Peripheral Neurostimulation for the Treatment of Chronic, Disabling Transformed Migraine

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Background.—Up to 5% of the general population suffers from transformed migraine. This study analyzes clinical responses of transformed migraine to cervical peripheral nerve stimulation.

Methods.—Headache frequency, severity, and disability (Migraine Disability Assessment [MIDAS] scores) were independently measured in an uncontrolled consecutive case series of 25 patients with transformed migraine implanted with C1 through C3 peripheral nerve stimulation. All patients met International Headache Society (IHS) criteria for episodic migraine, as well as suggested criteria for transformed migraine, and had been refractory to conventional treatment for at least 6 months. Responses to C1 through C3 peripheral nerve stimulation were recorded.

Results.—Prior to stimulation, all patients experienced severe disability (grade IV on the MIDAS) with 75.56 headache days (average severity, 9.32; average MIDAS score, 121) over a 3-month period.

Following stimulation, 15 patients reported little or no disability (grade I), 1 reported mild disability (grade II), 4 reported moderate disability (grade III), and 5 continued with severe disability (grade IV), with 37.45 headache days (average severity, 5.72; average MIDAS score, 15). The average improvement in the MIDAS score was 88.7%, with all patients reporting their headaches well controlled after stimulation.

Conclusions.—These results raise the possibility that C1 through C3 peripheral nerve stimulation can help improve transformed migraine symptoms and disability. A controlled study is required to confirm these results.

Key words: headache, migraine, transformed migraine, peripheral nerve stimulation, MIDAS score, neurostimulation

Abbreviations: PNS peripheral nerve stimulation, MIDAS Migraine Disability Assessment

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Up to 5% (approximately 2200000) of the general population experiences frequent headache symptoms with features of both migraine and tension-type headache called *transformed migraine*.[1]

Transformed migraines are chronic daily or almost-daily headaches (more than 15 days per month) and are nonparoxysmal (lasting more than 4 hours). Patients have a prior history of International Headache Society (IHS)-diagnosed episodic migraine with increasing headache frequency and decreasing severity of migrainous features.[2] Transformed migraine most often develops in the setting of symptomatic medication overuse with a severity and progression that is commonly disabling, incapacitating, and refractory to current treatment.[3]

Current treatment for transformed migraine may include hospitalization or intensive outpatient parenteral treatments. The goal is to interrupt the daily headache pattern with parenteral protocols, discontinue offending analgesics if rebound is present, implement effective preventive and abortive treatment, and treat behavioral and neuropsychiatric comorbidities. Treatment has varied responses. Fifty percent to 75% of patients gain prolonged benefit; relapses can occur.[4] Overall, parenteral medicines benefit these patients.

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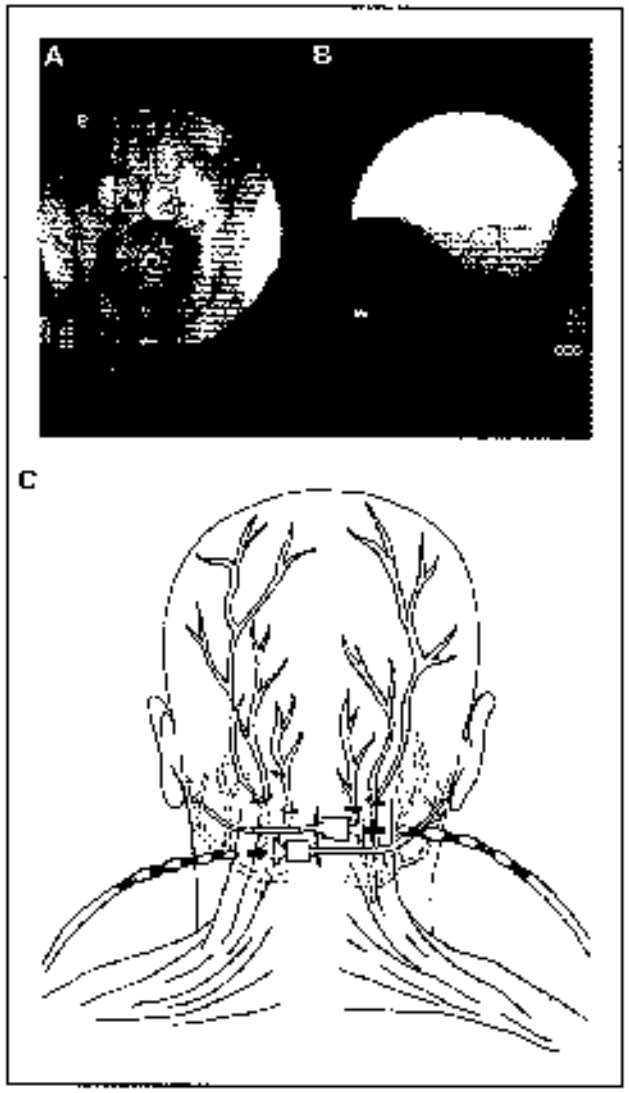

