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DOUBLE-BLIND, RANDOMIZED PLACEBO-CONTROLLED CLINICAL TRIAL OF BENFOTIAMINE FOR SEVERE ALCOHOL DEPENDENCE

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Abstract

Background—Alcohol dependence is associated with severe nutritional and vitamin deficiency. Vitamin B1 (thiamine) deficiency erodes neurological pathways that may influence the ability to drink in moderation. The present study examines tolerability of supplementation using the high-potency thiamine analogue, benfotiamine (BF), and BF's effects on alcohol consumption in severely affected, self-identified, alcohol dependent subjects.

Methods—A randomized, double-blind, placebo-controlled trial was conducted on 120 non-treatment seeking, actively drinking, alcohol dependent men and women volunteers (mean age=47 years) from the Kansas City area who met DSM-IV-TR criteria current alcohol dependence. Subjects were randomized to receive 600 mg benfotiamine or placebo (PL) once daily by mouth for 24 weeks with 6 follow-up assessments scheduled at 4 week intervals. Side effects and daily alcohol consumption were recorded.

Results—Seventy (58%) subjects completed 24 weeks of study (N=21 women; N=49 men) with overall completion rates of 55% (N=33) for PL and 63% (N=37) for BF groups. No significant adverse events were noted and alcohol consumption decreased significantly for both treatment groups. Alcohol consumption decreased from baseline levels for 9 of 10 BF treated women after 1 month of treatment compared with 2 of 11 on PL. Reductions in total alcohol consumption over 6 months were significantly greater for BF treated women (BF: N=10, −611±380 Std Dev; PL: N=11, −159±562 Std Dev, p-value=0.02).

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Contributors

Ann Manzardo was the primary study investigator responsible for the oversight of all aspects of study design, implementation, data analysis and interpretation and is primarily responsible for composing the manuscript.
Jianghua He conducted the majority of statistical analyses and contributed significantly to drafting the manuscript
Albert Poje participated in subject recruitment and data collection and contributed to the interpretation of study findings.
Elizabeth Penick contributed to the development of the study protocol and the interpretation of study findings.
Merlin Butler contributed to the interpretation of study findings and the preparation of the manuscript.
Jan Campbell contributed to the study design and provided medical oversight during data collection. She also contributed to the interpretation of study findings.

Conflict of Interest

No conflict declared

Conclusions—BF supplementation of actively drinking alcohol dependent men and women was well-tolerated and may discourage alcohol consumption among women. The results do support expanded studies of BF treatment in alcoholism.

Keywords

Alcoholism; Thiamine; Benfotiamine; Female alcohol consumption

1. INTRODUCTION

Chronic alcoholic drinking is commonly associated with serious nutritional and vitamin deficiency (Green, 1983; Hoyumpa, 1980; Laureno, 2012; Lieber, 2003; Thomson, 2000; Thomson et al., 2012; World et al., 1985). The poor dietary habits of individuals suffering from severe alcoholism are often compounded by the direct effects of alcohol which actively interfere with the absorption and use of dietary nutrients (Green, 1983; Hoyumpa, 1980; Lieber, 2003; Said, 2006; Subramanya et al., 2011; Thomson, 2000; Thomson et al., 2012; World et al., 1985). Deficiency of B vitamins is especially problematic in the context of alcoholism due to their physical properties including high water (rather than fat) solubility which limits cellular storage within the body (Hoyumpa, 1980; Said, 2006; Subramanya et al., 2011). In addition, several B vitamins have key roles in carbohydrate metabolism and are preferentially depleted by high rates of alcohol metabolism (Singleton and Martin, 2001; Martin et al., 2003). Severe thiamine (vitamin B1) deficiency is rare but can be associated with a serious illness (beriberi) and neurological problems which can lead to significant disability and death. Neurological syndromes in alcoholics are typically manifested as a progressive loss of central and peripheral white matter believed to result mainly from alcoholism-related thiamine deficiency (He et al., 2007; Laureno, 2012; Mellion et al., 2011).

1.1 Prevalence of Thiamine Deficiency in Alcoholism

Nationalized fortification efforts to alleviate nutritional deficiency have reduced the occurrence of acute thiamine deficiency in most western countries even in the context of alcoholism (Backstrand, 2002); but yet, deficits in circulating thiamine has been reported in 30–80% of alcoholic inpatients (Brust, 2010; Mancinelli et al., 2003; Thomson et al., 1987). Functional deficits in the activation of thiamine dependent enzymes have been reported in 35% of alcoholics (Butterworth et al., 1993; Herve et al., 1995; Thomson et al., 1987; 2012), and neuropathological brain lesions characteristic of thiamine deficiency have been reported in 12.5% of autopsied brain samples from alcoholics (Harper, 2006; Harper et al., 2003). Further, inherited differences in thiamine binding and utilization have been associated with an increased vulnerability toward thiamine deficiency in certain individuals which may be exacerbated by alcoholism (Blass and Gibson, 1977; 1979; Martin et al., 1993; Mukherjee et al., 1987).

