Protecting your brain from stress – Part 1

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Protecting Your Brain from Stress – Part 1

by Jonathan E. Prousky, ND, MSc, MA, RP(Qualifying)
Professor, Chief Naturopathic Medical Officer
Canadian College of Naturopathic Medicine

Abstract

This two-part series focuses on integrative treatments that can bring improved regulation to the stressed brain. Concepts from stress research, i.e., allostasis, allostatic load, and allostatic overload, are defined and referred to within the article's chronic stress framework so as to enumerate treatments that mobilize allostatic systems to improve brain and psychological health, as well as physical health. The treatments advocated include natural health products to lower the intensity of emotional overwhelm and to reduce the pathophysiological harms to the brain and body. Other recommended treatments include diet, exercise, nature, meditation, sleep, the avoidance of substances, psychotherapy and/or social support, as well as an assortment of psychological and behavioral recommendations. The integrative approaches, such as those mentioned in this article, should serve as models of the kinds of interventions that can realistically and dramatically affect the course of chronic stress and prevalent medical diseases via allostatic brain mechanisms.

Introduction

When the brain is stressed, the limbic system (i.e, includes the amygdala, hippocampus and other brain structures) seems to dominate the prefrontal cortex (PFC). A functional disconnection between these brain areas ensue, such that the PFC cannot effectively modulate emotions and attenuate the resulting stress response.[1] When this becomes an enduring problem, as happens from chronic stress, many pathophysiological impacts result, including mental morbidity, psychiatric illness, and medical disease (Table 1 provides an explanation of the common terms used in this paper).[1]

Given the inherent challenges to working with chronically stressed patients, it is imperative that treatment aims to restore their biological regulation. First, a thorough clinical evaluation needs to be done to rule-out diseases that would continue to wreak havoc unless properly treated. Then, various therapeutic interventions should be used to mitigate the psychological and physical harms accrued from being chronically stressed. This article will describe numerous integrative treatments that target allostatic mechanisms within the brain, and also other physiological systems when needed, to increase patients' quality of life (i.e., healthspan), and maybe even longevity (i.e., lifespan).

Using Natural Health Products to Lessen the Impacts of Chronic Stress

The conventional approach involves pharmaceutical intervention, which can be extremely helpful and potentially lifesaving. In their article discussing stress- and allostasis-induced brain plasticity, McEwen and Gianaro stated the ➤

Table 1: Definitions

Allostasis: Coined by Sterling and Eyer,[2] refers to biological adjustments that allow an individual to adapt to particular challenges that happen over the lifespan. Adapting to such challenges demands the synchronous though non-linear activation of many different physiological processes, such as neural, neuroendocrine, and neuroendocrine-immune mechanisms.[3] Allostasis begins with the brain and happens or is instigated by how an individual perceives and interprets any given situation. Allostasis is about adaptation, but the physiological adaptations may not ensure survival because they can become deleterious over time and cause irreversible damage.

Homeostasis: Is about ensuring survival, and refers to "physiological parameters like blood oxygen and pH" that are "maintained within a narrow range" (p.37).[3]

Chronic stress: Defined as "ongoing demands that threaten to exceed the resources of an individual in areas of life such as family, marriage, parenting, work, health, housing, and finances," p.638).[4] In physiological terms, chronic stress refers to a "pathological state that is caused by prolonged activation of the normal acute physiological stress response, which can wreak havoc on immune, metabolic, and cardiovascular systems" (p.56).[5] When an individual is faced with chronic stress, which is common among most psychologically distressed patients, it may seem enduring and without a clear ending.

***Allostatic load (AL), and allostatic overload* (AO):** AL represents body degradation that results from repeated allostatic responses during stressful situations.[6] This results when an allostatic system fails to habituate to the recurrence of the same stressor, fails to shut off following overwhelming stress, and/or whose response is deficient resulting in heightened activation of other, normal counter-regulatory systems.[3,7] AO is thus an extension of AL, which often results in irreversible damage to body organ systems, and/or mental illness. Thus, unmitigated chronic stress that results in AL and AO will typically cause all sorts of psychological distress signals, especially among individuals vulnerable to mental illness.

