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Physiology Optimization is the key for Migraine Management

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Goal

- to evaluate the effect of a physiology optimization with the use of multimodal treatment program in migraine management

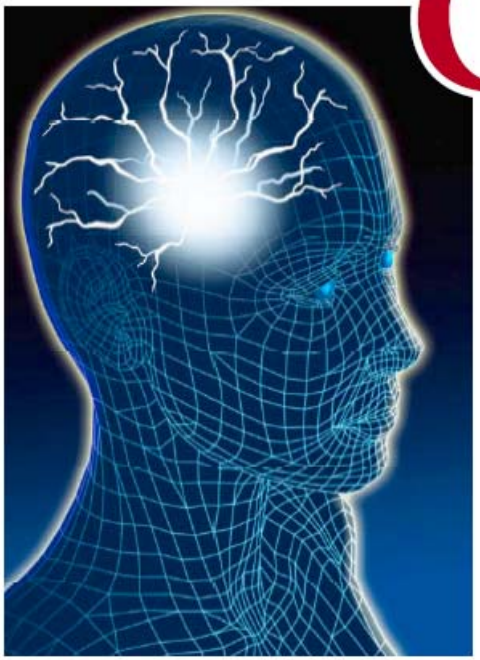
- to test a new hypothesis of migraine as a specific consequence of imbalanced neurohormonal and metabolic integrity

Migraine is one of the most mysterious diseases.

“Headache from hell”

Are You Ready to Get Your Life Back—And Be Permanently Free From The Crippling Pain of Migraines?

The Migraine Cure

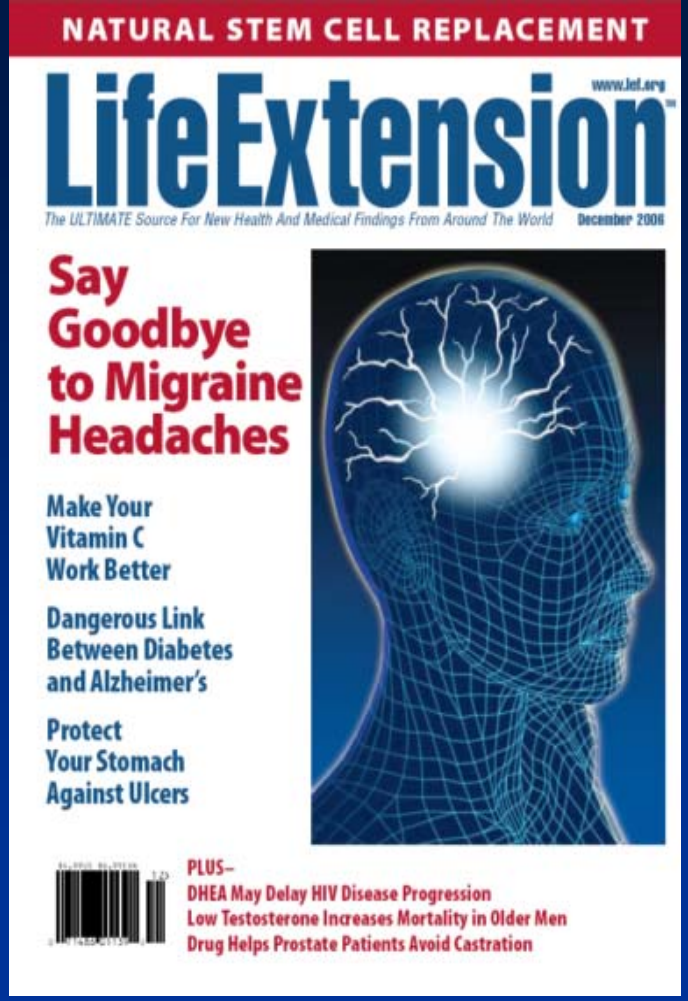


- **No more potentially destructive (and expensive) drugs!** The Migraine Cure is all natural and releases you from the tyranny of powerful medications—forever.
- **No need to change your diet!** The Migraine Cure requires no dietary changes or restrictions to be 100% effective.
- **No lifestyle changes!** The Migraine Cure is not dependent on exercise, environment or climatic changes to guarantee success.
- **No more guesswork, futility and frustration!** The Migraine Cure identifies and delivers exactly what YOU PERSONALLY need in order to be permanently migraine-free—and this is a guarantee.

