Depression, Fibromyalgia, Chronic Fatigue and Pain: Shared Neurobiological Pathways and Treatment

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Introduction

In clinical practice, it is commonplace for patients to present with one chief concern, but with discussion, it is uncovered that there are a few diagnosable conditions going on at the same time. There may be no better example of this challenge than the continuum of conditions articulated individually as major depression (MD), fibromyalgia (FM), chronic fatigue syndrome (CFS) and/or neuropathic pain (NP).

MD is a mood disorder in which feelings of sadness, loss, anger, or frustration interfere with everyday life for weeks or longer. FM is characterized by widespread pain, abnormal pain processing, sleep disturbance, fatigue and often psychological distress. CFS features debilitating exhaustion with a constellation of neurological and immunological symptoms. NP has been defined as pain that is initiated or caused by a primary lesion or dysfunction in the nervous system.

High rates of comorbidity occur among these, ranging from 30 to 60%. Some or all of these conditions not only occur together, but can make treatment more challenging. For example, those patients exhibiting NP have a much poorer recovery from MD. And depressed patients respond poorly to fibromyalgia and pain care. Each condition seems to promote the other: clinicians can expect that patients with FM to be up to 4.3 times as likely to develop depression.

Common Neurobiological Ground

The terms 'depression', 'fibromyalgia,' neuropathic pain,' 'chronic fatigue' and 'neuropathic pain' are all adequate for raising awareness about a patient's experience and symptomology (feeling emotionally low, in neural pain, muscular pain and exhausted, respectively), but none of these words remotely propose etiology.

While these conditions span the variegated disciplines and diagnoses of psychiatry, rheumatology, and neurology, there are clear underlying principles that bind them. These disorders represent an intersection of genetic and biologic underpinnings with environmental causality. The purpose of this article is to discuss the neuro-immuno-endocrine commonalities among them to help identify patient specific natural treatments aimed to correct the underlying causes, thus decreasing the need to chase symptoms. Below are 8 underlying considerations and 16 treatments that I have seen help make great clinical strides in patients with these conditions.

1- Genetics

MD, FM, CFS and NP share many symptoms. As such, it makes sense these conditions would have shared genetics. While these genes do not single-handedly cause these conditions to manifest, they will predispose the nervous system and physiology to threats that will result in inflammation, pain, poor mood, and fatigue. In epigenetic fashion, pre and postnatal stress is a recognized major aggravating factor in the expression of these genes.

2 - Stress and Evolution

From an evolutionary standpoint, fear response and physical pain have survival value: an organism that can effectively raise anxiety, feel pain or lay low when needed gains survival advantage. In the short term, these responses are healthy and can get the organism out of danger and process information. But humans in today's modern world sustain long-term stress which create persistent and skewed processing of emotional, painful and stressful signals. Combined with genetic predisposition and environmental influence, neuroplastic changes make these signals more permanent and lasting, thus driving chronic symptoms of depression, muscular and nerve pain, as well as fatigue.

3 - HPA Axis and Glucocorticoid Resistance

The hypothalamus is the nexus for our body's clock, nervous system, immune system and endocrine system. Hyperactivity of the hypothalamic pituitary adrenal axis (HPA) causes increased levels of glucocorticoids, including cortisol. The long-term effect results in glucocorticoid resistance, a condition well described in MD, FM CFS and NP. Glucocorticoid resistance is analogous to insulin resistance as found in type II diabetes: the more the hormone is around, the less the body cells respond to it.

Glucocorticoids are vital hormones that are released in response to stress. Cortisol helps clamp down an overactive inflammatory cascade, supporting neuronal survival and neurogenesis. Via direct action on the brain, glucocorticoid resistance augments inflammation and further stimulates HPA axis activity in a vicious cycle. In these conditions increased pro-inflammatory cytokines also induce brain neurodegeneration.

