

Advancing Nutrition

for Professionals

Feeling anxious
– nutritional and
functional
approaches
explored

**Optimising sporting
performance**

Astaxanthin
– nature's powerful gift

The skin
– an in-depth look

The labelling maze
– gluten explained

**What does organic
really mean?**

A nutritional approach to anxiety

Anxiety affects everyone at some point in their life: whether it's chronic general anxiety or at specific times, such as when flying or encountering that spider lurking in the bathtub. In this article, we will explore nutrients that can be used for chronic general anxiety, otherwise known as generalised anxiety disorder (GAD). The words anxiety and GAD will be used interchangeably in the article.

by Shannon Feely BSc ND



Shannon Feely BSc ND is a Canadian Naturopathic Doctor with a practice in Greenwich, London. She trained at the Canadian College of Naturopathic Medicine; one of only two schools in Canada allowed to grant the designation of Naturopathic Doctor. Shannon also teaches at the College of Naturopathic Medicine in London. More information can be found at www.shannonfeely.com.

GAD involves anxiety and worry that is excessive and unrelenting. The symptoms can range in severity, from people who go about everyday activities but are filled with exaggerated worry and tension, to people that experience symptoms that prevent everyday functioning⁽¹⁾. GAD affects over a million people in the UK, and is slightly more common in women⁽²⁾.

What causes anxiety?

We know that GAD is caused by a wide range of bio-psycho-social factors. Possible causes or contributing factors include: hypothyroidism, serotonin deficiency, nutrient deficiencies (particularly co-factors needed in neurotransmitter synthesis), fibromyalgia, sex hormone imbalances and related conditions such as menopause and PMS, excessive consumption of caffeine, chronic alcohol intake, medication side effects, opioid deficiency, hypoglycaemia, cerebral insufficiency, chronic stress, low stomach acid, excess glutamate, high homocysteine levels, excessive oxidation and excessive lactate production⁽³⁾.

Pathophysiology of anxiety

The pathophysiology of anxiety is poorly understood. On a general level, it involves communication between both the central nervous system and the autonomic nervous system, especially the sympathetic division.

Research has been searching for a common biological denominator in the cause of anxiety but has yet to find one. Instead, we are finding that anxiety is the result of complex interactions between multiple neurotransmitters and peptides.

In an attempt to summarise what we do know about the pathophysiology of anxiety, there appear to be four major systems involved: serotonin, gamma-aminobutyric acid (GABA), norepinephrine and acetylcholine. Other systems, such as dopamine, high levels of corticotropin-releasing factor (CRF), cortisol and lactic acid also contribute, but possibly to a lesser degree^(4,5). There are also conflicting results about the role of the nitric oxide (NO), L-arginine and cyclic guanosine monophosphate (cGMP) pathways in anxiety⁽⁶⁾. Anxiety often accompanies depression, suggesting common physiological pathways with this condition as well.

We know that increased norepinephrine and decreased serotonin are the major mediators of anxiety symptoms. We also know that GABA is the primary inhibitory neurotransmitter of the central nervous system, while acetylcholine is the main neurotransmitter of the parasympathetic nervous system and is antagonistic to adrenaline⁽⁷⁾. GABA sends inhibitory messages to other neurons, helping to balance and offset excitatory messages, such as from norepinephrine. It is speculated that people with GAD may have low amounts of GABA, or that their GABA receptors have reduced sensitivity⁽⁸⁾. Serotonin levels are affected by genetic

and environmental factors. For example, polymorphisms on various serotonin genes are associated with depression⁽⁹⁾. The hypothalamic-pituitary-adrenal (HPA) axis plays a significant role in anxiety, through its effects on hormones in responses to stress. For example, chronic stress activates the HPA and causes high levels of cortisol. This may alter special proteins that are needed for serotonin receptor function and lead to a state of low serotonin⁽¹⁰⁾. Stress also increases the need for various nutrients, such as magnesium and calcium, as studies have found increased urinary excretion of these nutrients with subjects under stress⁽¹¹⁾.

