An N-of-1 Placebo-Controlled Trial in Clinical Practice: Testing the Effectiveness of Oral Niacinamide (Nicotinamide) for the Treatment of Anxiety

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Abstract ***Background:*** *Many patients with anxiety often turn to complementary and alternative medical (CAM) treatments. Because of the popularity of CAM among patients with anxiety, it is important that emerging CAM treatments are researched for safety and efficacy. One emerging CAM treatment that shows potential as an anxiolytic agent is the amide form of vitamin B-3, also known as niacinamide (nicotinamide).*
Objectives: *To evaluate the efficacy and safety of niacinamide in a participant with anxiety symptoms.*
Design: *Double-blind, placebo-controlled N-of-1 trial of niacinamide versus placebo for the treatment of anxiety symptoms.*
Setting: *The Robert Schad Naturopathic Clinic, the outpatient clinic of the Canadian College of Naturopathic Medicine (North York, Ontario).*
Intervention: *Following a 2-week washout cycle, the 26-year-old female participant was allocated to a 4-week treatment Period (Block) where she was provided with 3000 mg/day of niacinamide, or an equivalent-looking placebo, at 2-week intervals. Following another 2-week washout cycle, the same procedure was followed.*
Main outcome measures: *Beck Anxiety Inventory (BAI) questionnaire, Measure Yourself Medical Outcome Profile (MYMOP) questionnaire, 14-day medication diary for side effects and pill counts, and laboratory testing to monitor safety and possible toxicity.*
Results: *The BAI results did not demonstrate a statistically significant difference in favour of the niacinamide for Periods 1 and 2 (p=0.07). There were no statistically significant differences in favour of the niacinamide for all the dimensions of the MYMOP, which include Symptoms 1 (p=0.30) and 2 (p=0.40), Activity (p=0.13), and Wellbeing (p=0.09) over the duration of the study. The baseline and end-of-trial evaluations (i.e., physical examination and laboratory testing) were within normal limits. None of the participant's transaminase levels were abnormal during the trial.*
Conclusions: *Niacinamide is safe at dosages as high as 3000 mg/day. Treatment with niacinamide produced no favourable therapeutic effects upon the participant's symptoms of anxiety and anxiety scores per the BAI and MYMOP questionnaires.*
Trial Registration: *Natural Health Products Directorate of Canada, Bureau of Clinical Trials and Health Science, File #:128210*

Introduction

Anxiety disorders are the most common psychiatric disorders in the United States, affecting 18% of adults (about 40 million) age 18 years and older in a given year.[1] In Canada, 12% of the entire adult population (15-64 years of age) has an anxiety disorder, with 9% of men and 16% of women being diagnosed during a one-year period.[2] Whether a patient has a primary anxiety disorder or another type of anxiety, the fact remains that a patient presenting with severe anxiety symptoms requires treatment. If symptoms cannot be lessened, the patient will continue to suffer needlessly. When the anxiety is not associated with a general medical condition, the initial approach to treatment usually involves nonpharmacologic therapies such as short-term counselling, psychotherapy, stress management, exercise, or meditation.[3] However, if the patient presentation is marked by significant emotional distress and obvious functional impairment, then the use of benzodiazepines or other medications (e.g., selective serotonin reuptake inhibitors, buspirone, imipramine or trazodone) would be necessary and is thought to outweigh any of the potential hazards (e.g., dependence and abuse) associated with their use.[3,4]

A significant amount of patients having anxiety also turn to complementary and alternative medical (CAM) treatments. A 1998 study demonstrated that 43% of anxiety suffers in the United States use some form of CAM therapy.[5] A more recent population-based 2001 study from the United States showed that of 9% of respondents with anxiety attacks, 57% have used some form of complementary medicine.[6] Some of the reasons why patients with mental health problems turn to CAM treatments is because of the perception that they have fewer or no side-effects or because of the ineffectiveness of conventional treatments.[7]

Because of the popularity of CAM among patients with anxiety, it is important that emerging CAM treatments are researched for safety and efficacy. One emerging CAM treatment that shows potential as an anxiolytic agent is the amide form of vitamin B_3, also known as niacinamide (nicotinamide). Niacinamide is readily available over-the-counter in most drugstores and health food stores. The use of large pharmacological doses (≥ 1500 mg/day) of niacinamide has been shown in several published case reports to improve symptoms of anxiety.[8-10]

Some of the hypothetical reasons for niacinamide's anxiolytic effects might be due to its ability to either increase the production of serotonin and/or augment the benzodiazepine receptor complex in the central nervous system. In terms of serotonin production, niacinamide might increase the synthesis of serotonin because a deficiency of vitamin B_3 has been associated with a deficiency of serotonin. 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-hydroxyindolacetic acid (5-HIAA).[11] The use of vitamin B_3 was also shown to increase the production of serotonin in a rat study, in which the administration of 20 milligrams of niacin (another form of vitamin B_3) resulted in increased levels of 5-HIAA and decreased levels of xanthurenic acid via the kynurenine pathway.[12] Taking pharmacological doses of niacinamide might, therefore, increase the production of serotonin, by diverting more dietary tryptophan to become substrate for the production of serotonin.

The other hypothetical reason for niacinamide's anxiolytic effects likely has to do with its presumed benzodiazepine-like properties. In a previous review of the literature by Hoffer, niacin and niacinamide were both shown to have some sedative activity, and were able to potentiate the action of sedatives, anticonvulsant medications, and certain tranquilizers.[13] Hoffer and his co-authors observed that 3,000 mg/day of niacin potentiated the action of barbiturates when the vitamin was given concomitantly to patients. They also observed that the usual quantities of sedatives when administered to schizophrenic and senile patients produced unexpected sleepiness and

sedation when combined with niacin and niacinamide. In a published case report by myself, a review of the literature was undertaken to determine the biological mechanism for niacinamide's anxiolytic effects.[8] It appears that niacinamide has therapeutic effects comparable to benzodiazepines. I concluded that 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 receptor.[14-19]

The use of niacinamide dates back to the 1940s when internist, Dr. William Kaufman, began to use therapeutic doses to correct a syndrome that he referred to as, "aniacinamidosis."[20] He used the term to denote a deficiency state that could not be ameliorated by dietary modifications, but required between 150 to 350 mg of niacinamide each day to reverse its clinical manifestations. Some of the psychological symptoms associated with aniacinamidosis are similar to the symptoms exhibited by many patients with anxiety. From the mid 1950s to the present, the clinical work of Hoffer demonstrated that 1,500-6,000 mg of niacinamide per day is safe for patients with psychiatric syndromes.[21,22]

At present, the biochemical and clinical data pertaining to the anxiolytic effects of niacinamide are lacking. Even though there are numerous biochemical publications suggesting a relationship between niacinamide and the gamma-aminobutyric acid system (including other neurotransmitters), it is unclear if this information is applicable to human beings. The published case reports are not considered the highest level of evidence since they are subject to bias and contain numerous confounding variables. For these reasons, it was necessary to study niacinamide in a more controlled and scientific manner. Although funding was unavailable to pursue a randomized controlled pilot trial, more rigour could still be applied when using a single subject (N-of-1) design. Here, I report the results from an N-of-1, placebo-controlled trial, designed to investigate the efficacy and safety of niacinamide in a participant with anxiety symptoms.

