A Randomized Controlled Pilot Study of the Clinical Effectiveness of Enzyme Therapy on Gluten Sensitivity

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ABSTRACT

OBJECTIVES: The purpose of this pilot study was to determine if digestive enzyme supplementation reduces symptoms (that have been shown to decrease in patients who adhere to a gluten-free diet) in subjects who continue to consume gluten. The surveyed symptoms included: ataxia, learning disorders, depression, headache, diarrhea, abdominal pain, gas, joint pain, tiredness, dermatitis, bloating, nausea, poor stool consistency, constipation, and anxiety.

METHODS: A double blind, randomized placebo-controlled crossover study was undertaken. Participants were randomized into two groups. Participants food-journaled for one week to confirm that they were consuming gluten regularly and completed a symptom survey to establish baseline. Participants continued a gluten containing diet throughout the study. Each participant kept a food/supplement journal throughout the study to track that gluten was being consumed regularly with supplements. The groups received enzymes to aid in gluten digestion for two weeks and placebo for two weeks. Symptoms were evaluated using a symptom survey at the conclusion of each week.

RESULTS: Change in tiredness was the only partially statistically significant result. Tiredness was also inversely related to participant compliance.

CONCLUSIONS: This pilot study allowed the examiners to identify areas where changes would be made to a larger study to ascertain more statistically significant results.

KEY WORDS*: Gluten, Enzyme, Non-Celiac Gluten Sensitivity, Ataxia, Learning Disorders, Depression, Headache, Diarrhea, Abdominal Pain, Gas, Joint Pain, Tiredness, Dermatitis, Bloating, Nausea, Poor Stool Consistency, Constipation, Anxiety*

INTRODUCTION

In clinical practice, some patients have symptoms that respond well to a gluten-free diet, yet they have no known markers of celiac disease. The published scientific literature is largely devoid of serological evidence of "non-celiac gluten intolerance," yet this sensitivity is believed to be very common due to the wide range of symptom relief some patients experience when on a gluten elimination diet. [1,2,3,4,5,6,7] Numerous difficulties exist for the scientific community to properly study the effects of gluten: patient compliance, incidental exposure, and subjective symptomatology, among countless others.

In 2010, global sales of gluten free products were almost 2.5 billion dollars.[8] According to Packed Facts, the United States "gluten free" market is expected to reach 6.6 billion by 2017.[9] Despite the steady increase in gluten-free purchases, diets for those who do not have celiac disease to control gastrointestinal and extra-intestinal symptoms is still not appealing because it is relatively inconvenient and more expensive. [10]

Gluten is a rather large dietary protein that contains proline and glutamine in sizeable quantities. Proline and glutamine inhibit exogenous alpha amylases, endogenous alpha amylases, trypsin and chymotrypsin from completely breaking down the protein, leaving toxic oligopeptides that reduce F-actin and alter zonulin in human intestines.[11, 12] These alterations in physiology cause intestinal inflammation, creating an environment where the immune system is exposed to molecules that, under normal physiology, it would not be in contact with. Gluten contains 60 different inflammatory peptides that cause intestinal inflammation with hyper-permeability which has become known as "Leaky Gut" syndrome.[13] "Leaky Gut" exposes the immune system to intestinal contents and creates autoimmune reactions throughout the body. It is thought to be the mechanism by which gluten affects non-celiac individuals.[14]

Because a gluten-free diet is relatively inconvenient and more expensive, adding a supplement to the diet could be more appealing than totally eliminating gluten.[10] It is hypothesized that enzyme supplementation will degrade the gluten molecule in the stomach into non-inflammatory, non-immune reactive, amino acids before reaching the intestines.[15] Research on the efficacy of enzyme therapy in computer modeled human systems and specifically for gluten digestion in rats has been successful. [16,17,18] Dr. Howard Loomis, D.C. has used supplemental digestive enzymes to clinically improve functional physiology since 1985, but due to the difficulties in trials of supplementation, published human trial research is sparse.

There are a number of symptoms associated with gluten intolerance. The purpose of this pilot study was to determine whether digestive enzyme supplementation reduces

those symptoms in participants who continue to eat a diet containing gluten. The surveyed symptoms included: ataxia, learning disorders, depression, headache, diarrhea, abdominal pain, gas, joint pain, tiredness, dermatitis, bloating, nausea, poor stool consistency, constipation, and anxiety.[1,2,3,4,5,6,7] (Table 1).

Table 1. Measured outcomes.