There is also one common body structure that appears to play a major role in anxiety⁽¹²⁾. This is the amygdala, a small structure inside the brain. The amygdala communicates with the sympathetic nervous system to relay perceived danger to other centres of the brain and then stores a memory of these dangers. Interestingly, this memory storage can cause these stressful memories to stimulate the sympathetic nervous system when the body and mind “perceive” that danger⁽¹³⁾. In anxiety, the perceived danger is often out of proportion to actual danger, but the body has stored that memory as being dangerous.

Overall, evidence shows that it is dysregulation in a range of nervous system pathways, and a problem with the body's ability to adapt to the stress, that leads to GAD⁽¹⁴⁾. Clearly, more research is needed in this area.

Nutrients for anxiety

L-tryptophan: It is well researched that serotonin is critically important in mood and anxiety⁽¹⁵⁾. Serotonin is synthesised from the amino acid tryptophan and serotonin levels depend on the amount of tryptophan that crosses the blood-brain barrier. Research shows that dietary sources of tryptophan can have significant effects

on serotonin synthesis⁽¹⁶⁾. For example, when a diet is deficient in tryptophan, it triggers anxiety pathways, leading to increased release of corticotropin-releasing factor (CRF) from the hypothalamus, increased plasma cortisol and worsening of depression symptoms⁽¹⁷⁾. However, using diet alone to raise tryptophan and, thus, serotonin levels is not efficient because of competitive inhibition with other large amino acids to cross the blood-brain barrier⁽¹⁸⁾. Interestingly, lactalbumin may be a way to bypass this problem, as, taken orally, lactalbumin enhances the production of serotonin, lowers cortisol and decreases symptoms of anxiety⁽¹⁹⁾.

Stress also impacts the body's use of tryptophan. High levels of cortisol appear to decrease the concentration of plasma tryptophan. Insulin has an opposite effect and decreases the concentration of amino acids except tryptophan⁽²⁰⁾. This may partially explain the links between carbohydrate cravings and anxiety.

5-Hydroxytryptophan (5-HTP): 5-HTP is made from l-tryptophan and is the pre-cursor to serotonin. However, keep in mind that 5-HTP has differences to tryptophan. 5-HTP is not affected by the presence of other amino acids, easily crosses the blood-brain barrier, and cannot be shunted into other pathways such as niacin or protein production, as tryptophan can⁽²¹⁾. Oral consumption of 5-HTP also skips the rate-limiting enzyme in serotonin synthesis and increases serotonin in the central nervous system⁽²²⁾.

A systematic review of the effects of tryptophan and 5-HTP on depressive disorders found a large number of studies showing that effects of these substances on depression were better than a placebo, but the quality of the studies were not sufficient to be reliable, and many side effects were reported⁽²³⁾.

Nutrients as co-factors:

Neurotransmitters such as acetylcholine, serotonin and GABA all require a series of biochemical reactions to occur before they can be produced. These biochemical reactions require specific nutrients:

- GABA is produced from **glutamine**, and low plasma glutamine levels are seen in depression. One of the enzymes that converts glutamine into GABA is dependent upon **pyridoxine**⁽²⁴⁾. If pyridoxine is not available in sufficient amounts, glutamine can be converted into glutamic acid, an excitatory neurotransmitter, rather than GABA⁽²⁵⁾. Glutamate and glutamic acid are main excitatory neurotransmitters in the brain. GABA production is also dependent

on **magnesium, vitamin C** and **zinc**⁽²⁶⁾.

