Optimizing Neuropathic Pain Relief With Scrambler Therapy

A review and retrospective study on the effectiveness of scrambler (stimulation) therapy to reduce noncancer-related neuropathic pain syndromes, with apparent, maximal pain relief achieved at 1 to 2 weeks.

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Minimizing the incidence of medication dependence in patients with chronic neuropathic pain (NP) poses significant difficulty for treating physicians. A recent increase in accidental deaths related to prescription opioid use has boosted the investigation of novel techniques for the treatment of chronic pain.[1] In addition to the risk of opioid dependence, chronic pain patients suffer from a wide range of secondary medical conditions, including mental health difficulties and physical disabilities.[2] Given the need for simultaneous treatment for chronic pain and associated comorbid conditions, pharmacological interventions alone are often inadequate when managing complex chronic NP syndromes.[3]

Scrambler therapy alleviates chronic pain relief with a novel, noninvasive stimulation. Photo credit: Edmond Boese, MD, Eagle, ID

Efforts to minimize risk of harm to chronic NP patients and their families prompted the development of noninvasive and nonpharmacological interventions.[4] This trend toward more comprehensive and personalized standards of care will likely aid in appropriately relieving pain in patients suffering from NP syndromes, and will allow physicians to more directly address any associated medical conditions.

Among the novel alternative treatments for chronic NP syndromes is a patient-specific neurostimulative technique called scrambler therapy (ST). Scrambler therapy uses a noninvasive transcutaneous electrostimulation device that has shown promise for providers and patients seeking alternatives to traditional pharmacological pain relief techniques. Scrambler therapy works by introducing a pleasant sensation that acts as a distraction by sending a new message to nerve fibers that were used to receiving pain signals.

This retrospective review aims to shed light on the nature and extent of pain relief experienced during and across stimulation visits. The authors hypothesize that ST will reduce pain ratings for patients with a variety of chronic NP syndromes across and within stimulation visits.

Scrambler Therapy Promises Sustained Relief From Chronic Pain

Scrambler therapy was designed primarily as a method for treatingcancer-related pain syndromes like chronic chemotherapy-induced peripheral neuropathy (CIPN).[5] Researchers explored the application of ST as a way of alleviating pain in cancer patients when metastases in the epidural space prevented use of nerve blocks and opioids from offering sufficient relief, and when adverse side effects prohibited achievement of adequate pain relief.

A preliminary case series reported findings of effective pain relief for 3 patients who were affected by severe cancer pain.[6] In a separate pilot study of patients with CIPN, ST reduced pain scores by 53%, tingling by 44%, and numbness by 37%.[7] This same study indicated that pain-relieving benefits of ST were sustained through 10 weeks of follow-up care. In another study, Coyne and colleagues measured changes in pain level on the Numerical Pain Rating Scale (NPRS)—a pain rating scale with 0 corresponding to “no pain” and 10 corresponding to “worst pain imaginable.” They found that when cancer patients were allowed to mark decimal points, pain ratings decreased from 6.6 before treatment to 4.6 over 3 months.[8]

Initial success in alleviating cancer-related NP syndromes allowed ST to emerge as a potentially successful treatment for a broader category of NP syndromes, including postherpetic neuralgia, low back pain, polyneuropathy, and peripheral neuropathy.[4] Marineo et al aimed to directly compare ST to guideline-based drug therapy for patients grouped into a larger category of poly- or mono-radiculopathy.[4] This randomized pilot study provided preliminary evidence that the neurostimulative technique may successfully alleviate pain better than pharmacology, reporting a mean rate of pain reduction of 91% in the first month of ST.[4]As personalized noninvasive treatments develop, growing evidence has been presented in favor of these devices to successfully alleviate chronic pain over time.[7,9]

In a recent examination of ST, this method produced a reduction in chronic pain from a pretreatment score of 7.41 to 1.60 pain score (based on NPRS) following 10 sessions of treatment.[9] This comprehensive study also divided patients into several broad categories of chronic pain, ultimately suggesting that the ST's efficacy may be dependent on pain type. While promising, these pain rates and time frames for pain relief in patients with general chronic pain syndromes differed from those reported in the studies examining ST in a population of CIPN patients.[7,8]

Reports of inconsistent rates and time spans for achieving pain reduction reflected an urgent need for further research concerning the mechanism and efficacy of ST. Of particular interest to researchers was identifying the length of time necessary for ST to achieve consistent, maximal benefit. Additional considerations in pursuing this research included whether specific types of NP syndromes, pain locations, and severity levels were better suited to favorable treatment response with ST.