Standard inpatient care for alcoholism typically incorporates nutritional support in the form of high-dose vitamin intravenous therapy which appears effective in alleviating acute symptoms of thiamine deficiency (Markowitz et al., 2000; Thomson et al., 2012). However, the duration of these interventions, typically 2 to 3 days, may be inadequate to restore functional activity of chronically down-regulated thiamine-dependent enzymes in the brain and other tissues (Thomson et al., 2012). In addition, the efficacy of subsequent follow-up care which currently relies upon traditional, water-soluble, oral thiamine supplements is limited by alcoholism-related impairments in thiamine absorption and activation (Baker and Frank, 1976; Thomson et al., 2012). In light of these factors, a need exists for an effective adjuvant therapy capable of producing a sustained elevation of blood thiamine in outpatient settings, particularly in the presence of continued alcohol abuse by the patient.

1.2 Alternative Thiamine Analogues

Benfotiamine (BF) is a synthetic thiamine analogue in a class of natural products referred to as allithiamines (Anonymous, 2006). Allithiamines are lipid-soluble molecules that are produced by plants from the *Allium* genus, in the garlic family (Lonsdale, 2004). These compounds are widely recognized for their ability to dramatically increase the bioavailability of thiamine pyrophosphate (TPP), in the blood, cerebrospinal fluid and urine (Fujiwara, 1976; Loew, 1996). First discovered in Japan in the 1950's, BF was patented for use in the United States in 1962 but was never marketed. The supplement has been widely used in Japan and Europe for decades where it is well-tolerated with no reports of serious adverse events (Anonymous, 2006). BF was licensed for use in Germany for the treatment of sciatica nerve pain in 1993. As a synthetic compound, rather than an extract, BF supplements can be purchased in a pure form.

BF is a lipid-soluble provitamin and rapidly converted to thiamine pyrophosphate (TPP) in the body (Bitsch et al., 1991). Studies of BF pharmacodynamics have confirmed its ability to elevate TPP bioavailability and to dramatically increase the activity of thiamine-dependent enzymes in alcoholics with thiamine deficiency (Bitsch et al., 1991; Greb and Bitsch, 1998; Loew, 1996; Schreeb, 1997). BF supplementation has been reported to increase erythrocyte transketolase enzyme activity by 3 to 4 fold compared to maximal increases of 25% reported for traditional, water-soluble, supplements of thiamine hydrochloride (Baker and Frank, 1976; Greb and Bitsch, 1998). Clinical trials with BF supplementation in Europe have identified significant improvements in the symptoms of alcoholic and diabetic neuropathy with little to no adverse effects (Anonymous, 2006; Ayazpoor, 2001; Babaei-Jadidi et al., 2003; Haupt et al., 2005; Simeonov et al., 1997; Stracke et al., 1996; 2001; Woelk et al., 1998).

1.3 Thiamine Deficiency and Alcohol Consumption

Research in animal models have suggested that deficiency of certain B vitamins, particularly thiamine deficiency, in acute alcoholism may contribute directly to pathological drinking (Brady and Westerfeld, 1947; Eriksson et al., 1980; Impeduglia et al., 1987; Mardones, 1951; 1954; 1960; Mardones et al., 1953; Pekkanen, 1979; 1980; Pekkanen et al., 1978; Pekkanen and Rusi, 1979; Zimatkin and Zimatkina, 1996; Zimatkina et al., 2000). Rats exposed to dietary thiamine depletion or treatment with thiamine antagonists show increased total alcohol consumption that was readily reversed after thiamine rescue (Brady and Westerfeld, 1947; Eriksson et al., 1980; Impeduglia et al., 1987; Pekkanen, 1979; 1980; Pekkanen et al., 1978; Zimatkin and Zimatkina, 1996). The findings of these early studies with rats suggest subclinical levels of thiamine deficiency moderate alcohol consumption and that restoration of thiamine blood levels could help to normalize drinking behaviors.

We hypothesize that improvements in central neurological functioning in response to BF treatment will correlate with improved cognitive functioning and enhanced behavioral control which may reduce alcohol consumption- similar to effects observed in animal models and enhance recovery from alcoholism. Here, we examined the dose tolerability and effect of thiamine replacement with the high potency thiamine analogue, BF, on alcohol consumption in a group of severely alcohol dependent subjects in a double-blind randomized placebo-controlled clinical trial.

2. METHODS

2.1 Participants

Study participants included 120 adult men and women with a mean age of 47.5 ± 7.9 years (range: 21 to 59 years) who met DSM-IV-TR (American Psychiatric Association, 2000)

criteria for a current Alcohol Use Disorder according to a structured interview administered by an experienced trained psychiatric nurse. Eligible subjects defined alcohol as their primary substance of abuse that was active within the previous 30 days. Intellectually impaired and seriously medically ill subjects were excluded but other comorbid psychiatric and medical illnesses were permitted. Formal inclusion and exclusion criteria were as follows.

Inclusion criteria was: DSM –IV-TR criteria for an Alcohol Use Disorder; active alcohol use or < 30 days of abstinence from alcohol; age 18 to 60 years with a local address; ability to read and understand English. Exlusion criteria was: individuals failing to meet DSM-IV-TR diagnostic criteria for an Alcohol Use Disorder; abstinence for >30 days; age <18 or > 60 years; intellectual disability or serious physical illness.