- **Vitamin B3, folic acid, calcium, B6, vitamin C, zinc, magnesium** and **iron** are all required for the synthesis of serotonin⁽²⁷⁾. Folic acid is a co-factor in the rate-limiting step of serotonin synthesis and studies have shown an inverse relationship between low folate levels and low mood⁽²⁸⁾.
- **Folic acid** and **vitamins B6** and **B12** are involved in the synthesis of s-adenosylmethionine (**SAMe**). **SAMe** plays a big role in the formation of a key brain compound called tetrahydrobiopterin (BH4). In turn, BH4 is essential to the synthesis of serotonin^(29,30). Studies show patients supplemented with BH4 have dramatic improvements of depression symptoms, possibly due to the SAMe⁽³¹⁾. (BH4 is not commercially available.)
- Acetylcholine production is dependent upon vitamins **B3, B1, B2, B5, magnesium, potassium, lipolate, choline** and **various amino acids (Iso, Leu, Lys, Phe, Try)**⁽³²⁾.
- Lactate levels can rise with **vitamin B3** or **magnesium** deficiencies⁽³³⁾. High levels of lactic acid can perpetuate anxiety symptoms. **Niacinamide** may have anti-anxiety effects, through increasing the conversion of lactate to pyruvate and so preventing the build up of lactic acid-induced anxiety⁽³⁴⁾.

Choline: research into choline for anxiety is starting to emerge. Choline is a precursor needed to make the neurotransmitter acetylcholine. Remember that acetylcholine is the main neurotransmitter of the parasympathetic nervous system and is antagonistic to adrenaline^(35,36). Acetylcholine's role in anxiety is not well understood, but we do know that acetylcholine suppresses anxiety in the hippocampus and anxiety occurs when its release is prevented, in animal research⁽³⁷⁾.

Cholinesterase is the enzyme that converts acetylcholine to choline and acetate. This breakdown is needed to allow the neuron to return to its resting state, after activation by acetylcholine. Choline esterase activity has been found to be high in anxiety states, due to an increased release of the enzyme from tissues^(38,39,40). This may suggest a number of possible scenarios:

- The high amounts of cholinesterase activity possibly decrease the amount of available acetylcholine and, thus, cause anxiety.
- People with anxiety use choline at a greater rate than non-anxious people because the cholinergic neurons are in a constant state of activation.

The next question could be: Are choline levels low in people with

anxiety? Well, recently, a large population-based study, called the Hordaland Health Study, found that choline concentrations were inversely associated with anxiety, but not with depression symptoms⁽⁴¹⁾. Multiple small studies have also found a correlation between generalised anxiety disorder and low levels of choline⁽⁴²⁾. Inositol has also been shown to have a calming effect, reducing the severity and frequency of panic attacks⁽⁴³⁾. Inositol is closely associated with choline and biotin. It is found in lecithin and works with vitamins B5, B6 and folic acid.

Huperzine (from firmoss) has been shown to inhibit acetylcholinesterase and, therefore, raise acetylcholine levels, by preventing degradation.

In another, older study, six people suffering from acute anxiety were treated daily with injections of a choline substance for two weeks and relief from the anxiety resulted in all cases. Anxiety symptoms resumed on withdrawal of the choline substance⁽⁴⁴⁾.

Acetyl-l-carnitine has been shown to raise acetylcholine levels in the brain and has protective effects on the mitochondria⁽⁴⁵⁾. Phosphatidylcholine seems to decrease the body's stress response and can increase levels of acetylcholine in the brain^(46,47). Lecithin is a popular source of phosphatidyl choline.

L-theanine: Theanine, an amino acid present in green tea is emerging as a promising nutrient for controlling anxiety. Theanine can cross the blood-brain barrier and has been shown, in rats, to increase both serotonin and dopamine production and may also play a role in GABA formation⁽⁴⁸⁾. It can prevent the binding of glutamic acid to glutamate receptors, suggesting it may increase GABA function as well⁽⁴⁹⁾.

Theanine also decreases both psychological and actual physiological symptoms of stress, possibly through modulation of the sympathetic nervous system⁽⁵⁰⁾. For example, it reduces heart rate and salivary IgA responses under acute stress conditions⁽⁵¹⁾. Theanine also increases alpha brain wave activity; a sign of an alert and relaxed state^(52,53). Theanine did not increase theta brain waves, which are brain waves indicative of dozing sleep⁽⁵⁴⁾.