This retrospective review was conceived to bolster the current evidence basis by examining the efficacy of repeated ST treatments over time through a lens of specific NP conditions.

Pain Relief From ST Assessed Across Multiple Conditions

A retrospective chart review was conducted among 25 patients who received ST as administered by a neurologist between 2014 and 2015 at an outpatient pain management clinic in Hopewell, New Jersey.[10] Basic demographic factors, including age and sex, were gathered. Pain-related data was also collected for pain diagnosis or classification, areas of pain, and descriptive characteristics of reported pain. Concomitant medications and pre- and post-stimulation blood pressure were noted.

Stimulation treatment details were gathered, including side effects, frequency (volume) of stimulation, location of treatment, dates of treatment, and number of treatments.

Institutional review board approval was obtained for this chart review,[10] which met compliance standards and ethical guidelines set by the participating institution.

Assessment and Collection of Pain Experiences

During patient visits, baseline diagnoses of pain were ascertained through physician consultation and completion of a Diagnosing Neuropathic Pain Questionnaire (DN4). The DN4 used pain characteristics such as burning, painful cold, electrical shock, tingling, pins and needles, numbness, itching, touch hypoesthesia, and pinprick hypoesthesia. The pain assessment revealed characteristics of pain from which pain types were categorized for each patient. Concomitant medications were also noted prior to treatment. Each patient sat in a recliner chair while a technician examined the skin for excoriations or lesions. Then, stimulation was delivered by the FDA-approved MC5-A Calmare Device (Fairfield, Connecticut).[11] Stimulation sessions to deliver pain relief typically lasted 45 minutes per patient. The number of stimulation sessions and location of surface electrodes varied based on the individual course of treatment. Visits 1-10 were attended by 16, 16, 14, 10, 9, 7, 6, 6, 6, and 4 patients, respectively.

Like the conventional transcutaneous electrical nerve stimulation (TENS) devices, the average scrambler stimulation will deliver a charge of 38.8 C.[11,12] ST has been found effective and safe for treatment of CIPN and a variety of neuropathic pain conditions, but it is contraindicated in patients with implanted pacemakers or automatic defibrillators, aneurysm clips, vena cava clips, skull plates, the presence of hardware (eg, cage and rods), intrathecal pumps, and spinal cord stimulators, as well as patients with a diagnosed psychosis or other severe uncontrolled mental illness.[10,12] Upon initiation of the stimulation, patients reported experiencing a reduction in pain and felt a sensation of pressure or rippling instead.[11,13] The procedure was intended to introduce a painless message, rather than introduce an exogenous process.[13] In other words, through changes in brain plasticity, the process was expected to create a new pain sensation that prompted the brain to anticipate a non-pain signal, preferring it to the prior pain. The outcome of this procedure was intended to have the patient arrive at an improved state of homeostasis.[13]To reach a new level of plasticity, the treatment regimen usually required 10 30-minute to 1-hour sessions.

Patients' pain scores were recorded at 3 intervals: prior to receiving stimulation; 15 to 20 minutes into the procedure; and post-stimulation, using the NPRS. Patients were

instructed to complete pain diaries, keeping track of both NPRS pain rating and narrative comments in between treatment periods. Patients who experienced varying degrees of pain severity were treated with the Calmare device regardless of their comorbidities or intensity of pain. Descriptive statistics and independent samples t-tests were used when appropriate.

Charts from 25 patients were reviewed to gather results of pain response to ST. This retrospective review included data from 9 men and 16 women, 28 to 83 years old. The range of diagnoses included idiopathic peripheral neuropathy (upper and lower extremities), complex regional pain syndrome (CRPS), radiculopathy of the back, trigeminal neuralgia, neuropathic groin pain, and postherpetic neuralgia (Figure 1). Of the patients, 68% were concomitantly taking medications, including pregabalin, gabapentin, topiramate, alprazolam, clonazepam, carbamazepene, primidone, lorazepam, and diazepam. Pain diaries revealed that no adverse events occurred as pertained to the ST.[10]