Symptoms Measured:
Ataxia, learning disorders, depression, headache, diarrhea, abdominal pain, gas, joint pain, tiredness, dermatitis, bloating, nausea, poor stool consistency, constipation, anxiety and overall symptoms

MATERIALS and METHODS

Patients:

Patients were recruited between September 17 and October 1, 2012. Students from a small private university were recruited through class announcements, approved fliers and the university newsletter. Additionally fliers were distributed to each of the university's satellite locations. (Appendix A).

This pilot study was a simple, randomized, double-blinded, controlled crossover trail with no washout period.

This pilot study design allowed for up to 30 participants. The inclusion criteria consisted of age > 18 years, self-report of ataxia, learning disorder, depression, headache, diarrhea, abdominal pain, gas, joint pain, tiredness, dermatitis, bloating, nausea, poor stool consistency, constipation, or anxiety and regular consumption of gluten. (Appendix B). The exclusion criteria consisted of patients with celiac disease, ulcers, or history of any gastrointestinal surgery, use of any type of gastrointestinal prescription medications or any type of gastrointestinal over the counter medication who were unwilling or unable to discontinue its use for one-week prior to and during the five-week study. Pregnant volunteers were excluded from the study. (Table 2). Enzyme supplementation has previously been demonstrated to be safe; therefore participant allergy status was not considered.[19] Nineteen participants that met the inclusion criteria were accepted into the study. Participants included 7 females and 12 males. The median age was 29 years (range 21-53y). All participants signed an informed consent document. (Appendix C).

Table 2. Study entrance criteria

Inclusion	Exclusion
• Self-report of: ataxia, learning disorder, depression, headache, diarrhea, abdominal pain, gas, joint pain, tiredness, dermatitis, bloating, nausea, poor stool consistency, constipation, or anxiety • Regular consumption of gluten in diet • Age > 18 years	• Current use of gastrointestinal prescription medications or gastrointestinal OTC medication • Celiac disease, ulcers, or history of any gastrointestinal surgery • Pregnancy

Study Protocol:

Participants were randomly assigned into two initial groups: group A (n=9) and group B (n=10). Randomization was accomplished through a computer generated simple randomization on RANDOM.ORG. During week 1, all participants were instructed to record all food and alcohol intake to confirm gluten was included in their diet. (Appendix D). At the end of week 1, participants completed the symptom survey outcome measure tool to document baseline symptoms with their normal diet. (Appendix E). During weeks 2 and 3, group A received GlutenEase, an enzyme supplement, and group B received placebos. Participants were asked to return unused capsules following week 3 to ensure compliance and prevent possible mix-up of leftover capsules. During weeks 4 and 5, group A received a placebo and group B received GlutenEase. Participants continued on their regular diet throughout the study. They were asked to consume 1 capsule per meal, snack or alcoholic beverage with the first bite or drink. Each participant was initially allotted 35 capsules per week but more were available upon request. Participants kept a weekly food journal and completed a symptom survey at the conclusion of each week.

Patients unable to continue the study due to intolerable symptoms or other issues were permitted to cease the study. The Logan College of Chiropractic Institutional Review Board approved the protocol.

Outcome Measure:

The symptom survey (APPENDIX A) created by the researchers was the primary outcome measure tool of the study; it included 14 symptoms and 1 overall scale. Each of the 15 scales was measured over 70 mm with 0 being no symptoms and 70 being unbearable. Symptoms measured included abdominal pain and nausea, satisfaction with stool consistency, diarrhea, constipation, bloating, flatulence, tiredness, headaches, trouble concentrating, anxiety, depression, skin conditions (rashes,

eczema, psoriasis), muscle coordination problems/trouble with balance, joint pain, and overall symptoms. The primary outcome measure was the change in overall and individual symptoms as assessed by the symptom survey 70-point scale.

Supplement Preparation:

Approximately 2000 placebos were prepared for the experiment. Bob's Red Mill Organic White Rice Flour was used for the placebo base. Each placebo contained approximately 400mg of flour in a size 1 gelatin capsule. Enzyme capsules were also size 1. Capsules were filled by investigators using a Cap-m-quik device and were separated into groups of 35 and placed into zip-lock snack baggies.