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following in reference to pharmaceutical interventions:

> Sleeping pills, anxiolytics, beta blockers, and antidepressants are all used to counteract problems associated with allostatic overload. Likewise, drugs that reduce oxidative stress or inflammation, block cholesterol synthesis or absorption, and treat insulin resistance or chronic pain can help deal with the metabolic and neurological consequences of chronically stressful experiences. All of these agents have value, but each one has side effects and limitations that are based in part on the fact that all of the systems that are dysregulated in allostatic overload interact with each other and perform normal functions when properly regulated (pp.439-440).[8]

Similar to pharmaceutical interventions, natural health products (NHPs) can be used to attenuate AL and AO. They are often of great importance to patients because they typically possess fewer adverse effects compared to pharmaceutical interventions. Many NHPs can be safely integrated with standard approaches or can sometimes be used as an alternative. NHPs can be used to modulate the activity of the PFC and/or limbic system to presumably improve the functional connection of these brain circuits, thereby, assisting the PFC with improved top-down control and processing, and/or attenuating limbic activity to dampen bottom-up control. NHPs can also mitigate pathophysiological harms from AL and AO, such as high blood pressure, insulin resistance, and other medical problems.

Information known about pharmaceutical interventions can be extremely helpful when postulating how NHPs assist with improving PFC and limbic functionality and connectivity. The essential aim of a modern treatment strategy is to deconstruct the psychiatric illness in question, then consider a treatment or set of treatments that hypothetically improves or attenuates malfunctioning neurocircuitry by targeting specific neurotransmitters in that circuit, which then relieves symptoms and improves overall functionality.[9] Antidepressant medications are good examples of pharmaceutical interventions that possess specific pharmacological effects to modulate implicated neurocircuits. They can increase the availability of serotonin and other monoamines between the synapses of neurons. The release of serotonin at target neurons, for example, activates receptors that are widely expressed in the hippocampus, amygdala, and PFC, and which mediate fear, anxiety, stress, and cognitive function.[10]

Antidepressants also increase brain-derived neurotrophic factor (BDNF) expression, which is believed to be responsible for the time lag prior to an antidepressant response, since it takes several weeks for the pharmacological actions to augment the expression of BDNF.[11] Antidepressants may help to compensate for the levels of BDNF in specific brain areas (i.e., the PFC and hippocampus) that are presumed to be insufficient as a consequence of chronic stress.[11]

Depression is also associated with perceiving social cues as more negative, including the tendency to focus on more aversive information, and even recalling more "negative than positive information about oneself" (p.4).[11] Antidepressants can reverse this core psychological process, known as ***negative affective bias***, by increasing the processing of positive affective information.[11]

Table 2. NHPs that putatively possess therapeutic effects similar to antidepressant medication

Treatment	*Suggested Daily Dose*	*References*
5-HTP (timed- or sustained-release formulations)	400-1200 mg	13,14
Acetyl-L-carnitine	1000-4000 mg	15,16
Chamomile extract (1.2% apigenin)	500-1500 mg	17,18
Curcumin extract (BCM-95)	1000 mg	19,20
Rhodiola rosea extract (3% rosavins and 1% salidroside)	300-1360 mg	21-23
Saffron extract	30-100 mg	21,24
SAMe	1600-3200 mg	25,26
St. John's wort extract (0.3% hypericin)	900-1800 mg	27,28
Theanine	200-400 mg	29,30

The chronic stress of depression is also related to an increased amount of extracellular glutamate within the brain, which contributes to excitotoxic damage.[11] There is reason to believe that antidepressant treatment can act as glutamatergic modulators and attenuate excitotoxic damage though more studies are certainly needed.[12]

Overall, these specific effects resulting from antidepressant use should be capable of modulating the implicated brain circuits to reduce symptoms of emotional overwhelm, improve functionality, and lessen the pathophysiological effects of AL and AO. The same logic about antidepressants can also be extended to specific NHPs (Table 2) that possess mechanisms of action that: (1) augment serotonin or other monoamine neurotransmitters; (2) augment BDNF expression; (3) increase the processing of positive affective information; and/or (4) attenuate glutamatergic excitotoxicity. The majority of the published data on these specific NHPs were derived from clinical trials, though some systematic reviews and meta-analyses were also referenced. All of these NHPs have an adverse effect profile that is superior to antidepressants. Extracts of St. John's wort and *Rhodiola rosea* should not be combined with antidepressant medication. Though it is sometimes clinically valuable, ongoing clinical vigilance is advised when combining 5-hydroxytryptophan (5-HTP) or S-adenosylmethionine (SAMe) with antidepressants.