One study showed that theanine might only have relaxing effects under resting conditions⁽⁵⁵⁾. A different study also found theanine significantly increased the amount of tryptophan in the brain, but the amount of serotonin decreased⁽⁵⁶⁾. The authors concluded that theanine might decrease serotonin synthesis but may enhance the degradation, or suppress the release, of serotonin⁽⁵⁷⁾.

Omega 3 fatty acids: Omega 3 fatty

acids play both direct and indirect roles in improving anxiety. Omega 3 fatty acids support healthy cellular membranes and promote optimal function of neurotransmitter receptors. They also reduce arachidonic acid (AA) release⁽⁶⁸⁾. AA increases glutamine release and blocks re-uptake of glutamate, so essential fatty acids act indirectly as glutamate antagonists⁽⁶⁹⁾. Although larger studies are needed, much research supports the need for the use of omega 3 fatty acids in anxiety disorders^(60,61).

Magnesium: Magnesium, although used widely for muscle tension and many other conditions, has only a moderate amount of research on its use for anxiety. These studies do show positive results for magnesium supplementation in improving anxiety⁽⁶²⁾. We also know that magnesium prevents excitatory glutamate receptor function, which suggests a role in increasing GABA⁽⁶³⁾. Also, during levels of high lactic acid and low carbon dioxide (such as in a panic attack), the kidney increases the excretion of bicarbonate. The bicarbonate ion and magnesium work together to prevent intracellular acidity and extracellular alkalinity, which, if not prevented, causes further hyperventilation⁽⁶⁴⁾. A magnesium deficiency may increase hyperventilation in people prone to panic attacks⁽⁶⁵⁾.

Taurine: Research is just starting to explore taurine's role in anxiety. Taurine is an amino acid found abundantly in excitable tissues⁽⁶⁶⁾. It is also an antioxidant and can be made from cysteine and vitamin B6, as well as methionine. Taurine's main action in anxiety is through lowering neuroexcitation by controlling glutamate metabolism⁽⁶⁷⁾. Taurine is best used to enhance the effectiveness of other treatments that have a direct effect on GABA⁽⁶⁸⁾. Glutamine supplementation increases plasma taurine⁽⁶⁹⁾.

Studies on mice found that supplementing chronically with taurine can be anxiety-causing, whereas acute injections of taurine were anxiolytic. An additional study found that taurine, given acutely and orally, did have a significant anti-anxiety effect, but that it may not be linked to the GABA receptor⁽⁷⁰⁾.

Taurine also has many positive side effects such as reducing blood pressure, glucose regulation and promoting biliary cholesterol secretion^(71,72). At this time, there are no systematic reviews for taurine's use in anxiety, indicating further research is needed in this area.

Additional nutrients to investigate: Melatonin precursors, glycine, phenylalanine, selenium, calcium, vitamin D and vitamin A are also

important nutrients to consider and research is emerging for their use in anxiety. For example, one study found that the lower the level of selenium in the diet, the more reports of anxiety, depression, and tiredness. These symptoms decreased after five weeks of selenium therapy⁽⁷³⁾.

Clinical message

The take-home message from this brief exploration into using nutrients for anxiety is that their clinical use should focus on:

- Ensuring all nutrient co-factor deficiencies are addressed.
- The role of multiple biochemical pathways in anxiety. The main ones are serotonin, acetylcholine, norepinephrine and GABA. If you don't get results with one approach, then consider a nutrient that affects a different pathway. Ideally, target multiple pathways and choose products that have multiple relevant nutrients.
- The need for more research on the complex web that is the pathophysiology of anxiety as well as the nutrients that affect this pathophysiology.