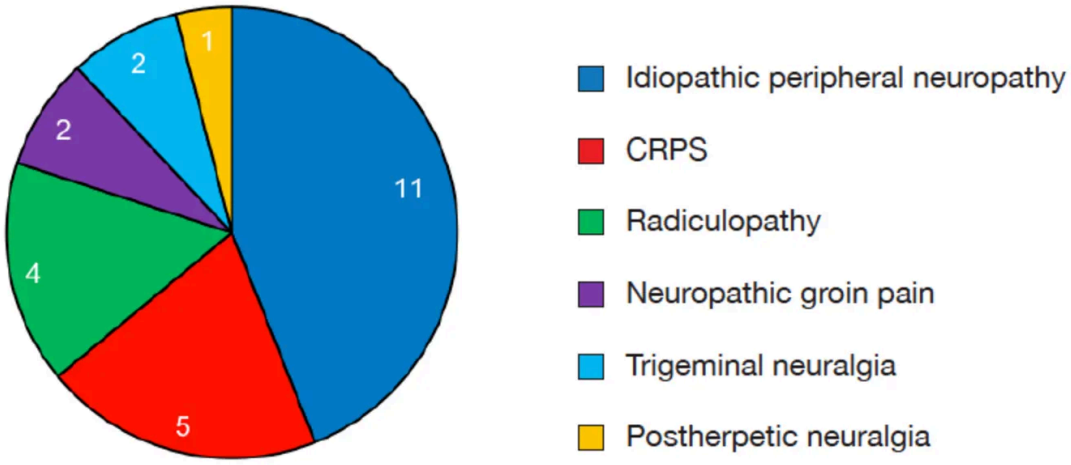

Figure 1. Patients categorized by type of neuropathic pain (n = 25).
CRPS, complex regional pain syndrome

Across all patients and visits, the mean pain ratings were 3.6 ± 1.4 for pre-treatment response, 2.0 ± 0.9 at mid-therapy, and 1.9 ± 0.8 at the end of treatment.[10] Overall, pain decreased across individual ($P < 0.03$) and multiple treatment visits ($P < 0.02$) (Figure 2).