Long term high cortisol levels are toxic to the body. As protection, cortisol production begins to wane in the long term. Most studies report that conditions of FM, chronic pain, and fatigue as well as atypical depression (depression that is characterized by excess sleeping, increased appetite, and profound fatigue) are characterized not by hypercortisolism, but instead decreased cortisol production and release. In support of this concept of lowered cortisol and glucocorticoid resistance, it has been shown that giving hydrocortisone (a cortisol analogue), although not widely used due to toxicity (likely why the body probably becomes resistant to endogenous cortisol), can improve symptoms of MD, CFS, and pain. Studies of subjects administered cortisol or prednisone prior to exposure to stressors report less distress and less fatigue. The administration of hydrocortisone to aging veterans with PTSD was even shown to enhance both episodic and working memory.

4 - Flattened Diurnal Rhythm

In healthy individuals, cortisol production peaks around early morning and then falls thereafter, save for transient increases in response to eating meals. In MD, FM, CFS and NP, cortisol levels are lower around wakening, show more disorganized variability during the day and do not fall sufficiently in the evening. Such flattening predicts subsequent development of chronic widespread pain in medically healthy individuals, even increased mortality in patients with cancer. Cortisol flattening impairs the production and release of brain derived neurotrophic factor (BDNF). BDNF is a key player to stimulating both the growth of new neurons and pathways that the nerves use to communicate and create better mood.

5 - Autonomic nervous system imbalance

Correlated with HPA imbalance and enhanced inflammatory tone is autonomic function (ANS) imbalance. Increased sympathetic function and decreased parasympathetic activity is a feature of MD, FM, CFS and NP. In vulnerable individuals, chronic stress can result in persistent sympathetic overdrive, with the resulting diminution of parasympathetic tone and inability to control inflammation. Manifestations include increases of heart rate at both rest and stress response, blood pressure, vascular resistance, whole body sympathetic activity, as well reductions in overall heart rate variability (HRV).

6 - Inflammation

Inflammation is the mark of an immune system on high alert trying to ready itself for a fight or injury, or to kill something it thinks does not belong – and the casualty of this war becomes the brain and overall health. MD, FM, CFS and NP have all been described as disorders of low-grade systemic inflammation.

As predoctoral fellow in the mid 1990's, my research group at the NIH were one of the first to find interleukin-1 (IL-1) gene receptor expression in brain blood vessels.[1] What we learned from this work is that the brain is uniquely readied to respond to stress, injury and pain via inflammatory changes. IL-1 elaboration here effects production of nitric oxide and other inflammatory factors. While these can insure short-term protection and reparative effect, in the long term, the effects are deleterious. In the long term, these changes will further the symptoms of MD, FM, CFS and NP and encourage HPA brain hyperfunction in susceptible individuals.

Patients with MD, FM, CFS, and NP exhibit all of the cardinal features of inflammation, including elevations in inflammatory cytokines, chemokines, adhesion molecules, prostaglandins, and acute phase reactants like C-reactive protein (CRP). Patients with CFS or CFS symptoms such as pain, fatigue and sleep disturbance have significantly higher levels of plasma CRP than controls, highlighting an especially close link between somatic symptoms and inflammatory activity.

7 - Brains on Heavy Metal

We have established that the genetic predisposition and the stress/HPA response will ultimately result in underlying inflammation contributing to mood disorder, pain and fatigue. When discussing neurobiology and pathologic contributors, we must consider that environmental factors may also play a strong role in this process. Heavy metals and other toxic chemicals will affect inflammatory levels in the brain. In a cyclic fashion, inflammation makes brain cells more vulnerable to a number of toxins.

The brain uses a very elaborate system to remove glutamate, a neurotransmitter which can be very toxic to brain cells. It has been shown that mercury, aluminum and other toxins can easily damage re-uptake proteins the brain uses to remove glutamate, thus rendering the brain cells more easily damaged. Furthermore, increased basal cytokine production in conditions of MD, FM, CFS and NP will also affect the efficacy of these reuptake proteins, allowing smaller amounts of toxin to have a greater effect in inflamed patients.

