Supplemental Niacinamide Mitigates Anxiety Symptoms: Three Case Reports

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Abstract

The purpose of this report is to highlight the potential of niacinamide for the treatment of anxiety disorders. Three patients were prescribed large pharmacological doses of niacinamide (2,000-2,500 mg per day). Each of the patients had considerable relief from their anxiety when regularly using niacinamide. The possible biochemical reasons for niacinamide's effectiveness might be related to the correction of subclinical pellagra, the correction of an underlying vitamin B_3 dependency disorder, its benzodiazepine-like effects, its ability to raise serotonin levels, or its ability to modify the metabolism of blood lactate (lactic acid). Adverse effects did not occur with these doses, but nausea and vomiting can occur when doses as high as 6,000 mg per day are used. These positive case reports suggest that niacinamide might be helpful for the treatment of anxiety disorders. However, definitive proof requires properly conducted randomized controlled trials to assess niacinamide's actual therapeutic effects and adverse effects profile.

Introduction

Anxiety disorders are very prevalent conditions treated by primary care providers. In a recent survey of 2,316 randomly selected patients (aged eighteen-years and older) seen by general practitioners, 42.5% of all patients had evidence of a threshold/subthreshold psychiatric disorder.[1] In the same survey, anxiety disorders were found in 19% of all patients. In a survey of 88 outpatients in an internal medicine clinic, 30% of patients had mixed anxiety features, 33% had generalized anxiety symptoms, almost half reported obsessive-compulsive personality symptoms, and about one-quarter had marked levels of worry.[2] The investigators concluded that anxiety disorders are more common in primary care settings than what had been previously reported.

Anxiety disorders are classified into various categories such as obsessive-compulsive disorder (OCD), panic disorder (PD), social phobia/social anxiety disorder (SAD), and generalized anxiety disorder (GAD). This report will not differentiate the various categories of anxiety disorders as described in the *Diagnostic and Statistical Manual of Mental Disorders*.[3] Considering their high prevalence, it is paramount that effective treatments are offered to patients due to the obvious suffering that accompanies anxiety disorders. Heart racing, muscular tension, sweating, flushing, nervousness, constant worry, and panic characterize some of the debilitating symptoms of anxiety disorders. It is unfortunate that many patients seeking standard (mainstream) treatment for anxiety disorders remain untreated and underdiagnosed many years after their initial diagnoses, leading to unremitting impairment in functional status and quality of life.[4]

I evaluate and treat patients every day suffering from unremitting anxiety symptoms. In my efforts to mitigate their anxiety, I have been prescribing the amide of niacin (nicotinic acid) known as niacinamide (nicotinamide). Both niacin and niacinamide are commonly referred to as vitamin B_3. The biochemistry of vitamin B_3 is well known in that it is involved in some two hundred enzymatic reactions, mostly including dehydrogenases within the human body. Its active forms or its coenzymes are both nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP).

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Vitamin B_3 can be absorbed directly from the stomach, but most of its absorption occurs within the small intestine. The liver contains the most concentrated amounts of the nicotinamide coenzymes, but all metabolically active tissues require these vital metabolic products.

The most common uses of nicotinamide and niacin are for the treatment of pellagra. Pellagra is a disease caused by a cellular deficiency of the nicotinamide coenzymes due to inadequate dietary supply of tryptophan and vitamin B_3 (as either niacin or nicotinamide). Diarrhea, dermatitis and dementia characterize this deficiency disease. Although is it not usually fatal, when the three Ds are present, death can occur. The adult intake of vitamin B_3 necessary to prevent pellagra is 20 mg per day. The body can manufacture approximately 1 mg of niacin equivalents from 60 mg of tryptophan obtained mostly from dietary protein sources. This *in vivo* conversion makes it rather difficult to develop frank pellagra in affluent, industrialized countries. Rare forms of pellagra, however, do occur. Pellagra has been found among patients with anorexia nervosa,[5] hypothyroidism,[6,7] alcoholism,[8,9] homeless men,[10] and from taking anticonvulsant medications.[11,12]

Here, I report on three cases where the use of large pharmacological doses of nicotinamide considerably improved the symptoms of anxiety.[13] In each of the cases frank symptoms of pellagra were absent, even though neuropsychiatric and gastrointestinal manifestations were present. Niacinamide's therapeutic mechanism of action was likely related to the correction of subclinical pellagra, the correction of an underlying vitamin B_3 dependency disorder, its benzodiazepine-like effects, its ability to increase the production of serotonin, or its ability to modify the metabolism of blood lactate (lactic acid).

