Niacinamide's Potent role in Alleviating Anxiety with its Benzodiazepine-like Properties: A Case Report

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Abstract

Anxiety disorders are extremely debilitating and are the most common psychiatric disorders in the United States. Such patients have greater chances of developing other medical illnesses such as chronic obstructive pulmonary disease, diabetes and hypertension. The underlying anxiety that exists in these patients also tends to prolong the course of any additional medical illnesses that they may develop. The conventional approach to severe anxiety involves pharmacotherapy with benzodiazepines, selective serotonin re-uptake inhibitors (SSRIs), or other medications such as buspirone, imipramine or trazodone. A case report demonstrated that the use of 2500mg of niacinamide (nicotinamide) per day ameliorated severe anxiety in a 34-year-old male patient. It appears that niacinamide has therapeutic properties similar to the benzodiazepines. However, the therapeutic effects of niacinamide likely have little to do with it acting as a ligand for the benzodiazepine receptor. Niacinamide might exert its effects through its modulation of neuro-transmitters that are commonly unbalanced in those areas of the brain associated with anxiety. Niacinamide might also reduce anxiety by shunting more tryptophan toward the production of serotonin and/or by simply correcting a vitamin B_3 dependency. The use of niacinamide for extended periods of time appears to be safe, but megadoses can cause sedation, nausea and vomiting. More case reports, research and rigorous controlled trials are needed to properly evaluate niacinamide's therapeutic effectiveness, safety and mechanisms of action for the treatment of anxiety.

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Introduction

Anxiety disorders are the most common psychiatric disorders in the United States.[1] Anxiety disorders are extremely debilitating for the suffering individual, disrupting one's ability to engage in a full, functional life. The consequences of anxiety are profound emotional, occupational and social impairments. Some of the common physical (somatic) symptoms of anxiety are difficulty breathing, facial flushing, hyperhydrosis, muscle tension and tachycardia. The typical emotional symptoms of anxiety are not independent of the somatic manifestations, but present as agitation, irritability, fearfulness, feelings of "impending doom," nervousness and shyness. Most patients with anxiety disorders seek help from a primary care physician rather than a psychiatrist,[2] and commonly report their health as poor,[3] smoke cigarettes and abuse other substances.[4] These patients have an increased chance of developing chronic medical illnesses (e.g., chronic obstructive pulmonary disease, diabetes and hypertension) compared to the general population.[5] When they do acquire a medical illness it is often prolonged as a result of the anxiety.[4]

The conventional approach involves cognitive therapy and relaxation for mild anxiety.[6] More serious cases of anxiety often require pharmacologic treatment with benzodiazepines, SSRIs, or other medications such as buspirone, imipramine or trazodone.[6] Here, I report on a case where psychological therapy, SSRIs, buspirone, and numerous natural agents were ineffective in the treatment of severe anxiety. The only medications that completely resolved this patient's anxiety were benzodiazepines. In an effort to wean off the benzodiazepine, the patient took increasing doses of niaci-

namide (nicotinamide). As demonstrated in the following case report, niacinamide was effective for addressing the benzodiazepine withdrawal symptoms and managing anxiety.

Case Report

A 33-year-old Caucasian male presented with a history of anxiety for the past 20 years. When the patient was 13, his homeroom teacher would embarrass him every week by having him stand-up in front of the class and remain as such until he was noticeably red in the face, at which point the teacher would comment about how red he was. The entire class would laugh at this. Over time, this patient became increasingly nervous and fearful about social situations and involvement in activities that could draw attention to him. Throughout junior high and high school, the patient would have pronounced anxiety and panic when making presentations and conversing with his peers, friends or girls. Typically his symptoms were facial flushing, profuse sweating, increased heart rate, muscle tension, burning in the stomach and the need to get away.

These symptoms persisted throughout university and when the patient was 22, he finally sought professional help for his anxiety. The clinical psychologist diagnosed the patient with social phobia, panic disorder, and mild agoraphobia. The patient underwent once- or twice-weekly sessions of psychodynamic and cognitive-behavioural therapy for the next six months. During this time the patient's symptoms improved only slightly, but the patient somehow convinced the psychologist that he was completely cured and that therapy was no longer necessary.