8 -The Brain-Gut Axis: Inflammatory and Neurotransmitter Considerations

Given the large digestive surface area and associated amount of Gut and Mucoid Associated Lymphoid Tissue, the gut immune system is a major player in global inflammation production. Chronic stress and HPA activation affects digestion by lowering blood circulation to the intestines which compromises digestion and leads to excessive inflammation, thus encouraging poor mood, fatigue and pain susceptibility. Not surprisingly, MD, FM, CFS and NP patients often present with gastrointestinal inflammations and autoimmune disease, as well as with cardiovascular disease, neurodegenerative disease, type 2-diabetes and even cancer, all of which have chronic low-grade inflammation as a significant contributing factor.

Dubbed 'the second brain' [2] the digestive tract and its enteric nervous system plays a major role in the production of neurotransmitters. Neurotransmitter imbalances are implicated in the dysfunction of MD, FM, CFS and NP. Produced in the GI tract's enterochromaffin cells, serotonin have been found to be low in some studies of FM and MD. It seems the delicate process of converting tryptophan, the amino acid which converts to 5-hydroxytryptophan, and ultimately to serotonin, is vulnerable to malabsorption and inflammatory problems in the digestive tract. Other research implicates imbalances in receptor function and neurotransmitter levels for GABA, dopamine, epinephrine, and glutamate.

One neurotransmitter note: while the mainstream medical world centers its treatments around neurotransmitters, we are reminded of the old joke about the drunk man at night looking for his keys in a mostly dark parking lot. After circling for hours in the same lit spot, another sober fellow asks "how do you know your keys are here, when there's the rest of this lot to check?" The drunk man answers, "well, it could be out there somewhere too, but the light is better here."

As holistic practitioners, it is our job to start shining the light on the other parts of the pathological parking lot. Like a patient's good health, neurotransmitters are likely a casualty of the HPA-inflammation problem. While neurotransmitters may play a role, for most cases of MD, CFS, FM and NP, there are a multitude of other factors to consider in order to create an effective recommendation plan.

Therapies Aimed At the Underlying Causes

So, given the above mechanisms, what is the best plan to treat the conditions of MD, CFS, FM and NP? I have listed a few below that I have found especially useful to aim at said mechanisms.

Please note that this article focuses on the neurobiological underpinning of these conditions. To keep to the scope of this article, there may be other salient therapies for these conditions not discussed. For example, while not addressing HPA axis disruption, giving thyroid support for previously undiagnosed and subclinical hypothyroidism can play a strong role in the amelioration of both FM and MD.

1 -Sleep

Non-restorative sleep with frequent wakening is present in most patients with MD, FM, CFS and NP. Disturbed sleep may be both a causative factor as well as a symptom of these conditions. Therapies aimed at restoring proper circadian rhythm, raising flattened morning cortisol, and lowering elevated evening cortisol are imperative. Some of the treatments in my practice include proper sleep hygiene, orange light therapy in the evening, and the use of melatonin (0.5 – 3mg hs) to help fall asleep, sustained released melatonin or l-tryptophan (1000mg) for staying

asleep, or valerian and Chinese herbs, individualized specifically to the patient.

2 - Hydration

Approximately 78% of the human brain is water.[3] As such, adequate hydration is a key to structure and function. Dehydration can create a rise in osmolality and advent of thirst which is associated with activations in the brain's hypothalamus, thalamic, limbic, somatosensory cortical, insular, and cerebellar areas.[4] Water is needed for tryptophan to be transported into the brain. Dehydration may limit the amount of tryptophan available to the brain.[5]

3 - Food:

Eating regularly, small frequent meals, as well as following the Chinese medicine axiom to 'eat like a king for breakfast, queen for lunch and pauper for dinner" are recommended for normalizing cortisol diurnal variation. Since eating a meal is known to stimulate cortisol, it is best to refrain from eating at least a few hours before bed.