Case #1

An 11-year-old female first presented to my office on November 10, 2003. Her chief complaints were nervousness, anxiety and excessive worrying. The onset of her symptoms occurred when her father tragically died in September of 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 that were reported included some facial acne, frequent blushing, stomachaches, and sweatiness. Her past medical history was unremarkable, except for asthma that was diagnosed approximately one year earlier. The asthma was not a concern since her symptoms were reported to be mild with the rare use of an inhaler as needed. Apart from the inhaler, she was on no other medications at the time of the visit. A complete physical examination was performed and all findings were within normal limits. The only notable sign was some acne along her cheeks and chin. She was diagnosed with PD, with some elements of social phobia. She was prescribed a daily multiple vitamin/mineral preparation, 25 mg of zinc, 100 mg of pyridoxine, 400 of magnesium, and 500 mg of niacinamide twice daily.

A follow-up appointment occurred on December 13, 2003. The patient reported a slight improvement with her anxiety. She did not like taking all the supplements and agreed to continue with just the multiple vitamin/mineral preparation, zinc, and niacinamide. She also 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, now 12 years old,

reported a striking improvement with her anxiety. She did not always take her pills daily, but was happy with the results. 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 1,000 mg of niacinamide twice daily. Her anxiety remained much improved and was no longer interfering with her ability to engage in a regular life.

Case #2

A 28-year-old female 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 would also occur when she simply thought about possibly feeling nervous and expelling gas. She also reported fears of embarrassment and worried about being criticized from others. She had been on paroxetine for one year but had not noticed any improvement. She reported feeling depressed due to the anxiety and would get apathetic when her anxiety was at its worst. Baths, lying in bed, walking, and exercising helped to slightly reduce her anxiety. She was unable to correlate any of her symptoms with foods. This patient also had a history of thrombocytopenia for the past five years for which she was being regularly monitored by her family physician. She did report easy bruising but did not have any history of widespread bruising and bleeding. The rest of her past medical history was unremarkable.

Physical examination revealed a well nourished woman with normal vital signs. All her systems were within normal limits. She was subsequently diagnosed with GAD with some social phobia, and thrombocytopenia. Lab tests were requisitioned and she was prescribed niacinamide at an initial dose of 500 mg three times daily for three days, and then was instructed to increase it to 1,000 mg every morning, 500 mg at lunch, and 1,000 mg at dinner. She was also prescribed 5-hydroxytryptophan (5-HTP) at a dose of 100 mg twice daily for her mild depression, and 2,000 mg of vitamin C to be taken daily for the thrombocytopenia.

The patient had a follow-up appointment on May 31, 2004. She had difficulty swallowing the niacinamide pills due to their bitter taste. Despite this, she was taking the recommended dose of 2,500 mg per day. Her anxiety was much improved and she experienced only three minor panic attacks since the initial visit. Prior to the treatment her anxiety was chronic, occurring daily, with the sensation or need to pass gas. The patient continued to complain of depression, which she felt was more pronounced prior to menses. Her complete blood count was normal, except that her platelets were low at a value of 79 (reference range, 150-400 x 10^9/L). The patient was unsure if the treatments were working due her time away from teaching. We agreed that she would discontinue all prescribed treatments except for the vitamin C until June 14, 2004. After this date, the patient would resume the 5-HTP, niacinamide, take 250 mg of vitamin B_6, and 400 mg of 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 due to being 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 female first presented to my private practice on May 16, 2004, for chief complaints of constipation and anxiety. About three weeks ago her father had been diagnosed with advanced carcinoma of the stomach. For three days following his diagnosis the patient experienced very soft stools once or twice daily. For her entire life she had been constipated, requiring regular laxatives in order to have a daily bowel movement. The patient reported additional gastrointestinal symptoms of bloating, gas, and right-sided abdominal pain. She had taken fiber therapy in the past but had never stayed on it long enough to see the benefits. She was not concerned about the constipation since she had been having at least one-to-two soft stools per day.

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 twenty-four-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. Even though her mother currently has heart disease, the rest of her family history was unremarkable. She was diagnosed with panic attacks, dyspepsia (possible irritable bowel syndrome), and mild obesity. She was advised to continue with her liquid multiple vitamin/mineral preparation, take 500 mg of niacinamide three times each day for two days, and was told to increase the dose to 1,000 mg twice daily. Two capsules of lactobacillus acidophilus were prescribed every morning upon rising.

