



Therapeutic Nutrition

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Sickness Syndrome: The Link Between Inflammatory Diseases and Depression: Part II

In Part I of “Sickness Syndrome,” (*Townsend Letter*, 2006;279:58-61) I discussed the causes and effects of this relatively new medical phenomenon. Sickness Syndrome can be identified by a host of non-specific symptoms, directly caused by peripheral inflammatory cytokines triggering the local production of inflammatory cytokines in the brain. It can result from a variety of problems, from mood disorders and cognitive disturbances to an overall reduction in the patient’s immune system functioning.

Stress, both physical and psychological, has been identified as one of the primary causes of Sickness Syndrome. Typically, the body responds to stress by producing glucocorticoids (e.g., cortisol), which serve as the main regulator of the expression and action of pro-inflammatory cytokines in the brain and at the peripheral level. In this article, I will focus on this physiologic response and its relationship to depression and highlight some of the treatment modalities that can address this condition.

The Inflammation-Depression Link

It has long been established that stress can increase levels of plasma IL-6 as well as activate nuclear factor (NF) κ B, a family of transcription factors that plays a central role in the inflammatory signaling cascade. In patients suffering from major depression, this response is further exacerbated by an increase in the level of plasma proinflammatory cytokines such as interleukin (IL)-6.¹⁻⁴

A study¹ was undertaken by researchers at the Emory General Clinical Research Center to determine the innate immune system activation in patients with major depression and increased early life stress who were subject to psychosocial stress. Twenty-eight males (half of whom were identified as having current major depression as determined by Structured Clinical Interview for DSM-IV) participated in the study, which measured the inflammatory response to stressful situations – specifically, plasma interleukin (IL)-6, lymphocyte subsets, and DNA binding of nuclear factor (NF) κ B in peripheral blood mononuclear cells.

While all participants displayed an increase in plasma IL-6 concentrations during Trier Social Stress Test challenge over time ($F=10.32$, $df=1.92$, 48.10 , $p<0.001$), depressed patients had higher IL-6 concentrations

than comparison subjects at baseline and 90 minutes poststressor, and also displayed a greater IL-6 response (IL-6) to the Trier Social Stress Test than comparison subjects (Mann-Whitney $U=44$, $p<0.05$).

While this study demonstrated the increased inflammatory response in patients with major depression, we also know from previous research^{5,6} that administering inflammatory cytokines to a non-depressed patient will trigger the local production of proinflammatory brain cytokines, which then causes depression. A connection has also been established between those patients having inflammatory diseases and the increased incidence of depression.⁷

As I mentioned in Part I of this series on Sickness Syndrome, cortisol is the main brake on the expression and action of proinflammatory cytokines, both at the periphery and in the brain. We know that cortisol production is enhanced by cytokines. However, its negative feedback on cytokines production and action is operational *only if there is no cortisol resistance*.^{5,8} It is reasonable to assume, then, that utilizing specific alternative approaches to modulate the stress response – and in particular cortisol production – to inhibit the production of inflammatory cytokines, and/or to counter their effects will prove to be a significant and beneficial approach to dealing with the depression-stress-inflammatory response link. Based on my research, I have compiled a selection of treatment modalities that have proven to be effective countermeasures against the effects of Sickness Syndrome, particularly for patients suffering from major depression.

Nutraceuticals

Through research, I have identified 12 nutraceuticals that can be taken to combat the effects of Sickness Syndrome. While each has key properties specific to its chemical composition, they all share an ability to address Sickness Syndrome symptoms in one or more ways:

- mediating hypoglycemic actions through cortisol-regulating activity
- regulating corticosteroid-induced inflammation and insulin resistance
- inhibiting lipooxygenase, cyclooxygenase 2, leukotriene

- providing anti-inflammatory and antibacterial benefits

Within this overall classification, I have further subdivided the nutraceuticals into two categories by virtue of their primary mechanisms of action.

Category I

The following eight nutraceuticals offer the following mechanisms of action: they act as anti-inflammatory and NF Kappa B modulators; they are able to traverse the blood-brain barrier; and they provide antioxidant protection. Their specific benefits are detailed below.