Working with food allergies and sensitivities is beneficial for those experiencing MD, FM, CFS and NP. One double-blind 30 person study found correlation between sublingual exposure of known allergens and increased cognitive-emotional disruption and heart rate variability,[6] both known indicators of HPA inflammatory dysfunction.

Exorphins are morphine-like molecules derived from incomplete digestive breakdown of the common food allergens dairy and grain.[7, 8] Five exorphins have been discovered in digests of gluten and eight others in milk digests.[9] Exorphins modulate mood and pain by depressing levels of serotonin, dopamine and norepinephrine in the central nervous system.[10] Type I mediated hypersensitivity reactions in the gut caused by individual food allergens can induce mast cells to release inflammatory mediators such as prostaglandins, leukotrienes and histamine, as well as extra serotonin, which can create long term deficiency of this neurotransmitter.

One study reported a prior history of psychiatric treatment in a high proportion of adults with celiac disease, even years before diagnosis.[11] Untreated celiac patients have significantly lower plasma tryptophan compared with gluten free and control groups.[12] This suggests that abnormally low tryptophan levels in patients with depression and behavior disorders are a likely marker of serotonergic dysfunction due to impaired availability of tryptophan. Importantly, this can be reversed to normal in those who use a gluten free diet.[13]

As with gluten in sensitive populations, when allergenic/sensitive foods for an individual are taken into the digestive tract, the tract produces large amounts of inflammation as well as serotonin to increase movement so that the gut empties. This may be why some people with mood disorders and people who go through high stress have accompanying diarrhea. The immune response in the digestive tract is known to lead to sickness behavior including flu-like symptoms of fatigue, anxiety, and of course, depression.

Besides demonizing the likely culprits of gluten and dairy, we need to realize that many of the foods we eat humanity has had only a relatively minimal time period on the evolutionary calendar to which to adapt. According to one hypothesis, the rise of carbohydrate intake (and concomitant reduction of fat and protein consumption) may be the greatest reason for the increase of many Western diseases. According to the hypotheses, it can be shown that the spread of agriculture from the Near East to the West and North of Europe with the accompanying differences in time for the adaptation to the new carbohydrates foodstuffs easily explains the geographic differences in the disease frequency of civilization, which is highest in places like Northern Ireland, Scotland and Finland, where carbohydrates appeared last.[14]

In patients with high CRP, special concern with eating foods cooked at low temperature has value, for advanced glycation end products, which are formed from cooking foods at high temperature, will increase levels of CRP[15, 16] in patients, as well as increase perpetuation of pain in patients with FM.[17] High dietary fiber intake (around 20 to 30 grams per day) is also protective against high CRP levels and other inflammatory molecules.[18] Notably, vitamin C,[19] 1 gram qd, and 1200iu vitamin E is helpful to reduce both elevated CRP and interleukin-6.[20]

4 - Exercise

Exercise balances the ANS. One three-week study utilized both exercise with cognitive behavioral therapy for 12 female patients with FM. Researchers found a normalization of cortisol plus an increase in glucocorticoid receptor-alpha mRNA expression, which suggests an improvement in glucocorticoid resistance in these patients.[21]

Another study of 207 people given mental stressors found that a person's level of fitness was associated with attenuated parasympathetic inflammatory cytokine response to acute mental stress, improved HPA axis function, corticosteroid sensitivity, parasympathetic control, and inflammatory response.[22] Exercise also increases BDNF, thus helping to protect the brain.[23] Overall, exercise and physical fitness act as a buffer to the detrimental effects of psychosocial stress exposure and should be employed in any plan designed to help MD, FM, CFS or NP.

