An Innovative New Treatment for Migraine

By Dr. Sergey A. Dzugan

The following article details a groundbreaking treatment program that achieved a 100% success rate for the cessation of migraine headaches during the study period. The cause and relief of migraine is an extremely complex issue involving hormonal balance, neurochemicals, and metabolic integrity. While this article may appear somewhat complicated, it summarizes years of research that can now deliver relief from migraine. If you or someone you know suffers from migraine, we encourage you to read the following article very carefully and to share it with your physician.

While recent advances in treatment have reduced the symptoms of suffering for millions of migraine patients, the underlying causes of migraine continue to be a focus of debate. In this article, we will present an innovative treatment that cured all patients treated for migraine in a recent study. This study was initially conducted at the North Central Mississippi Regional Cancer Center in Greenwood, MS, in association with Dr. Arnold Smith, and was continued at the Life Extension Foundation.

The Continuing Mystery of Migraine

The history of the treatment of headaches in general, and migraine in particular, predates the current millennium. Around 1500 BC, the Pharaoh's courts of ancient Egypt provided the first descriptions of unilateral headaches accompanied by vomiting and malaise. Of all medical disorders, migraine has one of the longest histories of recognition without sufficient understanding. Beset by myths, uncertain etiology, and inadequate treatment, migraine remains one of the most undertreated neurological conditions today. It seems frustrating that despite the long history of migraine, treatment for this ancient complaint, irrational at times and empirical at others, has evolved slowly and tortuously, yet is still without a universal standard.[1]

Migraine affects about 10-15% of the population in various countries.[2-4] Migraine may occur at any age, but its prevalence increases from childhood up to 40 years of age.[5] Migraine is more common in women than in men. According to the American Migraine Study, 17.6% of females and 6% of males in the US currently suffer from severe migraine.[6]

POPULAR THEORIES TO EXPLAIN MIGRAINE

- Inadequate regulation by the autonomic nervous system[11,12]
- Faulty interaction between the autonomic nervous system and hormones[13]
- Serotonin effect[14]
- Prostaglandin effect[15,16]
- Platelet abnormality[17-19]
- Reaction to decreased oxygen in the blood and tissues[20]
- Vasospasm[21,22]
- Muscle hypercontractility[23]
- Genetic predisposition[24]
- Neural hyperexcitability[25]
- Disruption of normal pain pathways[26]

The numerous theories and hypotheses that have been advanced concerning the causes of migraine are a subject of dispute among experts on the disorder.[7] For example, the theory of migraine as a result of dilated blood vessels in the brain was suggested in the early 1850s by Brown-Sequard and Claude Bernard. Their theory was rebutted, however, when Du Bois-Reymond proposed constriction of the brain's blood vessels as the cause of migraine in 1860.[8]

Today, no single hypothesis readily explains the mechanism underlying migraine.[9] Because of this, new hypotheses continue to emerge but defy acceptance,[10] as shown in the accompanying sidebar. While sufficient scientific data exist to support many disparate hypotheses, scientists have yet to promulgate a single hypothesis that explains all the laboratory findings and clinical observations.

Current Treatment Approaches

From a traditional standpoint, migraine appears to be a primary disorder of the cerebral vessels.[27] Current treatments for migraine includes dietary changes, stress management, proper sleep, hormone replacement therapy, supplements, and prescription drugs.

As one might expect, each hypothesis is accompanied by its own recommended treatment regimen and no single treatment is effective for everyone, or even for a given person with every migrainous attack.

As a result, it is not surprising that so many migraine sufferers (migraineurs) express dissatisfaction with their treatment and discontinue treatment despite continued debilitating migraine. Indeed, 44.5% of patients surveyed reported adverse events after using various drugs for migraine, and these side effects were considered serious in 1.7% of those treated.[28] The adverse events, including dizziness, nausea, headache, tingling of the fingers or toes, difficulty in thinking, and fatigue, are evidence of the need for safer, more effective medications for the treatment of migraine.[29,30] While behavioral management and relaxation training are important complements to pharmacological therapy, drugs remain the mainstay of migraine therapy.[31-37]

In reviewing the medical literature in an effort to determine the cause of migraine, one repeatedly encounters several consistently documented abnormalities:

1. widespread derangement of serotonin metabolism and excessive release of neurotransmitters;[38]
2. hyperexcitability of the brain as a result of low intracellular magnesium levels or increased neurotoxic amino acids; and
3. hormonal imbalance.

