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Change in Psychiatric Symptomatology after Benfotiamine Treatment in Males is a Function of Lifetime Alcoholism Severity

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Abstract

Background—Severe alcoholism can be associated with significant nutritional and vitamin deficiency, especially vitamin B1 (thiamine) which is associated with serious illness and neurological deficits that influence mood and cognition. We previously reported reduced alcohol consumption among female but not male alcoholics after supplementation with the high potency thiamine analog benfotiamine (BF). As a follow-up, we have examined the relationship between lifetime alcoholism severity and psychiatric symptoms among the alcohol dependent men from this cohort and their response to BF treatment.

Methods—Eighty-five adult men (mean age = 48 ± 8 yrs) meeting DSM-IV-TR criteria for current alcohol dependence participated in a randomized, double-blind, placebo-controlled trial of 600 mg BF vs placebo (PL) for 6 months. Psychometric testing included a derived Lifetime Alcoholism Severity Score (AS), Symptom Checklist 90R (SCL-90R), and the Barratt Impulsivity Scale (BIS) at baseline and at 6 months with data analyzed using ANOVA and MANOVA modeling.

Results—Baseline SCL-90-R scale scores for men with high alcoholism severity (AS ≥ 24; N=46 HAS) were significantly greater than for men with low alcoholism severity (AS < 24; N=39 LAS), but BIS scores did not differ. MANOVA modeling identified a significant treatment effect ($F=2.5$, $df=10$, $p<0.03$) and treatment x alcoholism severity level interaction ($F=2.5$, $df_{num}=10$, $dfd_{en}=30$, $p<0.03$) with SCL-90-R scores showing a reduction in symptoms among BF treated, high severity males.

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Trial Registration: #NCT00680121 High Dose Vitamin B1 to Reduce Abusive Alcohol Use

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

Tiffany Pendleton contributed to the interpretation of study findings and preparation of 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 preparation of the manuscript.

Conflict of Interest

No conflict declared

Conclusion—BF appears to reduce psychiatric distress and may facilitate recovery in severely affected males with lifetime alcohol dependence and should be considered for adjuvant therapy in alcohol rehabilitation.

Keywords

Alcoholism; Benfotiamine (BF); Vitamin B1; Thiamine Deficiency

1. INTRODUCTION

Chronic alcoholism is frequently associated with significant nutritional and vitamin deficiencies, including thiamine (Green, 1983; Hoyumpa, 1980; Laureno, 2012; Lieber, 2003; Thomson, 2000; Thomson et al., 2012). The role of B vitamins in carbohydrate and alcohol metabolism can rapidly deplete naturally low cellular stores within the body (Hoyumpa, 1980; Martin et al., 2003; Said, 2011; Said and Mohammed, 2006; Singleton and Martin, 2001). Severe thiamine deficiency is rare but can be associated with serious illness (Wernicke-Korsakoff syndrome) and neurological problems leading to significant disability and death. Despite nationalized fortification efforts to reduce acute thiamine deficiency, approximately 30–80% of alcoholic inpatients are thiamine deficient (Brust, 2010; Mancinelli et al., 2003; Thomson et al., 1987). Typical inpatient care for alcoholism with intravenous high-dose vitamin therapy appears to adequately improve the acute symptoms of thiamine deficiency (Markowitz et al., 2000; Thomson et al., 2012). However, this short-term intervention may be insufficient to restore chronic thiamine deficits. Traditional, water-soluble, oral supplements may be of limited value due to the impairments in thiamine absorption and activation related to alcoholism (Baker and Frank, 1976; Thomson et al., 2012). An important 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.