By the time he was 24 years old, he entered medical school and his anxiety worsened. He was so upset by his inability to just "go with the flow," or "feel comfortable in [his] own skin" that he again sought the help of a psychiatrist. This time the psychiatrist assessed and diagnosed him with social phobia, panic disorder, dysthymia and mild agoraphobia. He was started on Zoloft (sertraline HCl) 50 mg daily. After the first 2 weeks the patient's anxiety slightly improved, but he had noticeable side effects from the medication such as lethargy, apathy, and anorgasmia. By 4 weeks of use, the Zoloft seemed to work fairly well, as the patient had some days without any anxiety. His dose of Zoloft was increased to 100 mg daily. The patient was also put on 5 mg of Buspirone (BuSpar) 3 times each day. After 3 months of use, the patient had no significant improvement and his anxiety symptoms continued to be debilitating. He found his tendency to avoid social situations increased due to severe fears of blushing. He also avoided interactions with his professors and peers as much as possible. He preferred to stay at home and only go out when necessary. At this point he discontinued both the Zoloft and BuSpar due to their ineffectiveness.

From age 25 to 28, the patient investigated a variety of natural approaches for the treatment of his anxiety. From his readings, he decided to take the following nutrients daily: 6-12 g of vitamin C; 800 IU of vitamin E; 50 mg of zinc; a B-complex containing 100 mg of each of the B vitamins; 1000 mg of calcium; and 400 mg of magnesium. Although he followed this plan diligently, his anxiety did not lessen. After six months of the vitamin plan, he added a standardized extract of Kava two to three times each day. Within 2 weeks his anxiety symptoms were markedly improved. He was able to be in stressful social situations without blushing or appearing nervous. However, by the fourth week of continual Kava use, he experienced pronounced depression. The depression became so unbearable that he felt it necessary to discontinue the Kava. After a few days of discontinuing the Kava, the patient's depression completely lifted. In an attempt to see if the Kava was the problem, the patient resumed taking Kava. Once again, the anxi-

ety significantly improved, but his depression came back. He discontinued the Kava, and shortly thereafter the depression lifted once again. By the time the patient was 28, he had also tried St. John's Wort, adrenal extract, constitutional homeopathic medicine and amino acids such a gamma-aminobutyric acid (GABA), inositol, and L-taurine. None of these natural approaches helped.

At the tail-end of 28 years old, the patient's anxiety worsened. Even though he did not notice any reduction in anxiety, he continued to take the following nutrients daily: 6-12 g of vitamin C; 800 IU of vitamin E; 50 mg of zinc; a B-complex containing 100 mg of each of the B vitamins; 1000 mg of calcium; and 400 mg of magnesium. During his medical residency, he purposely avoided his assigned patients, his condition significantly interfering with his ability to perform. Due to the urgency that he felt, he once again sought the help from a medical doctor who prescribed 0.5 mg of Ativan (lorazepam) twice daily. Within two days all of his anxiety symptoms resolved and the patient felt normal for the first time in his life. He could function and perform with confidence and his anxiety did not interfere or prevent him from completing the residency program.

From ages 29 to 33 the patient continued with the benzodiazepine medication. At one point his medical doctor changed the Ativan to Klonopin (clonazepam, 0.5mg twice daily) since he was told that this preparation was better for long-term use. He had no more anxiety symptoms, but never felt good about taking the benzodiazepine medication. When he was 32, he went off the Klonopin for 1 month. During the first week, he experienced severe insomnia at night and during the day he experienced recurrent bouts of panic and anxiety. Almost 2 weeks later, the insomnia resolved but his anxiety returned to its pre-treatment state. He was completely debilitated. He resumed the Klonopin and once again felt complete relief.

When he turned 33, he did somewhat of a literature search on anxiety and found intriguing information on niacinamide. He informed his psychiatrist of his plan to wean himself off the Klonopin and take niacinamide. The psychiatrist encouraged the patient to do so but wanted the patient to contact him if he were to experience withdrawal symptoms such as recurrent anxiety, insomnia and irritability. For the first week, the patient took 0.5mg of Klonopin every morning along with 500 mg of niacinamide, 500 mg of niacinamide at lunch and 1000 mg at bedtime. He experienced no recurrences of his anxiety or insomnia during the first week of weaning. In the second week, the patient discontinued the Klonopin and took 1000 mg of niacinamide in the morning, 500 mg at lunch and 1000 mg at bedtime. The patient felt great and could not distinguish between taking Klonopin and niacinamide. The patient was completely free of benzodiazepine medication as of August 1st, 2002. The psychiatrist was so impressed with the outcome and commented that it gave him hope that a patient could actually go off benzodiazepine medication and not chronically depend on them.