The enzyme supplement chosen for this trial is made by Enzymedica under the trademark GlutenEase. GlutenEase contains plant-based protease DPP-IV with a marketed pH range of 2-10, in the amount of 95,000 HUT and 1000 DPPU, and gluco-amylase 15,000 DU and 15 AGU with no fillers.[20, 21] Serving size was 1 capsule. The vegetarian capsules did not have an enteric coating.[22]

Placebos and enzymes varied slightly in color, the placebo was white in color, and the enzymes were tan in color. To ensure investigator blinding, the divided placebos and enzymes were taken to a research department to be placed in opaque blue and white paper bags and stapled closed by department personnel. The department documented the true contents of the bags. Content information was held by the research department and study advisor to protect blinding. Those receiving placebos received blue paper bags, and those receiving enzymes received white paper bags.

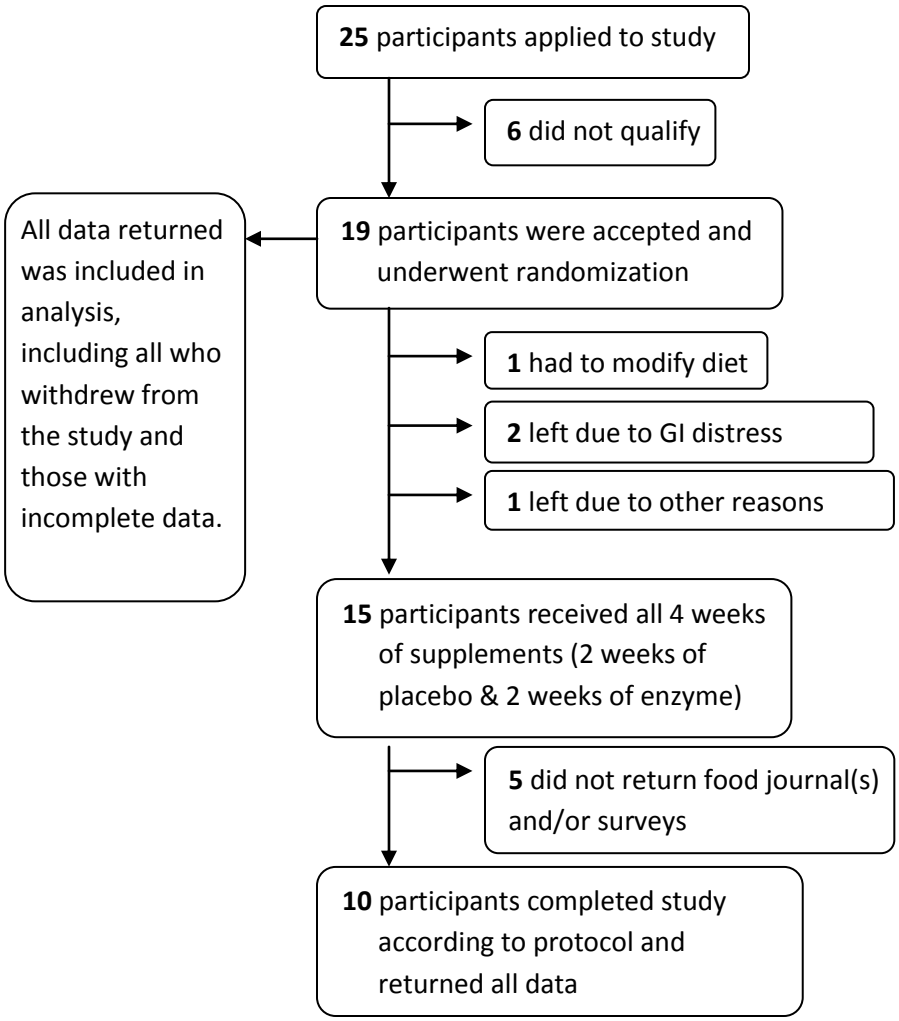
STATISTICAL METHODS

The symptom severity score across the treatment period was compared between baseline, effect of enzymes, and the effect of placebo on the fifteen measured outcomes using ANOVA, then by Tukey-Kramer post-hoc analysis. The relationship of enzyme compliance on symptom severity scores across the treatment period was analyzed using Pearson correlation coefficient to identify trends. It was assumed that placebo and baseline values would be equivalent to a zero percent compliance for enzyme ingestion. Enzyme compliance was calculated as a percentage of instances when gluten was consumed that the participant ingested the enzyme supplement. Significance was set at $p<0.05$.

All statistical analyses were conducted using InStat 3 statistical software package, made by Graph Pad.