Methods

Setting

This N of 1 trial took place at the Robert Schad Naturopathic Clinic (RSNC), the outpatient clinic of the Canadian College of Naturopathic Medicine (CCNM) in North York, Ontario. The 14-week study commenced in February 2008 and ended in May 2008, and involved one participant.

Participant

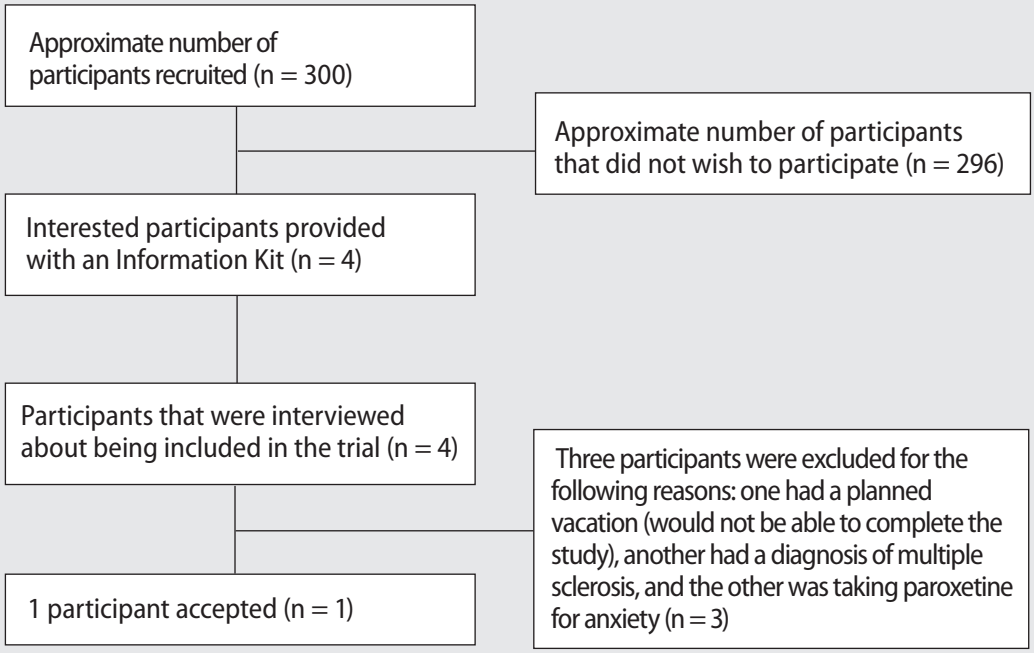
The participant was required to be either male or female, and needed to be 20 years of age or older to be eligible for the study.

Inclusion Criteria

The participant was eligible for this trial if the following inclusion criteria were met:

1. Males or non-pregnant females age range 20 or more years (non-pregnant females must agree to use an acceptable form of birth control during the trial, such as condoms, abstinence, etc).
2. Beck Anxiety Inventory (BAI) score of >21.
3. Mentally competent and able to adhere and understand the given protocol and treatments administered as interventions.
4. Student at CCNM or a patient of the RSNC.
5. Agreeing to not take any other natural health products for the duration of the trial.
6. Must be "healthy" and have no diseases of any kind (e.g., chronic active hepatitis, cirrhosis, past history of gout or active gout, peptic ulcer disease, gastric cancer, adrenal disease, thyroid disease, cardiac arrhythmia, eating disorders, coronary, artery disease and diabetes mellitus).
7. Normal on physical examination at the pre-study intake, and in the case of abnormalities the medical practitioner considers them to be clinically insignificant.
8. Must have a family doctor that they have seen in the last 12 months.
9. Must not be pregnant or have the intent to become pregnant in the next 6 months.
10. Must not have a severe psychiatric condition such as alcoholism, bipolar disorder, schizoaffective disorder, schizophrenia, or substance dependency.

Figure 1. Participant recruitment flow diagram



11. Must not have a previous episode or history of intolerance or allergy to niacin (nicotinic acid) or niacinamide (nicotinamide).
12. Must not have a previous episode or history of intolerance or allergy to any of the ingredients in the placebo (cellulose/microcrystalline cellulose, calcium phosphate/dicalcium phosphate dihydrate, and octadecanoic acid magnesium salt/magnesium stearate).
13. Must provide written and valid consent.

Sampling and Recruitment

Members of CCNM and the RSNC were invited to participate, as the number of eligible participants from these two sites was expected to be several hundred. Posters were distributed throughout CCNM and the RSNC and were placed on bulletin boards throughout the college campus. Several 5-10 minute information sessions were held at the beginning of lectures for years 1-3 to provide basic information about the study. Posters were also handed out during these information sessions, which involved a total of approximately 300 potentially eligible participants. Interested parties contacted me directly, either by phone or e-mail and provided their name, telephone number, preferred time of contact, and mailing address. Interested participants were also given an Information Kit, which included complete study information and a consent form. All potential participants were instructed to complete the BAI. A score above 21 indicates that the anxiety is moderate and clearly more than the usual stresses of everyday life. A score greater than 21 on the BAI, as well as the absence of any contraindications found on the initial intake, was used to determine eligibility for the study. Therefore, of the total 300 potentially eligible participants, four were interviewed, and one was chosen. Only data for the one participant was included in the final analysis (**Figure 1**, above). The selected participant demonstrated a high level of commitment to the trial, an ability to attend all appointments, and

an interest in furthering the knowledge of a potential nutritional treatment for anxiety symptoms.