As of November 7, 2003, this 34 year old patient has been able to practice as a doctor without any impairments or restrictions, and continues to do very well approximately 15 months after stopping the Klonopin. He no longer feels that anxiety is a problem, and believes that the niacinamide is equally as effective as benzodiazepine medication, but is potentially safer to take for long-term use.

Discussion

It is of no surprise that this patient benefited tremendously from the benzodiazepines. Benzodiazepines bind to a macromolecular complex that is found within the CNS and is referred to as the GABA-benzodiazepine receptor-chloride ion channel complex.[7] When benzodiazepines bind onto or near this macro-

molecular 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.[7] The net result is the reduction of anxiety and related symptoms via the diminution of neurotransmission (i.e., neuronal firing) among many brain regions such as the spinal cord, hypothalamus, hippocampus, substantia nigra, cerebellar cortex and cerebral cortex.[7]

It appears that niacinamide has similar anxiolytic properties to that of the benzodiazepines. This is supported by the fact that the patient did not feel any difference, in terms of response and effectiveness, between the benzodiazepines and niacinamide. He was able to switch with little difficulty from the daily use of a benzodiazepine to niacinamide. Furthermore, during the transition he did not experience common withdrawal symptoms such as insomnia, recurrent anxiety or panic attacks. However, unlike the benzodiazepines, the pharmacologic data pertaining to the anxiolytic properties of niacinamide are not well known since its precise mechanisms of action upon the central nervous system (CNS) have yet to be conclusively determined.

Möhler et al. suggested that niacinamide is pharmacologically similar to benzodiazepines due to its presynaptic inhibition, as demonstrated in the cat lumbo-sacral spinal cord, anticonflict effect, and anticonvulsant, muscle relaxing and hypnotic effects.[8] Based on these results, these investigators suggested that the endogenous ligand for the benzodiazepine receptor in the mammalian brain was niacinamide.

Slater and Longman used a rat head-turning model as a method of evaluating whether niacinamide and inosine affect the GABA-mimetic actions of diazepam in vivo.[9] Diazepam caused a highly statistically significant slowing of the head-turn, which is to be expected when injected into the globus pallidus. However, when diazepam was combined with niacinamide, the slowing of the head-turn initially produced by diazepam, reversed to its pretreatment time. In other words, niacinamide may have negated or abolished the effects of diazepam. From these results, it was assumed that niacinamide antagonized the effects of diazepam, therefore interacting with the benzodiazepine receptor in vivo. However, niacinamide administered by itself did not result in reduced head-turning behaviour, and did not mimic the benzodiazepine properties of diazepam when tested with the head-turning model. The authors concluded that niacinamide probably does have benzodiazepine-like properties at different benzodiazepine receptor sites in the CNS, but its effects are unrelated to the actions of GABA.

In rat studies, Kennedy and Leonard assessed the similarity between the action of niacinamide and diazepam on neurotransmitter metabolism.[10] They considered neurotransmitter turnover of serotonin, noradrenaline (norepinephrine), dopamine and GABA. In their three experiments on rats, they found that niacinamide had a qualitatively similar effect to that of diazepam. It was further concluded that niacinamide exerted its effects by influencing the turnover of serotonin, noradrenaline, dopamine and GABA in those areas of the brain thought to be unbalanced in anxiety.

Lapin compared the effects of putative endogenous benzodiazepine receptor ligands (i.e. niacinamide, inosine and hypoxanthine) against kynurenine and pentylenetetrazol, agents that have benzo-diazepine receptor affinity and induce seizures in mice.[11] Niacinamide decreased the kynurenine-induced seizures in C57BL/6 adult male mice and prolonged the latency of pentylenetetrazol seizures. 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. However, it was not yet conclusively determined if niacinamide's action was indeed related to its occupation of the benzodiazepine receptor.

