

Effects of Neurobiology Formula 12397

(marketed as SerotonaTM and SeratoninTM)

on the Headaches of Chronic Migraineurs

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Neurobiology Formula 12397 is trade marked as SeratoninTM
by Allergy Research Group

Abstract:

Purpose: Neurobiology Formula 12397 is a relatively new and unexplored natural supplement intended for the prevention of migraine headaches. This research was done to see what effects, if any, the Formula has had on the lives of migraineurs who have taken it. Methods: A survey was mailed to 20 individuals across the United States who were known to take the Formula. Surveys contained questions addressing demographic information, migraine symptomatology, therapy course with Neurobiology formula, as well as effects on 6 dependent variables: days missed from work/school, household work, and social events, severity of migraines, frequency of migraines, and impaired productivity. 15 surveys were returned complete. Results were analyzed using descriptive statistics. Results: Of the participating subjects, 93% were female and 60% older than 45 years of age. Most subjects (60%) were diagnosed with migraines before the age of 18. All participants claimed to experience at least one associated symptom during migraine attacks. Photophobia was reported by all participants, more than 70% of subjects reported suffering from phonophobia and nausea, and greater than 50% noted vomiting with their headaches. More than half of subjects had taken Neurobiology Formula for at least a year while the other half had taken the formula longer. No participants had taken the formula more than 3 years. Compliance with taking the formula was as follows: 26.7% never missed a dose, 46.7% rarely missed a dose, and 26.7% occasionally missed a dose. The dependent variables collectively showed positive results. Participants were asked to state the number of days in a three-month period that problems in question were encountered due to their migraines. Before taking Neurobiology Formula, over 30% of participants missed more than 10 days of work/school or social events. Over 40% missed household work more than 10 days. Impaired productivity on the job was encountered more than 10 days by over half of those surveyed. More

than 70% stated they experienced greater than 10 headaches over this time period with an average severity of 8.7 on a scale of 1 to 10. Results concerning the time after subjects had started taking the formula were much different. Approximately 60% of those surveyed reported missing only 0-1 days of work/school, household work and social events over three months, while less than 10% reported missing more than 10 days. More than 40% of subjects experienced only 0-1 days of reduced productivity in the time surveyed. Additionally, subjects experienced fewer headaches with a majority (>50%) having less than 4 headaches over three months. Headache severity also reduced to an average of 4.3 on a scale of 1 to 10. Conclusions: There are limited prophylactic therapies for migraine sufferers. With approximately 28 million Americans coping with migraine pain and direct and indirect costs totaling near 17.2 million dollars annually for this condition, it is imperative to continue looking for helpful treatment regimens. This research was done to determine the effects of Neurobiology Formula 12397 on chronic migraine headaches. It was hypothesized that those taking it would see positive changes in their headache pattern. Reviewing the analyzed results shows that this hypothesis was supported. With only 15 surveys to analyze, there is no way to state that this research is conclusive for the entire migraine population; however, the relief experienced by participants while taking the formula warrants further, more controlled research on this supplement.

Problem:

Migraine is the 2nd most common primary headache disorder in the United States. (Cutrer and Moskowitz, 2000, p.2066) Approximately 28 million Americans, or 13% of the US population, are tasked with managing migraine pain. Nearly one in four US households is home to a migraine sufferer. (Lipton, Diamond, Reed, Diamond and Stewart, 2001) While research has progressed over the last decade with the development of new migraine treatments and preventative therapies, the pain of migraine is still disabling for many. (Mauskop, 2001) Of those migraineurs treated for their pain by a health care provider, 70% are unsatisfied with the results. (Lipton and Stewart, 1999)

Looking past the pain and suffering migraineurs must learn to cope with is an economic impact on society that should also be considered. (Lipton et al., 2001; Schwartz, Stewart, and Lipton, 1997) Migraine pain is often the cause of missed work, with a nationwide total approaching 100 million lost workdays annually. (Aukerman, Glen, Knutson, Doug and Miser, 2002) The combination of direct and indirect costs due to missed days and lost productivity in the workplace, as well as medical costs, has been estimated at \$17.2 billion annually in the United States, an economic burden felt by both the patient and society. (Sensenig, Marrongelle, Johnson, and Staverosky, 2001)

In order to relieve the suffering of migraineurs and try to resolve the economic ramifications of the chronic condition, it is imperative the medical field continue to improve upon current treatments and investigate new options for migraine therapy. Neurobiology Formula 12397 is a new and unexplored natural supplement intended to prevent migraine pain, currently taken by several people across the United States. This research will show what impact, if any, taking Neurobiology Formula has had on their lives and migraine pain. It will also

determine the need for further research concerning the role of this supplement in the treatment of others with this disabling condition.