5 - Sunlight

Consistent with the increase in MD and FM this last century is the decrease is human exposure to the sun. Modern life is replete with sunblock: buildings, pollution, vehicle travel, clothes, as well as sunblock lotion and emphatic medical advise to avoid sunburn. Sunlight exposure suppresses daytime melatonin, which affects wake and sleep cycles and can help reestablish diurnal cortisol response.

6 - Phototherapy and Vitamin D

Another likely mechanism towards healthful mood is sunlight's production of the immune-balancing vitamin D through the exposure to ultraviolet B ray. One study investigated the effect of exposure of skin to ultraviolet light, which converts cutaneous 7-dehydrocholesterol to vitamin D_3. The participants exposed to UV therapy over 6 weeks reported they were more relaxed and less tense.[24] Another 6 week pilot study of 19 individuals with FM resulted in greater positive affect, well-being, relaxation, and reduced pain.[25] Low vitamin D have been implicated in fibromyalgia[26], CFS,[27], depression[28] and pain.[29] Testing of 25-OH vitamin D and supplementation, of vitamin D3 should also be a strong consideration for patients with MD, FM, CFS and NP.

7 - Protection Against Heavy Metals

Intake of minerals such as calcium, magnesium, zinc, selenium and manganese can competitively inhibit the absorption and utilization of toxic metals like lead, mercury, and aluminum.[30] It is possible that poor digestive absorption and nutrient deficiency of these may also increase one's ability to absorb unwanted metals. Since these minerals are low in patients with FM, DM, CFS and NP[31], repletion with these may be beneficial. Chelation therapy may also provide benefit, especially in cases that have a strong toxicity history.

8 - Transcranial Magnetic Stimulation (TMS)

In late 2008, the FDA cleared TMS as a noninvasive device that delivers MRI-strength high frequency magnetic pulses directed at the dorsolateral prefrontal cortex of the brain to lower excitability of the motor cortex. One study found a single session was enough to modulate HPA axis

function, as evidenced by reductions in salivary cortisol concentrations, although mood was not affected.[32,33] Other studies suggest need for two week treatments.[34] One 6-week randomized, placebo-controlled, double-blind study of 164 patients with moderate to severe MD found significantly improvement compared to placebo. A meta-ananlysis of TMS for fibromyalgia looked at 9 studies and found analogous pain reductions as well as considerably fewer side effects compared to pharmaceuticals.[35]

TMS treatment is administered during a 40-minute outpatient procedure typically every day for 4–6 weeks.[36] Patients reports are negative for systemic side effects, adverse effects on concentration or memory, or seizures. The discontinuation rate resulting from adverse events was less than 5%. The most commonly reported side effects were mild, including transient headaches and scalp discomforts at the stimulation site. One major side effect was to the wallet, for TMS is expensive.

9 - Essential Fatty Acids:

Well known as a important anti-inflammatory and depression treatment, epidemiologic studies link intake of omega-3 fatty acid with an improved HRV.[37] As discussed earlier, suboptimal HRV is a key marker of autonomic dysfunction.

10 - Melatonin

Melatonin is known to be a powerful antioxidant scavenger of reactive oxygen species and free radicals and prevents the reduction of membrane fluidity caused by lipid per oxidation.[38] As sunlight or phototherapy can be used in the morning hours, supplementation with melatonin can be used in the evening to re-establish circadian rhythms.[39] For example, 3 mg to 5 mg of melatonin used with or without fluoxetine resulted in significant reduction in both total and different components of FIQ score compared to the pretreatment values. In conclusion, administration of melatonin, alone or in a combination with fluoxetine, was effective in the treatment of patients with FMS.[40]

11-DHEA

Made by the adrenals, dehydroepiandrosterone (DHEA) levels also decrease in the long term along with cortisol. It has been suggested that DHEA may protect against the adverse effects of early raised circulating cortisol. DHEA is low in patients with MD and CFS, [41] and declines with psychological challenge and stress.[42]

While boasting dosages of 100 to 450mg qd in various studies, these are supra-physiologic doses that should be used with caution. In this author's opinion, if lab tests of DHEA and DHEA sulfate are low, it is best to start with lower doses of 5 to 15mg qd and increase if needed, while monitoring blood levels and side effects.