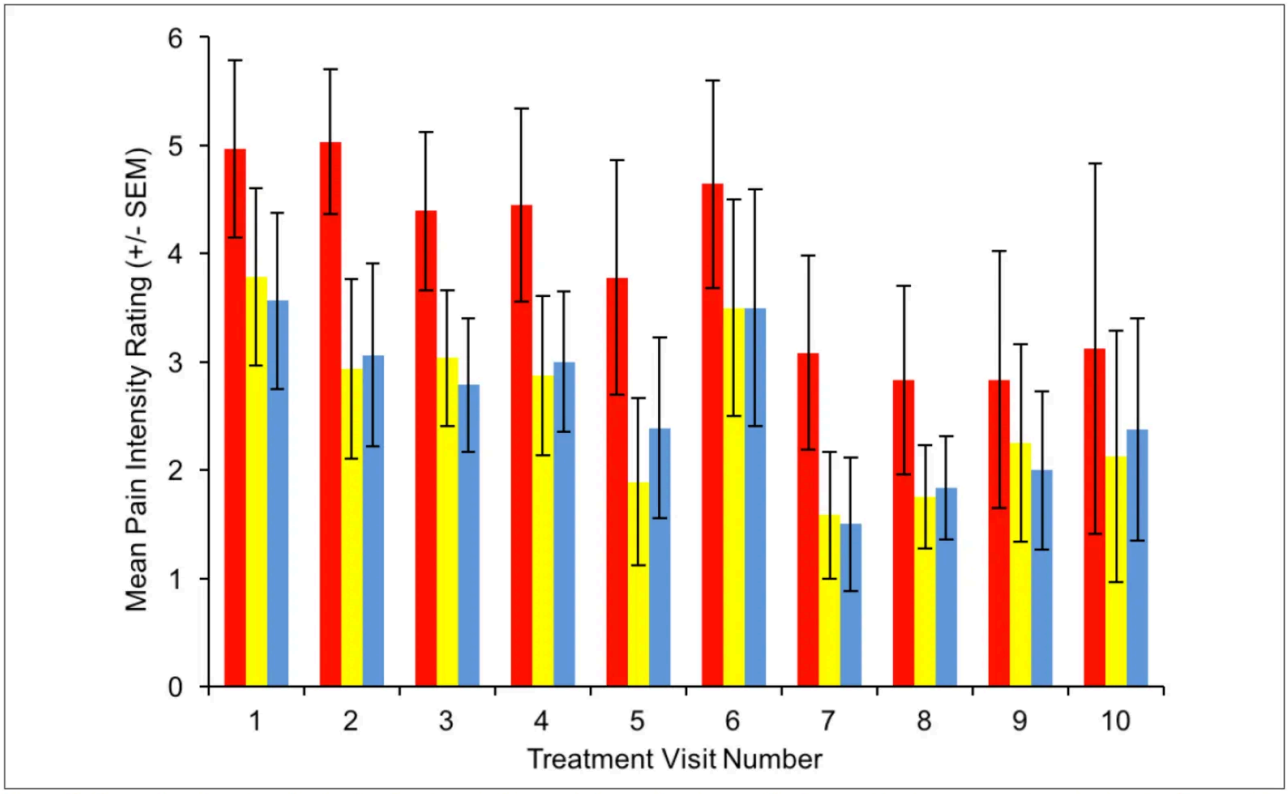

Figure 2. Mean pain ratings for patients attending visits 1-10, pre-, during, and post-scrambler therapy. Blue bars represent pre-treatment ratings, red for during treatment ratings, and green for post-treatment ratings. Asterisks indicate significant decreases in pain ratings found from pre- to post- and from pre- to during ratings ($P < 0.05$). Patients who did not attend more than 1 visit were excluded from this figure (n = 9). Visits 1-10 were attended by 16, 16, 14, 10, 9, 7, 6, 6, 6, and 4 patients, respectively.

While no significant interaction was found between reduction in pain over the course of single and multiple visits, the data offered the possibility for an interaction ($P \leq 0.1$). Of the 16 patients who attended more than 1treatment visit, significant decreases in pain ratings were found in comparing the pre- and mid-treatment ratings for visits 1, 2, 3, 4, 5, and 7 ($P < 0.05$). Similarly, significant decreases in pain ratings were found between pre- and post-treatment ratings for visits 1, 2, 3, 4, 5, and 7 ($P < 0.05$).

The number of patients attending visits decreased over the course of treatment, with a noticeable drop-off after the first visit. The first visit was free of charge and gave patients an opportunity to assess the potential benefit of the treatment. Continuation of treatment presented a significant financial burden and may explain the reason many patients decided not to continue treatment. Another possible explanation for the patient drop-offs in treatment was the extended time commitment, in both lost work or child-care hours, and need for transportation for 10 sessions. For those patients who continued treatments, this may be a reflection that they felt the treatment worked effectively; they stopped when they felt they did not need further stimulation.

Fifteen patients were also treated for secondary pain that was musculoskeletal in nature. In most cases, baseline pain was lower than that reported for the primary pain site. For secondary areas of pain that were not related to musculoskeletal pain, no significant pain reduction was observed across visits (P = 0.1) or stimulation time frame (P = 0.4).[10]confirming prior observations by others.[7]

Patient Pain Response Following Stimulation Therapy

There is mounting evidence for the efficacy of ST stimulation in decreasing chronic pain across several pain types.[7,9,14] However, reliability in the observed rate of pain reduction has remained variable.[4,7,8] The variability of pain reduction may have occurred as a result of differing study parameters, the many different types of pain, locations of pain, or starting pain severity.[15] Difficulties in identifying the mechanism or root of pain also may have contributed to difficulties in diagnosing and distinguishing between different types of pain.[16,17] Given the challenges in measuring changes in pain experiences, ST may need to be examined through the lens of specific NP syndromes in order to provide satisfactory evidence of reduced pain in patients with NP.[18]

The types of chronic pain discussed in prior studies included postherpetic neuralgia, chronic low back pain, polyneuropathy, peripheral neuropathy, and CIPN.[7,9] A few studies examined the therapy with respect to 1 specific type of pain. One study reported pain reduction as a result of ST in patients with cancer-related pain induced by bone and visceral metastases.[11]Patients with postherpetic neuralgia have also been examined separately to determine whether pain relief is experienced with stimulation.[14] In addition to cancer-related pain syndromes and postherpetic neuralgia, low back pain has been examined with regard to efficacy of ST.[19]Preliminary findings of this sham-controlled study suggested that low back pain can be decreased significantly with 10 sessions of stimulation; however, Starkweather et al called attention to significant differences in pain sensitivity and differential mRNA expression of 17 pain genes as well.[20] Positing that mRNA expression and pain sensitivity are altered as a result of ST may serve as a first step toward identifying the mechanism of cutaneous electrostimulation.

The change in mRNA expression may indicate that ST can have long-lasting or sustained therapeutic qualities, especially if the stimulation affects an individual's pain sensitivity. This finding further complicates an understanding of pain outcomes given the involvement of various locations and types of pain, which may have responded differently.

These findings in conjunction with the timing of pain reduction identified by the small retrospective study may aid in elucidating the timeline for efficacy of ST in the subcategory of NP syndromes.