Markin & Murray looked at several compounds with reported benzodiazepine receptor binding affinities.[12] The calculations, according to graph theoretical indices, demonstrated that niacinamide was structurally dissimilar to the benzodiazepine receptors. This suggested that niacinamide did not act as a specific ligand for the benzodiazepine receptor, but instead had a weak binding affinity for the receptor.

It appears that niacinamide does possess pharmacologic properties that are similar to benzodiazepines. A 1992 study found that niacinamide and its analogs possessed properties similar to benzodiazepines at various zones of the cerebral cortex by influencing the GABA-ergic system.[13] While it is impossible to conclude that the effects of niacinamide are due to its interaction upon the benzodiazepine receptor, it does appear to influence neurotransmitter metabolism in a manner that is comparable to benzo-diazepines by a route as yet undetermined. Even though most of the studies dealt with animal rather than human models, the results suggest that niacinamide has a potent benzodiazepine-like action on the CNS.

Besides its benzodiazepine-like effect, there are other possible reasons for niacinamide's therapeutic effectiveness. Inadequate vitamin B_3 or protein intake results in reduced feedback inhibition upon the kynurenine pathway which diverts more tryptophan to the kynurenine pathway, making less substrate available for serotonin synthesis, and resulting in decreased levels of the serotonin breakdown product, urinary 5-hydroxyindolacetic acid (5-HIAA).[14] It has also been reported in a rat study that the administration of 20 milligrams of niacin resulted in increased levels of 5-HIAA and decreased levels of xanthurenic acid via the kynurenine pathway.[15] In other words, taking niacinamide or any other form of vitamin B_3 might increase the production of the very important anxiolytic neurotransmitter, serotonin, and divert more tryptophan into being utilized as substrate for serotonin synthesis. This might be one of the mechanisms responsible for the amelioration of anxiety in this one patient.

Another way in which niacinamide might therapeutically help is in the correction of a vitamin B_3 dependency. A vitamin B_3 dependency denotes an increased metabolic need for the vitamin, as has been described in other publications.[16-18] The cause of a vitamin B_3 dependency is unknown, but Hoffer (2000) suggests that it might 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.[17] Over time, this disruption would impair all the biochemical processes dependent upon a constant supply of the vitamin, and necessitate a daily intake of vitamin B_3 in amounts far greater than what could be obtained from dietary sources alone in order to sustain adequate health. Individuals having a vitamin B_3 dependency tend to have disturbances in mood (i.e., anxiety, depression and fatigue) and vague somatic complaints, but do not manifest the same clinical features of frank vitamin B_3 deficiency or pellagra (i.e., diarrhea, dermatitis, dementia and death).[17] Corrective treatment of a vitamin B_3 dependency requires using megadoses of the vitamin to normalize the presumed underlying metabolic dysfunction.[19] Therefore in the previously discussed case report, the patient's therapeutic response to niacinamide might have been the result of correcting a long-standing vitamin B_3 dependency disorder. This correction might have nothing to do with niacina-

mide's potential role in serotonin production and/or its benzodiazepine-like effect.

Megadoses of niacinamide appear to be necessary in order to achieve therapeutic results. With regards to optimal dosage and safety, Hoffer (1995) has reported that: (1) about 2% of patients experience a cutaneous flush from niacinamide; (2) megadoses of niacinamide can cause nausea once the daily dose has exceeded the optimal dose; (3) vomiting occurs if the nausea-producing dose has not been reduced/adjusted; (4) the optimal daily dose appears to be the amount just below the amount that induces nausea; (5) the daily megadoses of niacinamide need to be tailored to the individual patient; and (6) few patients can tolerate more than 6 g per day of niacinamide.[16] The most common side effect with niacinamide is sedation.[20] It should be noted that large doses (9 g daily) have been reported to cause hepatic toxicity in one patient.[21] However, the concern over hepatic toxicity should not prevent the clinician from trying this approach. In fact, the remarkable therapeutic indexs of niacinamide (and other forms of vitamin B_3 allows for megadose amounts to be used for extended periods of time without serious risks of toxic side effects.[22,23]

Conclusion

More case reports, research and rigorous controlled trials are needed to properly evaluate niacinamide's therapeutic effectiveness, safety and mechanisms of action for the treatment of anxiety. In light of the positive results accomplished from using megadoses of niacinamide in this case report, perhaps this nutritional agent is indicated for the management of anxiety.