How to Forever Banish The Curse of Migraines—Using a 100% Effective, 100% Safe, Clinically-Proven, Yet Drug-Free, Medical Breakthrough

Sergey Dzugan, MD, PhD With Deborah Mitchell

A Lynn Sonberg book



Successfully treated patients from around the world

From our point of view migraine is a very complex disorder in several systems and requires Multimodal treatment program

Epidemiology of Migraine

- affects about 10-15% of the populations in different countries [1-3]
- may occur at any age, but prevalence increases from childhood up to 40 years of age [4]
- more common in women than in men. According to the American Migraine Study, 17.6% of females and 6% of males in the United States currently suffer from severe migraine [5]
- has been known for many centuries but despite a decade of progress, migraine remains a prevalent, disabling, underdiagnosed, and undertreated condition [2]

Etiology, Pathogenesis and Pathophysiology

- the specific cause of migraine remains unknown
- the studies on the pathogenesis of migraine have developed into a vast scientific movement in the last years.[6] There are a number of theories and hypotheses concerning the pathogenesis of migraine, but they are frequently conflicting. [7]
- the pathophysiology of migraine is also still incompletely understood [8,9]

A brief list of suggested and investigated migraine theories and hypotheses:

- a neuroendocrine hypothesis [12]
- serotonin (5-HT) involvement in migraine [13]
- central biochemical dysnociception [14]
- vascular theory [10]
- vasoactive effect of prostaglandins [15,16]
- a platelet hypothesis [17-19]
- reactive hyperaemia due to hypoxia [20]
- inadequate regulation by the autonomic nervous system [10,11]

A brief list of suggested and investigated migraine theories and hypotheses (cont.):

- over-reactive temporal artery or skeletal muscle response to stress [21]
- association of lipoprotein abnormalities with children's migraine [22]
- sensory cortex and hypothalamus as initiating sites for migraine [23]
- migraine as a state of central neuronal hyperexcitability[24]
- diffuse disruption of central pain-modulating system as reason for migraine [25]

Current treatments for migraine:

- prescription drugs
- hormone replacement therapy
- supplements
- stress management
- proper sleep
- dietary changes

Drugs used in the treatment of migraine:

- antiemetics (anti-nauseants)
- anxiolytics (anti-anxiety)
- NSAIDs (Non-Steroidal Anti-Inflammatory Drugs)
- ergots
- steroids
- tranquilizers
- narcotics
- selective serotonin agonists
- other miscellaneous drugs

Ref. 26-34

Preventive migraine agents include:

- beta-blockers
- calcium channel blockers
- antidepressants
- serotonin antagonists
- anticonvulsants
- behavioral management and relaxation training as complementation to pharmacologic therapy