2.2 Recruitment and Screening

This study was conducted under the authority of the University of Kansas Medical Center Office of Research Compliance who reviewed the study protocol and monitored study activities to ensure that appropriate steps were taken to protect the rights and welfare of humans participating as research subjects. Participants were recruited by advertisement in a local newspaper and word of mouth from the Greater Kansas City Metropolitan area between August 2008 and August 2011. Subjects were remunerated for study participation earning up to $245 for compliance with all elements of the study. Subjects were referred to an outpatient clinic and a 12-step program but no formal alcoholism treatment was offered. Subjects were not recruited from treatment programs, required to seek treatment or make a special effort to abstain from alcohol in order to participate. An initial phone screening interview of potential subjects was conducted to assess eligibility prior to enrollment.

2.3 Study Design

The study was a randomized, double-blind, placebo-controlled clinical pilot. Eligible and consenting subjects were randomized to one of two study arms: placebo (PL) or 600 mg BF once daily by mouth. PL was prepared by Great Plains Compounding Center (Lenexa, KS) and identically matched to BF capsules purchased from Nutraceutics Rx (Denver, CO). In order to control for variations in severity of illness attributable to familial characteristics, the study randomization was stratified by family history of alcoholism. Family history positive (FH+) for alcoholism status was defined as the presence of one or more first degree relative (parents, siblings or children) with alcoholism or a grandparent based upon subject report. Treatments were administered as 4 capsules (150mg BF or PL) taken orally once daily for a period of 24 weeks, and study subjects were instructed to return the unused bottle of capsules to assess and maintain subject compliance. Study progress was assessed every 4 weeks using brief clinical ratings of behavior, mood and physical status and monthly follow back drinking calendars. Subjects were also administered a series of psychometric tests, structured interviews and a 6 month follow back drinking calendar at intake and 6 month follow-up interviews. After each study visit, subjects were provided sufficient study supplements and scheduled to visit a study investigator in 4 weeks. Subjects were asked to return to the University of Kansas Medical Center for follow-up every 4 weeks for the remainder of the 6 month study.

2.4 Study Instruments

Following the initial screening procedure at baseline, a comprehensive interview was performed to 1) determine final study eligibility based upon DSM-IV-TR diagnostic criteria for Alcohol Dependence and 2) to establish the family history status of each eligible subject. The psychosocial interview is a pre-coded, structured interview, with high test-retest reliability that was administered by a trained research nurse. This interview included the

Alcohol Severity Scale, the Sobel Drinking Calendar, and the interviewer's rating of the Global Assessment of Functioning (GAF) scale (American Psychiatric Association, 2000; Knop et al., 2009; Sobell et al., 1996; Sobell and Sobell, 2000).

The Alcohol Severity Scale (ASS) is a 33-item scale based upon the alcoholism module of a structured, multidimensional criterion-referenced psychiatric diagnostic interview designed to assess the lifetime prevalence of 18 syndromes, including alcohol abuse and dependence (Knop et al., 2009; Othmer et al., 1989, 2000). The ASS reviews all of the major clinical characteristics and sequelae of alcohol abuse and dependence with good reliability and validity (Knop et al., 2009). Each item of the scale represents a symptom of alcoholism and higher totals indicate increased overall severity. Items were keyed to represent both the lifetime of the individual as well as the previous six months.

The Timeline Followback method employed by Sobel (Sobell et al., 1996; Sobell and Sobell, 2000) is a validated and widely used assessment tool for measuring alcohol consumption (Sobell et al., 1996; Sobell and Sobell, 2000; Pedersen and LaBrie, 2006). The interview was designed to obtain information about sociodemographic characteristics, lifetime and current drinking activities, family history of alcoholism and ratings of psychological functioning. Many of the items were keyed to reflect the six months prior to entering the study. A modified version of the Psychosocial Interview was completed at the end of the study at 6 months.

The Symptom Checklist 90-R (SCL-90-R) which assesses psychiatric symptomology in the past week was administered at baseline and 6 months (Derogatis and Savitz, 2000). A short psychosocial interview was also conducted at each followup visit to measure drinking patterns and drinking sequellae since the previous study visit.

Although there have been no previous reports of adverse events associated with the use of BF, even at very high doses, a brief survey of potential side effects was conducted at each of the monthly assessments. This survey included a standard list of 15 adverse events including gastrointestinal problems, headache, fatigue, restlessness, hives and other reactions. The occurrences of adverse events were carefully monitored and recorded at each visit throughout the course of the study.

2.5 Concomitant Medications and Supplements

No restrictions were placed on the use of additional supportive medications, but information about concomitant medications and supplements were collected throughout the course of the study. Participants were not precluded from taking multivitamin supplements even if supplements contained thiamine hydrochloride.

2.6 Randomization

Consenting subjects who completed the screening process and baseline assessment were stratified into family history positive (FH+) and family history negative (FH−) groups before they were randomized to the active drug and PL groups by the University of Kansas Medical Center's research pharmacist using a random number generator. No other participant characteristics were taken into consideration in the randomization. All study personnel and participants were blinded to treatment group assignments throughout the course of the study.