Our retrospective study[21] reflects the general trend in research, suggesting that ST may be an effective treatment for reducing pain intensity in patients with various types of NP syndromes. The chart review of patients with NP syndromes shows an overall decrease in pain across individual and multiple ST treatment visits. This general finding supports the few existing studies concerning the therapy's efficacy, but does so in a population affected more specifically by noncancer-induced neuropathic conditions: idiopathic peripheral neuropathy, CRPS, radiculopathy, trigeminal neuralgia, neuropathic groin pain, and postherpetic neuralgia. These conditions include some neuropathies not previously studied for efficacy of treatment with ST.

In addition to the overall pain reduction observed, our findings show significant decreases in pain from pre- to post-treatment ratings within each visit. Visits with significant decreases in pain from prestimulation to during, and from pre- to poststimulation include 1, 2, 3, 4, 5 and 7. As sample size was reduced with patients dropping out, the statistical power became too small to see significant differences in pain relief from visits 6 and 8 through 10. These data provide preliminary insight into how many treatment visits may be necessary for optimal pain relief in the short term. There is currently very little quantitative data that speaks to the longevity of the therapy's efficacy. Subsequently, a prospective study may aid in determining the number of treatment visits, the length of stimulation, and stimulation parameters necessary to achieve the best pain relief over the longest period of time.

Alternatively, this study only displayed a significant decrease in pain when primary areas of pain were being treated with ST. This suggests that the severity of pain, in addition to the location of pain, plays a role in ST's ability to alleviate symptoms. These findings are consistent with the notion that ST is better suited for those patients with neuropathies as opposed to musculoskeletal pain.[9] Thus, more research regarding how severity and location of pain influences ST's efficacy are warranted.

This retrospective study has significant limitations inherent to the methodology. Patients with a variety of pain syndromes, pain intensity, comorbidities, and medications were included in the study. The small sample prevents a meaningful posthoc analysis that

would elucidate the effect of ST on function and either synergistic or negative effect of concomitant medications. Future prospective studies should consider the use of standardized outcome measures to glean the efficacy with regard to improvement of daily function. Despite the limitations of sample size and retrospective nature, this study supports ST as a pain relief device. Additionally, the findings prompt more comparison of the length of treatment, the number of areas being treated, the severity of pain in areas being treated, and specific classification and/or type of pain diagnosis.

Conclusions

This small retrospective study highlights the possible role of ST in alleviating pain in a number of NP syndromes. Although 1 treatment may alleviate pain and is a predictor for responsiveness to treatment, the current recommendation is to treat until the pain has resolved, with a maximum of 10 treatments. Findings from this retrospective study support the use of ST as a potential method for reducing chronic pain for a variety of neuropathic conditions, particularly CRPS.[10] In conjunction with the growing body of literature, this study offers support to clinicians who are looking to recommend a noninvasive stimulation technique as an alternative or supplement to pharmacology or invasive pain reduction strategies.

Larger controlled studies are necessary to validate these findings and provide more definitive evidence for the efficacy of ST for the relief of NP.

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SOURCES

Neurohormones in Pain and Headache Management: New and Emerging Concepts

The authors discuss a special set of neurohormones with pain-related functions, which if tapped for their intrinsic use, may diminish the need for opioids.

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The recent discovery and awareness that the central nervous system (CNS) makes specific hormones for intrinsic use in addition to those for peripheral use is a profound finding that is critical to clinical pain and headache management. Some neurohormones provide the physiologic effects of neuroprotection and neurogenesis that are essential for pain reduction, prevention, and treatment.

Following is an attempt to provide an early status report on what we do (and don't) know about the function of neurohormones relative to pain management. Be clearly advised that this report is elementary and, undoubtedly, will be subject to expansion and revision as more basic science and clinical experience are accumulated. This review looks at 8 neurohormones that are in early clinical use.

Definition of Neurohormones

The CNS, including the pituitary gland, produces numerous hormones, but relatively few are known to have pain-related functions within the CNS.[1-22] For the purposes of this article, we define a neurohormone as a hormone that is produced, retained, and has functions within the CNS that promote pain control. Additional hormones surely will be found.

Table 1 lists the 8 neurohormones that have been identified as affecting pain. Five of these are called neurosteroids because they have the steroid moiety (4 carbon rings) as part of their chemical structure.[9-10] These are dehydroepiandrosterone (DHEA), estradiol, pregnenolone, progesterone, and testosterone. The 3 remaining neurohormones are human chorionic gonadotropin (HCG), human growth hormone (HGH), and oxytocin.