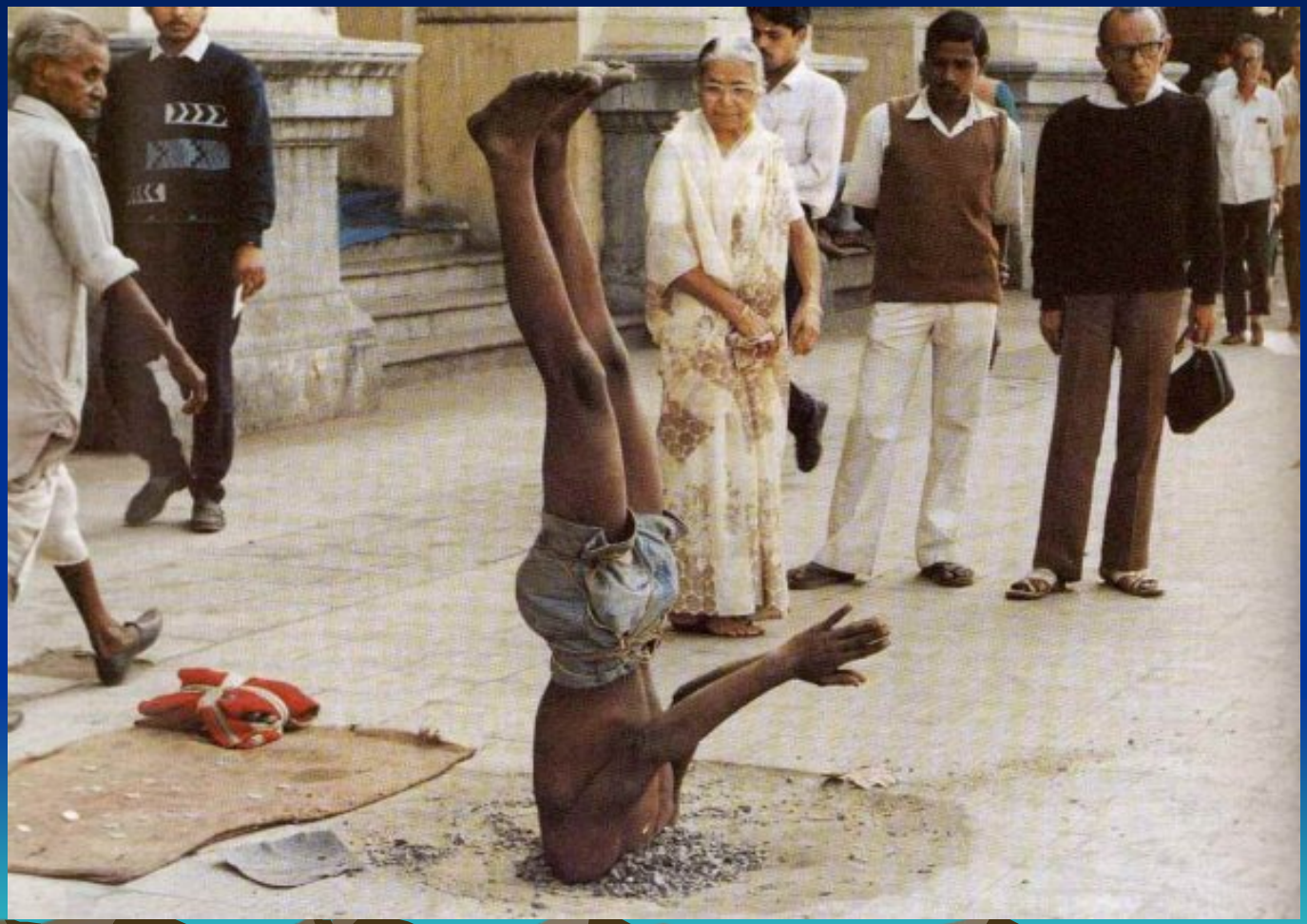
Ref. 26-33

Supplements used in treatment and prevention of migraine:

- magnesium [35]
- vitamin B2 (riboflavin) [36]
- feverfew (*Tanacetum parthenium*) [37,38]
- butterbur (*Petasites hybridus*) [39]
- glucosamine [40]
- fish oil [41]
- coenzyme Q10 (CoQ10) [42]
- melatonin [43,44]

Natural folk “CURES” ☺

Natural folk “CURES” ☺



Why do we need a new method?

Low effect of current therapies and a high frequency of side effects with using drugs (were seen in 44.5% of patients, 1.7% were rated as serious) require the need to find better, safer regimens for migraine management. [45-47]

According to historical data and clinical studies the following observations appear to have a solid basis:

- systemic derangement of serotonin (5-HT) metabolism, relevant to the peripheral vascular component of migraine pathophysiology
- changes in neuroexcitatory amino acids and magnesium
- hormonal fluctuations which seem important to set the threshold for a migrane attack
- catecholaminergic changes suggesting sympathetic overactivity

Ref. 48

The information which played a key-role in the suggestion of a new hypothesis:

- migraine affects more women than men, and is often related to menses
- steroid hormones in physiological concentrations are capable of interacting with serotonin transport system[49,50]
- controversial results of using estrogens, progestogens, androgens, and DHEA for migraine.[51-53] It is unclear - what is the problem here - too much or too little estrogen/progesterone?
- migraine is under control of multiple factors: neurogenic, chemical, metabolic, and myogenic [54]

The information which played a key-role in the suggestion of a new hypothesis (cont.):

- vascular disturbances have connection with biochemical and central neuronal disorders [9]
- multiple researches have led to concept that migraine is generated from a hyperexcitable brain
- the causes for hyperexcitability of the brain include low cerebral magnesium levels, mitochondrial abnormalities, dysfunctions related to increased nitric oxide or the existence of a P/Q type calcium channelopathy [55]
- the available evidence suggests that up to 50% of patients during an acute migraine attack have lowered levels of ionized magnesium [35]

The information which played a key-role in the suggestion of a new hypothesis (cont.):

- numerous experiments and clinical observations have credited magnesium with a positive influence on the incidence of migraine attacks [56,57]
- migraine is a primary biochemical disorder of the central nervous system involving neurotransmitters, specifically serotonin. The pineal gland, a primary source of central serotonin and melatonin. [58,59]
- migraine is a recurrent clinical syndrome characterized by combinations of neurological, gastrointestinal and autonomic manifestations [60,61]

The information which played a key-role in the suggestion of a new hypothesis (cont.):

- hypothesis describes hypercholesterolemia as a compensatory mechanism for age-related decline of steroidal hormones production [62]
- migraineurs were more likely to have an unfavorable cholesterol profile (TC >240 mg/dL) and to be using oral contraceptives [63,64]
- our clinical experience with hypercholesterolemia treatment. It is not rare when patients said about cholesterol:

✓ "My cholesterol is 335. I have tried every medication for this but they give me migraines".