3. DATA ANALYSIS

Data analysis focused on changes in outcome variables during seven months (every 4 weeks is considered one month), including one baseline month and 6 months of intervention. Alcoholism treatment protocols typically measure progress as a function of the duration of

abstinence from alcohol consumption (e.g., number of days abstinent; time to relapse) among participants recruited from treatment settings in a fully detoxified, abstinent state. However, abstinence measures may not accurately reflect progress for the present study population of non-treatment seeking, active drinkers. Therefore, we chose to examine the effects of BF treatment on the related measure of alcohol consumption recorded as standard drinks (SD) according to the U.S. definition of 0.6 fluid ounces (18ml) or 14 grams of pure alcohol. Daily consumption information was summarized into monthly data. For example, the mean daily alcohol consumption of each month was calculated as the total SD of alcohol consumed within the 4-week period divided by the total number of days in the month with alcohol consumption information. Any month with less than 14 days of drinking information was considered a missing month with one exception. One subject had 8 days of drinking information for the baseline month but the mean daily consumption was still calculated as the subject would be completely excluded from the analysis without the baseline measure.

Summary statistics were used to describe subjects at baseline. For the primary analyses, Wilcoxon rank sum test was used to compare the pre-post change in mean daily alcohol consumption based on completers who had both baseline and month 6 data. As this is a pilot study, several additional exploratory analyses were conducted to identify potential effects of BF. First, the (expected-observed) total 6-month alcohol consumption for completed subjects was compared between groups using the Wilcoxon rank sum test.

Expected total consumption assuming the baseline mean daily alcohol consumption is sustained for 6 months:

$$C_e = X_0 * 28\,(days/month) * 6\,(months)$$

X_0 = Mean daily alcohol consumption for the baseline month

Observed total consumption extrapolated from the daily consumption for each month:

$$C_0 = \sum_{t=1}^{6} X_t * 28\,(days/month)$$

X_t = Mean daily alcohol consumption of month in treatment, t = 1, 2, …, 6.

Estimated reduction in total alcohol consumption in 6 months: $C_0 - C_e$.

This approach is more powerful for detecting differences in consumption in the presence of interacting alcohol use trajectories (e.g., if alcohol consumption in both groups decreases to similar levels by the end of the study, but one group starts decreasing earlier than the other). Second, a mixed model was used to model the trajectory of mean daily alcohol consumption by comparing monthly mean alcohol consumption from baseline to month 6 for all participants. This approach is more powerful in detecting differences in trends in alcohol consumption for the two groups as monthly repeated measures were included for analysis. This intent-to-treat approach accommodates subjects with missing monthly information and may provide more reliable results than the previous approaches based upon study completers only. Men and women were analyzed separately to test gender differences in response to BF. SAS 9.2 (SAS Institute Inc. Cary, North Carolina, USA) was used for analysis of the demographic data and STATA 11 MP (StataCorp, College Station, Texas, USA) for analysis of changes from baseline to month 6.

4. RESULTS

4.1 Baseline Subject Characteristics

The study sample baseline demographic characteristics are presented in Table 1. The sample was predominantly male (71%) and African-American (72%) and the majority (85%) reported a family history of alcoholism among first degree relatives and/or grandparents; only 15% of the subjects (including just 1 female subject) were negative for a family history of alcoholism. Subjects reported drinking alcohol abusively for a mean duration of 33 ± 8.8 years. Of the 120 randomized subjects, 70 subjects completed the entire 6 month study. The remaining 50 subjects decided to drop, were dropped for non-compliance or were lost to follow-up prior to study completion. Randomization and stratification of study subjects resulted in appropriately balanced treatment groups across age, race, gender and alcoholism severity (Table 1).

4.2 Completion Rates and Blinding

Seventy (58%) of the 120 enrolled subjects completed the entire 24 week study which is within the expected range of retention (30 to 60%) for similar studies examining pharmacotherapy in alcohol dependent populations (Correa Filho et al., 2012; Oncken et al., 2001; Prisciandaro et al., 2011); 37 (53%) of the 70 completers were randomized to the BF arm and 33 (47%) were randomized to the PL arm (Table 2). The completion rate was 55% for the PL group and 63% for the BF group and these rates were not significantly different. Among the completers, there were 21 women and 49 men. In order to examine for a subjective bias toward treatment, study completers were asked to predict their treatment assignment at the final 6 month assessment. Sixty-five percent (N=45) of study completers believed that they had been assigned to the BF rather than the PL arm of the study. However, the perceived treatment assignment was not related to the actual treatment assignment (Wald χ^2=0.01, df=1, p=0.91; Table 2); thus, confirming the success of the blinding procedure.

4.3 Side Effects and Tolerability

BF was generally well-tolerated with no reports of serious adverse events during the course of the study, and no reports of differences in side effects that might have biased or otherwise compromised subjective responses to the study supplement. There were no significant differences in the frequency of any specific side effect associated with treatment, race or gender. The average number of reported side effects (out of 15 measured) decreased significantly from a mean (Std Dev) of [7.0 (2.9)] at study initiation to [5.3 (3.1)] at 6 months (t=4.8; p<0.001) with no difference observed between treatment groups (t=0.06; p=0.9).