Fig. 1.—(A and B) Anteroposterior and lateral images of dual quadripolar peripheral C1 through C3 neurostimulating electrodes (Pisces-Quad Plus, Medtronic, Minneapolis, Minn). (C) Artist rendition of percutaneous peripheral placement of C1 through C3 neurostimulating electrodes.

Twenty-five consecutive patients who met IHS criteria for episodic migraine and suggested criteria for transformed migraine were implanted with C1 through C3 peripheral nerve stimulation (PNS) (Figures 1A, 1B, and 1C).

There is a known longstanding clinical efficacy of PNS in the treatment of neuropathic pain. The rationale for applying PNS involved the distinct neuropathic quality of the patients' symptoms within the C1 through C3 neural distribution. Applying PNS may dampen the chronic bombardment of sensory input to the trigeminocervical complex and thus lessen progressive sensitization. Without other reports of implanted stimulators for the treatment of transformed migraine, this uncontrolled case series may be of interest.

METHODS

Twenty five consecutive patients meeting IHS criteria for episodic migraine and suggested criteria for transformed migraine, underwent history and physical examination in an outpatient neurological/pain management setting, most of whom had been treated with intensive outpatient parenteral treatments to interrupt their daily headaches. Magnetic resonance imaging (MRI) was used to rule out structural causes (intracranial and cervical) for patients' symptoms. All patients gave a history of progressive pain into the posterior occipital, vertex, or retroorbital regions and had failed polypharmacologic therapy (preventive and abortive). On average, the patients had failed 7 pharmacologic treatments. (Failed abortive treatment was defined as failing to obtain sustained pain-free responses. Failed preventive treatment was defined as the inability to reduce frequency of headaches by 50%.) Seventy-six percent of patients reported symptomatic overuse of medications including simple analgesics; combination analgesics, and narcotics for a minimum of 6 months. Attempts were made to discontinue overuse of medications prior to PNS with no success. Most patients had been to the emergency department for headache treatment within the prior month. Pertinent physical examination findings included posterior occipital muscle tension and tender points over the distal C2 through C3 nerve branches at the nuchal ridge. All responded temporarily (duration of the local anesthetic) to bilateral occipital nerve blockade. All patients completed a successful 5- to 7-day trial of outpatient stimulation with an externalized quadripolar (Medtronic Pisces-Quad, Minneapolis, Minn) electrode system. Again, there were no patients that failed external stimulation.

Permanent implant technique included placing two quadripolar electrodes positioned transversely through a subcutaneous midline incision over C1 and

attached to an implantable pulse generator. More specifically, electrodes (Pisces-Quad Plus/Synergy, Medtronic Neurological, Minneapolis, Minn) were placed subcutaneously, at the level of C1, superficial to the cervical muscular fascia and transverse to the affected C1 through C3 (occipital) nerve under fluoroscopic control (Figures 1A, 1B, and 1C).[3] Confirmation of electrode position was achieved when patients localized peripheral C1 through C3 stimulation paresthesias in their posterior occipital regions.

Measurements.—A postimplant telephone survey and Migraine Disability Assessment (MIDAS) Questionnaire were conducted at uniform times to document prestimulation and poststimulation responses. Data were collected retrospectively via patients' charts and telephone interviews. Patients were queried for: gender, current age, age at implant, age of initial headache, symptomatic medication overuse, and historical headache frequency, severity, and symptom type (episodic, continuous, progressive, transformed, aura). Stimulation responses, parameters, use patterns, satisfaction, and complications were recorded. The MIDAS Questionnaire was used to measure migraine disability. It does so with high internal consistency, test-retest reliability, and phase validity.[9]

Statistical Analysis.—All measurements are reported as group mean values with standard deviation and range unless otherwise noted. Data were analyzed (SPSS Inc, Chicago, Ill) using paired *t* tests to measure subjects' preresponses and postresponses. To evaluate the reduction of MIDAS severity grade, Wilcoxon signed rank statistics were used. A two-tailed *P* value <0.05 indicated a significant difference.

