Introduction

Anxiety disorders are life altering psychiatric conditions that severely impair the quality of life of those suffering from them. They are the most common psychiatric disorders in the United States, and are characterized by numerous somatic symptoms, such as facial flushing, hyperhydrosis (excessive sweating), muscle tension, paresthesias (numbness and tingling), shallow breathing, syncope (fainting), and tachycardia (rapid heart rate). The emotional symptoms of anxiety disorders occur simultaneously with the somatic ones and include agitation, derealization (feelings of unreality), fearfulness, feelings of impending doom, irritability, nervousness, and shyness. Patients with anxiety disorders often report escape and avoidance behaviors that merely reinforce and perpetuate their ongoing anxiety. They also tend to engage in catastrophic thinking by over-predicting the negative consequences of events. Patients tend to misinterpret benign bodily sensations as warning signals for more serious conditions. For example, heart palpitations are common among the anxiety sufferers, yet this symptom is often misinterpreted as being a heart attack.

Anxiety sufferers desperately want their anxiety to go away, but they cannot control it. What these patients suffer from is a heightened autonomic nervous system (ANS) reaction to a perceived threat. There might even be some link between the anxiety of modern times and the lifesaving mechanism that was required of our prehistoric ancestors. For example, when the early hominids had to hunt and kill to feed themselves, they had to mobilize and react to real threats to their survival. By contrast, the anxiety sufferer of today manifests the same mobilization as if fleeing from a predator, but this mobilization is out of proportion to the actual threat. In some of us, anxiety might actually be built into our genes. Evolution might favor those who have anxiety because it makes sense to have a built-in system that ensures survival.

Best of Naturopathy

Orthomolecular Treatment of Anxiety Disorders

by Jonathan E. Prousky, ND, FRSH

Table 1:

Lifetime Consequences of Anxiety

Most sufferers of anxiety:
- commonly report their health as poor.
- have a higher risk of suicide.
- smoke cigarettes and abuse other substances.
- have an increased chance of developing chronic medical illnesses (e.g., chronic obstructive pulmonary disease, diabetes and hypertension) compared to the general population.
- have medical illnesses that are often prolonged as a result of anxiety.
- will remain untreated and undiagnosed many years after their initial diagnoses, leading to unremitting impairment in functional status and quality of life.

Table 2:

Questions To Ask The Anxious Patient

- Is the anxiety constant or intermittent? If intermittent, the work-up should focus on psychomotor epilepsy, pheochromocytoma, insulinoma, or intermittent cardiac arrhythmia, such as paroxysmal supraventricular tachycardia or atrial fibrillation.
- What is the patient's age? Young or middle-aged patients likely have an anxiety disorder. Older patients, by contrast, might be suffering from cerebral arteriosclerosis or other types of dementia.
- Is the tachycardia present during sleep? If present during sleep, causes such as caffeine or other drug effects and hyperthyroidism need to be considered.
- Has there been any weight loss? If there is weight loss and tachycardia, hyperthyroidism is very likely.

Is it better to have a system that gives more false positives than false negatives? The advantage might be survival, but at a tremendous cost to the sufferer due to a lifetime of discomfort (Table 1).

Even with the unfortunate reality that anxiety might "live in" the genes of those susceptible to it, patients do not have to endure a lifetime of suffering. Anxiety sufferers want viable treatment options that can lessen their anxiety and improve their quality of life. An orthomolecular approach does just that—it is simple, effective, reduces the somatic and emotional symptoms of anxiety, and dramatically improves quality of life. The first part of this report will focus on the diagnosis of anxiety disorders. The second part will examine orthomolecular treatment strategies and will include case reports demonstrating the effectiveness of this approach.

Diagnosing Anxiety Disorders

To diagnose anxiety disorders it is necessary to first rule out organic causes before a psychiatric diagnosis can be made. Certain questions should be posed during the history when evaluating the anxious patient for organic causes (Table 2).