The chosen participant was a 26-year-old female at the time of study commencement. On intake, she reported a history of feeling very anxious, beginning when she was 5-6 years old. She mentioned an extreme fear of doing presentations in front of people. She would often lose her voice when engaging in any type of public speaking. She also noted being very fearful of how people judge or evaluate her. Although she has never been provided with a psychiatric diagnosis, my intake revealed the possibility that she had social anxiety disorder. Although this diagnosis was not confirmed by a psychiatrist or psychologist, she was an ideal participant due to the chronic and marked nature of her anxiety.

Non-selected participants were provided with the RSNC telephone number and were encouraged to set-up appointments so that they could receive immediate treatment for their anxiety symptoms.

Study Design

The participant had her initial evaluation, which included a screening physical examination, and laboratory testing (i.e., complete blood count, fasting plasma glucose, serum urate, serum bilirubin, serum human chorionic gonadotropin, and serum transaminases). Then the participant underwent a two week washout cycle (days 1-14) where she was not allowed to take any natural health product. On the 14th day of the trial the participant had a visit, completed the BAI and Measure Yourself Medical Outcome Profile (MYMOP) questionnaires, received the two week medication diary, received the follow-up appointment dates and the end-of-trial date, and received instructions about getting her two week supply of medication (i.e., niacinamide or placebo) from the research assistant.

Plans were made with the participant to have follow-up visits every two weeks until the conclusion of the 12th week. During each two week follow-up visit, the participant provided her two week medication diary including any unused study product, received testing for serum transaminases, and completed the BAI and MYMOP forms. Once all the cycles were completed, the participant returned for her end-of-trial evaluation, which included a complete screening physical examination, laboratory tests (i.e., complete blood count, fasting plasma glucose, serum urate, serum bilirubin, serum human chorionic gonadotropin, and serum transaminases), and the completion of the final BAI and MYMOP questionnaires to determine the severity of her anxiety symptoms. The complete study period and clinical evaluations have been outlined in **Table 1** (p.200).

Blinding

The research assistant randomly chose (i.e., by coin toss) which treatment (i.e., niacinamide or placebo) the participant received, and kept hidden from both participant and doctor the treatment intervention. The intervention period ended at the 12th week (or day 84) of the trial. The research assistant was the only person with knowledge of the specific treatment intervention during the duration of the trial and did not communicate this information to anyone until the trial was completed.

Study Drugs

Swiss Herbal Remedies Limited (Richmond Hill, Ontario) provided the 500 mg immediate-release niacinamide in a white, round, standard biconvex tablet. A certificate of analysis of the finished product was furnished verifying the potency and safety of the tablet (i.e., acceptable levels of heavy metals, total plate count, and microbial impurities). The placebo was matched for colour and size, and contained microcrystalline cellulose, dicalcium phosphate dehydrate, and magnesium stearate.

Dosage Selection

The 3,000 mg/day dose of niacinamide was chosen for a variety of reasons. The foremost expert on the clinical use of niacinamide, i.e., the late Dr. Abram Hoffer, recom-

Table 1. Study period and clinical evaluations

Initial Evaluation		Day 0, the participant underwent a complete history, screening physical examination, and laboratory testing (i.e., complete blood count, fasting plasma glucose, serum transaminases, serum bilirubin, serum urate, and human chorionic gonadotropin).
Wash-out Cycle	Weeks 1 & 2 (days 1-14)	Participant discontinued all natural health products for 2 weeks.
Period 1	Weeks 3 & 4 (days 15-28)	On the 14th day of the trial, the participant had a visit and completed the BAI and MYMOP. Serum transaminases were done. The participant was instructed to take 2 tablets (1000 mg) of niacinamide or 2 identical placebo tablets, three times each day.
	Weeks 5 & 6 (days 29-42)	On the 28th day of the trial, the participant had a follow-up visit, completed the BAI and MYMOP, and returned any unused study product. Serum transaminases were done. The participant was instructed to take 2 tablets (1000 mg) of niacinamide or 2 identical placebo tablets, three times each day.
Wash-out Cycle	Weeks 7 & 8 (days 43-56)	On the 42nd day of the trial, the participant had a follow-up visit, completed the BAI and MYMOP, and returned any unused study product. Serum transaminases were done. The participant discontinued treatment, and did not take any natural health products during the proceeding 2 weeks.
Period 2	Weeks 9 & 10 (days 57-70)	On the 56th day of the trial, the participant had a follow-up visit and completed the BAI and MYMOP. Serum transaminases were done. The participant was instructed to take 2 tablets (1000 mg) of niacinamide or 2 identical placebo tablets, three times each day.
	Weeks 11 & 12 (days 71-84)	On the 70th day of the trial, the participant had a follow-up visit, completed the BAI and MYMOP, and returned any unused study product. Serum transaminases were done. The participant was instructed to take 2 tablets (1000 mg) of niacinamide or 2 identical placebo tablets, three times each day.
End-of-Trial Evaluation		On the 84th day of the trial, the participant had a follow-up visit, completed the BAI and MYMOP, returned any unused study product, and underwent a complete history, screening physical examination, and laboratory testing (i.e., complete blood count, fasting plasma glucose, serum transaminases, serum bilirubin, serum urate, and human chorionic gonadotropin).

mended 1,500-6,000 mg/day to all patients with psychiatric disorders.[21] Niacinamide (in doses up to 3,000mg/day) have been safely used in children, adolescents, and adults for a few months to several years without any serious adverse reactions.[22-26] Niacinamide at 3,000mg/day has been used in several randomized controlled trials without any serious adverse reactions.[26]

Other reasons for using 3,000 mg/day involve its presumed quick onset of action and quick termination (i.e., offset) of action once the vitamin has been discontinued. Animal studies have demonstrated that niacinamide exhibits clinical effects similar to those obtained from benzodiazepine medications. This is important since benzodiazepines are known to have a quick onset of action in alleviating symptoms of anxiety. I have also observed the swiftness of niacinamide's onset of action in my clinical practice and have published several case reports describing niacinamide's anxiolytic effects. When discontinued, the beneficial effects from a 3,000 mg/day dose of niacinamide would presumably be negated within 24 hours. In a published study pertaining to the pharmacokinetics of niacinamide in humans and mice, a 3,000 mg dose of niacinamide in human subjects generally achieved peak drug levels within the first 45 minutes, with the peak plasma level calculated to be 70.3 μg/ml (± 7.5).[27] There was no identifiable niacinamide in the plasma of the human subjects 24 hours after taking 3,000 mg of the vitamin. In addition, the mean elimination half-life in the human subjects given the 3,000 mg dose was 5.9 hours (± 0.6). Based on this data, within 24 hours of discontinuing niacinamide, there would no identifiable amounts of the vitamin in the plasma, and presumably its favourable therapeutic effects would cease to exist.