RESULTS

Headache Demographics (Table 1).—All 25 patients met IHS criteria for episodic migraine and proposed criteria for transformed migraine. Seven patients (28%) had migraine with aura and 18 (72%) had migraine without aura. Nineteen (76%) reported symptomatic overuse of medication including simple analgesics, combination analgesics, narcotics, or triptans on a daily basis (more than 15 doses per month). Twenty-two patients (88%) were women with an average age of headache onset at 25 years. All patients reported an average of 10 years with episodic migraines and 10 years with chronic transformed migraines.

Table 1.—Patient Demographics[a]

Feature	Study Group (N = 25)
Sex	
Female	22 (88)
Male	3 (12)
Age, mean (range), y	45 (31-65)
Age at headache onset, mean (range), y	25 (11-40)
Type of headache	
Migraine with aura	7 (28)
Migraine without aura	18 (72)
Episodic migraine, median (SD), y	10 (7.41)
Range	2-30
Transformed migraine, median (SD), y	10 (9.22)
Range	1-30
Symptomatic medication overuse	
Yes	19 (76)
No	6 (24)

[a]Values are number (percentage) unless otherwise indicated.

Implant Demographics (Table 2).—The average length of follow-up was 18.3 months. The average age at the time of stimulator implant was 43.8 years. Patients applied low frequencies (mean 55), low voltages (mean 3.2), wide pulse-widths (mean 400), and activated a mean of 2.3 cathodes per electrode to achieve optimal control of headaches. These settings were independent but not randomly preferred by patients during postimplant programming sessions. Sixty percent of patients used stimulation intermittently, while 40% applied it continuously (usually at lower levels) even in the absence of headache. Patients chose the mode of stimulation (intermittent or continuous) depending on their symptom profiles. They used it intermittently if they were able to completely abort headaches, and continuously only after headache cessation to maintain pain-free periods. The baseline characteristics between these 2 groups did not differ. Average stimulation time to stop a headache was 24.5 minutes.

Complications included traumatic migration in 6 patients (motor vehicle accident and fall) and spontaneous migration in 3 (unknown cause). All migrations were successfully repositioned. One pa-

Table 2.—Implant Demographics[a]

Feature	Study Group (N = 25)
Implant follow-up, mean (SD), mo	18.3 (8.201)
Range	9-36
Age at implant, mean (range), y	43.82 (20-64)
Frequency, mean (range)	55 (25-80)
Pulse-width, mean (range)	400 (250-450)
Power setting, mean (range)	3.2 (1.8-7.5)
Cathodes/electrode, mean (range)	2.3 (1-3)
Stimulation use patterns	
Time to cessation, mo	24.5
Use intermittently to abort, %	60
Use continuously, %	40
Complications, No.†	
Traumatic electrode migration	6
Spontaneous electrode migration	3
Infection	1
Total device experience, mo	457

[a]All patients implanted with bilateral Pisces-Quad Plus electrodes attached to a single Synergy Dual Programmable Internal Pulse Generator (Medtronic Neurological, Minneapolis, Minn).
†All traumatic migrations were incident related (motor vehicle accident, fall, etc). All migration and the single infected patient underwent successful electrode repositioning.

Table 3.—Headache Stimulation Responses[a]

Feature	Study Group (N = 25)
Headache frequency, mean (SD)/90 days	
Prestimulation	75.56* (26.81)
Poststimulation	37.45* (7.49)
Headache severity, mean (SD), 0-10	
Prestimulation	9.32* (1.28)
Poststimulation	5.72* (3.31)
Positive responders, %	88
MIDAS disability reduction, mean (SD), %†	88.7 (5.72)
Range	50-100
MIDAS score, mean (SD)	
Prestimulation	121 (56)
Range	29-240
Poststimulation	15 (25.1)
Range	0-90

[a]Paired-sample t test, $P<.001$. Defined by 50% or greater improvement in frequency or severity of headache. MIDAS indicates Migraine Disability Assessment.
†Migraine Disability Assessment scores are obtained by simply summing the five items covering activity limitations in uniform units of days of missed activities.[6]

rient suffered an infection 6 months postoperatively and was reimplanted successfully 2 months after explantation. Total reported device experience is 457 months.