Once a thorough history has been obtained the diagnostic work-up involves various tests depending on the nature of the anxiety. If the anxiety was found to be intermittent, it might be necessary to perform a wake-and-sleep electroencephalogram (EEG) and possibly a computed tomography (CT) scan to rule out a cerebral tumor. In addition, the work-up might require a 24-hour urine collection for catecholamines (to rule-out pheochromocytoma) or a 24-hour Holter monitor (to rule-out paroxysmal cardiac arrhythmia). If the anxiety is more constant than intermittent, the work-up involves other tests such as a thyroid panel (to rule-out hyperthyroidism), a drug screen, and an EEG. In cases of
chronic anxiety, a 24-hour Holter monitor might also be helpful.

When the work-up does not reveal an organic cause, or when the history strongly indicates a non-organic cause of anxiety, a psychiatric diagnosis needs to be considered. Anxiety disorders are classified into various categories such as generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), panic disorder (PD), posttraumatic stress disorder (PTSD), and social phobia/social anxiety disorder (SAD). See Table 3 for a brief description of the main types of anxiety disorders. To make an appropriate psychiatric diagnosis, it is necessary that certain criteria be met for the anxiety disorder being considered.

Orthomolecular Treatment Strategy #1: Niacinamide (Nicotinamide)

The main treatment approach for anxiety disorders is to use a high enough dose of certain nutrients to diminish the ANS reaction, eliminate the fear of anxiety, and improve quality of life. One of the most effective ways to accomplish this is through the use of the amide of niacin (nicotinic acid) known as niacinamide (nicotinamide). This B-vitamin has remarkable therapeutic benefits for those suffering from anxiety. In a recent report, a review of the literature was undertaken to determine the biological mechanism for niacinamide’s anxiolytic effects. It appears that niacinamide has therapeutic effects comparable to the benzodiazepines, a class of medications commonly used for GAD, PD, and SAD. Benzodiazepine medications bind to a macromolecular complex that is found within the central nervous system (CNS), referred to as the GABA (gamma-aminobutyric acid) benzodiazepine receptor-chloride ion channel complex. When benzodiazepines bind onto or near this macromolecular complex they potentiate GABA-ergic synaptic inhibition through membrane hyperpolarization, thus enhancing the conductance of the chloride ion by increasing the frequency of channel-opening events. The net result is the reduction of anxiety and related symptoms via the diminution of neurotransmission (e.g., neuronal firing) among many brain regions such as the spinal cord, hypothalamus, hippocampus, substantia nigra, cerebellar cortex, and cerebral cortex.

Niacinamide’s therapeutic effects are likely not related to it acting as a ligand for the benzodiazepine receptor, even though it acts centrally and might have a weak binding affinity for the benzodiazepine receptor. Both the benzodiazepines and niacinamide exert similar anxiolytic effects through the modulation of neurotransmitters commonly unbalanced in anxiety. Table 4 summarizes niacinamide’s benzodiazepine-like effects. The three following case reports demonstrate niacinamide’s superb anxiolytic properties.

Case #1
An 11 year-old girl first presented to my office on November 10, 2003, with chief complaints of nervousness, anxiety, and excessive worrying. The onset of her symptoms occurred when her father tragically died in September 2003. The patient reported anxiety when she had to sit for examinations and when she was around her classmates. The most concerning symptom was her fear of being kidnapped, which was instigated by a well-publicized kidnapping of a young Asian girl in the city where she lives. She also reported having approximately two panic attacks each month since September for which she had learned to deal with them by “leaving the situation to get air.” Other symptoms she reported included some facial acne, frequent blushing, stomachaches, and sweating. She was diagnosed with PD, with some elements of SAD. A complete physical examination was performed and all findings were within normal limits. She was prescribed a daily multiple vitamin/mineral preparation, 25 mg of zinc, 100 mg of pyridoxine, 400 of magnesium, and 500 of niacinamide twice daily. A follow-up appointment occurred on December 13, 2003. The patient reported a slight improvement with her anxiety. She was only taking the multiple vitamin/mineral preparation, zinc, and niacinamide. She agreed to increase the dose of niacinamide to 1000 mg twice daily. No side effects were reported. A second follow-up occurred on February 7, 2004. The patient reported a striking improvement with her anxiety. Her panic attacks completely stopped and her acne was much improved as well. In a recent email from the patient, she reported to be taking only the 1000 mg of niacinamide twice daily. Her anxiety remained much improved and was no longer interfering with her ability to engage in a regular life.
Anxiety