End Points

Primary Outcomes

The primary outcomes for this study were the BAI and MYMOP questionnaires that were repeatedly measured during the trial. The BAI questionnaire is designed to measure subjective symptoms of anxiety, as well as discriminate between anxiety and depression. The BAI consists of 21 items, each describing a common symptom of anxiety. The items are summed to obtain a total score that can range from 0-63. The scale has high internal consistency.[28,29] In addition, the BAI has been demonstrated to have good test-retest reliability, good convergent validity with other measures of anxiety, good divergent validity with measures of depression, and to be a sensitive enough scale that changes with treatment.[30] The BAI was chosen since it provided a score rating the severity (intensity) of the participant's symptoms; a score that would presumably drop if her anxiety improved.

The MYMOP is a patient-centered outcome questionnaire with internal consistency and construct validity.[31-33] It has been used in primary care and complementary medicine settings as a means of collecting and quantifying qualitative patient experiences.[31,34] It requires the participant to specify two personally relevant symptoms that are the most bothersome (of greatest importance to their individual health) and to rate them numerically on a 7-point visual analogue scale (0-6). The MYMOP also contains a question where the participant writes down some activity (i.e., physical, social, or mental) that has been hindered/affected by her problem, and asks the participant to rate the severity of it numerically. Lastly, the MYMOP asks about wellbeing and again the participant is to rate this numerically. Higher scores correspond to a lower satisfaction (i.e., worse) level of health as it pertains to individually selected symptoms. There are also a few questions pertaining to medication use, but these were not applicable since no medications (other than niacinamide or placebo) were allowed during the trial.

Safety

The patient underwent safety evaluations at the initial visit (day 0), at each subsequent visit (days 14, 28, 42, 56, and 70), and at the end of the trial (day 84). Adverse events were elicited at each visit, their in-

tensity graded as none, mild, moderate, or severe, and their relation to the study drug determined. A screening physical examination (including vital signs) and a battery of laboratory tests were assessed at baseline and at the end of the trial. Serum transaminases, which refer to alanine transaminase (ALT) and aspartate transaminase (AST), were assessed repeatedly during the trial to monitor hepatic function and ensure the absence of hepatitis.

Adherence

Pill counts were conducted on return visits to determine compliance. The selected participant was also instructed to maintain a medication diary during each two week cycle for the eight week intervention period. The participant recorded the dosage of medication that was taken each day, including any side effects or other noteworthy changes. After each two week cycle, the patient returned her diary for evaluation, as well as any unused study product. While the completion of a daily medication diary has been shown to be positively correlated with patient compliance in medication intake, [35] other studies have shown that such diaries may increase patient burden,[36] and are not always filled-out at the appropriate time.[37] Despite its limitations, the use of a medication diary was the only practical and cost-effective method utilized to increase the participant's compliance during this study.

Statistical Analysis

Data were entered into a Microsoft Excel spreadsheet (Microsoft Corp., Redmond, Wash.) and analyzed using the StatsDirect statistical software (StatsDirect Ltd., Cheshire, Engl.). The data analyst was not blinded to allocation. A paired t-test was used to determine the magnitude and consistency of the differences between placebo and niacinamide on the BAI and MYMOP scores using a two-tailed P-value < 0.05 as the threshold of significance.

Relevant lab values (i.e., transaminase levels) were subjected to the same statistical analysis to ascertain if niacinamide and placebo treatments had different effects upon hepatic function. A paired t-test was used to determine the magnitude and consistency of the differences between the effects that placebo and niacinamide had upon transaminases using a two-tailed P-value < 0.05 as the threshold of significance.

Ethics

The institutional review board of CCNM approved the protocol, and the participant gave written and valid consent prior to study inclusion. In addition, the Natural Health Products Directorate of Canada, Bureau of Clinical Trials and Health Science, formally approved of the study in its entirety based on the study protocol, safety, and chemical and manufacturing analysis of the study drug. The Declaration of Helsinki was adhered to during all phases of the study.

Results

Primary Outcomes

The data were analyzed, and the paired t-test was used to determine the magnitude and consistency of the difference between the niacinamide and placebo treatment. The standard deviation, standard error, and confidence intervals were not reported due to the low degrees of freedom in this study. The niacinamide was expected to produce substantial changes in the BAI and MYMOP scores, and the placebo should have produced little-to-no effects. Thus, there should have been a consistent difference in favour of the niacinamide that was unlikely to have occurred by chance.

Unfortunately, the BAI results did not demonstrate a consistent difference in favour of the niacinamide. Improvements (declines) from the initial BAI were observed in both the placebo and niacinamide treatments, with greater declines occurring while the participant was taking the placebo tablets. In **Table 2,** (p.203) the BAI scores for the placebo decreased by 17 in Period 1 and decreased by 11 in Period 2. For the niacinamide, the BAI scores increased by 2 in Period 1 and increased by 4 in Period 2.

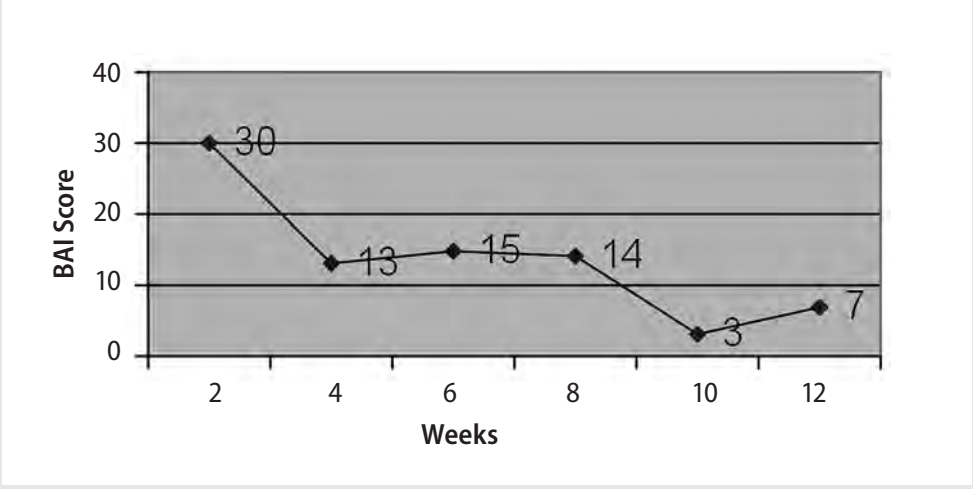
Figure 2 (p.203) demonstrates a con-

Table 2. BAI Results for Periods 1 and 2

Treatment	PERIOD 1: BAI Score After Weeks 1&2 (Washout)	BAI Score After Weeks 3&4	BAI Score After Weeks 5&6	PERIOD 2: BAI Score After Weeks 7&8 (Washout)	BAI Score After Weeks 9&10	BAI Score After Weeks 11&12
Niacinamide	30	N/A	15 (+2)	14	N/A	7 (+4)
Placebo		13 (-17)	N/A		3 (-11)	N/A