Headache Stimulation Responses (Table 3).—Significant reduction in headache severity, frequency, and disability was seen with C1 through C3 PNS. Prior to stimulation, patients reported 75.6 headache days (average severity, 9.32 on a scale of 0 to 10) over an average 3-month period. After stimulation, this dropped to 37.5 days (average severity, 5.72) over the same time frame. Eighty-eight percent of patients were positive responders as defined by 50% or greater improvement in frequency or severity of headache. Average reduction in the MIDAS score was 88.7% (range, 50% to 100%), with the average MIDAS score before stimulator placement of 121 and after stimulator placement, 15. Patients who did not achieve or lost paresthesia of the C1 through C3 dermatomes had immediate relapse of their head pain symptoms.

Pain Relief, Disability Scores, Patient Satisfaction, and Symptomatic Overuse.—Prior to stimulation, all patients experienced severe disability (grade IV). Following stimulation, 15 patients reported little or no disability (grade I), 1 reported mild disability (grade II), 4 reported moderate disability (grade III), and 5 continued with severe disability (grade IV). However, all patients reported that their headaches remained well controlled (successful pain relief), beginning immediately after implant and thereafter maintained over the duration of the study, and that they would repeat the implant procedure again. Twenty patients (80%) reported 75% or greater pain relief, 5 reported 50% or greater pain relief, and none reported less than 50% relief. Symptomatic medication overuse, as defined by more than 15 doses per month, was present in 76% of patients prior to stimulation. After stimulation, most patients used less than 15 symptomatic medication doses per month for residual symptoms.

COMMENTS

Significant reduction in headache severity, frequency, and disability was seen with C1 through C3

PNS. Prior to stimulation, patients reported 75.6 headache days over an average 3-month period. After stimulation, this dropped to 37.5 days. Prior to stimulation, average severity was 9.3 on a scale of 0 to 10. After stimulation, average severity was 5.7 (both over a 3-month period). Average reduction in the MIDAS score was 88.7%, with the average MIDAS score before stimulator placement of 121 and after stimulator placement, 15. Eighty-eight percent of patients were positive responders as defined by 50% or greater improvement in frequency or severity of headache.

In our study, patients were able to reduce transformed migraine frequency, severity, and disability. These results could reflect placebo response, regression to the mean, or spontaneous improvement. Nine of our patients after stimulator placement still had grade III or IV MIDAS scores. However, these 9 patients had a 69% reduction in their overall MIDAS score. In addition, all 9 patients either had a 50% or greater reduction in the frequency or severity of their headaches. Thus, one can appreciate how these 9 patients still felt their headaches were well controlled. In the end, the overall robust results of the study raise the possibility of a true treatment response.

Recent studies have suggested that the activation of peripheral nociceptors, increased on-cell activity, and decreased pain inhibition may act at the trigeminocervical complex to produce transformed migraine.[1] Could C1 through C3 PNS modulate these neuronal circuits creating a true treatment response?

Understanding functional neural anatomy such as the trigeminocervical complex and how information from anterior intracranial structures, dura mater, and blood vessels project to this anatomic area is important in formulating potential treatment options (Figure 2).[8]

The possibility that just as the trigeminocervical complex received input from sensory afferents of meningeal vessels and dura, it may also receive continuous bombardment from C1 through C3 sensory afferents in patients with transformed migraine (Figure 2).[9]

By altering the incoming peripheral sensory nociceptive input from C1 through C3 with stimulation, we could potentially abort central sensitization (Figures 3 and 4). Acting at the trigeminocervical complex, it appears we may be polysynaptically reducing excitatory transmitters that augment pain. The dorsal horn is the site of state-dependent neuronal plasticity and structural modifications (Figure 4). In essence, if this cascade of events is interrupted preemptively, head pain response can be aborted or controlled, thus reducing headache frequency, severity, and disability (Table 3).