Case #2
A 28 year-old woman came to my private practice with a chief complaint of GAD on May 10, 2004. She had been struggling with this anxiety disorder for the past twelve years. She is a high school teacher and noted that her anxiety was more pronounced during the academic year. Her anxiety was worse in the morning with symptoms of frequent muscular tension, the passing of flatus, and chest pain. She reported a fear of smelling when she needed to expel gas. The anxiety also made it difficult for her to concentrate and focus on things. When she experienced anxiety symptoms she would feel the need to isolate herself from others. The same isolating need occurred when she simply thought about feeling nervous and expelling gas. She also reported fears of embarrassment, and worried about being criticized by others. She had been on paroxetine for one year but had not noticed any improvement. She reported feeling depressed due to her mild depression, and 2000 mg of niacinamide. The vitamin B-6 and magnesium. The vitamin B-6 and magnesium were prescribed for the premenstrual symptoms of depression. On June 4, 2004, I received an urgent telephone call from the patient. Since discontinuing the prescribed treatments on June 1, her anxiety symptoms returned promptly and she had difficulty functioning. She agreed to resume only the niacinamide tablets. On July 2, 2004, the patient emailed me with an update. She discontinued all the prescribed treatments except for the niacinamide. She found her anxiety and depression to be much relieved because she was at home and not teaching during the summer months. When she felt anxiety, she would take niacinamide and it would help. In her words: "I take the niacinamide and I'm fine afterwards."

Case #3
A 42 year-old woman first presented to my private practice on May 16, 2004, for chief complaints of constipation and anxiety. About three weeks earlier, her father was diagnosed with advanced carcinoma of the stomach. Since her father's diagnosis, she had been feeling very anxious with symptoms of shakiness, light-headedness, numbness of the extremities, and balance problems. Her medical doctor had her do a 24-hour Holter monitor and the results were normal. She was unable to correlate her anxiety with feelings of hunger. In the past, she would have the same kind of anxiety symptoms when stressful events occurred. Her medical doctor felt that the patient's anxiety was related to hyperventilation. On physical examination, the patient was well-nourished, slightly overweight, with normal blood pressure and normal heart sounds. All other systems were within normal limits. She was diagnosed with panic attacks, dyspepsia (possibly irritable bowel syndrome), and mild obesity. She was advised to continue with her liquid multiple vitamin/mineral preparation, take 500 mg of niacinamide, and to add a B-complex vitamin preparation (personal observation). The three patients tolerated the large pharmacological doses of niacinamide very well. On June 4, 2004, she called me to inform me that she had decreased her dose from 3000 mg per day to 2000 mg per day due to feelings of unreality. The 28 year-old patient had problems swallowing the niacinamide tablets. For this reason, it might be necessary to switch some patients to capsules or powder forms of niacinamide. Large pharmacological doses of niacinamide (1500-6000 mg per day) have been safely used in children and adolescents for extended periods of time without any adverse side effects or complications such as clinical hepatitis.20,21 The most common side effect with niacinamide is sedation,22 but dry mouth and nausea have been the most common side effects that I have observed among some of my patients. There has been one case report linking large pharmacological doses of niacinamide (9 grams per day) to hepatic toxicity.23 The patient in the cited report had no evidence of clinical hepatitis when taking 2000-3000 mg per day of niacinamide, but did develop clinical hepatitis when the dose was increased to 9000 mg daily. All clinical abnormalities did revert to normal once the niacinamide