A follow-up visit occurred on May 26, 2004. The patient felt a little better during the first week on niacinamide. However, she felt jittery and related this to her father's grim prognosis. Her sleep was unaffected, even though she did wake-up once each night to go to the bathroom. Overall, she felt much more under control. She was advised to increase the niacinamide to 1,000 mg three times each day.

On July 12, 2004, she came in for another visit. She cut back on the niacinamide since she felt that it caused her to have feelings of not being present. Instead of 3,000 mg daily she lowered the dose to 2,000 mg per day. Her constipation was not a problem and she was having one bowel movement daily. Her anxiety was much improved on this dose and the previous shakiness had completely resolved. In fact, she had not experienced any episodes of shakiness since the last visit. She was told to continue the prescribed treatments and to take a B-complex vitamin preparation and 1 mg of folic acid each day.

Subclinical Pellagra

These three case reports and an additional case report by this author,[14] demonstrate that niacinamide is capable of reducing symptoms of anxiety. All the patients responded favourably to large pharmacological doses of niacinamide (2,000-2,500 mg per day or as needed). These amounts were much greater than the amounts of vitamin B_3 or protein (containing tryptophan) that would be necessary to prevent full-blown pellagra. The initial symptoms of pellagra tend to involve the gastro-

intestinal system, which are known to precede the dermatological ones.[15] In these three patients, the gastrointestinal symptoms formed part of their clinical presentation. It was impossible to determine if these symptoms preceded their anxieties or neuropsychiatric symptoms. In case #3, the patient reported a long-standing history of constipation many years before the onset of acute anxiety. In the other two cases, the patients had anxiety symptoms with mild gastro-intestinal manifestations. The patient in case#1 had stomachaches when she felt anxious, and in case #2 the patient passed gas when she experienced anxiety.

It appears that these patients did have pellagra-like symptoms primarily involving the neuropsychiatric system. One of the earliest reports describing the psychological patterning of central nervous system impairments due to an inadequate supply of niacinamide came from the work of Kaufman.[16] He used the term "aniacinamidosis," to denote a deficiency state that could not be ameliorated by dietary modifications, but required daily pharmacological doses (150-350 mg) of niacinamide to reverse its clinical manifestations. Table 1, (below) describes some of the psychological symptoms associated with aniacinamidosis. Some of the symptoms listed in Table 1 are similar to the symptoms exhibited by the patients in these case reports.

Green, in his paper on subclinical pellagra, noted that mental symptoms occurred in patients without frank deficiency of vitamin B_3.[17] Similarly, Hoffer reported that the earliest symptoms of pellagra in its subclinical form manifest as modern mood disorders (e.g., anxiety, depression, fatigue, and vague somatic complaints) followed by the development of other symptoms.[18] It is evident that subclinical pellagra can present with symptoms primarily affecting the neuropsychiatric system, yet the reasons for its genesis remain un-

Table 1. Adult pattern of psychological symptoms in aniacinamidosis.

- He has not felt himself for weeks or years.
- Feels tense; can't relax.
- Is impatient and irritable.
- Frequently has unwarranted anxieties.
- Worries about unimportant things and can't seem to shake worries.
- Has the feeling of impending trouble.
- Not sure of his knowledge or abilities.
- Has uncertainties as to what the future will hold for him.
- Has lost his former interest in work, family, friends.
- Adjusts poorly to ordinary life situations.
- Lacks initiative.
- Not cooperative.
- Routine duties become particularly burdensome.
- Delays making decisions.
- Shuns and fears unfamiliar people, ideas, situations.
- Frequently wishes to be alone, to get away from everyone.
- Is unhappy, frequently without apparent cause.
- Frequently thinks that something is seriously wrong with him.
- Can't sleep right.

known. One possible explanation might involve a phenomenon known as a localized cerebral deficiency disease. Pauling discussed the possibility of having grossly diminished cerebrospinal fluid (CSF) concentrations of a vital substance while its concentration in the blood and lymph remain essentially normal.[19] This localized cerebral deficiency, according to Pauling, might occur from decreased rates of transfer (i.e., decreased permeability) of the vital substance across the blood-brain barrier, an increased rate of destruction of the vital substance within the CSF, or from some other unknown factor.[19] If the serum and CSF were to be examined for micronutrient status, extreme perturbations between these compartments might demonstrate the presence of a localized cerebral deficiency. For example, in a study involving 49 patients with organic mental disorders, deficient CSF levels of vitamin B_{12} (<5 pg/mL) were found in 30 of the patients.[20] 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. Given that serum levels of vitamin B_{12} can be normal yet deficient in the CSF, other micronutrients (such as vitamin B_3) might follow a similar pattern of deficiency if the CSF and serum were to be respectively analyzed. The correction of subclinical pellagra might be one of the reasons for niacinamide's effectiveness. Conversely, we need to understand the role of localized cerebral deficiency of niacinamide, including niacinamide's metabolism with the CSF, before this diagnosis can be given the confirmation it requires.