Anxiety or anxious feelings are other target areas of pharmaceutical interventions that differ from antidepressants. Reducing anxiety is an obvious and helpful component when mitigating the AL and AO that accompanies chronic stress. Commonly prescribed treatments are the benzodiazepines that should be reserved for short-term use, but are taken chronically by numerous anxious patients. All benzodiazepines target the benzodiazepine-binding site in the brain located on the chloride channel. They boost the effects of gamma-aminobutyric acid (GABA) on the frequency of the opening of the chloride channel, culminating in a hyperpolarization of the target cell, a decrease in the firing rate of these neurons, and pharmacological effects that include muscle relaxation, lowered arousal, and sedation.[31] Benzodiazepines also modulate the

activity of the HPA axis by mitigating the effects of CRH,[32] and reduce the limbic response to anxiety.[33]

The problems with taking benzodiazepines long-term are well known, and include dependence, withdrawal-associated problems, and addiction. They also prevent the brain from creating new pathways of growth, which undermines a patient's ability to effectively manage and/or overcome their anxiety.[34] There are published reports, for example, that have documented reduced effectiveness of exposure-based treatment when patients are taking benzodiazepines, and clinical benefits from exposure-based treatment when patients are not taking them.[34] When a patient comes off benzodiazepine treatment, they will almost always re-experience the same anxiety that they had when they first initiated treatment because the cumulative benefits from treatment are very limited. This class of medication can, however, be beneficial when used as needed and very judiciously, or for brief durations of time (i.e., 2-4 weeks).

Given what has been noted about benzodiazepines, it makes sense to consider specific NHPs (Table 3) as alternative treatments since they have mechanisms of action that interface with the benzodiazepine-binding site and/or the GABA system, but without serious adverse effects and problems of addiction, dependence, and withdrawal. Moreover, these specific NHPs likely reduce HPA axis activation, and assist with top-down PFC processing by attenuating the limbic response to anxiety. Though they can be combined with benzodiazepines, these NHPs will potentiate the clinical effects of benzodiazepines, and in some cases may be contraindicated because of too much sedation. All the published data on these specific NHPs involve clinical trials and/or aggregated datasets involving large numbers of patients (i.e., more than several hundred), except for niacinamide, which only has lower quality evidence in the form of published case reports discussing its benzodiazepine-like effects.

The final component involves the clinical use of NHPs (Table 4) that work similarly to pharmaceutical interventions used to mitigate AO represented by high cholesterol (i.e., an abnormal cholesterol profile), metabolic-based diseases (e.g., insulin resistance and obesity), oxidative stress, inflammation, and/or chronic pain. All of these medical problems contribute immeasurably to the burdens of chronic stress and should be managed aggressively. Specific NHPs will be highlighted here though clinicians are certainly encouraged to consider many more NHPs when attempting to lessen the pathophysiological effects associated with AO, and the consequential increased morbidity and premature mortality that normally follows. These NHPs have a superior adverse effect profile compared to commonly prescribed pharmaceutical interventions (e.g., statins and metformin), but several of them (i.e., berberine, curcumin extract, and resveratrol) can sometimes cause symptoms such as gastrointestinal upset, flatulence, constipation, and/or nausea. The published data is strongest for berberine, pantethine, and palmitoylethanolamide, while both curcumin extract and resveratrol require more clinical trials, systematic reviews, and meta-analysis to better support the indications listed in the table.