Prescribing Instructions
Most patients require 2000-4500 mg of niacinamide per day to achieve therapeutic results. These dosages were derived from the work of Hoffer, who recommended 1500-6000 mg of niacinamide per day for all patients with psychiatric syndromes.19 Patients usually experience relief of their symptoms within one month of taking the medication (personal observation). The three patients tolerated the large pharmacological doses of niacinamide very well. One patient needed to reduce her dose from 3000 mg per day to 2000 mg per day due to feelings of unreality. The 28 year-old patient had problems swallowing the niacinamide tablets. For this reason, it might be necessary to switch some patients to capsules or powder forms of niacinamide. Large pharmacological doses of niacinamide (1500-6000 mg per day) have been safely used in children and adolescents for extended periods of time without any adverse side effects or complications such as clinical hepatitis.20,21 The most common side effect with niacinamide is sedation,22 but dry mouth and nausea have been the most common side effects that I have observed among some of my patients. There has been one case report linking large pharmacological doses of niacinamide (9 grams per day) to hepatic toxicity.23 The patient in the cited report had no evidence of clinical hepatitis when taking 2000-3000 mg per day of niacinamide, but did develop clinical hepatitis when the dose was increased to 9000 mg daily. All clinical abnormalities did revert to normal once the niacinamide
was discontinued. I never prescribe more than 6000 mg per day of niacinamide since most patients will develop nausea and sometimes vomiting on a dose higher than this. There is hardly any need to go above 4500 mg per day when treating anxiety. If nausea does occur, decreasing the dose by 1000 mg usually corrects the problem.

Orthomolecular Treatment Strategy #2: L-Glycine
Glycine is a nonessential (or neutral) amino acid that has profound anxiolytic properties. It is considered to be an inhibitory amino acid since it increases membrane permeability to chloride ions, producing an inhibitory postsynaptic potential (IPSP), and preventing action potential generation. In other words, glycine works similarly to the benzodiazepines. Receptors for glycine are found in the vertebrate CNS, spinal cord and brain stem areas, and are equally distributed throughout mammalian tissues. The highest concentrations of glycine are found in the thalamus, amygdala, substantia nigra, putamen, and globus pallidus. The most unique aspect of glycine's mechanism of action has to do with its presumed antagonism of norepinephrine (NE). The neurons for NE are located in a part of the brain stem called the locus coeruleus, from which the NE neurons branch out to touch as many as half of all the cells in the brain (probably several billion) in the cerebral cortex. When an individual experiences anxiety or panic, NE is released from the locus coeruleus and affects a part of the brain known as the nucleus accumbens, leading to feelings of anxiety and panic. Glycine antagonizes the release of NE from the locus coeruleus and the ensuing signals to the nucleus accumbens, thus mitigating anxiety and panic, and feelings of over-arousal.

Prescribing Instructions
The best way to administer glycine is sublingually so that the gastrointestinal route is bypassed. This allows for quicker absorption, a faster onset of action, and swift entry to the CNS. At least 2–10 grams are required in order to stop a panic attack. It is very palatable and sweet tasting making it easy to administer sublingually. I have my patients place 2 grams under their tongue at the onset of an acute panic attack. They can take another 2 grams every few minutes until the panic attack subsides. It usually works within a matter of a few minutes. Side effects are very rare with high doses of glycine. There is one report that 14 grams given to a 70 Kg adult male produced nausea. However, 15-30 grams have been given to two manic patients producing no side effects except for cessation of the manic episode and calmness within one hour of supplementation. I have never found glycine to work better than niacinamide for daily use. It is best reserved for acute panic attacks or acute periods of anxiety.

Orthomolecular Treatment Strategy #3: Intramuscular (IM) Injections of Vitamin B12 (cobalamin)
Vitamin B12 (cobalamin) is involved in numerous biochemical reactions as a cofactor and coenzyme. Its main functions involve DNA synthesis, methionine synthesis from homocysteine, and conversion of proprionyl into succinyl coenzyme A from methylmalonate.

The psychiatric manifestations of vitamin B12 deficiency include irritability, personality change, mild memory impairment, dementia, depression, and psychosis. Patients most likely to develop vitamin B12 deficiency have clinical conditions such as atrophic gastritis, bacterial overgrowth of the small intestine, and pernicious anemia.

It is clear that vitamin B12 helps those who are deficient; yet, there are many patients who seem to benefit psychologically from regular vitamin B12 injections despite the absence of diseases and serologic evidence of vitamin B12 deficiency. In a study involving two subjects, each was randomized to receive weekly injections of hydroxocobalamin or placebo (phenolsulfonphthalein) for 25 weeks. Prior to the study and after the study, gastric analysis was performed and the subjects were found to have no absorption problems. Each week during the study, the subjects were given a questionnaire ranking various items such as the helpfulness of the injection, the duration of benefit, and if the injection improved energy, pep, strength, depression, nerves, appetite, tremor, fatigue, and outlook. Even though there were no differences found between the hydroxocobalamin or placebo, the subjects did report a benefit in terms of nervousness and fatigue from the hydroxocobalamin.