Background:

According to data from American Migraine Study II, the prevalence of migraine has remained stable over the past decade. Unfortunately, migraine-associated disability remains substantial and pervasive. 62% of migraineurs experience one or more headaches per month; 37% report experiencing one to three migraines per month; 11% of people cope with one severe headache every week. Regardless of headache frequency, 91% of migraineurs report functional impairment with their headaches. Half of those experience severe impairment that requires bed rest or cancellation of activities. When able to attend work or school, migraine pain can reduce productivity by at least 50% among half of migraineurs. (Lipton et al., 2001) For some, disability is related to more than their headaches. Many report the fear of their next attack has a significant impact on their quality of life between attacks as it disrupts their ability to plan social and family activities. (Sensenig et al., 2001) In a study determining predictors of lost workdays and reduced workday effectiveness, people with migraine headaches were at the greatest risk for both when compared to all other headache types. (Schwartz et al., 1997) Those reporting severe migraine attacks compared to mild or moderate headaches were found to be responsible for a majority of the indirect costs of migraines. (Edmeads and Mackell, 2002)

Many abortive treatments are available for migraine patients to explore. Because therapy is individualized, patients must often try different medications before finding the most effective regimen for them. (Massiou, 2000) The selective serotonin agonists (triptans) such as sumatriptan have improved the lives of many people; however, these drugs were found to be ineffective in 30% of patients, can cause unpleasant side effects in some patients, and can lead to serious side effects in a few people. (Mauskop, 2001) Moreover, they are ineffective at

reducing the number of attacks migraineurs experience. (Sensenig et al., 2001) Patients with heart disease, a history of stroke or transient ischemic attacks, peripheral vascular disease, Raynaud syndrome, high blood pressure, high cholesterol, diabetes, or smokers, must be cautioned and may be unable to take these medications. (“The Migraine Relief”, 2001)

While much has been accomplished in the effort to find acute treatments for migraine pain, prophylactic treatments have shown limited progress. (Sensenig et al., 2001) Some indications for preventive therapy include 1) two or more attacks a month causing 3 or more days of disability, 2) contraindications to or failure of migraines to respond to abortive treatment, and 3) the use of acute medicines more than twice a week. (Diener and Limmroth, 2001; Snow, Weiss, and Wall, 2002) Many agents are available for preventive migraine treatment: alpha-2 agonists, anticonvulsants, antidepressants, beta-blockers, calcium antagonists, ergots, methysergide, and NSAIDs have all been studied. Of these, only a few have proven efficacy and most have side effects significant enough to cause subject withdrawal when studied. (Gray, Goslin, McCrory, Eberlein, Tulskey, and Hasselblad, 1999; Snow et al, 2002) Research on the benefit of certain herbal therapies is in progress. Effectiveness has been seen with Feverfew over placebo, and it is the most recommended herb to those interested in herbal remedies. (Mauskop, 2001). Butterbur root, an extract from the rhizome *Petasites hybridus*, has shown a 60% reduction in the frequency of headache compared to baseline in recent research. (Grossman and Schmidrams, 2001) Further research of these natural alternatives is being conducted currently.