*N/A = Not applicable; minus (-) denotes an improvement and positive (+) denotes a decline in BAI scores

Figure 2. BAI results over time



tinuous decline over time in the BAI results. During weeks one and two, the participant was in the washout cycle of the trial. During weeks three and four, the participant was taking placebo and the BAI score at the end of the two weeks declined. During weeks five and six, the participant was taking niacinamide and the BAI score slightly increased. During weeks seven and eight, the participant was in the final washout cycle of the trial, and the BAI score was 14. Between weeks nine and 10, the participant was taking placebo and the BAI score declined once again. Between weeks 11 and 12, the participant was taking niacinamide and the BAI score increased. Even though there was an overall improvement in the BAI results over

time, whenever the participant was taking the niacinamide, her BAI scores increased (worsened).

Figure 3 (below) demonstrates a trend toward the placebo having an effect over the niacinamide. The participant's anxiety worsened while taking the niacinamide, and improved while taking the placebo. However, there was no statistically significant difference in the BAI results from the niacinamide and placebo treatments (p=0.0746) over the entire study period.

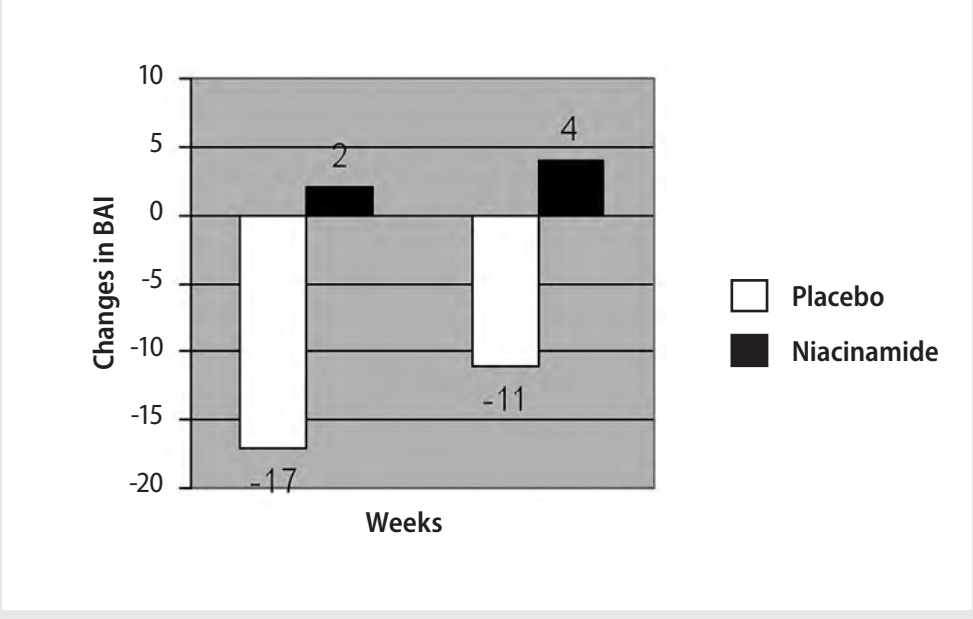
Similar to the BAI results, the MYMOP results did not demonstrate a consistent difference in favour of the niacinamide for Periods 1 and 2. Improvements (declines) during Periods 1 and 2 on the MYMOP scores were observed in both the placebo and niacinamide treatments, with greater declines occurring while the participant was taking the placebo tablets.

For Period 1, the MYMOP scores for the placebo and niacinamide were almost identical, except the scores for Symptom 2 and Wellbeing decreased (improved) while the participant was taking the placebo tablets and increased (worsened) while the participant was taking the niacinamide (**Table 3**, p.205).

For Period 2, some of the individual MYMOP dimensions worsened (increased) or did not change while the participant was taking the niacinamide, whereas some of the individual dimensions improved (decreased) while the participant was taking the placebo tablets (**Table 4**, p.206). Specifically, Symptom 2 worsened while the participant was taking niacinamide, but did not change while the participant was taking the placebo tablets. The Activity dimension worsened while the participant was taking niacinamide, and improved when the participant was taking the placebo tablets. The scores for Symptom 1 and Wellbeing improved (decreased) when the participant was taking the placebo tablets, and did not change when the participant was taking the niacinamide.

Figure 4 and **Figure 5** (p.207) demonstrate the change in the individual MYMOP dimensions that occurred when the participant was taking either the niacinamide

Figure 3. Changes in BAI over time



or placebo during the trial. Note that the changes in the individual MYMOP dimensions declined more often when the participant was taking placebo compared to when the participant was on niacinamide.

There were no statistically significant differences between the niacinamide and placebo treatments for all the dimensions of the MYMOP, which include Symptoms 1 and 2, Activity, and Wellbeing over the duration of the study. Thus, there were no statistically significant differences observed in Symptom 1 (p=0.30), Symptom 2 (p=0.40), Activity (p=0.13), and Wellbeing (p=0.09).