REFERENCES:

1. *HelpGuide.org. Generalized Anxiety Disorder. Available at: http://www.helpguide.org/mental/generalized_anxiety_disorder.htm [Accessed 30th March 2010]*
2. *Patient UK. Generalized Anxiety Disorder. Available at: <http://www.patient.co.uk/health/Anxiety-Generalised-Anxiety-Disorder.htm> [Accessed 30th March 2010]*
3. *Osiecki H. The Physician's Handbook of Clinical Nutrition. 7th Edition. Australia: Bio Concepts Publishing; 2008.*
4. *Rakel D, Rosenbaum J, Fava M, Biederman J, Rauch S. Integrative Medicine. 2nd Edition. Philadelphia: Saunders; 2007.*
5. *Stern T. Massachusetts General Hospital Comprehensive Clinical Psychiatry. 1st Edition. [Online] Philadelphia: Mosby; 2008. Available at: www.mdconsult.com [Accessed 29th March 2010]*
6. *Gilhotha N, Dhirgra D. Involvement of NO-cGMP pathway in anti-anxiety effect of aminoguanidine in stressed mice. Prog Neuropsychopharmacol Biol Psychiatry. [Online] 2009;13 (33(8)): pp. 1502-7.*
7. *Barlow D. Anxiety and its disorders: the nature and treatment of anxiety and panic. [Online] New York: The Guilford Press; 2004. Available at <http://books.google.co.uk/books> [Accessed 28th March 2010]*
8. *Stern T. Massachusetts General Hospital Comprehensive Clinical Psychiatry. 1st Edition. [Online] Philadelphia: Mosby; 2008. Available at: www.mdconsult.com [Accessed 29th March 2010]*
9. *Jones D, ed. Textbook of Functional Medicine. Washington: The Institute for Functional Medicine; 2005.*
10. *Jones D, ed. Textbook of Functional Medicine. Washington: The Institute for Functional Medicine; 2005.*
11. *Grases G, Pérez-Castelló JA, Sanchis P Casero A, Perelló J, Isern B, et al. Anxiety and stress among science students. Study of calcium and magnesium alterations. Magn Res. [Online] 2006; Jun;19(2):102-6. Available from: www.ncbi.nlm.nih.gov/pubmed (Accessed 30th March 2010)*
12. *Rakel D, Rosenbaum J, Fava M, Biederman J, Rauch S. Integrative Medicine. 2nd Edition. Philadelphia: Saunders; 2007.*
13. *Rakel D, Rosenbaum J, Fava M, Biederman J, Rauch S. Integrative Medicine. 2nd Edition. Philadelphia: Saunders; 2007.*
14. *Stern T. Massachusetts General Hospital Comprehensive Clinical Psychiatry. 1st Edition. [Online] Philadelphia: Mosby; 2008. Available at: www.mdconsult.com [Accessed 29th March 2010]*
15. *Jones D, ed. Textbook of Functional Medicine. Washington: The Institute for Functional Medicine; 2005.*