In another study, a double-blind crossover trial involving 28 subjects comparing of tiredness, injections of hydroxocobalamin or matching placebo were administered. The subjects were given 5 mg of hydroxocobalamin twice weekly for two weeks followed by a rest period of two weeks, and then a similar course of matching placebo injections. Symptoms were assessed by a daily self-ratings that included appetite, mood, energy, sleep, and general feeling of well-being. Those subjects who received the placebo in the first two-week period showed a favorable response to hydroxocobalamin in the second period in all measurements made. Specifically, statistical significance (p=0.006) was achieved with respect to general well-being, while “happiness” also showed statistical significance (p=0.032).

The data presented does indicate a potential anxiolytic benefit from regular IM injections of hydroxocobalamin. The case described below is an example of the clinical response that is possible with vitamin B12.

Case #4
A 25-year-old presented to my private practice on August 7, 2004, with chief complaints of anxiety and depression. The onset of the patient’s anxiety began two years ago when she started her new job as a graphic designer. She described symptoms of heart racing, sweating, dizziness, stomach pain, nausea, vomiting, light-headedness, and diarrhea. She also reported difficulties falling asleep, and would even wake-up with her heart beating very fast. She was currently on 25 mg of paroxetine daily, and had taken it for the past two years. The anxiety attacks mainly occurred at work, which often forced her to leave early. She also described a history of depression that began when she was only 12 years of age. The depression improved initially when she first started the paroxetine, but now it seemed to have worsened again. Physical examination revealed a slightly overweight female, with normal vitals and normal findings of all other systems. She was diagnosed with GAD, and was prescribed a program of 120 mg/day of Ginkgo biloba extract to help with her sexual dysfunction, 1 teaspoon of fish oil, and niacinamide at increasing doses until 1000 mg three times daily was reached. At a follow-up appointment on September 9, 2004, the patient complained of feeling sick and nauseous with the niacinamide. She also reported feeling paranoid and panic. The patient had anxiety for the previous two weeks and was crying all...
Anxiety

> the time. She was told to reduce the niacinamide to 500 mg three times daily, to add 50 mg of 5-HTP three times daily, and was given 1000 micrograms (mcg) of hydroxocobalamin by IM injection. For the next five weeks, the patient received injections of hydroxocobalamin twice weekly and discontinued all the other prescribed supplements on her own. On October 16, 2004, the patient described herself as being free of any anxiety and panic. She had not had a panic attack since September 9. About one-month later, on November 13, 2004, the patient returned for another vitamin B12 injection. She described a slight worsening of her anxiety and panic since stopping the twice-weekly injections. For the previous two weeks, the patient had spells of nausea and hot flushes; however, she had not needed to leave work early as she did in the past. Another 1000 mcg of hydroxocobalamin was administered IM, and she was instructed to return more regularly for the injections. In a follow-up email on November 17, the patient reported the following: "I've been panic free since the weekend, which is nice. I haven't had hot flashes or heart beating fast in the morning either. I'm starting to think it has a lot to do with how well I have been feeling!"

Prescribing Instructions

When trying to control symptoms of anxiety, it might be necessary for patients to receive regular injections of hydroxocobalamin. The dose should always be 1000 mcg and can be given once or twice every week until symptoms improve. The best form is injectable hydroxocobalamin as can be seen from Table 5.32

The only rare side effect from hydroxocobalamin is an acneiform exanthema, particularly in women.33 These lesions have been reported to result from oral supplementation, but I have seen the same eruption occur from hydroxocobalamin injections. The lesions consist of loosely disseminated small papules or papulopustules on the face, the upper parts of the back and chest, and can spread to the upper arm. They go away within a week once the regular injections have been discontinued.