The composition of Neurobiology Formula is grounded in research showing migraine headaches occur from a lack of neurotransmitters serotonin and norepinephrine in the brain. The proposed mechanism states that low levels of neurotransmitters lead to loss of vasomotor control, resulting in the vascular dilation responsible throbbing migraine pain. Many problems could lead to low levels of neurotransmitters: allergic reactions, inflammation, poor absorption of precursors into the brain, or poor metabolism of precursors in the brain. (Allocca, 1999) Studies have shown that levels of serotonin in the blood fall at the onset of a migraine attack and return to normal between attacks. Also, an increased urinary output of the serotonin metabolite 5-hydroxyindoleacetic acid has been observed during acute attacks. Additionally, the drug reserpine, which depletes serotonin supplies, can precipitate a migraine attack. (Larkin, 1997) Dr. Allocca (1999) found migraineurs have a higher than usual number of serotonin and norepinephrine receptors in their brains, which could mean they need more neurotransmitters and the nutrients to manufacture them.

TABLE 1-1	
Contents of NBF 12397	Proposed effects
L-5-Hydroxytryptophan	precursor to serotonin
L-Tyrosine	precursor to norepinephrine
Copper and vitamin C	required for the production of norepinephrine from Tyrosine
Dextrose	stimulates production of insulin to facilitate absorption of 5-Hydroxytryptophan across blood brain barrier
Magnesium Aspartate (chelated form of magnesium-making it more absorbable)	essential for metabolism of carbohydrates and proteins, activation of enzymes, and protein synthesis; decreased levels lead to vasodilation
Calcium and magnesium	required for normal nerve transmission
Magnesium and niacin	required for vasomotor control
Niacin	ensures tryptophan is not converted to niacin instead of serotonin
Quercetin	strengthens outer cell membranes/stabilizes cell surface; used to stabilize basophils and mast cells so they will not burst easily and release histamine and other inflammatory chemicals
Vitamin C	potent antioxidant required to convert pyridoxal dopamine to norepinephrine
Vitamin B6	important in production of neurotransmitters and prostaglandins
Choline	precursor to acetylcholine
Folic acid	facilitates the production of neurotransmitters

Neurobiology formula 12397, contents listed in Table 1-1, is a supplement containing precursors to serotonin and norepinephrine. It also contains antioxidants, anti-allergic substances

and cell membrane support substances that are intended to reduce allergic and inflammatory reactions. The formula does not contain a precursor to serotonin called L-Tryptophan, which has been associated with more than 900 cases of Eosinophilia Myalgia. Rather, it utilizes a different precursor, 5-Hydroxytryptophan, which has never caused adverse reactions. (Allocca, 1999)

Purpose:

Migraine sufferers are prevalent in American society. (Lipton et al., 2001) Despite research efforts targeted towards treatment for their condition, many are not relieved by current pharmacologic options for acute and prophylactic treatment. (Sensenig et al., 2001) Migraine sufferers need continual research in order to reduce the impairments they experience personally as well as the economic impact on society. Studying this cohort of individuals who were committed enough to themselves and their pain to try an unexplored regimen is an important step in generating information to add to the migraine treatment database. PA's and Physicians alike will see many patients with headaches in their lifetime. Because all migraineurs respond differently to treatments, having many options is important in caring for migraine patients. Neurobiology formula 12397 could offer an additional therapeutic option to patients unable to tolerate or minimally improving with current migraine therapies.

Hypothesis:

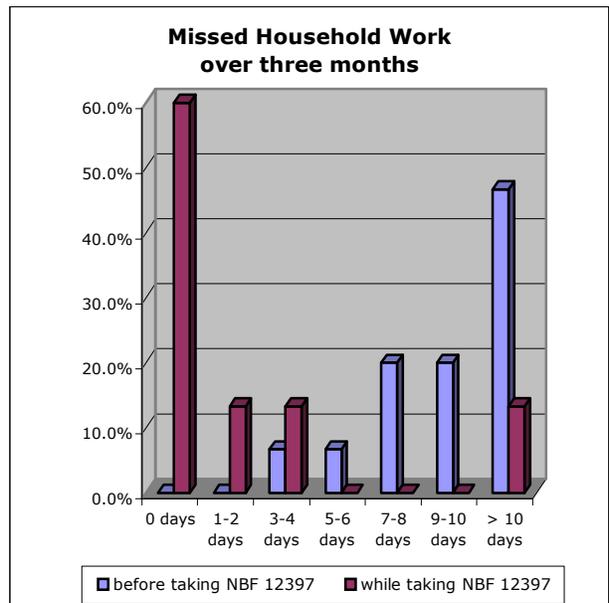
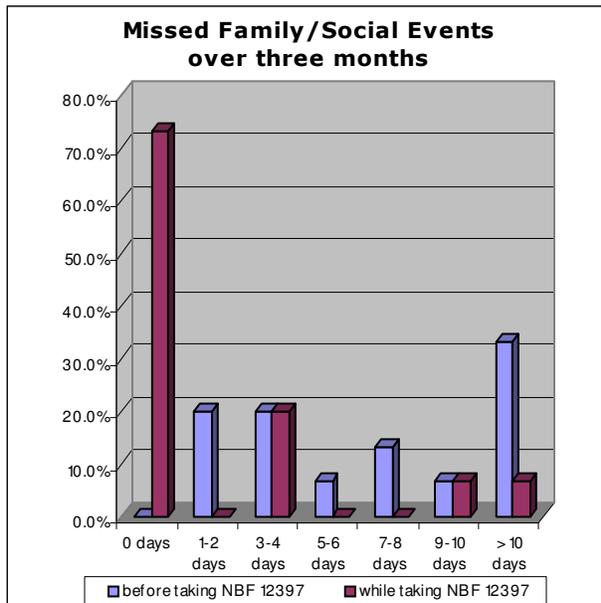
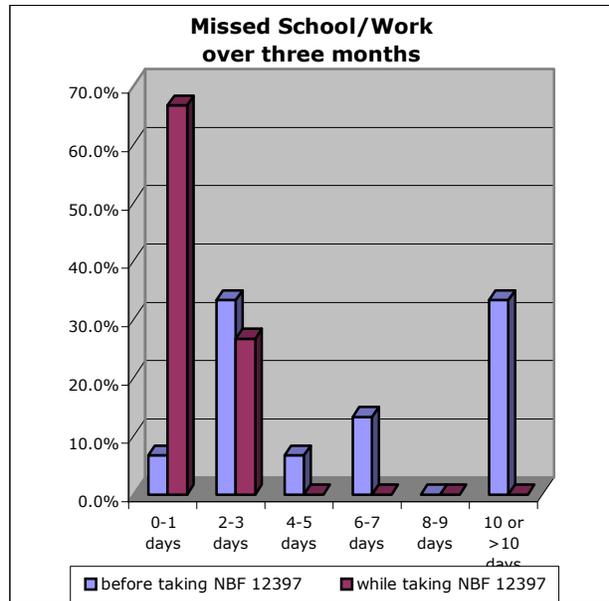
This research proposes several research questions. Does taking Neurobiology Formula lessen the number of days missed from school, work, household work and family and social activities? Does taking the formula lessen the number and severity of headaches a person experiences? Does taking the formula lessen functional impairment caused by migraine headaches? The hypotheses in question are that Neurobiology Formula 12397 has a positive effect on each of these variables.

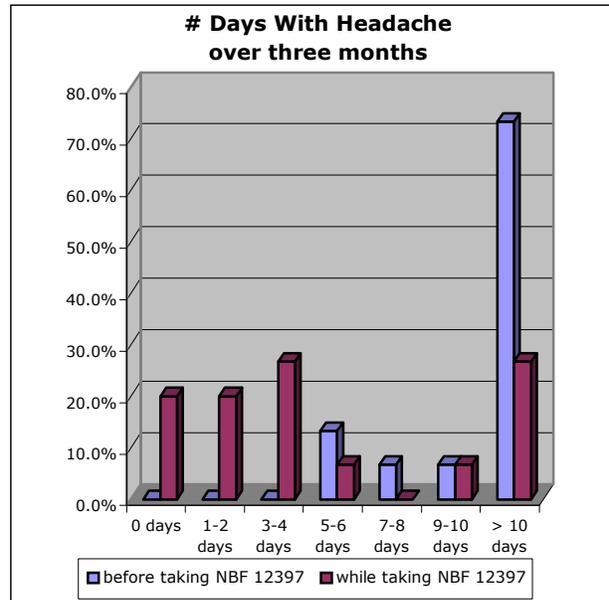
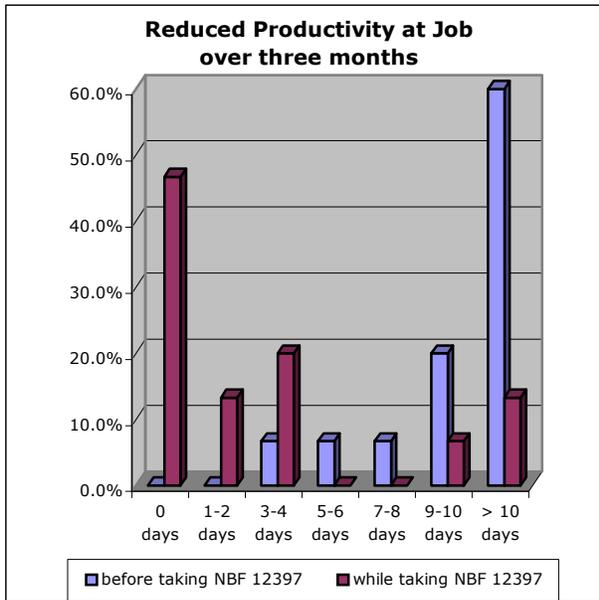
Method:

The study is a quantitative retrospective cohort study focusing on a group of individuals (n = 20) who began taking Neurobiology Formula for their own reasons, not for research purposes, and still actively take it. Because little is known about the supplement and its effects on migraine pain, few exclusionary criteria were utilized in order to maximize data gathering. Subjects 18 years or older taking the Formula and willing to participate in the study were included. Research was conducted on an individual basis using a survey (Appendix A) mailed directly to participants' homes. Because a small number of people take the Formula, a nonrandom selection process was used. John Carvalho of Dynamic Health Resources provided addresses of individuals taking the formula. Demographic questions including age, race, and gender were asked to determine how representative this population is of migraine sufferers nationally. In order to address the dependent variables, the survey included modified questions from the Migraine Disability Assessment (MIDAS) questionnaire, which is used to grade migraine sufferers according to the severity of the headache and its impact on their life. (Lipton and Stewart, 1999) It was necessary to include other questions addressing variables not covered by the MIDAS questionnaire, including compliance with the formula regimen, length of time taking the formula, and associated symptoms experienced. The survey utilized was written newly for this research and tested using a pilot study in July 2002. After pilot surveys were returned, questions were modified to make results more quantifiable. No questions were deleted or added, and the meaning of the questions remained the same. Surveys were then mailed to 20 individuals in August 2002 with self-addressed stamped envelopes. As surveys were returned throughout September and October, they were given a number and results were entered into a data spreadsheet (Appendix B). All data entry was finished in November.

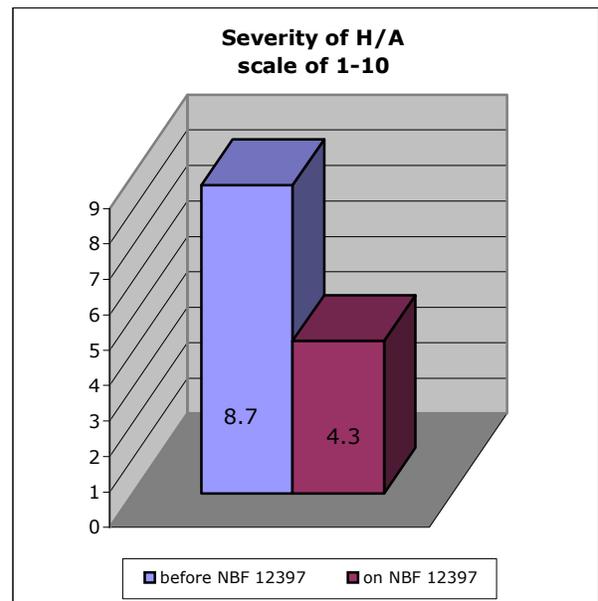
Results:

Of the 15 respondents to the survey, 93% were female, 86.7% were Caucasian, and 6.7% were Hispanic/Latino. All study participants were older than 25 with a majority (60%) older than 45 years of age. All participants were diagnosed with migraines before the age of 50, with most (60%) being diagnosed before the age of 18. All participants experienced at least one associated symptom during migraine attacks. Photophobia was reported by all participants, more than 70% of subjects reported suffering from phonophobia and nausea, and greater than 50% noted vomiting with their headaches. 53% of individuals had taken NBF less than 1 year at the time of the survey, 27% had taken it 1-2 years and 20% had taken it for 2-3 years. No participants had taken the formula > 3 years. Compliance with taking the formula was as follows: 26.7% never missed a dose, 46.7% rarely missed a dose, and 26.7% occasionally





missed a dose. All but two participants also made suggested dietary changes while taking the formula; 33.3% reported compliance always with those changes, 40% were usually compliant and 13.3% were sometimes compliant. Results addressing the research questions and hypothesis are represented in Charts 1-1 through 1-6.



Discussion:

The purpose of this research was to determine if Neurobiology Formula 12397 might have a role in the therapy of migraine headaches. The hypotheses stated that taking the Formula would have a positive impact on several dependent variables. Reviewing Charts 1-1 through 1-6 shows results that support these hypotheses. There are clear differences in response between subjects before and after Neurobiology Formula 12397 was initiated. While taking the Formula, migraineurs missed fewer days of work and school, experienced less functional impairment,

missed less household work and fewer social activities, noted a reduction in overall days with migraines, as well as a decrease in the severity of their headache pain.

Despite having only 15 subjects, the group as a whole seems similar to the migraine population. There were many more female participants than male and most of the participants are caucasian. As well, all participants reported associated symptoms with their headaches. Results show that close to 60% of survey respondents are over the age of 50 years. Additionally, 60% of individuals stated they were diagnosed with their migraines before the age of 18. These two findings are testaments to the chronicity of this condition.

There were many areas of this research open to flaws, bias and threats to validity. The limited number of study subjects confined the volume of information available for comparison. With such few results, it is difficult to say that the findings of this research are generalizable to a larger migraine population. Additional changes and revision of the survey should have occurred before the final mailing to participants. Answers to questions addressing dependent variables were written categorically instead of in open-ended format. Had answers been open-ended, results may have been more significant. Many people reported experiencing problems more than 10 days over a three-month period. Perhaps further impact could have been documented if the research were able to quantify how many more than 10 days those problems were experienced. An error while editing the survey left intervals answering one of the questions (days of work/school missed) different from other questions. This made comparing results between questions impossible, as the amounts were not equal. A majority of the questions asked participants to recollect six or more months prior to starting the Formula and the headache patterns associated with this time period. While headaches are quite disabling and memorable, recall bias is a potential problem depending on how long the subjects had taken the Formula.

This was not a controlled prospective study. Many of the subjects could have been taking OTC or prescription medications or using other natural therapies or alternative treatment strategies simultaneously. Because participants were not asked specifically if they were using any other regimens during their use of the formula, it is impossible to know how many of the effects were from the Formula alone and how many were from the Formula in addition to concurrent treatments.

As previously discussed, more than half of the subjects had only taken the Formula for less than a year at the time of the survey. Furthermore, only 27% of all individuals surveyed reported total compliance in taking the Formula daily. Further research conducted on this supplement done in a controlled environment ensuring total compliance would be of interest. In addition, it would be of significance to determine the average time of maximum response. Subjects in this study had taken the formula various lengths of time. A prospective study, utilizing subjects who have never taken the formula, would make possible comparison of subject responses over an equal amount of time.

Clearly, if we are to know more about Neurobiology Formula 12397 and its role in the therapy of migraine patients, further research is indicated. Results from this research show migraineurs taking the formula had an overall decrease in missed days from work, school and household work, fewer days experiencing impaired productivity, less missed family and social events as well as a decrease in the number and severity of headaches experienced. More research, including controlled, randomized, prospective studies with more participants would help correct for many of the biases and threats to validity encountered in this research. With limited truly effective preventive therapies available to migraine sufferers and the preliminary data reported here, it is implausible that further research would not be conducted. The results of

this research demonstrate hopeful signs that chronic migraineurs may see opportunities for relief with Neurobiology Formula in the future.

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