4.4 Pre-post examination of mean daily consumption for study completers

The primary outcome of this study was the change in the mean daily alcohol consumption recorded in standard drinks of alcohol per day (SD/day) from baseline to month 6 and total consumption for the BF vs PL treatment groups. For the 70 completers, the average daily alcohol consumption decreased from approximately 6.1 ± 4.3 SD/day to 2.8 ± 3.4 SD/day with both arms combined. Examination of the changes from baseline to month 6 found no significant difference between BF and PL groups using the Wilcoxon rank sum test (BF: N=37, −3.4 ± 3.6 SD/day; PL: N=33, −3.0 ± 4.6 SD/day, p-value=0.33). When men and women were analyzed separately using the same test, no difference was found for men (BF: N=27, −3.2 ± 3.8 SD/day; PL: N=22, −3.5 ± 4.6 SD/day, p-value=1.0) or for women (BF: N=10, −4.0 ± 3.0 SD/day; PL: N=11, −2.0 ± 4.8 SD/day; p-value=0.11).

A plot of trajectories of mean daily alcohol consumption from baseline to month 6 (Figure 1) suggests that women may respond to BF differently from men. The mean daily alcohol consumption among females randomized to BF decreased by 45% within 1 month of treatment initiation and 60% over the first 3 months of study participation. Women randomized to PL initially increased by 20% after 1 month and decreased by 13% over the first 3 months (Figure 1). For men, no obvious difference was observed between the two treatment groups. From previous analysis of pre-post changes, we can see that the pre-post change in alcohol consumption among BF treated women was 2 SD/day more (−4 vs. −2) than that of PL treated women. A post-hoc power analysis assuming an effect size the same as that observed for women completers in this study shows that 106 subjects will provide 80% power of detecting a difference using one-sided Wilcoxon rank sum at 0.05 level (G-power 3.1).

4.5 Mean daily consumption over 6 months for female completers

Figure 2 shows the trajectories of the mean daily consumptions of all female completers. The consumption time course for all individuals was centered at the baseline value to better capture the changes from baseline (all lines start from 0). Mean daily consumption decreased from baseline levels in the first month after treatment for 9 of the 10 women in the BF group while only 2 of the 11 in the PL group showed a decrease. Consumption also remained low in the later study period for most subjects in the BF group, only one subject showed an increase in daily consumption at month 6 compared to baseline. The consumption trajectories of subjects in the PL group showed no consistency: some subjects had continuing decreases through the study period yet others had increased consumptions. This difference in trend between two groups may not be detectable by comparing pre-post changes (section 4.4) as the pre-post changes are not very different between groups.

4.6 Observed vs expected total alcohol consumption among all female subjects

In order to take into consideration differences in the trends of alcohol consumption over time, total alcohol consumption during the study was compared between groups (Figure 2). If alcohol consumption decreased to the same level in both study groups but at an earlier time point for one, total consumption would differ even if the pre-post change was the same. This type of difference may also be clinically meaningful. Figure 3 shows box plots and distribution of the (observed- expected) total alcohol consumption for females in the two study groups. Examination of the (observed- expected) total alcohol consumption using Wilcoxon's rank sum test showed a significant difference (BF: N=10, mean= −611+380 Std Dev; PL: N=11, mean= −159+562 Std Dev, p-value=0.02). With an earlier decrease in alcohol consumption, women taking BF could consume less alcohol in total. No significant differences were found for men.

4.7 Longitudinal analysis of mean daily consumption including all participants

Since alcohol consumption may not drop in a linear fashion, we used a mixed model to capture the time trend of mean daily alcohol consumption considering the possibility of both linear and quadratic trends. The different trends of the two groups were tested using the interactions of treatment group and time. When all 120 enrolled participants were included, the interaction of treatment and the quadratic trend did borderline significance with p-value = 0.07; the interaction was significant in the model for women only (p-value = 0.03) and not significant for men (p-value=0.30). This result is consistent with the observed reduction in total alcohol consumption over 6 months

5. DISCUSSION

The results of the present pilot study provide evidence that high dose thiamine supplementation using the highly efficacious thiamine analogue, BF, is well-tolerated in actively drinking alcohol dependent subjects and may provide a useful adjuvant therapy to treat thiamine deficiency in alcoholism. No significant differences in the frequency of side effects were noted between BF and PL groups after 6 months of treatment. Alcohol consumption decreased among all participants and a preliminary examination of gender differences in the trajectory of alcohol use suggests that BF treatment may selectively reduce alcohol consumption in women and possibly facilitate recovery efforts. Mean pre-post change in alcohol consumption in BF treated women was 2 SD/day more (−4 vs. −2) than that of PL treated women. Although 2 SD/day difference is not statistically significant in this small pilot study, it is clinically meaningful and worthy of further exploration with a larger confirmatory study.

5.1 BF Treatment of Thiamine Deficiency

High-dose thiamine supplementation with BF has been shown to restore thiamine levels in alcohol dependent subjects and to slow/reverse the degenerative effects of peripheral alcoholic neuropathy (Ayazpoor, 2001; Bitsch et al., 1991; Greb and Bitsch, 1998; Loew, 1996; Schreeb, 1997; Woelk et al., 1998). The unique pharmacological properties of BF permit the rapid restoration of thiamine blood levels in the context of alcohol dependence (Bitsch et al., 1991; Greb and Bitsch, 1998; Loew, 1996; Schreeb, 1997) and its extremely high potency and favorable side effects profile is particularly suited to highly non-compliant populations with complex comorbid health histories. High potency thiamine analogues, like BF, have the potential to arrest or possibly even reverse some of the neurological damage associated with alcoholism and potentially restore neurological functioning and enhance cognitive control over alcohol use. Nevertheless, BF remains an understudied and underutilized resource for medical and psychiatric rehabilitation in alcoholism. The present study supports the safety of BF as an adjuvant therapy in alcoholics to treat thiamine deficiency even in the context of continued alcohol use.