17. *Jones D, ed. Textbook of Functional Medicine. Washington: The Institute for Functional Medicine; 2005.*
18. *Jones D, ed. Textbook of Functional Medicine. Washington: The Institute for Functional Medicine; 2005.*
19. *Jones D, ed. Textbook of Functional Medicine. Washington: The Institute for Functional Medicine; 2005.*
20. *Jones D, ed. Textbook of Functional Medicine. Washington: The Institute for Functional Medicine; 2005.*
21. *Pharmacorama. Serotonin. Available at: http://www.pharmacorama.com/en/Sections/Serotonin_2_1.php [Accessed 30th March 2010].*
22. *Birdsall TC. 5-Hydroxytryptophan: a clinically-effective serotonin precursor. Altern Med Rev. [Online]. 1998 Aug;3(4): pp.271-80. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9727088> [Accessed 1st April 2010].*
24. *Birdsall TC. 5-Hydroxytryptophan: a clinically-effective serotonin precursor. Altern Med Rev. [Online]. 1998 Aug; 3(4): pp.271-80. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9727088> [Accessed 1st April 2010].*
26. *Shaw KA, Turner J, Del Mar C. Tryptophan and 5-Hydroxytryptophan for depression (Review). The Cochrane Collaboration. [Online] Available at: http://www.mrw.interscience.wiley.com/cochrane/clsyrev/articles/CD003198/pdf_abstract_fs.html [Accessed 28th March 2010]*
27. *Jones D, ed. Textbook of Functional Medicine. Washington: The Institute for Functional Medicine; 2005.*
28. *Osiecki H. The Physician's Handbook of Clinical Nutrition. 7th Edition. Australia: Bio Concepts Publishing; 2008.*
29. *Pizzorno J, Murray M. Textbook of Natural Medicine. 3rd Edition. [Online] St. Louis: Churchill Livingstone; 2009. Available at www.mdconsult.com. [Accessed on 28th March 2010].*
30. *Pizzorno J, Murray M. Textbook of Natural Medicine. 3rd Edition. [Online] St. Louis: Churchill Livingstone; 2009. Available at www.mdconsult.com. [Accessed on 28th March 2010].*
31. *Jones D, ed. Textbook of Functional Medicine. Washington: The Institute for Functional Medicine; 2005.*
32. *Rakel D, Rosenbaum J, Fava M, Biederman J, Rauch S. Integrative Medicine. 2nd Edition. Philadelphia: Saunders; 2007.*
33. *Pizzorno J, Murray M. Textbook of Natural Medicine. 3rd Edition. [Online] St. Louis: Churchill Livingstone; 2009. Available at www.mdconsult.com. [Accessed on 28th March 2010].*
34. *Pizzorno J, Murray M. Textbook of Natural Medicine. 3rd Edition. [Online] St. Louis: Churchill Livingstone; 2009. Available at www.mdconsult.com. [Accessed on 28th March 2010].*
35. *Pizzorno J, Murray M. Textbook of Natural Medicine. 3rd Edition. [Online] St. Louis: Churchill Livingstone; 2009. Available at www.mdconsult.com. [Accessed on 28th March 2010].*
36. *Osiecki H. The Physician's Handbook of Clinical Nutrition. 7th Edition. Australia: Bio Concepts Publishing; 2008.*
37. *Werbach MR, Moss J. Anxiety. Textbook of Nutritional Medicine. CA: Third Line Press, Inc; 1999.*
38. *Byrne D. Anxiety: Recent Developments In Cognitive, Psychophysiological And Health Research. [Online] USA: Hemisphere Pub Corp; 1990. Available at <http://books.google.co.uk/books> [Accessed 28th March 2010].*
39. *Barlow D. Anxiety and its disorders: the nature and treatment of anxiety and panic. [Online] New York: The Guilford Press; 2004. Available at <http://books.google.co.uk/books> [Accessed 28th March 2010].*
40. *Südhof T, Starke K. (Eds.) Pharmacology of neurotransmitter release. [Online] Berlin: Springer-Verlag; 2008. Available at: www.googlebooks.co.uk [Accessed 21st March 2010].*
41. *Richter D, Lee M. Serum Choline Esterase and Anxiety. Journal of Mental Science [Online] 1942; 88: pp. 428-434. Available at: www.pubmed.com [Accessed 30th March 2010].*
42. *Ledowski T, Bein B, Hanss R, Tonner PH, Roller N, Scholz J. Pseudocholinesterase activity increases and heart rate variability decreases with preoperative anxiety. European Journal of Anaesthesiology. [Online] 2005 Apr; 22(4): pp. 289-92. Available at: www.pubmed.com [Accessed 30th March 2010].*
43. *Erzegovci S, Bellodi L, Smeraldi E. Serum cholinesterase in obsessive-compulsive disorder. Psychiatry Res [Online] 1995 Oct 16;58 (3): pp. 265-8. Available at: www.pubmed.com [Accessed 30th March 2010].*
44. *Bjelland I, Tell GS, Vollset SE, Konstantinova S, Ueland PM. Choline in anxiety and depression: the Hordaland Health Study. American Journal of Clinical Nutrition [Online] 2009 Oct; 90(4): 1056-60. Available at: www.pubmed.com [Accessed 30th March 2010].*

References continue on page 30.