1.1 Alternative Thiamine Analogues

Benfotiamine (BF) is a synthetic provitamin and a lipid-soluble analog of thiamine similar to a class of natural products called the allithiamines (Anonymous, 2006, Lonsdale, 2004). The lipid solubility of BF significantly increases the bioavailability of thiamine pyrophosphate (TTP) and dramatically increases the activity of thiamine-dependent enzymes even in alcoholics with thiamine deficiency (Bitsch et al., 1991; Greb and Bitsch, 1998; Loew 1996; Schreeb et al., 1997). The preparation is widely available and utilized over the counter in Japan and Europe and licensed to treat sciatica nerve pain in Germany (Anonymous, 2006). BF supplementation has proven to alleviate symptoms of alcoholic and diabetic neuropathy in human clinical trials with minimal side effects (Anonymous, 2006; Ayazpoor, 2001; Babaei-Jadidi et al., 2003; Haupt et al., 2005; Manzardo et al., 2013; Simeonov et al., 1997; Stracke et al., 1996; Woelk et al., 1998).

1.2 Pathology of Thiamine Deficiency

Thiamine deficiency can be linked to serious illness and neurological deficits affecting memory and cognition including acute Wernicke encephalopathy and Wernicke-Korsakoff syndrome which occur more frequently in alcoholics with deficits in executive function (de

la Monte et al, 2014; Dirksen et al., 2006; Harper, 2006; 2009; Jung et al., 2012; Kopelman et al., 2009; Oscar-Berman et al., 2004; Pitel et al., 2011; Victor et al., 1989). Depression and other psychiatric disorders have been associated with thiamine deficiency in both Wernicke-Korsakoff syndrome and in the elderly (Bell et al., 1992; Benton et al., 1995a, 1995b, 1997, 1999; Brozek and Caster, 1957; Heseker et al., 1995; Linton et al., 2002; Smidt et al., 1991; Zhang et al., 2013). The primary actions of thiamine deficiency on oxidative metabolism increases oxidative stress leading to secondary activation of microglia and inflammatory chemokines which are believed to contribute to neurodegeneration and exacerbation of the neurotoxic effects of alcohol (Calingasan et al., 1999; Desjardins et al., 2005; Gibson and Blass, 2007; Hazell and Butterworth, 2009; Ke et al., 2003; Yang et al., 2011). Thiamine deficiency is associated with alterations in hippocampal and cortical function impacting the extended amygdala which includes the central medial amygdala, nucleus accumbuns and stria terminalis associated with behavioral and mood disturbances and alcoholism pathophysiology (Nardone et al., 2013; Pires et al., 2001; 2005; Savage et al., 2010). Previous research in both human and animal models have suggested that thiamine deficiency in alcoholism may modulate consumption or contribute directly to pathological drinking (Brady and Westerfeld, 1947; Eriksson et al., 1980; Impeduglia et al., 1987; Pekkanen, 1979; 1980; Pekkanen et al., 1978; Pekkanen and Rusi, 1979; Manzardo et al., 2013; Manzardo and Penick, 2006; 2008; Zimatkin and Zimatkina, 1996). For example, Oliveira-Silva et al. (2014) recently reported that even mild thiamine deficiency was associated with sustained neurochemical abnormalities including acetylcholinesterase activity and increased alcohol consumption in rats.

We previously reported decreased alcohol consumption among alcohol dependent women but not men after 6 months of treatment with benfotiamine in a double-blind study (Manzardo et. al 2013). That study also reported a significant reduction in overall psychiatric symptoms and impulsiveness at the end of treatment but no difference between placebo and treatment groups. That study did not address the specific influence of the severity of alcoholic illness which could impact the degree of thiamine deficiency and thus the responsivity to thiamine supplementation. The present study considers the interactive influence of alcoholism severity and BF treatment on psychiatric symptoms in men from this cohort to determine whether BF treatment response is effective in reducing psychiatric symptoms in men with alcoholism.

2. METHODS

2.1 Participants

Study participants consisted of 85 unrelated adult males with a mean age of 48.5 ± 7.8 years (range: 21 to 59 years) and a current Alcohol Use Disorder (Alcohol Abuse or Alcohol Dependence) diagnosis based upon DSM-IV-TR (American Psychiatric Association, 2000) criteria determined by a structured interview administered by an experienced trained psychiatric nurse. Eligible males identified alcohol as their primary substance of abuse used within the previous 30 days. Participants met DSM-IV-TR criteria for an Alcohol Use Disorder with active alcohol use or <30 days of abstinence from alcohol. Participants had a local address and the ability to read and understand English (Manzardo et al., 2013).