In addition to the BAI and MYMOP evaluations, the participant also recorded noteworthy changes in the 14-Day Medication Diary that was provided to her at the beginning of each two week cycle. The participant ranked her overall stress level during each two week cycle as none, mild, moderate, or severe, and also provided additional information that she felt was important. She was not instructed to rank her stress level, but decided to do so anyway. During the two week washout in Period 1, she recorded her stress level as being "mild," and stated that she was "struggling with the course mate-

Table 3. MYMOP Results for Period 1

Treatment	MYMOP Scores After Weeks 1 & 2 (Washout)	MYMOP Scores After Weeks 3 & 4	MYMOP Scores After Weeks 5 & 6
Niacinamide			
Symptom 1 Self Confidence	5	N/A	2 (N/C)
Symptom 2 Concentration	5	N/A	3 (+2)
Activity Exam Preparation	5	N/A	2 (N/C)
Wellbeing	5	N/A	3 (+1)
Placebo			
Symptom 1 Self Confidence	5	2 (-3)	N/A
Symptom 2 Concentration	5	1 (-4)	N/A
Activity Exam Preparation	5	2 (-3)	N/A
Wellbeing	5	2 (-3)	N/A

*N/A = Not applicable; N/C = No Change; minus (-) denotes an improvement and positive (+) denotes a decline in MYMOP scores

Table 4. MYMOP Results for Period 2

Treatment	MYMOP Scores After Weeks 7 & 8 (Washout)	MYMOP Scores After Weeks 9 & 10	MYMOP Scores After Weeks 11& 12
Niacinamide			
Symptom 1 Self Confidence	3	N/A	2 (N/C)
Symptom 2 Concentration	2	N/A	3 (+1)
Activity Exam Preparation	3	N/A	3 (+1)
Wellbeing	4	N/A	1 (N/C)
Placebo			
Symptom 1 Self Confidence	3	2 (-1)	N/A
Symptom 2 Concentration	2	2 (N/C)	N/A
Activity Exam Preparation	3	2 (-1)	N/A
Wellbeing	4	1 (-3)	N/A

*N/A = Not applicable; N/C = No Change; minus (-) denotes an improvement and positive (+) denotes a decline in MYMOP scores

rial" for an upcoming immunology examination. Her BAI was recorded as a 30 and her MYMOP scores were 5s on all the individual dimensions. During the next two week cycle, when she was provided with the placebo tablets, her BAI and MYMOP scores dropped considerably. During this time her stress level was recorded as "severe" and she even indicated a "lack of sleep" in the diary. Then when she was given the niacinamide tablets during the next two weeks, she recorded her stress levels as being "moderate." Although the participant was less stressed than the previous two week cycle, her BAI and MYMOP scores increased (worsened) while she was taking the niacinamide.

Period 2 began with another washout period, and she recorded her stress level as "mild." She also noted that another set of exams were fast approaching. Following the washout, her BAI and MYMOP scores were lower than at the beginning of Period 1. While on placebo, she noted "moderate" stress and even noted that she had a fight with her father. Despite this, her BAI and MYMOP scores dropped (improved). When the intervention was changed

Figure 4. Changes in MYMOP Scores

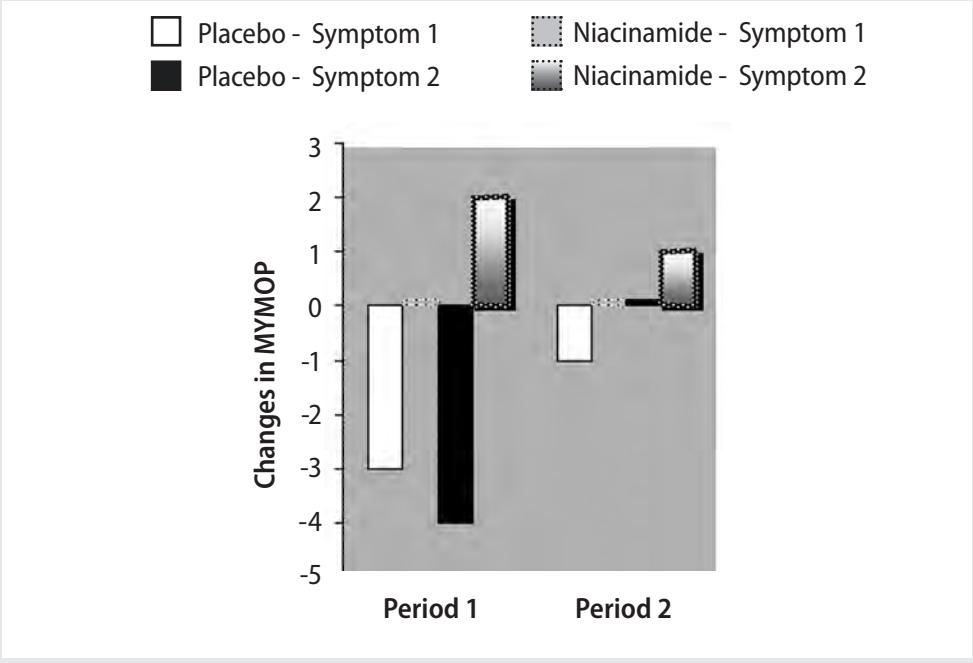
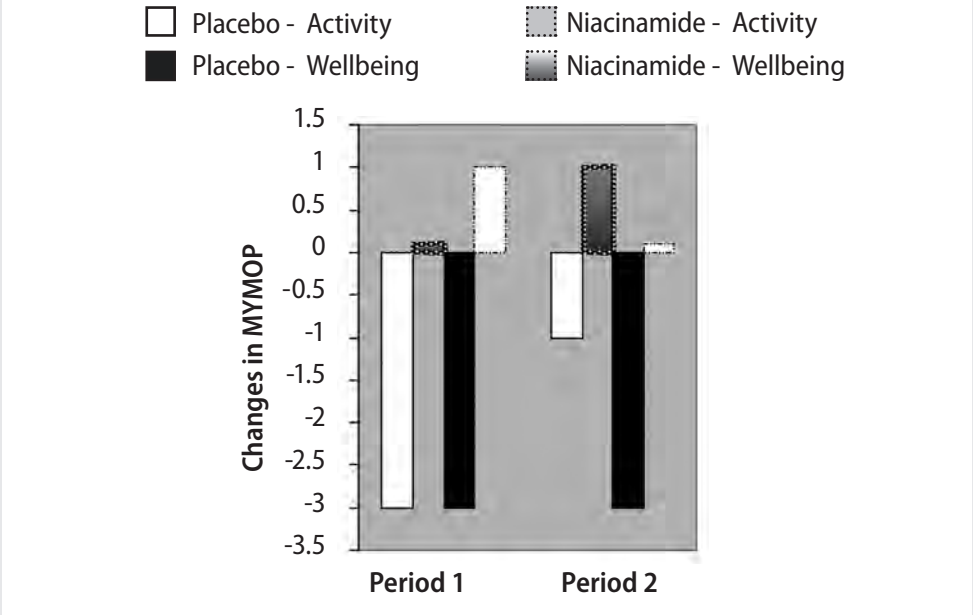


Figure 5. Changes in MYMOP Scores



to niacinamide for the next two week cycle, she reported her stress level as "severe" and that one of her close friends had "left her parent's home and was homeless." Similar to Period 1, her BAI and MYMOP scores generally worsened (increased) while on the niacinamide.