Using Lifestyle Modifications to Lessen the Impacts of Chronic Stress

In this section, I will review numerous lifestyle modifications that can be recommended to patients suffering from the deleterious effects of chronic stress. All of these lifestyle modifications do not have to be done in their entirety to improve enduring problems associated with AL and AO, but certainly several of them can become part of a comprehensive plan aimed at lessening the biological and psychological impacts resulting from chronic stress. This won't be an exhaustive review but will instead highlight salient research linking lifestyle modifications with reduced stress, increased psychological and physical health, and when possible, implicated brain mechanisms.

Diet. There should be no dispute about the enduring and negative health impacts from nutrient-poor and carbohydrate-rich diets, which are notably high in energy density, contain too much sugar and saturated fat, are low in fiber, and are abundantly processed. This type of diet has contributed to the exponential rise in obesity and associated metabolic diseases like type 2 diabetes mellitus and non-alcoholic fatty liver disease.[83,84] Type 2 diabetes mellitus is also associated with psychiatric illnesses, such as depression, since they both likely have the same underlying inflammatory pathophysiology.[83] A high-fat diet has been associated with anxiety and anhedonic behaviors due to cascading effects that adversely impact synaptic plasticity and insulin signaling/glucose homeostasis, which result in increased cortisol levels and inflammatory cytokines.[85] Unhealthy eating in an adult population was shown to be associated with an increased prevalence of anxiety, depression, and stress.[86] In that same study, the data showed that an excessive intake of sweets and low consumption of dairy products was particularly associated with a higher prevalence of psychological and sleep disturbances.[86]

Based on what has been noted, it is rather obvious as to what constitutes a healthier diet. Recommending well-balanced meals that are rich in fruits, vegetables, and fiber, with adequate protein, healthy fats, low levels of sugar ➤

Table 3. NHPs that putatively possess therapeutic effects that interface with the benzodiazepine-binding site and/or the GABA system

Treatment	*Suggested Daily Dose*	*References*
Ashwagandha extract (2.5-5% withanolides)	1000-1800 mg (providing approx. 45-50 mg of withanolides)	35-38
Broad-Spectrum Micronutrients	2-15 pills daily (depending on the recommended NHP)	39-41
Chamomile extract (1.2% apigenin)	500-1500 mg	42-44
Holy Basil	1000-1200 mg	45,46
Lavender extract	80 mg or 160 mg	47-50
Niacinamide/Nicotinamide (i.e., amide form of vitamin B3)	500-2500 mg	51,52
Passion Flower extract	425-1275 mg	53,54
Rhodiola rosea extract (3% rosavins and 1% salidroside	400-600 mg	55-57
Valerian root extract (0.8% valerenic acids)	500-1500 mg	58-61
Theanine	200-400 mg	62-64

➤

and carbohydrates (i.e., limiting foods with a high glycemic index), and lower amounts of food (i.e., meaning calories), is something that should be advocated to all patients.[85] In terms of a specific dietary approach, a clinical trial used a ***modified Mediterranean diet*** to treat patients with major depressive disorder (MDD), and the results showed remission among 32% of the treated patients and an impressive number needed to treat of 4.1.[87] A less rigorous evaluation showed that an increased consumption of plant foods consistent with a Mediterranean diet were positively associated with physical function and general health, and with reductions in trait anxiety, depression, and perceived stress.[88]

Even though there isn't just one dietary approach that would ideally help all patients with chronic stress, recommending a dietary approach that is similar to a Mediterranean diet seems to be the best one to approximate. Of course, compliance will always remain an issue, but it possesses broad health benefits that appear to additionally improve mental health symptoms. With respect to brain changes, adopting a Mediterranean diet has not specifically been linked to changes in brain morphology though in one cited study positive effects were observed in plasma BDNF levels among a subset of participants (i.e., it attenuated reductions in plasma BDNF levels).[89] In a couple of systematic reviews and meta-analysis on adults, the Mediterranean diet was shown to improve a variety of cognitive parameters known as cognitive domain composites (i.e., global cognition, memory, and frontal cognitive domains),[89] and cognitive functions (i.e., delayed recall, working memory and global cognition).[90] Mechanistically, its benefits are likely attributed to anti-inflammatory, antioxidant, microbiome effects, the lowering of the glycemic load and advanced glycation endproducts, and increasing dietary fiber and specific micronutrients (e.g., omega-3 essential fatty acids and polyphenols).[89]