Vitamin B_3 Dependency as a Result of Enzymatic Defects

The patients' positive responses to niacinamide suggest that this vitamin might have corrected an underlying vitamin B_3 dependency disorder. A vitamin B_3 dependency denotes an increased metabolic need for the vitamin. Its cause is unknown, but it has been purported to result from a combination of malnutrition and long-term environmental-genetic stresses that disrupts the *in vivo* conversion of dietary tryptophan into a sufficient amount of vitamin B_3.[18] Over time, this disruption would impair all the biochemical processes dependent on a constant supply of the nicotinamide coenzymes. In order to sustain adequate health, it would be necessary to obtain a daily intake of vitamin B_3 in amounts far greater than what could be accomplished from dietary sources alone.[21] This is not so unreasonable since many enzyme systems within the body require large pharmacological doses of vitamins to remedy defects in the synthesis of vital metabolic products to sustain adequate health. Pauling reported that, "…mental disease is for the most part caused by abnormal reaction rates, as determined by genetic constitution and diet, and by abnormal molecular concentrations of essential substances".[19] He described how megavitamin therapy would be necessary for the optimal treatment of mental disease since the saturating capacity would be much greater for defective enzymes that have diminished combining capacity for their respective substrates. In other words, an enzyme-catalyzed reaction could be corrected by pharmacologically increasing the concentration of its substrate when high doses of a particular micronutrient are provided.

Pauling's ideas were later confirmed by Abbey who found various B-vitamin dependent enzymopathies in 12 patients with agoraphobia.[22] All of Abbey's patients required 200-500 mg of the various B-complex factors in order to resolve both the associated enzymatic defects and symptoms of their anxiety and panic. In a more recent report, the need for large pharmacological doses of micronutrients were deemed necessary as a means to increase coenzyme concentrations and to correct defective enzymatic activity in some 50 human genetic diseases.[23] Certainly, there must be a

certain percentage of patients that would be responsive to large pharmacological doses of vitamin B_3 to correct both the disordered biochemistry and the resulting neuropsychiatric manifestations; presumably, the result of defective enzymatic activity.

Benzodiazepine-like Properties

Additional reasons for niacinamide's effectiveness likely have to do with its benzodiazepine-like effects. In a previous review of the literature by Hoffer, both niacin and niacinamide were shown to have some sedative activity, and were able to potentiate the action of sedatives, anticonvulsant medications and certain tranquilizers.[24] In a recent case report by this author, a review of the literature was undertaken to determine the biological mechanism for niacinamide's anxiolytic effects.[14] **Table 2** (p.174) summarizes this data.[25-30] It appears that niacinamide has therapeutic effects comparable to the benzodiazepines. Its therapeutic effects are probably not related to it acting as a ligand for the benzodiazepine receptor, although 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.

Niacinamide might also be helpful when weaning patients off their benzodiazepine medications. Benzodiazepine withdrawal symptoms include tinnitus, involuntary movements, paresthesias, perceptual changes and confusion. Twenty-eight patients who had been abusing flunitrazepam for at least six months were abruptly taken off the drug.[31] The patients were randomly assigned to receive intravenous nicotinic acid (xantinol nicotinate; 3 g in 1,500 mL of 10% glucose per day over the first 48 hours, followed by 1.5 g over the following 48 hours) or placebo (glucose solution alone). Although blinding was not specified, patients who received xantinol nicotinate had significantly fewer withdrawal symptoms than those who received placebo. These results suggest that intravenous administration of xantinol nicotinate can reduce withdrawal symptoms in patients withdrawing from flunitrazepam. Even though intravenous xantinol nicotinate would achieve higher blood concentrations than oral niacinamide, both nutrients are forms of vitamin B_3, and therefore, the parenteral and oral methods might similarly help to withdraw patients from their benzodiazepine medications.