RESULTS

Figure 1. Subject flow



More than seventy five percent of the applicants were deemed suitable for trial according to inclusion and exclusion criteria. The study occurred October 2nd through November 6th 2012. Subject flow is shown in Figure 1. Four participants withdrew themselves from the study; two were due to self-described adverse events. Five of the remaining participants did not return all food journals and/or symptom surveys. Ten completed the study and returned all data to researchers.

Of the four participants that prematurely discontinued the study, two were in the placebo arm and two were in the enzyme arm at the time of discontinuation. One participant discontinued the study after experiencing abdominal pain after ingesting 7 placebo capsules. One subject withdrew shortly after beginning the enzyme arm due to apparent gastrointestinal distress. This participant returned no further data.

All participants continued to consume a diet containing gluten during the study. An average of 15.5 meals containing gluten were consumed per week with an average of 2 non-compliance incidents per week (where gluten was consumed without GlutenEase). Participant-reported compliance of enzyme consumption with meals was calculated at 90 percent. Placebo arm participants were recorded as having 0% enzyme compliance.

The study sample size (N) had a baseline of 19 participants, 10 began in the placebo arm. All gathered participant data was included in analysis. Thirty-two weeks of placebo data and 30 weeks of enzyme data was collected.

The ANOVA and post-hoc analysis of the data yielded a statistically significant improvement ($p<0.05$) in tiredness severity between the baseline and enzyme groups. Though there was a greater improvement in tiredness severity between the enzyme and baseline groups than between the placebo and baseline group, it lacks statistical significance. There was no statistical significance between the placebo and enzyme group. (Table 3.).

Tiredness	baseline	placebo	enzyme
Mean	31.3	23.5	18.1
Standard deviation (SD)	19.100	18.400	15.600
Sample size (N)	19	32	30
Std. error of mean (SEM)	4.3818	3.2527	2.8482
Lower 95% conf. limit	22.094	16.865	12.276
Upper 95% conf. limit	40.506	30.135	23.924

Table 3. The ANOVA and post-hoc analysis of the data yielded a statistically significant improvement ($p<0.05$) in tiredness severity between the baseline and enzyme groups.

All other symptoms measured, including the overall symptom measure, were not significantly different when analyzed with ANOVA and post-hoc analysis. (Appendix F).

A Pearson correlation coefficient analysis revealed a relationship between enzyme compliance and tiredness severity scores across the treatment period ($r=-0.682$). All other symptoms measured, including the overall symptom measure, did not show any significant relationships when analyzed by the Pearson correlation coefficient. (Figure 2).

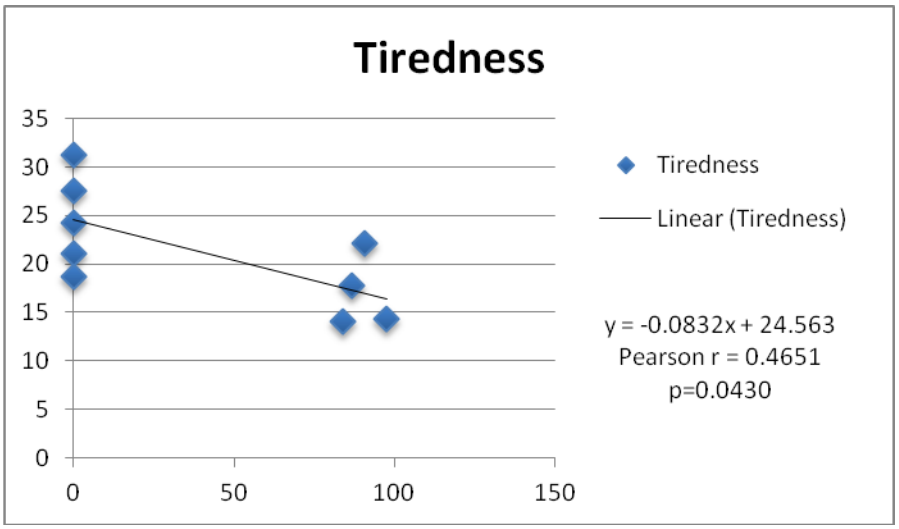


Figure 2: Pearson correlation coefficient analysis revealed a relationship between enzyme compliance and tiredness severity scores across the treatment period (r=-0.682).

DISCUSSION

The effect gluten has on the human body is becoming more specifically understood and documented in scientific literature. A pharmaceutical company is currently testing a drug to combat gluten's negative effect on intestinal permeability.[23] The side effects and potential interactions with other pharmaceuticals may not be fully understood before it is given to patients. Gluten sensitive patients would benefit from a less risky option to control their issues associated with gluten consumption. This double blind, randomized placebo-controlled trial supports the need for more research on digestive enzyme efficacy for gluten sensitivities as a safe, potential preventive measure.