✓ "My total cholesterol is 315. I have taken all the meds dealing with cholesterol but couldn't take any of them because they caused muscle aches or really bad migraine".

New hypothesis of migraine:

Neurohormonal and Metabolic Dysbalance Hypothesis of Migraine

This hypothesis implies that migraine is a consequence of a loss neurohormonal and metabolic integrity [65]

We followed the main principles considered for Scientific Method (1854) in suggesting a new hypothesis:

- **the recognition and formulation of a problem**
- **the collection of data through observation and experiment**
- **formulation and testing of Hypothesis**

From our point of view migraine is a complex disorder in several systems:

- neurohormonal system - includes hypothalamus, pituitary gland, and glands that produce steroid hormones
- sympathetic-parasympathetic nervous systems - imbalance leads to decreased pain threshold of brain nociceptive system
- calcium-magnesium ion system – imbalance can change electricity of cells membrane, and condition of calcium channels

From our point of view migraine is a complex disorder in several systems (cont.):

- pineal gland - decreased function of pineal gland with lower production of melatonin or decreased sensitivity of cells membrane to melatonin
- digestive system - changed intestinal flora with abnormal absorption

All these systems and changes within them are closely interrelated, and each can be a trigger mechanism for migraine.

Material and Method:[66]

- we analyzed 30 patients with migraine
- mean age – 46.4 (from 16 to 66 yr)
- male to female ratio – 1:9 (3-27)
- follow up duration – 5 - 77 months

Basic Lab – Serum:

- CBC, chemistry panel
- lipid profile
- pregnenolone
- DHEA Sulfate
- testosterone
- total estrogen
- progesterone
- cortisol
- aldosterone
- TSH, Total T3, Total T4
- serotonin
- prolactin
- homocysteine
- Vitamin D-3

Multimodal treatment program

- hormonorestorative therapy (HT) with bio (anthropo)-identical hormones
- simultaneous correction of the imbalance between sympathetic and parasympathetic nervous systems as well as between calcium and magnesium
- “resetting” the pineal gland
- improvement of intestinal absorption through restoration of normal intestinal flora
- cleanse from parasites (if necessary)

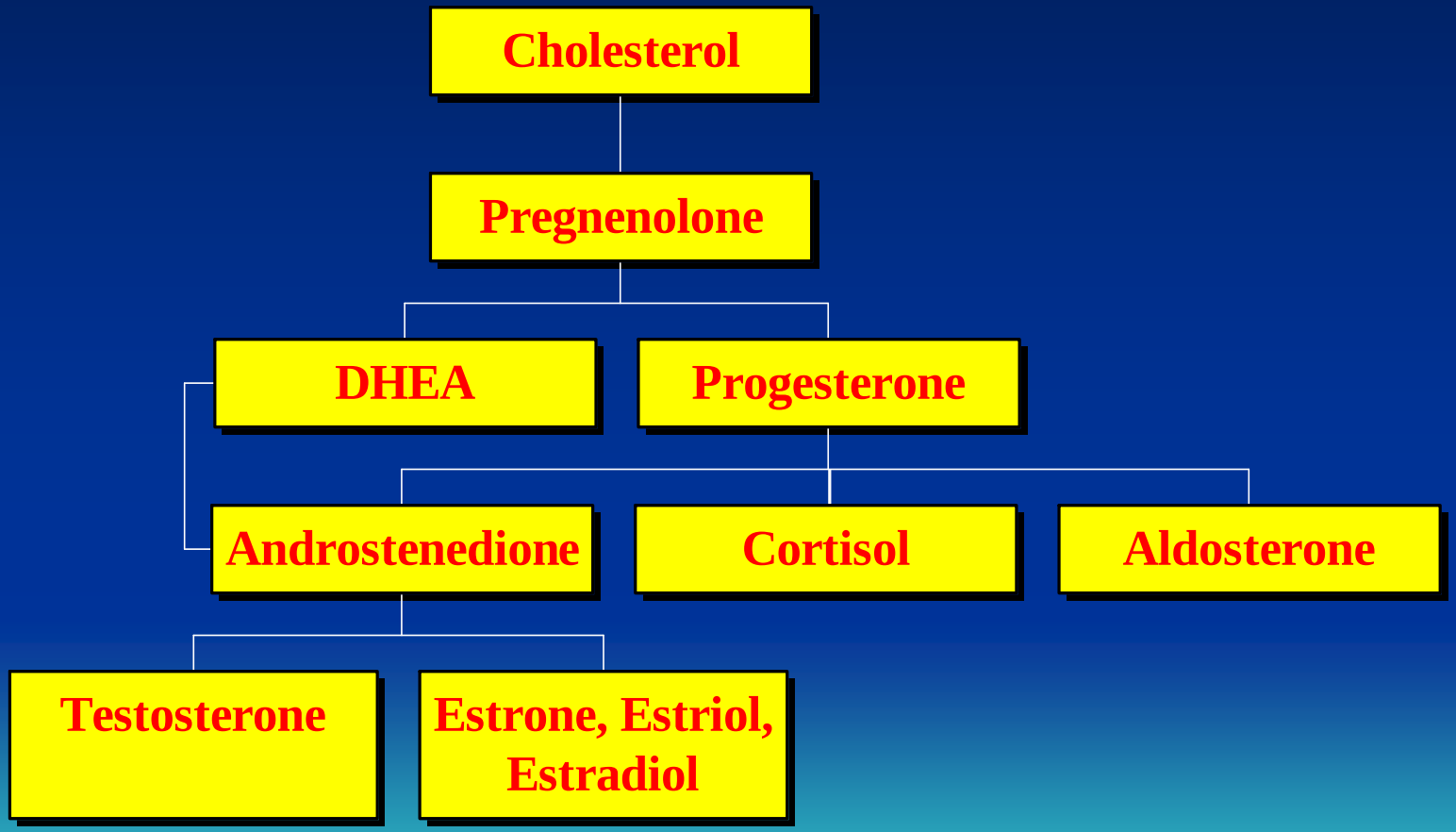
It is necessary to stress the fact that the above mentioned parts of the program cannot be separated.