DRUGS USED TO TREAT MIGRAINE

- Anti-nausea drugs
- Anti-anxiety drugs
- Anti-inflammatories
- Ergot
- Steroids
- Tranquilizers
- Narcotic pain relievers
- Serotonin promoters

DRUGS USED TO PREVENT MIGRAINE

- Beta-blockers
- Calcium channel blockers
- Antidepressants
- Serotonin blockers
- Anticonvulsants

Several studies performed since the 1960s have demonstrated that migraine is caused by a primary biochemical disorder of the central nervous system involving neurotransmitters, and serotonin in particular. Serotonin has long been implicated as a key neurotransmitter in migraine.[39] The body's serotonin level falls during a migraine attack.[40] Among its other actions, the release of serotonin results in blood vessel constriction in the brain and impaired neural transmission.

The pineal gland, a primary source of serotonin and melatonin, is also known to contribute significantly to migraine attacks.[41,42] Research has found that the pineal hormone melatonin is low in migraine patients,[43] suggesting impaired pineal function.[44] Additionally, several studies have demonstrated that the administration of melatonin to migraine sufferers relieved pain and decreased headache recurrence in some cases.[43,45] It has been suggested that the pineal gland could act as the intermediate causative factor of migraine, via a derangement of melatonin.[42] The melatonin precursor serotonin showed diurnal variations with opposite phases to melatonin synthesis.[46] What this indicates is that serotonin levels rise during the daytime and fall at night. Melatonin levels rise at night and decrease during the day. Stress and dietary habits lead to deficiencies of both serotonin and melatonin. A diminished ratio of melatonin to serotonin leads to a decline in adaptive processes.[47] Also, abnormal circadian rhythms of cortisol may occur in states of decreased melatonin.[48] Our research supports the hypothesis that migraine is a response to a pineal circadian irregularity, and that the administration of melatonin normalizes this circadian cycle;[45] that is, melatonin may play a role in resynchronizing biological rhythm to lifestyle, and may subsequently relieve migraine.

During the last 15 years, many researchers have proposed that migraine is generated by a hyperexcitable brain. A migraine attack can be triggered at any time, depending on the threshold of brain excitability, and in fact, the frequency of migraines is proportional to the excitability level. According to classic theory, a migraine attack is initiated by a cerebrovascular spasm followed by extracranial vasodilatation. This change may be caused by an imbalance in brain biochemistry. Decreased cellular oxygen can cause an increase in the flow of calcium from the extracellular fluid to the intracellular space, resulting in a calcium overload and cellular dysfunction.[49] Disturbances in mitochondrial oxidation reactions, magnesium deficiency, or abnormalities of cellular calcium channels may be responsible for the neuronal hyperexcitability between attacks.[50] We believe that the restoration of calcium-magnesium balance is one of the critical issues in migraine therapy.

Sex Hormones and Headaches

Migraine affects approximately three times as many women as men, suggesting that gonadal steroids may play a role. Furthermore, headaches have been linked to menstrual cyclicity. Migraine attacks occur during menses in 60% of women. Changes in estrogens levels at menarche and during menstruation, pregnancy, and menopause may trigger migraine. Indeed, the physiological decline in estrogens levels that occurs with menstruation, or a therapeutic withdrawal as occurs during hormonal blocking therapy, often precipitates migraine, whereas the sustained high estrogens levels that occur during pregnancy frequently result in relief from headaches.[51,52]

In some cases, estrogens replacement therapy for menopausal symptoms induces headache. The incidence and severity of migraine are also affected by use of oral contraceptives.[53] In migrainous women, 17-beta-estradiol levels are higher in both the follicular (before release of an egg) and luteal (after release of an egg) phases of the menstrual cycle, whereas progesterone concentrations and the ratio of progesterone to estradiol are lower than in healthy subjects during the luteal phase of the menstrual cycle.[54] Menstrual distress was highest during the luteal and menstrual phases of the cycle, and these symptoms were related to higher estradiol levels, higher ratios of estradiol to progesterone, and increased headache activity.[55]