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References

1. Kessler RC, McGonagle KA, Zhao S, et al: Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch Gen Psychiat,* 1994;51:8-19.
2. Shear MK, Schulberg HC: Anxiety disorders in primary care. *Bull Menninger Clin,* 1995; 59: A73-85.
3. Katon WJ, Von Korff M, Lin E: Panic disorder: relationship to high medical utilization. *Am J Med,* 1992; 92: 7S-11S.
4. Shader RI, Greenblatt DJ: Use of benzodiazepine in anxiety disorders. *New Engl J Med,* 1993; 328: 1398-1405.
5. Wells KB, Golding JM, Burnam MA: Psychiatric disorder in a sample of the general population with and without chronic medical conditions. *Am J Psychiat,* 1988;145:976-981.
6. Gliatto MF: Generalized anxiety disorder. *Am Fam Physican,* 2000;62:1591-1600, 1602.
7. Trevor AJ, Way WL: Sedative-hypnotic drugs. In. eds. Katzung BG. *Basic & Clinical Pharmacology.* 6th ed. Norwalk, CT, Appleton & Lange. 1995;338-339.
8. Möhler H, Polc C, Cumin R, et al: Nicotinamide is a brain constituent with benzodiazepine-like actions. *Nature,* 1979; 278: 563-565.
9. Slater P, Longman DA: Effects of diazepam and muscimol on GABA-mediated neurotransmission: interactions with inosine and nicotinamide. *Life Sci,* 1979; 25: 1963-1967.
10. Kennedy B, Leonard BE: Similarity between the action of nicotinamide and diazepam on neurotransmitter metabolism in the rat. *Biochem Soc Trans,* 1980; 8: 59-60.
11. Lapin IP: Nicotinamide, inosine and hypoxanthine, putative endogenous ligands of the benzodiazepine receptor, opposite to diazepam are much more effective against kynurenine-induced seizures than against pentylenetetrazol-induced seizures. *Pharmacol Biochem Behav,* 1981; 14: 589-593.
12. Markin RS, Murray WJ: Searching for the endogenous benzodiazepine using the graph theoretical approach. *Pharm Res,* 1988;5:408-412.
13. Akhundov RA, Dzhafarova SA, Aliev AN: The search for new anticonvulsant agents based on nicotinamide. *Eksp Klin Farmakol,* 1992;55:27-29 {Article in Russian; Abstract Only}.
14. Judd LE, Poskitt BL: Pellagra in a patient with an eating disorder. *Br J Dermatol,* 1991; 125: 71-72.
15. Shibata Y, Nishimoto Y, Takeuchi F, Tatsuma Y: Tryptophan metabolism in various nutritive conditions. A*cta Vitamin Enzymol,* 1973; 29: 190-193.

16. Hoffer A: Vitamin B-3: niacin and its amide. *Townsend Lett Doctors Patients,* 1995; 147: 30-39.
17. Hoffer A: Vitamin B_3 dependency: chronic pellagra. *Townsend Lett Doctors Patients,* 2000; 207: 66-73.
18. Hoffer A: *Vitamin B_3 & Schizophrenia: Discovery, Recovery, Controversy*. Kingston, ON. Quarry Press. 1998; 92.
19. Megadose refers to a daily intake of niacinamide in gram amounts that far exceed the milligram amounts obtained through diet alone.
20. Werbach MR: *Foundations of Nutritional Medicine.* Tarzana, CA. Third Line Press, Inc. 1997; 145.
21. Winter SL, Boyer JL: Hepatic toxicity from large doses of vitamin B_3 (nicotinamide). *N Engl J Med,* 1973; 289: 1180-1182.
22. Hoffer A: Vitamin B_3 and schizophrenia. *Townsend Lett Doctors Patients,* 2001; 213: 20-23.
23. Paterson ET: Vitamin B_3 and liver toxicity. *Townsend Lett Doctors Patients,* 2001; 207: 23.