12- Phenylalanine

Phenylalanine is a precursor of brain phenylethylamine (PEA), a likely neuromodulator and promoter of overall energy positive mood. [43] Phenylalanine converts to tyrosine, which is in turn converted to dopamine, and subsequently norepinephrine and epinephrine, and is known to mildly stimulate the nervous system. It is thought that phenylalanine also serves to promote enkephalin activity, by acting as an enkephalinase inhibitor. Enkephalin is an opioid that promotes analgesic effects in the nervous system.

Treating patients with forms of phenylalanine can potentiate pain relief and also ease depression in patients receiving opiates for chronic pain. In patients with NP, use of phenylalanine may amplify the analgesic efficacy of chronic opiate therapy, while enabling dosage reductions that minimize opiate side-effects. Analogously, this approach may complement the efficacy of acupuncture and other analgesic measures. Studies have used 150 to 200mg qd of D-phenylalanine for depression [44], and one author successfully reports using D-L phenylalanine 750 to 1500mg qd for chronic pain associated with depression.[45]

13 - SAMe

Originally described in 1952, SAMe is a naturally occurring molecule derived from L-methionine and ATP. SAMe acts as a methyl donor in the brain and is involved in the synthesis of various neurotransmitters in the brain. It has been in use for decades in Europe, and prescription-only in such countries as Italy, Spain, Germany and Russia. The American Psychiatric Association has recognized the benefit of SAMe to treat MD patients who prefer natural therapies.[46]

SAMe is known to effectively treat depression, with a number showing superior results and faster acting than antidepressants.[47,48] Several clinical trials have investigated the use of SAMe as a treatment for both FM, MD and pain. Out of a small group of 17 patients, administration of SAMe showed reduced pain at trigger points and improved depression versus placebo.[49] Other somewhat larger studies have shown favorability for FM treatment[50], while a few showed no statistical benefit.[51]

14 - Homeopathics

One FM study showed less depression and greater improvements in tender point count and tender point pain, quality of life, and global health using individualized classical homeopathic prescriptions.[52] Another study of chronic fatigue patients, two randomized controlled trials showed that homeopathy improved fatigue, function and symptom improvement.[53,54] While five short duration (1 week to 6 month) studies for common chronic pain conditions found a trend towards pain reduction, only one study reached statistical significance.[55]

15 - Acupuncture

Traditional Chinese Medicine theory regards low mood, pain and fatigue as a stagnation of qi (the energy force of life), which leads to disruption of normal internal organ function. Acupuncture has a clear history of benefit for both pain[56], CFS[57] and MD[58]. Acupuncture may increase natural opioids such as enkephalins or serotonin that help reduce pain through endogenous central nervous system analgesia pathways. A growing body literature supports acupuncture's benefit both as a monotherapy and as adjunctive in FM.[59]

16 - Psychotherapy, Biofeedback and Meditation:

The psychological aspects of the patient's condition is cardinal to healing and rebalancing cortical input to the hypothalamus. Psychotherapy helps to calm underlying ANS imbalance by increasing vagal tone,[60] which is useful in pain, MD, FM and CFS. Emotional processing is useful for low mood, especially when there is a pre-disposing past traumatic or depressing life event.[61]

Biofeedback teaches voluntary control of physiologic function. A small trial of 12 women with FM taught breathing at a slow resonant frequency twice daily for 10 weekly sessions. There were clinically significant decreases in depression, pain and improvement of function for a 3-month follow-up. For depression, the improvement occurred by Session 10. HRV improvements suggested an immediate response of the autonomic nervous system. Blood pressure, baroreflex and mood changes took improved in the longer run.[62]

Meditation may the most valuable treatment of all. It calms input to the HPA, returns ANS balance, restores healthy digestive function [63] and promotes brain neurogenesis [64]. Meditation has shown benefit in FM[65], pain syndromes.[66] Meditation may be the most elegant way to practically address underlying dysfunctions of the syndromes we are discussing.