Serotonin Synthesis

Another biochemical reason for niacinamide's anxiolytic effects might have to do with the vital role that it has upon the synthesis of serotonin. For example, in a patient with anorexia nervosa an insufficient supply of vitamin B_3 or protein resulted in reduced urinary levels of the serotonin breakdown product, 5-hydroxy-indolacetic acid (5-HIAA).[32] The authors of this report postulated that a deficiency of vitamin B_3 reduced the feedback inhibition upon the kynurenine pathway, resulting in more tryptophan being diverted to the kynurenine pathway, making less substrate available for the synthesis of serotonin. By contrast, the use of pharmacological doses of vitamin B_3 can increase the production of serotonin.[33] In a rat study, the administration of 20 mg of niacin resulted in increased levels of 5-HIAA and decreased levels of xanthurenic acid via the kynurenine pathway.[34] Taking pharmacological doses of niacinamide (or any other form of vitamin B_3) would increase the production of serotonin, by diverting more tryptophan to become substrate for serotonin synthesis. Niacinamide's therapeutic ability to increase serotonin production might explain why it was successful in reducing the anxiety symptoms of the three patients.

Modulation of Blood Lactate (lactic acid)

The final biochemical reason for niacinamide's favourable effect might have to do with its ability to modulate the metabolism

Table 2. Biochemical data summarizing niacinamide's benzodiazepine-like effects.

Reference	Results
25	Niacinamide modulated spinal cord activity, and had anticonflict, anticonvulsant, muscle relaxing and hypnotic effects. The potency of niacinamide was found to be equivalent to a highly potent benzodiazepine. Niacinamide had a low affinity to the benzodiazepine-binding site in the mammalian brain. This low affinity may have been the result of the binding assay used, or it may have been a reflection that more than one binding-site existed by which niacinamide exerted its benzodiazepine-like properties.
26	Niacinamide antagonized the effects of diazepam, therefore interacting with the benzodiazepine receptor in vivo. However, niacinamide did not mimic the benzodiazepine properties of diazepam when tested with the rat head-turning model. Niacinamide probably does have benzodiazepine-like properties at different benzodiazepine receptor sites in the CNS, but its effects are unrelated to the actions of gamma-aminobutyric acid (GABA).
27	Niacinamide had a qualitatively similar effect to that of diazepam. It was concluded that niacinamide exerted its effects by influencing the turnover of serotonin, noradrenaline (norepinephrine), dopamine and GABA in those areas of the brain thought to be unbalanced in anxiety.
28	Niacinamide could possibly be a competitive antagonist for the benzodiazepine receptor since it prevented the binding of kynurenine to the benzodiazepine receptor. It was further postulated that this action was more likely of central origin than peripheral origin. It could not be determined if niacinamide's action was indeed related to its occupation of the benzodiazepine receptor.
29	Niacinamide was structurally dissimilar to the benzodiazepine receptors. Niacinamide did not act as a specific ligand for the benzodiazepine receptor, but instead had a weak binding affinity for the receptor.
30	Niacinamide and its analogs possessed properties similar to benzodiazepines at various zones of the cerebral cortex by influencing the GABA-ergic system.

of blood lactate (lactic acid). Before this therapeutic mechanism is explained, it is necessary to review some of the studies that have explored the relationship between lactic acid and anxiety. This research will demonstrate a consistent link between PD and lactate provocation.

In a single-blind study using sodium

lactate infusions, 11 out of 15 patients with PD had panic attacks with the lactate.[35] The 15 control subjects did not experience panic attacks during the infusions. Even though no biochemical abnormalities were seen between the groups, it was hypothesized that the treatment group had an increased baseline arousal level causing them to be more susceptible to panic attacks. In another study, 72% of the treatment group (n=43) developed panic attacks with intravenous sodium lactate infusions.[36] The treatment group was comprised of patients with either PD, or agoraphobia with panic attacks. In the control group (n=20) none of the participants developed panic attacks with the infusions. There was increased activity of the central noradrenergic system in most of the patients in the treatment group who experienced panic attacks. A similar study involving 43 subjects having PD or agoraphobia with panic attacks were administered infusions of sodium lactate.[37] Thirty-one of the subjects panicked in response to the infusions, whereas none of the 20 subjects in the control group had any panic attacks. It was concluded that the lactate-induced panic attacks were associated with heightened central noradrenergic activity and hyperventilation. It now appears that the lactate-induced panic response involves angiotensin-II, which interfaces with the basolateral nucleus of the amygdala (BLA) and the autonomic nervous system in the generation of anxiety disorders.[38]