We did not include hormones that are produced in the peripheral endocrine system and then transported by arterial blood into the CNS for biologic actions, such as cortisol, epinephrine, thyroid hormones, or insulin.[11-13] Also excluded from discussion are endorphins, prolactin, melatonin, vitamins (ie, D2 and D3), dopamine, cytokines, and various releasing hormones because, although they may have a pain modulatory function, they are generally considered neurotransmitters or neuromodulators. At this time, many of these hormones cannot be readily measured in serum or formulated into compounds.

Neurohormones appear to have 3 basic pain control functions: analgesia or pain modulation; neuroprotection of CNS cells; and neurogenesis, defined as re-growth of damaged tissue.[14-21] Table 2 outlines the biologic actions of neurohormones. Neurohormones likely exert some neuromodulatory and transmission effects, and some appear to have direct analgesic properties. For example, oxytocin is known to surge during childbirth as a component of natural anesthesia.

Serum Testing: Why, When, and How

One of the best uses of hormone profiles is for chronic pain patients who have not responded to a standard treatment regimen and continue to have uncontrolled pain.[22] A hormone profile can measure all 5 neurosteroids; HCG, HGH, and oxytocin testing usually are only available through specialty labs that use early-phase testing protocols with non-standard assays.

A serum concentration of a hormone, such as pregnenolone, progesterone, or DHEA, has adrenal and gonadal sources, as well as CNS sources. Thus, it is unknown how much of a serum neurohormone concentration is from CNS versus peripheral sources. However, pain control requires hormone homeostasis in both the CNS and periphery, so a low serum level can be treated without concern as to which sources are not producing enough. Results from a hormone profile will give the practitioner some clues as to why a treatment regimen is not effective and provide enough information so the clinician can

take measures to help the patient adjust, or modify, his or her regimen to attain better pain control.[22] For example, serum testing is recommended before starting DHEA, pregnenolone, progesterone, testosterone, and estradiol.

Our recommendation is that hormone administration be restricted to patients who show serum deficiencies. A goal of hormone administration should be to bring serum concentrations into the normal or optimal range.

Neurohormones

Progesterone and Allopregnanolone

Although a great deal of basic science and animal research has been conducted on neurohormones,[23-53] prior to 2010 there was little interest in neurohormones other than testosterone for pain management. In 2010, Kilts et al observed that nearly half of veterans returning from the Middle East who experienced persistent pain had low serum levels of allopregnanolone,[23] a metabolite of progesterone.[25,29,43] It was theorized that the pain experienced by the veterans was due to a lack of progesterone, which has been shown in multiple studies to reduce neuroinflammation, oxidative stress, and brain damage in animals.[24,27,33,39] Progesterone also may be a precursor of cortisol, the central hormone in the stress response.

Progesterone is being studied in cerebral vascular accidents and traumatic brain injury (TBI).[39-42] Our preliminary open-label investigation of progesterone is encouraging, but no specific recommendations on its clinical use can be made yet.[27] However, it is important to take a broader look at the pain patient's hormonal status and measure it, even in young men and women. Progesterone cannot be considered ONLY the "baby" hormone anymore!

Dehydroepiandrosterone

DHEA is, on a quantitative basis, the most plentiful hormone in the human body. It circulates in abundance in the form of a sulfated reserve (DHEA-S).[54-73] DHEA, the levels of which decline with age,[59] has been well studied and used as a dietary and hormonal supplement for hyperlipidemia and cardiovascular disorders.[68-73] It also has been a favorite anti-aging and stress-relieving dietary supplement.

Enthusiasm for use of DHEA in pain management began in 1994, when it was found to suppress pain and pain flares in patients with systemic lupus erythematosus (SLE).[68] Since that time, a number of studies have confirmed its effectiveness in SLE. It clearly possesses anti-inflammatory properties and suppresses interleukin 10 synthesis in women with SLE.

In addition to having peripheral anti-inflammatory actions, DHEA also has been shown to be produced in the CNS and have additional critical properties related to pain management.[56] It is neuroprotective and inhibits tumor necrosis factor alpha (TNF-a) and CNS inflammatory markers by inhibiting production of monocytes, astrocytes, and microglial cells. Its neuroprotective action in the CNS is at least partially attributed to conversion to estrogen and estradiol.[54]

In our experience, serum DHEA and DHEA-S levels regularly are found to be low in patients with severe chronic pain and headache.[22] Many pain practitioners recommend DHEA as a dietary supplement, beginning with replenishment dosing. Some rheumatologists routinely prescribe 200 mg a day in SLE patients because this dosage has been found to suppress inflammation and prevent pain flares in SLE. To date, no studies have reported that DHEA at this dosage is effective in other causes of chronic pain.

