss is substantially equivalent or superior to the previously established efficacy of the full-coverage occlusal splint for the reduction of migraine and tension-type headaches and their associated symptoms.

There is no significant risk when using the NTI-tss device for the reduction of medically diagnosed migraine and tension-type headache.

In addition to reducing the muscular hyperactivity that leads to temporomandibular syndrome and pericranial tenderness, teeth are protected from traumatic occlusion by the NTI-tss device.

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Overview of these trials:

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