5.2 Impact of Thiamine Deficiency on Alcohol Consumption

Nutritional factors and thiamine deficiency specifically have been found to influence psychological functioning including mood and the expression of psychological symptoms that may moderate alcohol use and abuse (Abou-Saleh and Coppen, 1986; 2006; Bell et al., 1992; Benton and Donohoe, 1999; Benton et al., 1995a; 1995b; 1997; Botez et al., 1977; Brozek, 1957; Heseker et al., 1995; Linton, 2002; Smidt et al., 1991; Sterner and Price, 1973; Zhang et al., 2013). Neurological damage secondary to alcoholism and related nutritional deficiencies may contribute to the continuation of abusive drinking by impairing brain processes that regulate behavior (Manzardo and Penick, 2006; 2008; Pfefferbaum et al., 2000; 2009; Pitel et al., 2011; Sullivan and Pfefferbaum, 2005; Schulte et al., 2010). Previous research has reported gender differences in predisposition and response to thiamine deficiency and deficiency-related conditions such as Wernicke-Korsakoff syndrome that may be related to alcohol consumption and could impact upon drinking trajectories as observed in the present study (Benton et al., 1995a; 1995b; Martin et al., 1985; Rittmueller et al., 2012; Victor et al., 1971). Gender differences in dietary habits and risk for thiamine deficiency as well as differences in white matter volume, normally greater in females than males, may influence the neuropsychiatric and neurocognitive effects of thiamine deficiency and supplementation (Rittmueller et al., 2012). Furthermore, gender-based differences in dietary habits and risk for thiamine deficiency have been reported in alcoholism (Rittmueller et al., 2012) including selective enhancement of mood and cognitive function in healthy adult females after prolonged thiamine supplementation (Benton et al., 1995a; 1995b)

5.3 Strengths and Limitations

Our examination of BF safety and tolerability in an actively abusing alcohol dependent population tests the clinical utility of BF adjuvant therapy as a possible tool to improve health and motivate change in severely alcohol dependent individuals at the primary care level. This design differs from typical clinical efficacy trials of alcoholism pharmacotherapy which utilize fully detoxified, abstinent alcohol dependent participants and measure treatment outcomes as a function of abstinence from alcohol use (e.g., abstinence duration; time to relapse). This difference in strategy prevents a direct comparison with results of prior pharmacotherapy trials and limits our interpretation of study findings and their relevance to alcoholism recovery. Never-the-less, our approach provides a unique perspective on drinking trajectory and course of recovery in non-treatment seeking individuals for which we have developed a novel analytical strategy to assess therapeutic response that is based upon changes in total alcohol consumption. Alcohol consumption behavior in active drinkers is more variable than abstinence measures and may be less sensitive. An analytical approach was developed to accommodate the increased variance and improve analytical sensitivity, but the methodology has not yet been clinically validated. The two treatment modalities (abstinence vs consumption) likely encompass different behavioral constructs that may not be directly comparable, but we believe will be equally informative. The present study also lacks empirical measures of study compliance with benfotiamine supplementation which could have significantly impacted study results. A strong behavioral response to study participation (e.g., placebo effect) was observed that is consistent with previous literature reports, but in the absence of any formal behavioral intervention. Subgroup analysis supported a selective effect of BF treatment on consumption in females but lacked statistical power to achieve a conclusive result.

5.4 Conclusions

The results of the present study suggest that BF is safe and may be a useful adjuvant therapy to treat thiamine deficiency during alcoholism rehabilitation. More research is needed to characterize possible effects on behavior in severely alcohol dependent men and women and to elucidate the mechanism of observed effects on alcohol consumption. These preliminary results support the hypothesis that subclinical thiamine deficiency in alcohol dependence may contribute directly to pathological drinking among women, and that treatment with thiamine analogues may reduce alcohol consumption in cases of severe alcohol dependence. Broadly speaking, the data we have presented inspires a renewed consideration of the role of nutrition and impacted genetic factors in alcoholism and possibly in addictions and other psychiatric illness.