What is the mechanism that can account for the benefits of injectable hydroxocobalamin? In a study involving 49 patients with organic mental disorders, deficient CSF levels of vitamin B-12 (<5 pg/ml) were found in 30 patients.34 When the serum levels of vitamin B-12 were tested, normal values (200–800 pg/ml) were found in 45 of them, indicating a marked difference between both compartments. A group of ten patients were also given injectable hydroxocobalamin at a dose of 1000 mcg twice weekly for six weeks. This group was compared against a group of two patients given 0.1 mg of oral cyanocobalamin three times daily for six weeks. As can be seen from Table 6, the group given the injections achieved a much greater increase in their CSF levels of vitamin B12. Given that serum levels of vitamin B-12 can be normal yet deficient in the CSF, patients responding to regular IM injections of hydroxocobalamin might have an improvement in their anxiety due to marked (supraphysiological) increases in their CSF vitamin B12 levels, or from the correction of deficient CSF levels of vitamin B12. The best way to achieve high CSF levels of vitamin B12 is through twice weekly injections.

Orthomolecular Treatment Strategy #4: Eliminate Caffeine & Alcohol

Although the case reports did not specifically identify caffeine and alcohol as anxiety-triggers, these items should be eliminated in all patients with anxiety disorders. Caffeine is a stimulant and can sometimes be the underlying cause of a patient's anxiety. Caffeine toxicity is not uncommon and has been shown to cause symptoms such as lightheadedness, tremulousness, breathlessness, headache, and premature ventricular contractions in one patient.35 In the same patient, these symptoms went away once the caffeine was discontinued, and recurred on two separate occasions when caffeine was re-challenged after periods of abstinence.

Alcohol has been demonstrated to increase the lactate-to-pyruvate ratio, which can precipitate anxiety.36 Numerous studies to date have confirmed that lactate sensitivity or an increased responsiveness to lactate is a factor in provoking anxiety symptoms.37–40 Alcohol has also been shown under double-blind conditions to increase anxiety.41

Conclusion

More case reports, research, and rigorous controlled trials are needed to properly evaluate the therapeutic effectiveness, safety, and mechanisms of action of niacinamide, glycine, and vitamin B12. In light of the positive results accomplished from using these nutrients, perhaps these orthomolecular substances are indicated for the management of anxiety. In fact, these agents might be more effective than current contemporary medications for the treatment of anxiety disorders. Their safety profile is unmatched by most conventional agents due to the relative absence of negative side effects when large pharmacological doses are used.

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Table 5: Vitamin B12: Effectiveness and Route of Administration

<table>
<thead>
<tr>
<th>Route</th>
<th>Maximum increase from baseline</th>
<th>24-hour urinary excretion</th>
</tr>
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<tbody>
<tr>
<td>Oral</td>
<td>43%</td>
<td>0.009%</td>
</tr>
<tr>
<td>Sublingual</td>
<td>34%</td>
<td>0.004%</td>
</tr>
<tr>
<td>Parenteral (hydroxocobalamin)</td>
<td>106%</td>
<td>2.7%</td>
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<tr>
<td>Parenteral (cyanocobalamin)</td>
<td>78%</td>
<td>4.2%</td>
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Table 6: Cerebral Spinal Fluid (CSF) and Serum Differences Between Injectable & Oral Vitamin B12

<table>
<thead>
<tr>
<th>Group</th>
<th>Pre-Treatment Serum B12 (pg/ml)</th>
<th>Pre-Treatment CSF B12 (pg/ml)</th>
<th>Post-Treatment Serum B12 (pg/ml)</th>
<th>Post-Treatment CSF B12 (pg/ml)</th>
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</thead>
<tbody>
<tr>
<td>Injectable (10 patients)</td>
<td>310</td>
<td>&lt;5</td>
<td>&gt;2400</td>
<td>70</td>
</tr>
<tr>
<td>Oral (Patient #1)</td>
<td>430</td>
<td>14</td>
<td>2400</td>
<td>21</td>
</tr>
<tr>
<td>Oral (Patient #2)</td>
<td>450</td>
<td>&lt;5</td>
<td>&gt;2400</td>
<td>9.6</td>
</tr>
</tbody>
</table>
References


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