Because of these controversies, we maintain that the main problem is an imbalance between estrogens and progesterone levels rather than the absolute levels of these hormones. This can explain, for example, why migraine was relieved by using Zoladex®, which blocks estrogen release from the ovary and improves the ratio of estrogens to progesterone.[56] Menstrual migraine therefore represents a model that coincides with a neuroendocrine hypothesis.[13] Effects of hormonal imbalances and deficiencies on vasomotor control are clinically significant, and hormonal treatment is often effective in managing various conditions caused by abnormal blood flow, including migraine.[57]

In this way, estrogens are known to exert their influence by modulating sympathetic control of cerebral vasculature.[12] Not surprisingly, various trials have been conducted using estrogens,

progestogens, and dehydroepiandrosterone (DHEA) to manage migraine; the findings from these trials, however, have been inconsistent.[58-60] Despite copious research, the proper therapeutic use of hormones remains in question.[61,62]

The fluctuations in estrogens levels associated with migraine also produce biochemical changes in prostaglandin production, prolactin release, and endogenous opioid regulation. Prostaglandin E2 (PGE-2) is a well-defined mediator of fever and inflammation. PGE-2 increases vasodilatation and thereby induces pain. Estrogens increase the production of PGE-2. An excess of estrogens, deficit of progesterone, or dominance of estrogens can cause increased production of PGE-2, resulting in migraine. Elevation of the prolactin level or increased sensitivity to prolactin leads to a decreased level of prostaglandin E1 (PGE-1). Patients with migraine may have prostaglandin-induced hyper-sensitivity to prolactin. PGE-1 is a substance that in fact improves the microcirculation and leads to the development of collateral circuits with a consequent improvement in local hemodynamics. If the patient has a dominance of PGE-2, we would expect vasodilatation of major arteries with spasm of collateral circuits, which in turn can cause pain. Restoration of hormonal levels and balance between them can stabilize levels of prostaglandins.

Steroid hormones also influence the metabolism of calcium and magnesium. Estrogens regulate calcium metabolism, intestinal calcium absorption, and parathyroid gene expression and secretion, triggering fluctuations across the menstrual cycle. Alterations in calcium homeostasis have long been associated with many affective disturbances. Clinical trials in women with premenstrual syndrome have found that calcium supplementation may help alleviate most mood and somatic symptoms. Evidence to date indicates that women with symptoms of premenstrual syndrome have an underlying calcium abnormality.[63] A low brain magnesium level can be an expression of neuronal hyperexcitability of the visual pathways and be associated with a lowered threshold for migraine attacks.[64] Clinically, it is known that magnesium supplementation relieves premenstrual problems (for example, migraine, bloating, and edema) that occur late in the menstrual cycle, and that migraine, particularly in women, is associated with deficiencies in brain and serum magnesium levels. Testosterone was not shown to produce any significant alteration in magnesium levels, but estrogens and progesterone do.[65]

In some but not all studies, patients with migraine showed a significant reduction of testosterone and a significantly increased cortisol concentration.[66-69] We believe that a normal level of testosterone does not necessarily equate with an optimal level. Little attention has been paid thus far to androgens and their role, if any, in causing migraine.[70,71] Our clinical experience strongly supports the notion that migraine can be managed only when levels of all the basic hormones—pregnenolone, DHEA, testosterone, estrogen, and progesterone—are optimal with the physiological cycle.[72]

A New Hypothesis

The findings just described, in conjunction with our clinical observations, have led us to hypothesize that migraine is a specific consequence of the imbalance between neurohormonal and metabolic integrity. Based on our clinical experience, we have therefore suggested a unifying hypothesis, which we call the Neurohormonal and Metabolic Dysbalance Hypothesis of Migraine. Such a hypothesis not only brings together the many seemingly disconnected research findings for the first time, but also provides guidance for an effective treatment approach.

Migraine is not a single disorder, but a collection of disorders. According to our hypothesis, a migraine involves faulty hormonal feedback in the hypothalamic-pituitary-adrenal-gonadal axis.