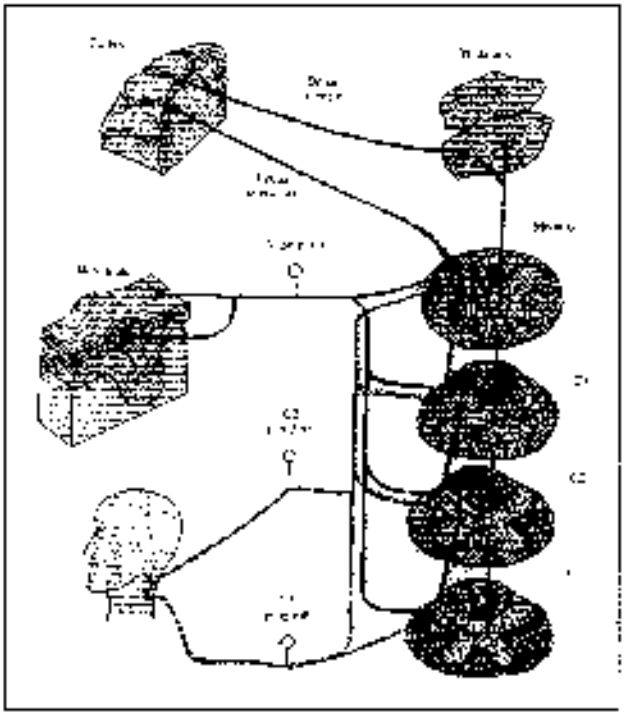

Fig. 2.—Pain transmission and modulation via trigeminovascular and trigeminocervical systems. Anterior intracranial structures dura mater, blood vessels via trigeminal ganglion, C1 through C3 input via C1 through C3 ganglion, and descending inhibitory pathways through the locus coeruleus converging on the same neuron of the trigeminocervical complex.[8]

Could we also be affecting other neuronal circuits such as on-cell activity and central pain inhibition that also process information at the level of the trigeminocervical complex?

Increased on-cell activity may enhance the central nervous system's (CNS) response to both painful and nonpainful stimuli, and modulate the activity of the trigeminal and dorsal horn neurons.[7,8] Also, symptomatic overuse in patients with transformed migraine may facilitate nociception via on-cells within the rostroventromedial medulla.[8] As seen, 76% of our patients were overusing symptomatic medications. Indeed, some forms of chronic daily headache may

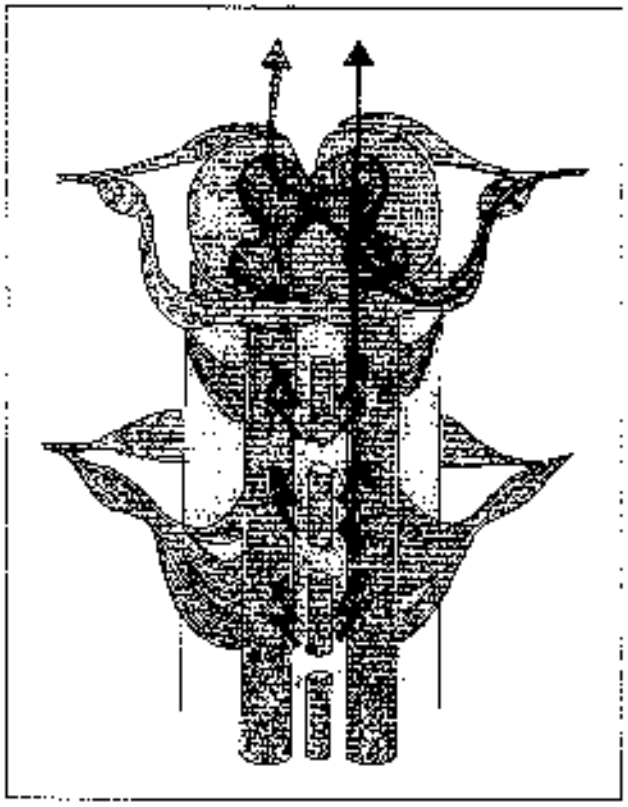

Fig 3.—Mode of action of spinal cord stimulation. Antidromic excitation of low-threshold fibers in dorsal columns is believed to activate inhibitory circuits in the dorsal horn. The simultaneous orthodromic activation of dorsal columns may activate supraspinal-gating mechanisms.[1]

result, in part, from neuronal activity in the trigeminal nucleus caudalis as a result of enhanced on-cell activity.[8]