Safety

Overall, the treatments were well tolerated with no reported adverse reactions to either niacinamide or the placebo during the trial. When elicited (i.e., questioned) about possible adverse reactions the patient reported none at each return visit. The baseline and end-of-trial evaluations (i.e., physical examination and laboratory testing) were within normal limits.

Table 5 and **Figure 6** (p.209) show the transaminase results for Periods 1 and 2. None of the transaminase results were abnormal during the trial. Although there were fluctuations in the levels of these hepatic enzymes, they remained stable and within normal limits during the course of the trial.

There were no statistically significant differences in transaminase levels when the participant was taking the niacinamide and placebo. Thus, there were no statistically significant differences observed in the AST (p=0.39) and ALT (p=0.62) values as a consequence of either treatment. **Table 6** (p.210) lists all the P-values for the entire study.

Adherence

Prior to each two week cycle the participant was provided with 90 pills in a clear container. Because she was taking six pills daily, she only needed 84 pills every two weeks. Six extra pills were provided at each two week cycle just in case any were lost. The participant was completely compliant during the trial and did not miss a single dose of medication. This was confirmed by questioning the participant, by having the participant return any unused pills (there were six unused pills at each return visit), and from reviewing the medication diary at each return visit.

Discussion

The results did not demonstrate any statistically significant and clinically significant differences between both treatments. Although there were noted improvements when the participant had taken placebo and noted declines when the participant had taken the niacinamide, the results demonstrated a consistent improvement in the participant's anxiety and related measures over time. This probably had little to do with both treatments and more to do with the "receiving" of a treatment believed to be beneficial by the participant. There are examples of this in the published literature. Recent evidence has demonstrated that the clinical effects of antidepressant medications (e.g., selective serotonin receptor inhibitors) are no different than those obtained from placebo.[38] The argument can be made that the participant in this trial improved as a result of simply being treated.

If the participant had not served as her own control it would have made it impossible to determine if variability in metabolism within the participant overshadowed the potential impact of niacinamide on anxiety symptoms. Examples of confounding factors that might have influenced variability within the participant included changes in stimulant use, sleeping habits, compliance to niacinamide or placebo, exercise frequency and intensity, and environmental stressors that may have occurred over the duration of the trial. These confounding factors appeared to have had a minor or insubstantial effect on the participant. In the participant's medication diary, she recorded her stress levels and other relevant information. Despite experiencing many stressful events during the study (e.g., she had numerous college examinations and oral/practical presentations), her anxiety continued to improve. Thus, the therapeutic effects of receiving treatment for her anxiety overshadowed any of the possible confounding factors that were present.

The study did demonstrate that niacinamide was safe at 3,000 mg/day. The participant's hepatic enzymes did not become abnormal as a result of the niacinamide. Both the initial and end-of-trial laboratory evaluations were within normal limits. There were no statistically significant differences

Table 5. Transaminase Results for Periods 1 and 2

Transaminase Reference Range	Period 1 Results After Weeks 1 & 2 (Washout)	Results After Taking Placebo During Weeks 3 & 4	Results After Taking Niacinimide During Weeks 5 & 6	Period 2 Results After weeks 7 & 8 (Washout)	Results After Taking Placebo During Weeks 9 & 10	Results After Taking Niacinimide During Weeks 11 & 12
AST (< 31 U/L)	23	17 (-5)	24 (+7)	20	20 (N/C)	22 (+2)
ALT (< 36 U/L)	25	15 (-10)	21 (+6)	16	20(+4)	19 (-1)

*Minus (-) denotes a decrease and positive (+) denotes an increase in the individual transaminase enzymes

Figure 6. Changes in MYMOP Scores

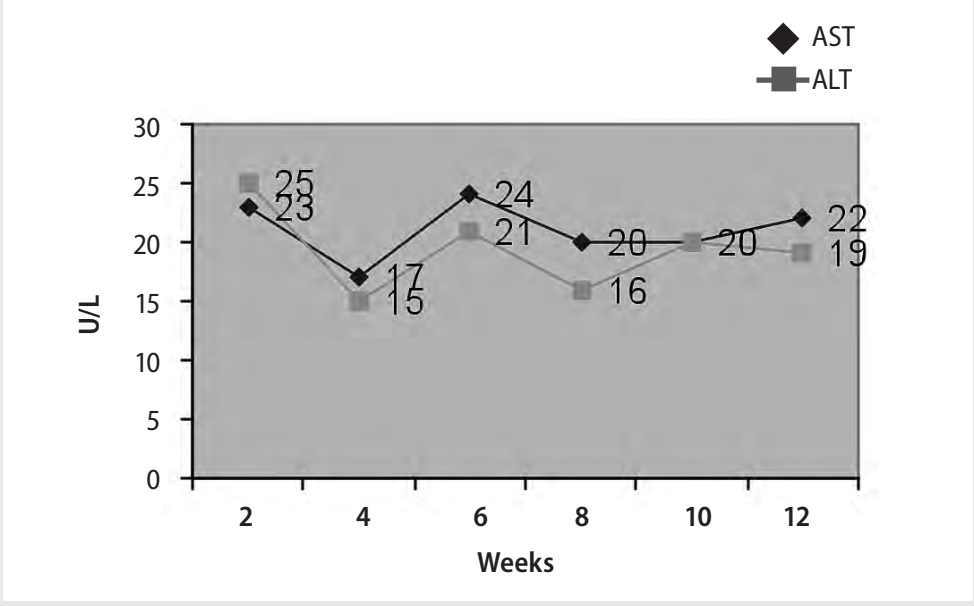


Table 6. Results Summary of P-Values

Measurement	P-value
BAI	0.07
MYMOP:	
Symptom 1 (Self Confidence)	0.30
Symptom 2 (Concentration)	0.40
Activity (Exam Preparation)	0.13
Wellbeing	0.09
AST	0.39
ALT	0.62

in the participant's transaminase levels resulting from niacinamide treatment. This is consistent with the published literature demonstrating that dosages up to and including 3,000 mg/day are well tolerated and safe when used in healthy individuals, and even among individuals with diseases such as arthritis, insulin-dependent diabetes mellitus, and schizophrenia.[39]

Strengths and Weaknesses of the Study

The strength of this study was the rigorous attention paid to blinding, randomization of treatment (e.g., niacinamide or placebo), safety (e.g., frequent laboratory testing), and compliance testing (e.g., 14-Day Medication Diary). One major limitation was that 3 treatment blocks or periods were not possible, although publications pertaining to N-of-1 trials recommend this due to increased odds of statistical significance between periods.[40-42] All clinical trials, including N-of-1, require Health Canada approval prior to commencement. The approval process began in November 2007 and was not granted until late January 22, 2008. The actual study did not commence until February 19, 2008 due to problems with recruitment (i.e., finding a suitable and willing participant). Thus, it was not possible to add any additional treatment periods once the study was approved. Any change to the protocol would have necessitated another submission, and a possible delay of several weeks to several months.