All of the patients in the case reports experienced frequent panic attacks in addition to their other anxiety symptoms. Lactate sensitivity or an increased responsiveness to lactate might have caused some of their anxiety symptoms. Only one of the patients (case #3) appeared to have hyperventilation as part of her clinical presentation. All of them had a therapeutic response to niacinamide demonstrating its ability to reduce panic attacks. Abbey suggested that an insufficient supply of NAD would inhibit the conversion of lactate back to pyruvate, which would contribute to a high lactate-to-pyruvate ratio and therefore to anxiety.[22] In 3 out of 12 patients, Abbey found deficient levels of urinary N^1 methylnicotinamide (indicating deficient intake of niacinamide) normalized when large pharmacological doses of B-complex vitamins were provided, to which she conjectured that an excess of NAD was required to drive the conversion of lactate to pyruvate. Buist also hypothesized that anxiety neurosis is associated with elevated blood lactate and an increased lactate-to-pyruvate ratio to which effective treatment requires increasing niacin status (i.e., increasing NAD levels) through supplementation.[39]

The formation of lactate by the enzyme, lactate dehydrogenase, is the final product of anaerobic glycolysis in eukaryotic cells. Niacinamide supplementation might result in an increased conversion of lactate to pyruvate, thus reversing the equilibrium of the pyruvate to lactate reaction. For example, when a patient with MELAS (mitochondrial encephalopathy, myopathy, lactic acidosis, and stroke-like episodes) syndrome was treated with 1,000 mg of niacinamide four times daily, large reductions (50% or more) in blood lactate and pyruvate concentrations occurred by the third day of treatment.[40] Large pharmacological doses of niacinamide appear to be capable of reducing blood lactate and pyruvate concentrations. Patients with panic attacks likely have a greater demand placed upon anaerobic glycolysis due to the rapidity or shallowness of breathing that so often accompanies their anxiety attacks. Therefore, a greater amount of NAD obtained by means of niacinamide supplementation might help the tissues of the body, including the central nervous system, to readily oxidize lactate (obtained from the blood) to pyruvate, and consequently mitigate panic attacks, and hyperventilation (if present).

Prescribing Instructions

In terms of proper dosing, most patients require a minimum of 2,000-4,500 mg per day to achieve therapeutic results. These dosages were derived from the work of Hoffer, who recommended 1,500-6,000 mg of niacinamide per day for all patients with psychiatric syndromes.[21] 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. Only one patient needed to reduce her dose from 3,000 mg per day to 2,000 mg per day due to feelings of not being present (perhaps derealization). 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 (1,500-6,000 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.[41,42] The most common side effect with niacinamide is sedation,[43] but dry mouth and nausea have been the most common side effects that I have observed among some my patients. There has been one case report linking large pharmacological doses of niacinamide (9 g per day) to hepatic toxicity.[44] The patient in the cited report had no evidence of clinical hepatitis when taking 2,000-3,000 mg per day of niacinamide, but did develop clinical hepatitis when the dose was increased to 9,000 mg daily. All clinical abnormalities did revert to normal once the niacinamide was discontinued. I never exceed 6,000 mg per day of niacinamide since most patients will develop nausea and sometimes vomiting on this dose.[21] There is hardly any need to go above 4,500 mg per day when treating anxiety. If nausea does occur, decreasing the dose by 1,000 mg usually corrects the problem.

Conclusion

Large pharmacological doses of niacinamide were effective in relieving the symptoms of anxiety in these three patients. Even though niacinamide's mechanisms of action have not been substantiated from controlled clinical trials, this agent does appear to have a wide spectrum of beneficial effects upon anxiety disorders. It is imperative that properly designed randomized controlled trials are developed in order to identify niacinamide's therapeutic effects and adverse effects profile. A head-to-head placebo-controlled trial of niacinamide and a benzodiazepine medication also seems to be worthy of consideration.

Clinical trials of niacinamide as an agent that mitigates symptoms of anxiety are warranted by the following:

1. the clinical observation from these three case reports and an additional one[14] demonstrate that niacinamide reduces symptoms of anxiety;
2. biochemical data showing niacinamide to have both benzodiazepine-like properties and the ability to increase serotonin synthesis;
3. by comparison, mainstream anti-anxiety medications similarly interface with the benzodiazepine and serotonergic systems;
4. niacinamide has other possible biochemical properties (corrects subclinical pellagra, corrects vitamin B_3 dependency, and favorably modulates blood lactate) that may perhaps make it a more effective agent than current contemporary medications for the treatment of anxiety disorders;
5. the relative absence of negative side effects when large pharmacological doses of niacinamide are used;
6. the wide availability of inexpensive niacinamide.

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