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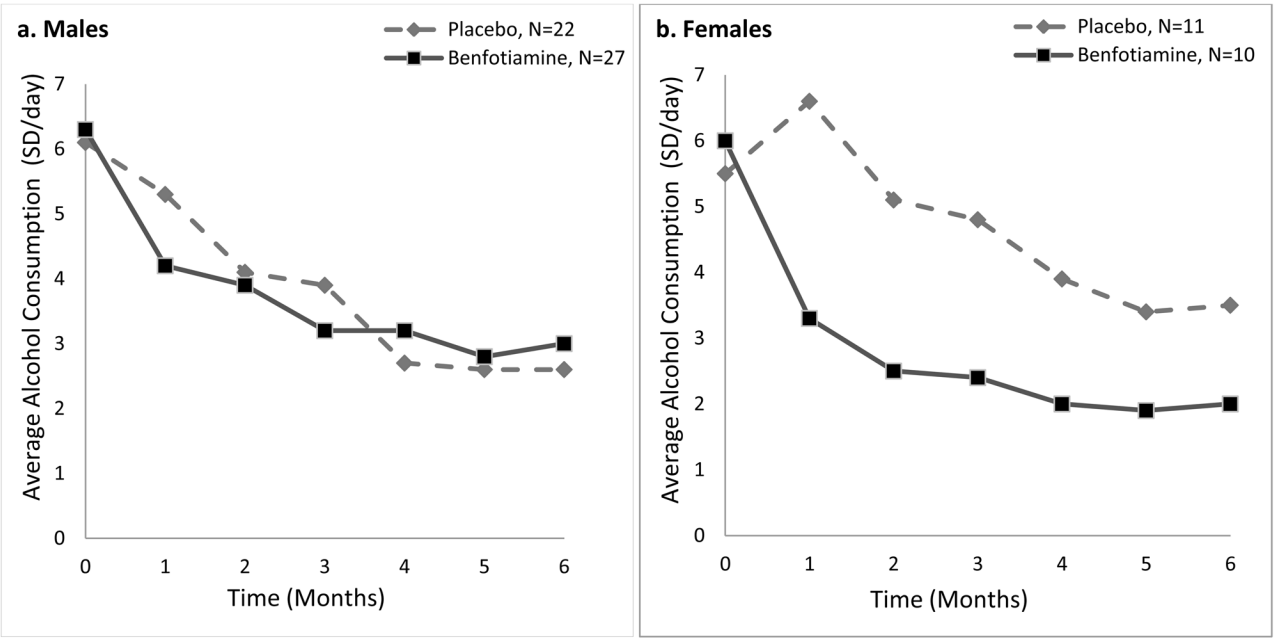

Figure 1. Average Daily Alcohol Consumption Based upon Timeline Followback Assessment

Mean daily alcohol consumption recorded as standard drinks (SD) equivalent to 0.6 fluid ounces (18ml) or 14 grams of alcohol calculated in 4 week blocks for completed male and female subjects.