The findings of significant improvement in tiredness severity between the baseline and enzyme groups and the correlation between enzyme compliance and tiredness severity over a two week period is promising for enzyme efficacy research. The estimated participant number needed for tiredness to be accurately measured within a 95% confidence level between enzyme and placebo groups would be 124 participants when following this study's protocol. The estimation is according to RSS with an alpha of 95% and a beta of 50%.[24] Future researchers may also investigate utilizing common standardized outcome measurement tools such as a true visual analogue scale or IBS SSS symptom survey. Standardized outcome measurement tools may support more powerful studies with fewer participants.

Although there are numerous hypotheses to explain the mechanisms by which the trend of reduction in tiredness when taking enzymes can be attributed, the investigators believe that there are two primary probable explanations. A reduction in the number of

intact gluten proteins reaching the intestines leads to less inflammation and less immune activation allowing the body to utilize energy for more conscious tasks and creating the perception of an increased energy level in the participant. Another possible explanation for this enzyme effect is simply the creation of more bioavailable amino acids from the participants' general protein intake. Participants may have had difficulty digesting all proteins optimally and once digestive enzymes were introduced into their diet, more nutrients were made bioavailable for ATP production. More human trials and serum/biopsy testing options are needed in this area.

The recruitment phase of the study had certain limitations. Recruitment occurred over a two-week period. A longer recruitment period would have been optimal in this small university setting. A future study that only includes participants who have had previous gastrointestinal surgery or are on gastrointestinal medications may provide additional valuable insight on the effectiveness of enzyme therapy. The extensive food journaling requirement was also a great limitation to public interest in participation.

No known previous studies have been conducted to determine the length of treatment required to accurately measure symptom reduction from digestive enzyme therapy. Therefore, this pilot study length was selected to accommodate both budget and time constraints.

The food-journaling requirement seemed to be a stressor to all participants. People do not food-journal on a regular basis and therefore find it very tedious to do so. Participant behavior regarding food journals lead the investigators to believe a large percentage of the completed journals contained incorrect documentation that probably lead to misleading data.

The study could have been lengthened to include a washout period between supplements to increase reliability; however, taking this particular participant pool into consideration, the benefit of a washout period was thought to be more burdensome than beneficial. A future study that did not require food journaling may allow for a longer run-time. As an alternative to the food-journaling requirement, a future study could educate participants on gluten containing foods.

When surveying the participants' food journals, investigators noticed comments on changes in bowl movement frequency and reflux, which could be other symptoms to evaluate in a future study. Multiple participants also verbally commented to investigators that the act of keeping a food journal and being more aware of their symptoms further confirmed their previous suspicion of gluten intolerance. The blinding technique of this trial was not measured. A future study should figure the K score to document the agreement between actual treatment and participant guessing.

When compared with another double blind study on gluten sensitivities, these results were not surprising. The trial on gluten sensitivity in Gastroenterology in 2011 also had a relatively small number of participants whose diet/compliance could not be fully controlled.[5] The inherent limitations of this research make a large sample size imperative. It is difficult to ascertain a true measurement of effect when independent variables are not fully controlled.

The study sample size had a baseline of 19 participants. All data returned was included in statistical analysis, including all who withdrew from the study and those with incomplete data. A future study should analyze only those participant's data that complete the entire study protocol to yield more accurate results.

There were many design flaws affecting the outcome of this pilot study. Lack of a washout period and more than one symptom being assessed were serious errors that a future study should not follow. A relatively short run-time, a non-proven symptom assessment tool, and a participant population where true compliance was questionable at best, all increased the chances of unreliable data. With more participants, a longer run-time, a washout period, use of the visual analog scale or other standard outcome assessment tool measuring only one symptom, and with a true compliance score of 90%, a study of this type would better document the use of digestive enzymes for gluten sensitivities.

Clinical implications of the study of gluten's affect on the human system are overwhelming. The implications go far beyond just gastrointestinal upset and the aforementioned symptoms. Monkeys have a reduced cancer risk when eating a diet without gluten.[25] Some children on the autistic spectrum improve when gluten is removed from their diet.[26] While not all people suffering from symptoms will improve on a gluten free diet, the possibility of dramatic remission in a wide range of disorders makes gluten digestion an important consideration for new treatment protocols by healthcare professionals.