Exercise. Recommending regular exercise to all chronically stressed patients makes logical sense. It is certainly preferable that patients have some type of planned exercise each week to overcome the psychological and biological burdens associated with being sedentary and/or bored. There is published data demonstrating specific mental health benefits from exercise in being able to attenuate mental health symptoms, improve social connectedness and functionality, and augment personal empowerment. In a systematic review that evaluated the impact of regular exercise among people with severe mental illness, the results showed improvements that included mood, alertness, concentration, sleep patterns and even psychotic symptoms. Unsurprisingly, the data revealed that exercise contributed to improved quality of life "through social interaction, meaningful use of time, purposeful activity and empowerment" (p.48).[91] A comprehensive literature review also showed that a broad range of exercise types was associated with different outcomes, such as reduced mental health symptoms, improved functionality, and/or better concentration.[92]

The biological factors associated with the improvements from regular exercise include increased levels of monoamine neurotransmitters, beta-endorphins, opioids, endocannabinoids, neurotrophic factors, and even specific (yet helpful) pro-inflammatory processes.[92] Specifically, exercise induces the following neurochemical alterations: increased serotonin levels decrease anxiety; increased norepinephrine levels increase alertness; increased dopamine levels increase pleasure; and increased levels of opioids and endocannabinoids

Table 4. NHPs that mitigate AO represented by high cholesterol, metabolic-based disease, oxidative stress, inflammation and/or chronic pain

Treatment	Primary Indication	Pharmacologic mechanisms of action	Suggested Daily Dose	References
Berberine	Cholesterol modification and insulin resistance	Insulin sensitization; increases glucose uptake; enhances glucose metabolism; stabilizes LDL receptor mRNA; and inhibits lipid synthesis within hepatocytes	500-1500 mg	65-68
Curcumin extract (80-95% curcuminoids)	Chronic pain (i.e., joint arthritis), inflammation, oxidative stress, and insulin resistance	Down-regulates nuclear factor-kappa B; modifies proinflammatory cytokines such as interleukin production, phospholipase A2, cyclooxygenase-2, and 5-lipoxygenase; reduces tumor necrosis factor; reduces inducible nitric oxide synthase; protects against advanced glycation as well as collagen crosslinking; and inhibits osteoclastogenesis	1000 mg	69-73
Pantethine	Cholesterol modification	Increases coenzyme A levels in cells; inhibits acetyl-CoA carboxylase and HMG-CoA reductase; and favorably modifies lipoprotein metabolism	900 mg	74,75
Palmitoylethanolamide	Chronic pain (irrespective of etiology)	Acts as a congener of the endocannabinoid anandamide; agonism of peroxisome proliferator-activated receptor-α; inhibits the release of proinflammatory mediators such as cyclooxygenase, and inducible and endothelial nitric oxide synthase; reduces mast cell migration and degranulation; and reduces over-activation of astrocytes and glial cells	1200 mg	76-78
Resveratrol	Inflammation, oxidative stress, and insulin resistance	Too numerous to note, but includes interactions with a large number of receptors, kinases, and other enzymes; and stimulates the activities of sirtuin 1 and adenosine monophosphate-activated protein kinase	1000 mg	79-82

increase euphoria and decrease anxiety. Additionally, neurotrophic factors such as BDNF and insulin-like growth factor-1 increase from regular exercise, and contribute to its experienced and durable benefits over time. Exercise also causes pro-inflammatory processes associated with durable benefits related to neurogenesis, angiogenesis and synaptogenesis.

Another biological model that explains the benefits from exercise involve a hypothesized mechanism known as ***transient hypofrontality***.[92] When a person exercises, the ensuing blood flow and energetic resources are diverted from the brain to motor activities. In doing so, there would be a transient hypofrontality because the brain's metabolic demands have been rightfully shifted. This has the net effect of attenuating psychiatric symptoms by temporarily deactivating involvement of the PFC (i.e., less hyperawareness, vigilance and attention), which then reduces the ensuing amygdala activation, resulting in less mental distress.