Pregnenolone

Pregnenolone is a hormone that is of interest in pain management. [74-99] Low levels of pregnenolone have been found in patients with headaches, migraines, chronic pain, and TBI.[76,79,89,98] It has multiple effects and properties that compel its consideration in all chronic pain patients. First, its history is interesting and instructive. It was first discovered and researched in the 1940s, with studies on energy, stress, and painful rheumatologic conditions.[93-97] Although reports of pregnenolone effectiveness in rheumatoid arthritis (RA) were quite positive, the commercial development of cortisone and prednisone put an end to further investigation of pregnenolone as an analgesic and anti-inflammatory agent.

Pregnenolone has been called the “grandmother” of hormones, secondary to cholesterol, its parent compound. Pregnenolone, which is synthesized in the CNS, adrenals, and gonads from cholesterol, is the most plentiful hormone in the CNS. It converts to progesterone, allopregnanolone, and DHEA.

Pregnenolone's reported pain-related functions in the CNS include neuroprotection; antagonism of the *N*-methyl-D-aspartate (NMDA) receptor, glutamate, and other receptor subtypes; inhibition and augmentation of the g-aminobutyric acid (GABA) receptor; and suppression of microglial neuroinflammatory responses.[88-92] Of particular interest are studies showing that spinal cord injury resolution is enhanced by pregnenolone.[76]

Serum assays are available through local commercial laboratories, and pregnenolone supplements are available without prescription from reliable commercial sources.[22] Serum levels in severe chronic pain and headache patients may be extremely low, according to our preliminary testing in our patients. Little is known about replacement or sub-replacement dosages. We normally recommend a starting dosage of 25 to 100 mg per day. Dosages can then be titrated upward or maintained to achieve a desired effect, such as reduced pain and opioid use, or increased mobility and energy. As much as 600 mg a day was used in the 1940s.[94,95]

Estradiol and Estrogens

Estrogens are produced in the adrenals, gonads, and CNS and peripheral nerves, as well as in microglia.[100-121]Estrogens are believed to modulate NMDA receptors and have some influence on inhibitory descending pain pathways. They, like the other CNS steroids and neurohormones, may suppress glial cell activity and neuroinflammation.[105,106,112]

Painful symptoms of menopause and migraine have been treated successfully with estrogen derivatives,[101,107] but most treatments use synthetic estrogenic substances that are not identical to the naturally occurring hormones. A monthly or bimonthly estrogen injection, primarily in women, is still common practice throughout the United States; more rarely, patients are prescribed implanted replacement pellets of estradiol. Although no one questions the analgesic and pain management potential of estrogens, there has been no consistent identifiable adoption of estradiol or estrogens into contemporary pain management.

There are 2 basic reasons for the lack of use of estradiol and other estrogens in pain management: 1) serum tests are too variable because estradiol levels depend upon age, sex, and menstrual status; and 2) exactly how estrogens modulate pain is extremely complex. For example, estradiol can increase migraine/headache severity in some women but can dramatically reduce or improve it in others.[100,111,117,118]

Without reliable serum ranges of a hormone, it is problematic to replace or replenish it. When a hormone exerts multiple and sometimes opposing analgesic effects, it is problematic to select appropriate patients for treatment. Part of the complexity is that estrogen receptors are located throughout the body, including in the joints, peripheral nerve endings, and CNS. Further, there are 3 derivatives of estrogens in humans: estradiol, estrone, and estriol. It is not known if 1 of these 3 has more relevance to pain/headache management.

The most exacting research with estrogens has been in patients with pain/migraines and RA. Although it is clear that estrogens may influence severity and treatment of these painful disorders, there is no specific consensus or recommendation relative to dosage, as exists partially with DHEA and SLE, and perhaps pregnenolone. Patients with a low estradiol serum level, appropriate for time of cycle and post-menopausal factors, may be given clinical consideration for a trial of low-dose, short-term estradiol. Male estradiol serum levels are available through commercial test laboratories, and low-dose trials in a few men with chronic pain syndrome suggest that further trials should be done. Estrogen should not be considered a “female” drug in pain management, nor should testosterone be considered a “male” drug.[103, 104]

Testosterone

Testosterone is the hormone that is most often addressed in pain management.[122-129]It is included here primarily because there are enzymatic mechanisms in the CNS that can produce testosterone and the other sex steroids.[123] In the CNS, the neurosteroids are highly interconnected and may even metabolize to one another. We know that testosterone is produced in peripheral organs, adrenals, and gonads, and migrates into the CNS, but we are unable to identify any studies that show any appreciable testosterone production in the CNS. Testosterone production is under pituitary control.