In addition, the CNS contains neural networks that inhibit/modulate pain transmission.[8] These include noradrenergic inhibitory projections from the insular cortex and hypothalamus which descend to the trigeminal nucleus caudalis and the upper cervical dorsal horn (Figures 2 and 4).[9] Dysfunction within this descending inhibitory system over time could facilitate the development of chronic headaches and may be important in the clinical evolution of transformed migraine.[9,10]

How physiologically could we affect various neuronal circuits related to pain transmission/modulation at the level of the trigeminocervical complex with peripheral nerve stimulation? It has been demonstrated that neuronal activity evoked by peripheral noxious stimuli in the deeper part of the dorsal horn may be

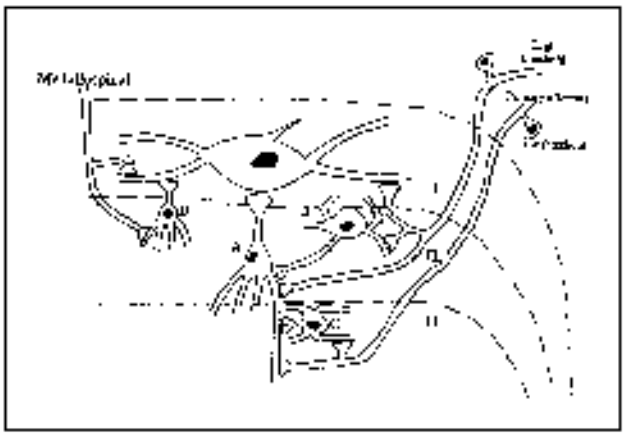

Fig 4.— Local circuitry in the superficial dorsal horn. Nociceptive inputs transmitted via high-threshold and low-threshold primary afferent fibers. The schema also illustrates possible descending control mechanisms (D). These may be exerted directly upon dorsal horn projection neurons. Polysynaptic inhibition and excitation occur.

inhibited by stimulation of the dorsal columns.[11–13] It is also known that stimulation of the dorsal columns gives rise to antidromic activation of collaterals in the dorsal horn.[11,12] This indirect activation via interneurons, or direct activation via presynaptic and postsynaptic neurons, may inhibit second-order nociceptive neurons (Figure 4, A, B, and C).[14] Thus, stimulation of low-threshold, primary afferent fibers may result in reduced nociceptive sensory input that subsequently reduces central sensitization. In addition, with reduced nociceptive sensory input, headache frequency and severity could be reduced leading to improvement in medication overuse. This yields a gradual return to less severe episodic headache patterns (Table 3). As the descending inhibitory projections converge at the trigeminocervical complex, stimulation may be modulating pain transmission by decreasing nociceptive transmission at the C1 through C3 level.

Patients who did not achieve or lost paresthesia of the C1 through C3 dermatomes had immediate relapse of their head pain symptoms.

In addition, with stimulation, our patients noted that touch, vibration, pressure, and hair movement sensibilities were altered in their occipital scalp (dermatomes C1 through C3). This suggests stimulation

activation of A alpha and beta fibers via the dorsal columns.

Furthermore, pinprick sensation remained unchanged with the stimulator on, corresponding with smaller-diameter A gamma and C fibers. This supports the supraspinal gate control theory, postulating that dorsal column stimulation effects are mediated via the dorsal horn (Figure 3).[5] These observations also highlight the importance of full activation of the dorsal columns, orthodromically and antidromically, to achieve headache symptom control (Figure 3).

CONCLUSION

Peripheral nerve stimulation of C1 through C3 was successfully used for reducing refractory transformed migraine severity, frequency, and disability. This modality may be influencing the trigeminocervical complex via the upper cervical dorsal horn, and thus represents a new treatment modality that may provide benefit to patients. In addition, this study may provide ideas for further research to refine our understanding of anatomy and physiology of neuronal circuits. With this knowledge, we may develop potential treatments with exclusive neural action. We must also, as yet, better understand the inhibition of pain transmission by reduction of such excitatory neurotransmitters as glutamate, substance P, and calcitonin gene-related peptide and the modulation of this transmission by inhibitory GABAergic interneurons. Both systems are present at the trigeminocervical complex. With ongoing neuromodulatory treatment, the potential for further disease modification is possible. Controlled prospective studies are warranted.

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