Hormonorestorative therapy - definition

Hormonorestorative therapy is multi-hormonal therapy with the use of a chemically identical formula to human hormones (anthropo-identical) and is administered in physiologic ratios with dose schedules intended to simulate the natural human production cycle and allows to restore the optimal level of hormones.

Metabolism of Cholesterol

(simplified version)



Basic components of Multimodal treatment program:

1. Basic Hormonorestorative Therapy (HT) :

- **pregnenolone**
- **DHEA**
- **progesterone**
- **testosterone**
- **triestrogen *(women)***
- **cortisol**
- **aldosterone**

Delivery systems for hormones:

Oral

1. Capsules

- pregnenolone
- DHEA
- melatonin
- aldosterone

2. Tablets

- hydrocortisone
- whole thyroid

(Armour thyroid, compounded thyroid)

3. Troche

- progesterone (100/200mg/troche)

4. Drops

- Tri-Est – 5 mg/ml (E3:E2:E1- 80:10:10)
- progesterone - 50 mg/ml
- testosterone - 50 mg/ml

Topical

Gels (micronized)

- Tri-Est gel – (E3:E2:E1 – 90:7:3) – 1.25-2.5 mg/ml
- progesterone 5-10% – 50-100 mg/ml
- testosterone 5-10% – 50-100 mg/ml

Parenteral

Subcutaneus

- HGH (human growth hormone)
- HCG (human chorionic gonadotropin)

Dosage

the recommended doses were determined by clinical data, serum hormonal levels, and the so-called the optimal range that was defined as a level of hormones in one third of the highest normal range for all steroid
hormones for healthy individuals between the age of 20 and 30.

Basic components of Multimodal treatment program (cont.):

2. magnesium citrate - dose 400-800 mg

(at bed time - 400 mg, or 200/400 mg in a.m. and 400 mg at bed time)

3. combination of melatonin (3-6 mg), *kava root extract* (250-500 mg) and *vitamin B6* (10-20 mg)

(30 minutes before bed time)

4. probiotic formula which includes:

- ✓ Lactobacillus group (L.rhamnosus A., L.rhamnosus B., L.acidophilus, L.casei, L.bulgaricus) - 3.5 Billion,
- ✓ Bifidobacterium group (B.longum, B.breve) - 1.0 Billion,
- ✓ Streptococcus thermophilus – 0.5 Billion

Most frequently used agents of the program:

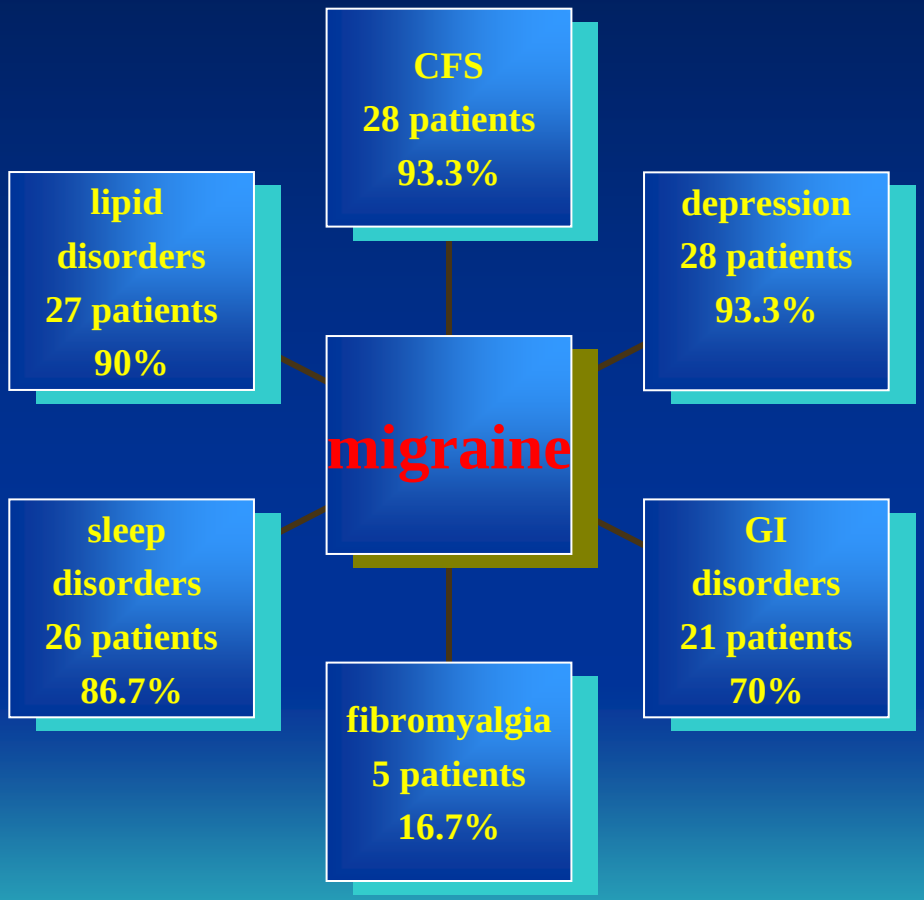
- 5-HTP 50-100 mg
- zinc -25-100 mg
- saw palmetto 160 mg
- 7-keto DHEA 25-100 mg
- anti-parasites formula

Results:

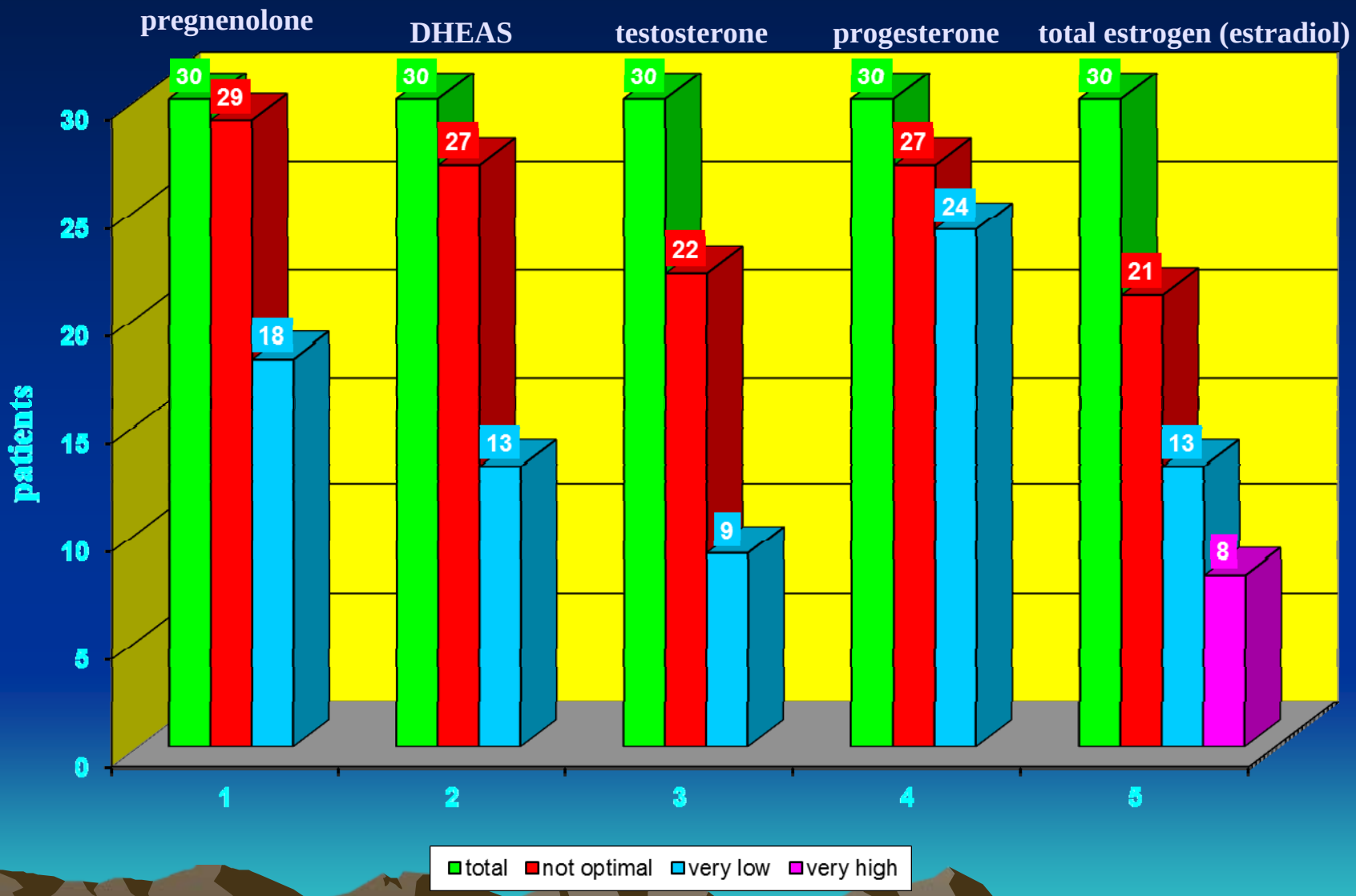
- duration of migraine - from 2 to 46 years
- prior to our program all patients have used drugs and/or tried supplements
- HRT or oral contraceptives have used 77.8% of patients (21 women)
- Lipid abnormalities were found in 27 (90%) patients:

✓ hypercholesterolemia - 24 (80%) patients (highest level - 360 mg/dL)
✓ hypocholesterolemia – 3 (10%) patients (lowest level – 86 mg/dL)

Results: concurrent illnesses



Lab results prior to therapy



Results:

- all patients responded to migraine management. We do not have any patients in this study who still have migraine after they started to use this program
- all patients were free of concurrent illnesses
- total cholesterol completely normalized in 22 (91.7%) patients
- acute morbidity of a multimodal program was zero

Case Study

Case study 1

Patient B. 54 y.o., female, first visit 04/13/1999

Diagnosis: hypercholesterolemia, hypertension, migraine, depression, insomnia, arthritis.

Complaints: severe migraine; high cholesterol; high blood pressure that was poorly controlled with prescription drugs; fatigue; depression; severe anxiety; irritability; poor libido; low sex drive; genital herpes; poor short-term memory; trouble falling asleep; weight gain; arthritis; and irregular menstrual cycle.

	TC	DHEAS	Pregn	Estr.(total)	Progest	Test	IGF-1
(nl - age 20-30)	(<200)	(65-380)	(10-230)	(61-437)	(0.2-28)	(14-76)	(>300)
04/13/1999	241	66	50	643	0.7	29	90
09/16/2003	182	350	182	315	14.4	49	250

(blood was drawn on 21 day of menstrual cycle in both cases)

follow up 09/16/2003 – occasionally, minimal morning neck stiffness

Case study 2

Patient F. 55 yr, female, first visit 06/11/02

Diagnosis: fibromyalgia, migraine, menopause depression, insomnia, fatigue, obsessive-compulsive disorder.

Complaints: fibromyalgia, migraine, fatigue, depression, suicidal attempts, insomnia, weight gain, short-term memory problems, sex disorder, constipation.