- Sesame Seed oil – Both sesamin and sesamol inhibit IL-6, TNF- α , and NF- κ B function activation. Precursors from sesame seeds are converted by bacterial microflora in the colon to mammalian lignans. As effective as flax seeds in producing lignans, sesamin has strong free radical-scavenging capability.^{9,10}

- *Curcuma longa* extract – Also known as turmeric, this extract of curcumin inhibits lipooxygenase, cyclooxygenase 2, leukotrienes, thromboxane, TNF- α , and IL-12.¹¹

- Proteolytic Enzymes – Potent anti-inflammatory proteolytic enzymes increase antioxidant enzymes (SOD, catalase, and glutathione peroxidase) while reducing inflammatory cytokines – specifically TNF- α , IL-1 β .¹²

- *Camellia sinensis* (standardized for EGCG) – The tea plant that is the source of green tea extract, *Camellia sinensis* is a weak NF Kappa B modulator.¹³ Keep in mind that we do not want to entirely shut down weak NF kappa B activity, due to its role in supporting immune function. The fact that this herbal medicine only weakly inhibits that activity speaks to the elegance of nature in its infinite wisdom: *Camellia sinensis* only modifies the actions of key biochemical players – enough to maintain balance. This cannot be said for pharmaceutical agents designed to entirely block the actions of this family of transcription factors.

- *Humulus lupulus* (terpenoids) – Also known as the common hops plant, it serves as a weak NF Kappa B modulator.¹⁹

- Pycnogenol® – A natural plant extract from the bark of the maritime pine tree native to the coast of southwest France, Pycnogenol is an antioxidant modulator of NF Kappa B.¹⁴

- *Boswellia serrata* – An Indian herb also known as Shallaki, its resin contains boswellic acids, which inhibit 5-lipoxygenase, leukotriene synthesis, and leukocyte elastase. Clinical trials report promising results supporting anti-inflammatory effects of *Boswellia* extract in Rheumatoid Arthritis (RA), Ulcerative Colitis (UC), and Crohn's.¹⁵⁻¹⁷

- *Withania somnifera* – Known as Ashwagandha in Ayurvedic literature, the extract derived from the root has anti-inflammatory properties. The methanolic extract also has antibacterial properties.¹⁸

Category II

The following four nutraceuticals provide the following physiologic benefits: they regulate cortisol/insulin/ blood sugar, nourish the adrenal glands, provide antioxidant protection, increase alpha brain wave activity, and offer overall adaptogenic actions. They each also offer specific benefits as detailed below.

- Wildcrafted Holy Basil – Referred to as the “Queen of Herbs” and the “incomparable one” in Ayurvedic Medicine, Wildcrafted Holy Basil mediates hypoglycemic effects through cortisol-inhibiting activity as well as through regulating corticosteroid-induced inflammation and insulin resistance.¹⁹

- *Rhodiola rosea* – Clinical trials have demonstrated *Rhodiola rosea*'s efficacy in reducing mental fatigue, improving cognitive functioning, enhancing sense of well-being, and regulating cortisol levels. An anti-inflammatory, it lowers C-Reactive Protein (CRP) levels after exhausting exercise and contains proanthocyanidins that cross the blood-brain barrier.²⁰⁻²²

- Suntheanine® – Research has shown that L-Theanine increases alpha brain wave activity, improves learning performance, heightens mental acuity, and promotes concentration while diminishing social anxiety.²³

- Schizandra berry extract – A creeping vine native to Northern China, extracts from its berries enhance and protect overall cellular vitality and maintain healthy nerve and adrenal gland function.^{24,25}

Additional Effective Approaches

In addition to the above nutraceuticals, both yoga and meditation have proven to be effective in regulating vagal output and decreasing stress levels, which decreases cortisol resistance. As a result, the inflammatory process is short-circuited and, with it, the production of proinflammatory brain cytokines that ultimately cause depression. Regulating vagal output prevents synthesis of proinflammatory brain cytokines that cause depression in Sickness Syndrome patients. In addition to regulating Vagal output, meditation and yoga increase activity in the left frontal region of the brain associated with positive emotions.^{26,27} Combined with the above-mentioned nutraceuticals, these two approaches are effective weapons against the effects of major depression, an illness considered the leading cause of disability in countries all over the world.²⁸

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Sickness Syndrome

Dr. Nick maintains patent protection for the treatment of Sickness Syndrome™ and is completing a new book on the condition. She will also be presenting new information about the diagnosis and treatment of Sickness Syndrome at the following events:

The Merging Medicine Series I: Stress, Inflammation and Cancer conference, November 4&5, 2006 at the San Diego Convention Center in San Diego, California. Register at www.calnd.org/events.asp, or call: 209-245-3521.

CAM EXPO West November 11, 2006 at the Hyatt Regency Century Plaza in Los Angeles, California: www.camexpo.com.

Notes

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