Conclusion

MD, FM, CFS and NP result from interaction of environmental input with

genetic predisposition, neuro-immune, gut-brain, and autonomic system dysfunctions that perpetuate states of emotional and physical discomfort.

While there is no single treatment modality to fix these common pathways, holistic care is uniquely positioned to offer a number of tools from the dietary, lifestyle, nutrient and psychotherapy-based worlds to create a combined approach that can not only help symptoms, but also actually restore balance.

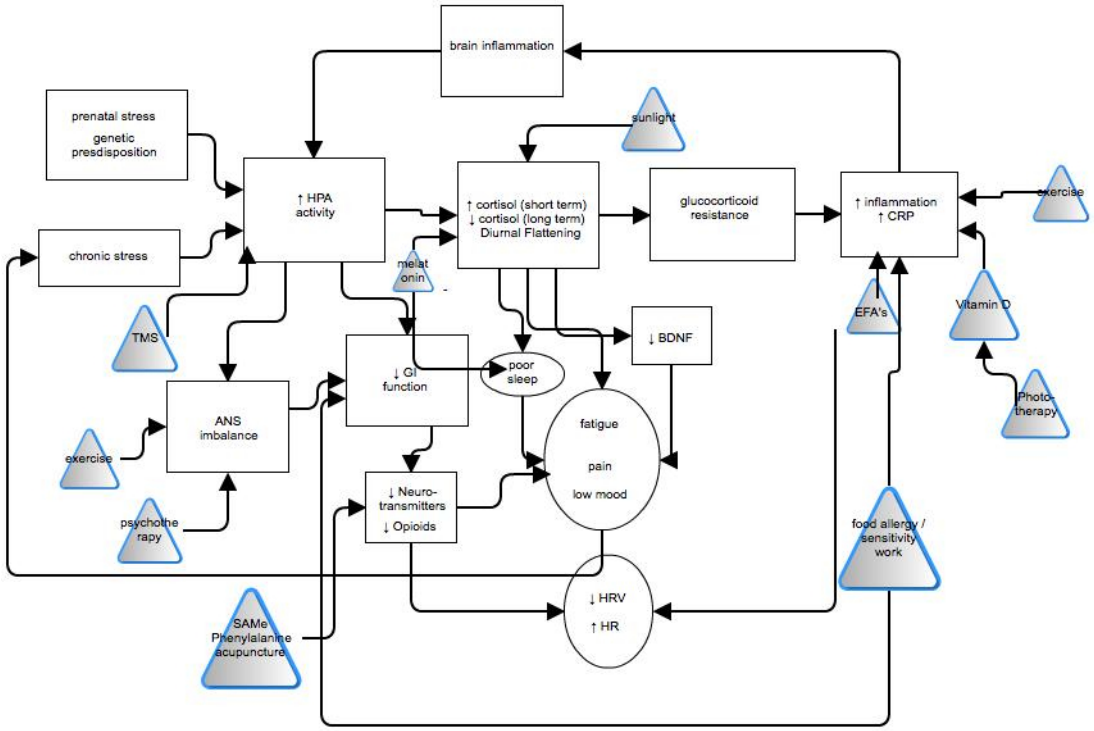

FIGURE: underlying causes in white boxes and circles.
Treatments in blue border grey triangles (not included in original publication)

BIO:

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A major contributor to the 3rd and 4th edition of the Textbook of Natural Medicine, Dr. Bongiorno authored the textbook Healing Depression: Integrated Naturopathic and Conventional Therapies for Depression. His most recent publication is How Come They're Happy and I'm Not?, *the complete natural program for healing depression for good* was released in October of 2012.

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