CONCLUSION

This pilot study was not registered as a randomized controlled trial. A future study should be registered for the possibility of publication. The goal of this study was to conduct a double-blinded randomized controlled trial that would measure the effect of digestive enzymes on those with symptoms often related to gluten sensitivities. Results indicated that the use of digestive enzymes warrants further evaluation.

Full details of the trial protocol can be found in the supplementary appendices. All materials can be found in the Logan College of Chiropractic research department.

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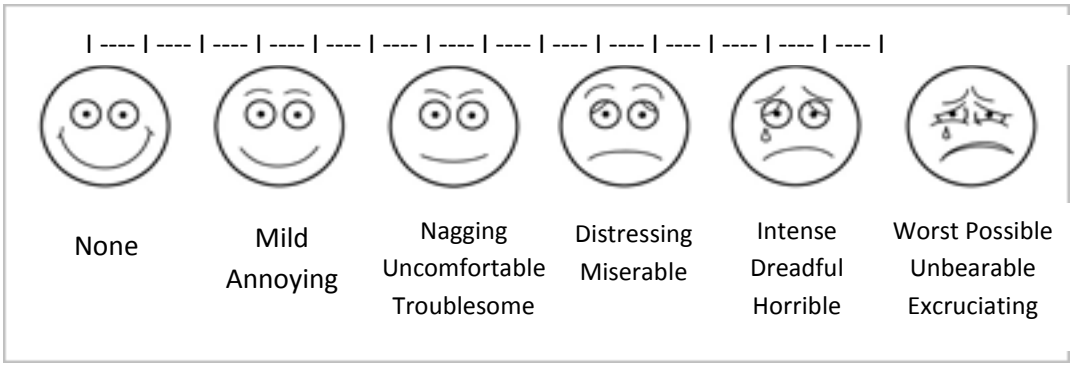
Appendix A

WEEK _____ Date_____ Student/Patient ID _____



During the past week I have had:

Abdominal Pain and/or Nausea

NO PROBLEMS I----I----I----I----I----I----I----I----I----I----I----I----I----I----I----I UNBEARABLE

Satisfaction with stool consistency

NO PROBLEMS I----I----I----I----I----I----I----I----I----I----I----I----I----I----I----I UNBEARABLE

Diarrhea

NO PROBLEMS I----I----I----I----I----I----I----I----I----I----I----I----I----I----I----I UNBEARABLE

Constipation

NO PROBLEMS I----I----I----I----I----I----I----I----I----I----I----I----I----I----I----I UNBEARABLE

Bloating

NO PROBLEMS I----I----I----I----I----I----I----I----I----I----I----I----I----I----I----I UNBEARABLE

Flatulence

NO PROBLEMS I----I----I----I----I----I----I----I----I----I----I----I----I----I----I----I UNBEARABLE

Tiredness

NO PROBLEMS I----I----I----I----I----I----I----I----I----I----I----I----I----I----I----I UNBEARABLE

Headaches

NO PROBLEMS I----I----I----I----I----I----I----I----I----I----I----I----I----I----I----I UNBEARABLE

Trouble Concentrating

NO PROBLEMS I----I----I----I----I----I----I----I----I----I----I----I----I----I----I----I UNBEARABLE

Anxiety

NO PROBLEMS I----I----I----I----I----I----I----I----I----I----I----I----I----I----I----I UNBEARABLE

Depression

NO PROBLEMS I----I----I----I----I----I----I----I----I----I----I----I----I----I----I----I UNBEARABLE

Skin Conditions (Rashes, Eczema, Psoriasis)

NO PROBLEMS I----I----I----I----I----I----I----I----I----I----I----I----I----I----I----I UNBEARABLE

Muscle Coordination Problems (ie:trouble with balance)

NO PROBLEMS I----I----I----I----I----I----I----I----I----I----I----I----I----I----I----I UNBEARABLE

Joint Pain

NO PROBLEMS I----I----I----I----I----I----I----I----I----I----I----I----I----I----I----I UNBEARABLE

Overall Symptoms

NO PROBLEMS I----I----I----I----I----I----I----I----I----I----I----I----I----I----I----I UNBEARABLE

DON'T FORGET TO LEAVE YOUR FOOD JOURNAL AND PICK UP YOUR SUPPLEMENTS!
PLEASE WRITE ANY EXTRA COMMENTS ON THE BOTTOM OF THIS SHEET.