Contributing to this hormonal abnormality is an imbalance between two of the three arms of the autonomic nervous system (the sympathetic and parasympathetic nervous systems), which causes a decline in the brain's pain threshold. Because of disequilibrium between intra- and extracellular calcium and magnesium, the polarity of the cell membrane is changed, which affects the electrical stability of the cell membrane and sensitivity to neurohormonal impulses (steroid hormones, melatonin, and serotonin). Lastly, the intestinal flora is altered, which results in abnormal absorption.

The Migraine Solution

The old approach of focusing on the treatment of symptoms was replaced in our study with treating the cause of the disease. Herein we present our clinical experience with a series of particularly difficult-to-treat migraineurs in whom we simultaneously restored neurohormonal and metabolic integrity. We offered our treatment to 23 patients (21 women and 2 men) from May 2001 to May 2004. The patients ranged in age from 29 to 66, with a mean age of 46.7. The main characteristics and clinical summaries of these patients before treatment are reported in Table 1 on the following page.

Table 1. CLINICAL SUMMARY OF PATIENTS WITH MIGRAINE BEFORE TREATMENT

					Concurrent symptoms or illness				
Patient	**Sex**	**Age**	**Illness duration** (years)	**Migraine medicine**	Fibromyalgia	Insomnia	Depression	Fatigue	**Previously used hormone replacement therapy or oral contraceptive**
1	F	52	20	+	+	+	+	+	-
2	F	29	10	+	+	+	+	+	+
3	F	58	9	+	+	+	+	+	+
4	F	52	9	+	-	+	+	+	+
5	F	56	6	+	-	-	+	+	+
6	F	53	6	+	-	+	+	+	+
7	F	42	17	+	-	+	+	+	+
8	F	33	14	+	-	-	+	+	+
9	F	51	20	+	-	+	+	+	+
10	F	53	2	+	-	+	+	+	+
11	F	64	20	+	-	+	+	+	+
12	F	55	13	+	+	+	+	+	+
13	F	38	5	+	-	+	+	+	-
14	F	44	15	+	-	-	+	+	+
15	F	43	30	+	-	+	+	+	-
16	F	39	23	+	+	+	+	+	+
17	F	30	15	+	-	+	-	+	+
18	F	38	20	+	-	+	+	+	+
19	M	35	12	+	-	-	+	+	-
20	M	47	30	+	-	+	+	+	-
21	F	46	34	+	-	+	+	+	+
22	F	66	36	+	-	+	+	+	-
23	F	51	19	+	-	+	+	+	+

All of our patients had attempted—without success—to prevent or treat migraine with up to four standard drugs for periods ranging from 2 to 36 years (with a mean of 16.7 years). Nearly three of four patients (73.9%) had used hormone replacement therapy or oral contraceptives. Concurrent illnesses were noted as follows: fatigue in 100% of patients; depression in 95.7% of patients; insomnia in 82.6% of patients; and fibromyalgia in 21.7% of patients. This was consistent with other reports.[73-76] Fibromyalgia, chronic fatigue, and primary headaches are common and debilitating disorders with complex interactions among each other.[77] We believe that this relationship is based on common abnormalities and that successful treatment is possible.

Following initial consultation, a baseline lipid profile was taken and levels of pregnenolone, dehydroepiandrosterone sulfate, progesterone, total estrogen, and total testosterone were determined through routine blood testing. Serial determinations were made thereafter during treatment.

All patients then underwent a comprehensive treatment program incorporating the following four components:

- hormonorestorative therapy with bio-identical hormones that included a combination of oral pregnenolone, DHEA, triestrogen, progesterone, and testosterone gels
- simultaneous correction of the imbalance between sympathetic and parasympathetic nervous systems and the ratio of calcium to magnesium
- "resetting" of the pineal gland through melatonin supplementation
- improvement of intestinal absorption through restoration of normal intestinal flora with the use of probiotics.

It must be stressed that these four components of the program cannot be separated; they are intertwined and work together. For example, by using estrogens and progesterone, we not only restored hormonal balance, but also helped restore a balance between the sympathetic and parasympathetic nervous systems. The same situation is associated with calcium and magnesium: by restoring metabolic integrity, we also restored balance between the sympathetic and parasympathetic nervous systems.