Another major limitation is that the results from this N-of-1 study cannot be generalizable to populations of subjects with anxiety disorders. Large randomized controlled trials allow for quality inferential statistical testing.[43] This enables important conclusions to be formed because a sufficient sample was drawn from a larger population. In other words, the conclusions would be based on a sample believed to be representative of a wider population. In this N-of-1 trial, the results (both statistical and graphical) regarding the effectiveness of niacinamide can only be applied to the participant in this study. The statistical testing that I utilized was of limited value because the data was so sparse and the possible inferences so limited. I decided to include statistics in this N-of-1 trial to show the results in another format. I am fully aware, however, that these results cannot be used to draw conclusions about the usefulness of niacinamide as a treatment for other individuals with anxiety.

Other limitations included insufficient washout cycles between treatments and

insufficient treatment durations. The participant was given placebo after an initial two week washout cycle. After the placebo treatment, she was immediately placed on niacinamide. It would have been more rigorous to have included a washout cycle between treatments and not simply at the beginning of each period. Even though data was presented that showed niacinamide to likely have a rapid onset and offset of action, a washout cycle between treatments would have eliminated any potential carryover effects. With respect to treatment durations, the exact period of time that the participant was on niacinamide or placebo (in two week intervals) was for a total of 56 days (eight weeks). It is unknown if this provided enough time to determine whether niacinamide produced clinically significant effects. Had niacinamide been administered for a longer period of time, it might have had an increased chance of producing observable therapeutic effects. On the other hand, longer treatment durations would not have necessarily demonstrated increased effects, but might have jeopardized the results through loss of the participant. Thus, it is unknown if the study duration allowed for accurate data collection on the effects of niacinamide and placebo.

The other notable limitation was financial. The participant was not charged for each visit, which amounted to a loss of approximately $420.00 Canadian dollars. My normal fee is $60.00 per half-hour. This total was arrived at by averaging the time I spent with the participant (approximately, 30-minutes/visit) at each of the required seven visits. I paid for all the laboratory tests in this study as well, which amounted to approximately $250.00 Canadian dollars. Since I had not sought out funding or financial sponsorship, I was only capable of designing and completing a study that I could happily afford.

Implications for Clinical Practice

The absence of hepatic toxicity in this study was consistent with published reviews demonstrating the relative safety of niacinamide.[22,26,39] This is important since CAM practitioners and medical doctors use niacinamide for various reasons (i.e., for the treatment of acne, anxiety, augmenting radiotherapy, and possibly Mycobacterium tuberculosis and human immunodeficiency virus) in clinical practice.[22,26,39,44-48] At the very least, this study contributes to a growing evidence-base demonstrating the safety of this commonly-used vitamin. The results, however, are only applicable to the participant in this study and cannot be generalized to other individuals seeking help for their anxiety. Should niacinamide be considered as a treatment option for anxiety? At present there are more questions than answers about the effectiveness or lack of effectiveness of niacinamide for anxiety. More study is certainly needed.

From participating in every aspect of this study (i.e., from inception to completion), I believe that there is tremendous value in N-of-1 trial designs and that they are very appropriate to the practice of CAM. The N-of-1 trial is a very appealing design in which to define efficacy on an individual basis. It is entirely possible to complete an N-of-1 trial in clinical practice and to generate data that is meaningful and less subject to bias. Most CAM practitioners rely on expert opinions and case reports to evaluate the outcome of particular therapeutic treatments.[42] If more CAM practitioners completed and published N-of-1 trials, the emerging evidence base would be less subject to bias and more credible with respect to conclusions about the effectiveness of many treatments. Mills and Johnston have reported on the value of N-of-1 trials as they relate to CAM, and have noted that single subject designs offer the following 6 possibilities or advantages: (1) they minimize the effects of drawing invalid conclusions about the effectiveness of particular therapies; (2) they can help develop better diagnostic tests; (3) they can be used to identify "individual responders" in patients presenting with heterogeneous clinical conditions; (4) they can be used to clarify optimal formulations of natural health products in individual patients; (5) they can be used to evaluate different dosing regimens of the same natural health product; and (6) they can serve as a tool to investigate the true placebo effect.[42]

I am now much more familiar with the type of attention and rigor that is required when conducting research in clinical practice. The potential to generate meaningful data is very achievable with N-of-1 trials. Clearly, this is a trial design that CAM practitioners should highly consider, as it can be easily implemented into clinical practice.

Conclusion

This study demonstrated that niacinamide was safe at the 3,000 mg/day amount. The use of niacinamide was not, however, associated with any favorable therapeutic effects upon the participant's symptoms of anxiety and anxiety scores per the BAI and MYMOP questionnaires. The results also showed a consistent improvement in the participant's anxiety that was likely the result of simply receiving treatment, with little to do with the type of treatment provided (i.e., placebo or niacinamide). Since the limitations of this study might have negatively impacted the results, more study of niacinamide is clearly warranted if its anxiolytic effects are to be properly evaluated. This study also underscores the importance of conducting rigorous N-of-1 clinical research in CAM office settings. N-of-1 study designs are achievable and would contribute to evidence that is less subject to bias and more credible with respect to conclusions about the effectiveness of many CAM treatments.

Competing Interests

The author has acted as a consultant to Swiss Herbal Remedies Limited in the past, i.e., the company that supplied the niacinamide and placebo tablets for this study. The author has no current financial relationship with them. Swiss Herbal Remedies Limited had knowledge of this study and manuscript, but has not seen the results or this manuscript.

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