Psychologically, regular exercise can induce a variety of positive states of being that reduce symptoms of mental distress.[92] Exercise can result in a state known as ***flow,*** which is related to focused concentration, being in the moment, and experiencing feelings of reward. ***Self-efficacy*** is another benefit from regular exercise, and relates to feeling a sense of accomplishment. Exercise also increases social interaction, which is known to assuage mental distress.

Different types of exercise have been studied (e.g., yoga, walking, weight-lifting, and running), and all of them produce benefits when they are done consistently, and for adequate durations of time (i.e., at least 90 minutes each week).[92] Exercise that is of moderate to high-intensity has been shown to produce greater therapeutic effects at attenuating psychiatric symptoms.[92]

With respect to specific brain changes, it is known that the volumes of the hippocampus and medial temporal lobes are larger in adults with a high level of fitness, and that exercise increases hippocampal perfusion.[93] In a randomized clinical trial, 6 months of regular aerobic exercise was shown to increase the size of the anterior hippocampus, resulting in spatial memory improvements.[93] Specifically, exercise increased hippocampal volume by 2%, which reversed age-related loss in volume by 1-2 years. The increased hippocampal volume was also associated with increased serum levels of BDNF.

Many natural health products can be safely integrated with standard approaches or can sometimes be used as an alternative.

Nature. An obvious lifestyle treatment that enhances mental health is that of ***nature experiences***, which "includes individuals' perceptions and/or interactions with stimuli from the natural world (from potted plants and private gardens to more expansive public green spaces and wilderness, weather, and the movements of the sun) through a variety of sensory modalities (sight, hearing, taste, touch, and smell)" and that "can occur through conditions of 'real' (in situ) contact, window views, representations (e.g., landscape photographs), or simulations (e.g., virtual reality; p.2)."[94] Evidence supports enhanced psychological well-being, positive affect, increased happiness, positive social interactions, improved sleep, increased meaning and purpose in life, and reductions in stress (i.e., as per self-reported improvements, and/or improvements in various physiological measurements and biomarkers of acute and chronic stress) when engaging in nature experiences.[94] Other published data has shown improvements in working memory, cognitive flexibility, and attention control when being exposed to nature experiences.[95] Being in nature also increases ***hedonic well-being*** (i.e., feeling good and experiencing a sense of satisfaction), and ***eudaimonic well-being*** (i.e., meaning, autonomy, vitality, and feelings of transcendence).[96]

Several hypotheses have been proposed to explain the benefits of nature experiences and include the ***biophilia hypothesis*** (that we have an innate drive to be in nature), the ***stress reduction hypothesis*** (that there is a resultant physiological response that reduces stress levels), and the ***attention restoration theory*** (that nature reloads cognitive resources and re-establishes the capacity to concentrate and pay attention).[96]

Even though no direct published research was cited about nature experiences and brain mechanisms, it seems likely that increasing these types of exposures would enhance the functional connectivity between the cortico-limbic systems. Nature experiences should therefore be capable of providing protection against chronic stress by preventing (or moderating) decoupling between the PFC, amygdala, and hippocampus. ◆

References and article are available online at www.townsendletter.com.

Dr. Jonathan E. Prousky graduated from Bastyr University (Kenmore, Washington) in 1998 with a doctorate in naturopathic medicine. He furthered his clinical training by completing a family practice residency sponsored by the National College of Naturopathic Medicine (now the National University of Natural Medicine). In 2008 he obtained a master of science degree in international primary health care from the University of London, which focused on clinical epidemiology and evidence-based research. In 2016 he obtained a master of arts degree in counselling psychology from Yorkville University.

At the Canadian College of Naturopathic Medicine, Dr. Prousky's primary responsibility is the delivery of safe and effective naturopathic medical care in his role as the chief naturopathic medical officer. He was the first naturopathic doctor to receive the "Orthomolecular Doctor of the Year" award in 2010. In 2017 he was also the first naturopathic doctor to be recognized for his longstanding commitment to mental health by being inducted into the "Orthomolecular Hall of Fame." Dr. Prousky is the author of several texts, such as *Textbook of Integrative Clinical Nutrition*, and *Anxiety: Orthomolecular Diagnosis and Treatment.*