Hormonorestorative therapy includes a formula that is chemically identical to human hormones and is administered in physiological doses according to schedules intended to simulate natural human hormone production. Patients received treatment with oral pregnenolone, DHEA, and dermal applications of triestrogen (estriol 90%, estradiol 7%, estrone 3%), progesterone, and testosterone gels. All patients had steroid hormone deficiencies before beginning hormonorestorative therapy, with deficiencies in pregnenolone most prominent. Recommended doses to different patients varied significantly and were determined by serum hormone levels obtained during serial testing.

We did not use a standard dose, rigid protocol, or traditional design for this study. Doses were individually selected to produce youthful physiological serum levels. We administered hormones in doses sufficient to achieve circulating plasma levels observed in younger healthy adults between the ages of 20 and 30, who register the highest naturally

occurring levels of all steroid hormones. These levels are at the high end of the normal range specified by the testing laboratory. Sixteen patients (69.6%) had been taking from one to three steroid hormones before beginning hormonorestorative therapy; none of the 16 reported obtaining any relief from these therapies, and all were still experiencing migraine before starting our program. All agents such as equine conjugated estrogens, medroxyprogesterone acetate, and methyl testosterone were switched to bio-identical hormones during treatment. Estrogens were always used in conjunction with progesterone.

Kava Leaf

Throughout the period of hormonorestoration, all of our patients were provided with an oral dose of 420 mg of magnesium citrate taken at bedtime. Patients were also given 3-6 mg of melatonin and 100-250 mg of kava root extract at bedtime. Kava has been shown to be effective as an alternative treatment in mild to moderate cases of anxiety. The pharmacological properties of kava are postulated to include blockade of voltage-gated sodium ion channels, enhanced ligand binding to gamma-aminobutyric acid (GABA) type-A receptors, diminished excitatory neurotransmitter release due to calcium ion channel blockade, reduced neuronal reuptake of noradrenaline (norepinephrine), reversible inhibition of monoamine oxidase B, and suppression of the synthesis of the eicosanoid thromboxane A(2), which antagonizes GABA(A) receptor function.[78] In this study, kava was used as part of the program without side effects. While kava remains on the market, you may wish to substitute L-theanine because of concerns about kava-induced liver toxicity. For the restoration of healthy natural intestinal flora and improvement of absorption, 3.5 billion of the Lactobacillus group (L. rhamnosus A, L. rhamnosus B, L. acidophilus, L. casei, L. bulgaricus), 1 billion of the Bifidobacterium group (B. longum, B. breve), and 0.5 billion of Streptococcus thermophilus were introduced. Migraine is a recurrent clinical syndrome characterized by combinations of neurological, gastrointestinal, and autonomic manifestations.[79] We believe that restoration of natural intestinal flora is a very important element of our program.

Much to our satisfaction, all patients responded to migraine management with this multimodal treatment strategy. None of the patients suffered from migraine after initiating this program (a 100% success rate), indicating that migraine is not only treatable but also curable. Furthermore, the associated symptoms of fibromyalgia, insomnia, depression, and fatigue were resolved entirely.

During the follow-up period, no complications or side effects related to this regimen were cause for concern. Most important, all patients described a significant improvement in their quality of life

Summary

Analysis of the medical literature and our own experience convince us that migraine is a complex disorder that comprises malfunctions in several systems: the neurohormonal system, which includes a feedback loop mechanism between the hypothalamus, pituitary gland, and glands that produce steroid hormones; the sympathetic-parasympathetic nervous systems; the calcium-magnesium ion system; the pineal gland; and the digestive system. All these systems and changes within them are closely interrelated, and each can be a trigger mechanism for migraine. Contradictory results with other migraine treatments—for example, using medications that modulate serotonin—offer additional evidence that the problem is not high or low sympathetic nervous system activity, but rather an imbalance between the sympathetic and parasympathetic nervous systems.

Following this logic, the basic method of migraine treatment must be directed toward restoring integrity between these different systems. In our hands, the simultaneous restoration of neurohormonal and metabolic integrity was an effective approach to the successful

management of migraine.

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