	DHEAS	Pregn	Estr.(total)	Progest	Test
(nl - age 20-30)	(65-380)	(10-230)	(61-437)	(0.2-28)	(14-76)
06/11/02	100	32	59	0.6	50
15/01/03	326	180	250	8.4	67

	TC	TRG	HDL	LDL	VLDL
06/11/02	203	75	58	131	15
15/01/03	172	70	46	112	10

follow up 01/15/03 – no complaints

Case study 3

Patient L. 34 y.o., female, first visit 12/10/03

Diagnosis: migraine, PMS, depression, insomnia, constipation.

Complaints: migraine (2-3 times weekly) since age 15, fatigue, insomnia, PMS, no libido, poor sex drive, constipation, overweight.

	TC	DHEAS	Pregn	Estr.(total)	Progest	Test
(nl - age 20-30)	(<200)	(65-380)	(10-230)	(61-437)	(0.2-28)	(14-76)
12/10/03	207	81	87	128	0.8	42
10/18/04	178	205	172	274	17.7	47

(blood was drawn on 21 day of menstrual cycle in both cases)

follow up 10/18/04 – no complaints

follow up 01/17/08 – no complaints

Case study 4

Patient CH. 58 y.o., female, first presentation 01/07/05

Diagnosis: hypercholesterolemia, migraine (38 years history), CFS, depression, insomnia, menopause.

Complaints: daily migraine, hypercholesterolemia, CFS, depression, body aches, insomnia, constipation, hot flashes, vaginal dryness, no libido, poor sex drive, short-term memory problems, overweight.

	TC	DHEAS	Pregn	Estradiol	Progest	Test
(nl - age 20-30)	(<200)	(65-380)	(10-230)	(19-528)	(0.2-28)	(14-76)
01/07/05	300	86	<10	19	0.4	51
09/12/05	195	340	190	217	5.9	61

follow up 09/12/05 – no complaints

follow up 12/12/07 – no complaints

Case study 5

Patient M. 48 y.o., female, first visit 11/18/08

Diagnosis: migraine (>40 years), high cholesterol, menopause, anxiety, depression, fatigue, insomnia, irritable bowel syndrome, acid reflux.

Medications before program: Klonopin, Metherginel, Effexor, BusPar, Corgard. All of these are supposed to be migraine preventatives. Most of them make patient lethargic, chronic dry mouth, and blurry vision. Also, patient takes Treximet, Imitrex and Indocin for abortives. If these do not work, then she goes to her Family Practitioner or the ER for Dilaudid and Vistaril. Also, patient takes Rhinocort and Prilosec.

	TC	TRG	HDL	LDL	VLDL	Vit D-3	homocysteine
	<200	<150	>35	<130	5-40	(32.0-100)	<15.0
11/13/08	309	155	53	225	31	35.9	6.0
09/14/10	181	140	45	108	28	43.5	9.6

	DHEAS	Pregn	total Est	Progest	Test	Cortisol	Serotonin
(nl - age 20-30)	(65-380)	(10-230)	(61-437)	(0.2-28)	(14-76)	(4.3-22.4)	(0-420)
11/13/08	23	17	22	<0.2	31	6.5	4
09/14/10	294	183	310	6.9	54	15.8	266

follow up 09/28/10 – no complaints

Case study 6

Patient M. 27 y.o., female, first visit 09/10/09

Diagnosis: daily debilitating migraine (>4 years), depression, extreme fatigue, insomnia, hypotension

Medications before program: Vicodin, Percocet, Lorazepam, Klonopin, Phenergan, Zofran, Indomethacin, Norflex, Amerge, Nortriptyline, Lyrica, Progestrone as an oral apothecary compound, Thyroid medication - apothecary compound, and NuvaRing (releases a low dose of a progestin and an estrogen over 3 weeks).

Supplements before program : Migraine relief, feverfew, prenatal vitamin, iron, Valerian Root, 5-HTP, DHEA, Fish Oil, Inderal, calcium, vitamins C, D, B-Complex, Co Q-10, folic acid, melatonin, Butterbur, potassium iodide, Milk Thistle, extract Artichoke, extract Vitex, Sea Kelp, etc.

	TC <200	DHEAS (65-380)	Pregn (10-230)	total Est (61-437)	Progest (0.2-28)	Test (14-76)	Cortisol (4.3-22.4)	Serotonin (0-420)	aldo (5-41)
09/10/09	171	25	7	<50	<0.2	<14	17.5	25	6
10/18/11	132	312	212	290	18.8	65	18.0	280	30

(blood was drawn on 21 day of menstrual cycle in both cases)

follow up 12/02/11 – no complaints

Case of Migraine

Conclusion

- our results support a new hypothesis of migraine
- physiology optimization with the use of multimodal treatment program could be an effective and an inexpensive approach in migraine management

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