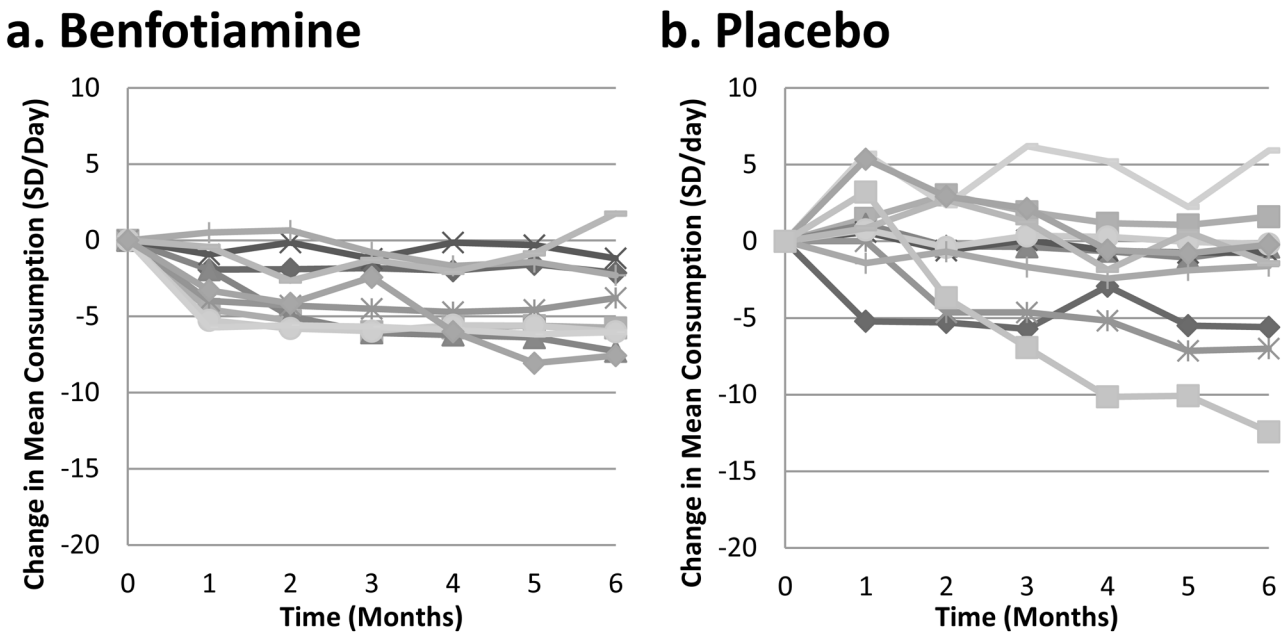

Figure 2.
Change in Mean Daily Alcohol Consumption in Completed Females

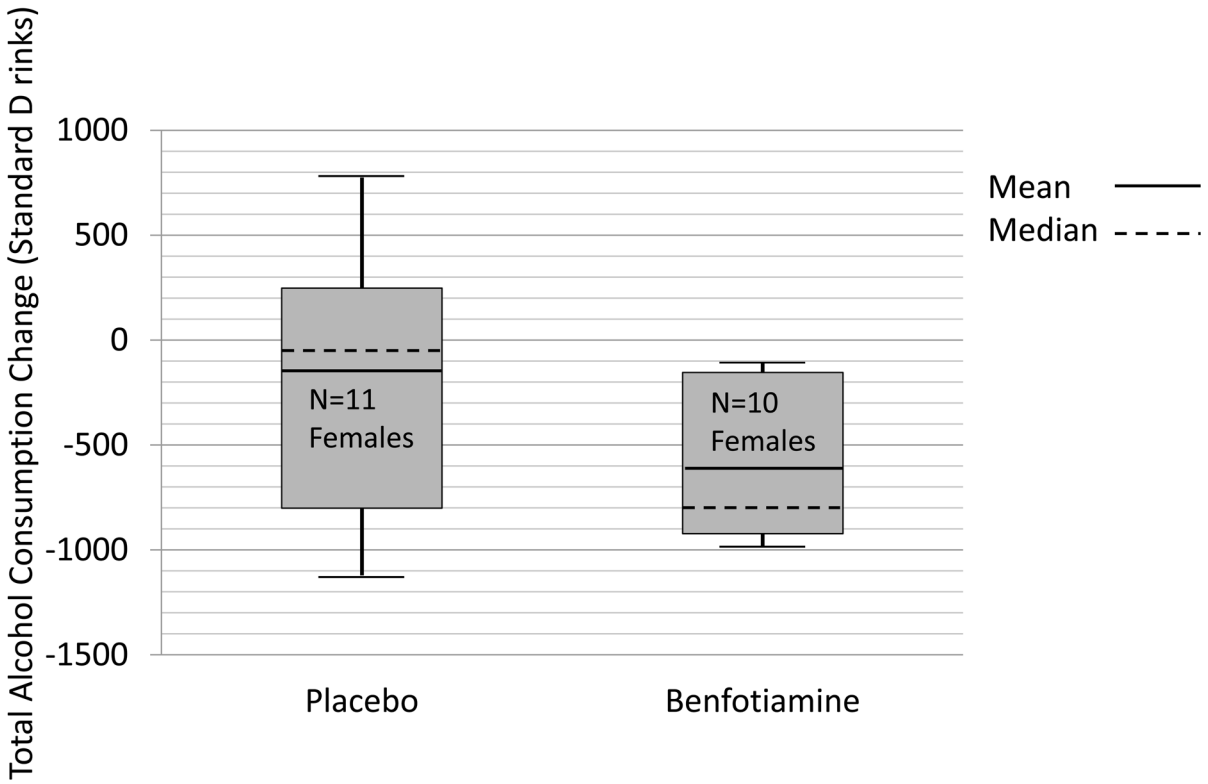

Figure 3. Change in Total Alcohol Consumption among Female Completers

Box plots represent the distribution of the calculated change (observed – expected) in total alcohol consumption within each treatment group. The “expected” total alcohol consumption assumes that the mean daily alcohol consumption is sustained for 6 months while the “observed” alcohol consumption reflects the sum of the mean daily consumption over the 6 month study time interval. The extended bars for each box show the minimum and maximum values of the respective sample distributions

Table 1

Baseline Demographic Characteristics

Measure	Overall N = 120	Randomized, N=120		P-value
		Benfotiamine	Placebo	
FH Alcoholism				
FH+	102 (85%)	51 (43%)	51 (43%)	Stratified
FH−	18 (15%)	9 (7%)	9 (7%)	
Gender				
Male	85 (71%)	43 (36%)	42 (35%)	
Female	35 (29%)	17 (14%)	18 (15%)	P=0.84
Race				
African American	86 (72%)	43 (36%)	43 (36%)	
Caucasian	28 (23%)	15 (13%)	13 (11%)	
Other/unknown	4 (3%)	1 (1%)	3 (3%)	P=0.54
Age				
Mean (Std Dev)	47.5 (7.9)	48.1 (6.9)	46.9 (8.7)	
Min/Max	21/59	27/58	21/59	P=0.40
Alcoholism Severity *(6 months, 33 total)*				
Mean (Std Dev)	17.2 (5.8)	16.4 (5.3)	17.9 (6.2)	
Min/Max	4/30	7/30	4/29	P=0.13
Duration of Abuse *(yrs)*				
Mean (Std Dev)	32(8.8)	33(7.6)	31(9.8)	
Min/Max	4/46	8/45	4/46	P=0.35
Age 1st Drinking *(yrs)*				
Mean (Std Dev)	16(4.3)	15(3.2)	16(5.2)	
Min/Max	6/35	8/25	6/35	P=0.70

Table 2

Study Completion Rates

Total N=70 (58%) Subject Group	Benfotiamine N (%)	Placebo N (%)	p-value
Subject Completion	37 (53%)	33(47%)	P=0.35
FH Alcoholism			
FH+	33(47%)	27(38%)	P=0.38
FH−	4(6%)	6(9%)	
Gender			
Male	27(39%)	22(31%)	P=0.56
Female	10 (14%)	11(16%)	
Race			
African American	29(42%)	29(42%)	P=0.41
Caucasian	7(10%)	4(6%)	
Other/unknown	0(0%)	0(0%)	
Subject Prediction			
Active	24(34%)	21(30%)	P=0.91
Placebo	13(19%)	12(17%)	