Testosterone has well-known analgesic effects, and pain patients who demonstrate serum deficiencies and undergo replacement report better pain and headache/migraine control.[122-127] Unfortunately, testosterone levels are decreased in both genders when opioids are used for pain control. This data is well-known. Unfortunately, testosterone is not always tested for in patients with chronic pain, headaches and/or migraines, and mood and sleep disorders, especially women. We recommend short clinical trials of testosterone in both sexes when low serum levels are detected.[126]

Human Growth Hormone

Little is known about the relevance of HGH[130-133]to pain and headache management. The increasing interest in neurogenesis and curative measures likely will lead to much more interest in this neurohormone. The paucity of knowledge likely is related to its lack of availability and extreme expense. In recent years, the little available commercial supply essentially has been restricted to use in pituitary deficiencies, primarily in pediatric and head trauma patients.

Bennett et al published a few reports on use of HGH in fibromyalgia patients.[130,131] In a double-blind study, HGH provided significant pain relief.[131,133] In 2015, Thomas Romano, MD, PhD, reported at the Academy of Integrative Pain Management (formerly American Academy of Pain Management) in San Antonio, Texas, that patients with fibromyalgia had low serum levels of insulin-dependent growth factor (IGF) and were, therefore, deficient in HGH secretion, providing a rationale for its use in pain management.[134]

Recently, HGH secretagogues and pure HGH have become more widely available and less expensive, with potential indications for chronic debilitating diseases. We have begun preliminary clinical trials but, as of yet, have little to report; however, JCK has anecdotal, positive data indicating that using HGH to improve IGF1 levels improved headaches and fatigue in patients with post-concussive TBI.

Human Chorionic Gonadotropin (HCG)

HCG originally was named because it was believed to be produced only in the placenta of pregnant women.[135-145]Later, it was clearly determined that HCG is produced daily in the pituitary glands of males and females.[135-138] Although it formerly was believed that HCG's primary function was to maintain placental integrity, it is now known that it is composed of 2 separate chemical units, each with a unique biologic function.[138,141-145] One unit provides hormone stimulation and the other angiogenesis and neurogenesis. One hormone unit of HCG actually is a long chain of amino acids that incorporates duplicates of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and thyroid-stimulating hormone (TSH).

One of the uses of HCG is treatment of hypogonadism. In the pain management arena, deficiencies of testosterone, estradiol, progesterone, and thyroid hormone are common,

and HCG may elevate 1 or more of these hormones.

The authors find HCG to be a safe alternative to testosterone replacement in females. The angiogenesis/neurogenesis unit appears to be of clinical benefit in many patients with chronic pain. Open-label trials indicate that HCG may reduce pain and opioid use, enhance energy and mental function, and promote a generalized feeling of well-being.[135]

Compounding pharmacies throughout the country now supply HCG as a sublingual troche, sublingual solution, or subcutaneous injection. Starting dosages are 125 to 250 units 2 to 3 times a week.

Oxytocin

Preliminary studies of oxytocin,[146-158] including one small, double-blind study, indicate that oxytocin has analgesic properties and has a place in both acute and chronic pain management.[147-151, 157] Although its mechanism of action is unclear, it appears to act by inhibition of some neurons that connect the brain and spinal cord.[146, 153-155] Oxytocin is, like the other neurohormones, becoming accessible through local compounding pharmacies. It can be used intranasally or sublingually. Starting doses range from 20 to 40 units a day.

Summary

Over the last 2 decades, research has shown that the CNS produces and retains a special set of neurohormones that have pain control functions. In addition, almost all neuroprotective and neurogenic biologic mechanisms are under some hormonal control. The revelation that a number of hormones with pain-related functions are produced in the CNS without apparent pituitary control compels pain management clinicians to investigate the use of these hormones in clinical practice. DHEA has found solid footing in SLE patients at a dose of about 200 mg per day to reduce pain intensity and flares. Testosterone testing and replacement are now commonplace in pain management since low serum levels are associated with inferior pain control, especially in the setting of opioid management of pain.

There are practitioners throughout the country who are attempting to determine how best to clinically use neurohormones. To date, there are no serious reported complications. Open-label observations suggest that neurohormones are a good adjunct to symptomatic

pain/headache care. They appear to reduce baseline pain and flares, diminish the need for opioids, and, possibly, produce some neurogenesis and healing properties.

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