2.2 Recruitment and Screening

This study was monitored through the University of Kansas Medical Center Office of Research Compliance to ensure the rights and welfare of the research subjects were protected. Participants were recruited from the Greater Kansas City Metropolitan area between August, 2008 and August, 2011 by an advertisement in a local newspaper and word of mouth. The participants were compensated 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 or required in order to participate. Participant eligibility was assessed by an initial phone screening interview.

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 identically matched to BF capsules purchased from Nutraceutics Rx (Denver, CO). The study randomization was stratified by family history of alcoholism, defined as the presence of one or more first degree relatives with alcoholism or a grandparent based upon the participant's report. Treatments were administered as 4 capsules (150mg BF or PL) taken orally once daily for a period of 24 weeks and study progress was assessed every 4 weeks using various instruments. Please see previous study for further details (Manzardo et al., 2013). Subjects were also administered a series of psychometric tests and structured interviews at intake and 6 month follow-up interviews.

2.4 Study Instruments and Procedures

After the initial baseline telephone screening, a comprehensive interview was completed to determine subject's final eligibility based upon DSM-IV-TR diagnostic criteria for alcohol dependence and the family history status of each eligible subject. The psychosocial interview was administered by a trained research nurse and included the 33 item lifetime 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 interview was designed to obtain information about sociodemographic characteristics, lifetime and current drinking activities, family history of alcoholism and ratings of psychological functioning. A modified version of the Psychosocial Interview was completed at the end of the study at 6 months. A short psychosocial interview was conducted at each follow-up visit to measure drinking patterns and secondary psychosocial and behavioral effects of heavy drinking since the previous study visit.

The Symptom Checklist 90-R (SCL-90-R) was performed at baseline and 6 months to assess psychiatric symptomology over the past week (Derogatis and Savitz, 2000). The SCL-90-R consists of 90 items with subject rated responses that range from 1 to 4 that is scored to produce 9 primary symptom dimensions and generate two measures: mean raw scores and normative scores relative to non-psychiatric controls. The Barratt Impulsivity Scale (BIS) was also performed at baseline and 6 months to measure impulsiveness. The BIS is a 30-item questionnaire with subject rated responses (Rarely/Never, Occasionally, Often, Almost

Always/Always) that are scored to yield a total score, six first order factors and three second order factors (Patton et al., 1995).

2.5 Concomitant Medications and Supplements

There were no restrictions on the use of additional supportive medications, but information was 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, eligible subjects were stratified by family history (positive (FH+) and negative (FH−) and then randomized into active drug and PL groups 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.

2.7 Blood Collection

Optional blood collection (5 ml) was carried out for consenting participants using sodium heparin vacutainer tubes. Blood was processed at 4ºF within 30 minutes of collection and stored frozen at −80ºC until used. Plasma thiamine levels were assessed, when available, for completed subjects randomized to the active treatment arm. Analyses were performed commercially using high pressure liquid chromatography according to standard protocols by ARUP Laboratories (Salt Lake City, UT).

2.8 Data Analysis

Data analysis examined changes in outcome variables over the course of six months, including baseline and 6 months of therapy using intent to treat methodology. Descriptive statistics (mean, standard deviation) and data analyses were performed using SAS 9.4 software (SAS Institute Inc. Cary, North Carolina, USA). Subjects were grouped into “high” (HAS) and “low’” (LAS) alcoholism severity categories based upon a median split of the 33 item lifetime alcoholism severity scale with high lifetime alcoholism severity being AS ≥ 24. Standard SCL-90-R scale scores were derived from mean raw scores of 99% non-psychiatric Caucasian male controls and presented as area T-scores with a mean=50th centile and a standard deviation=10. Mean raw SCL-90-R scale and BIS scores were compared by severity group using analysis of variance or a general linear model with a Bonferroni correction for multiple testing where appropriate. Mean SCL-90-R and BIS raw scores at baseline and 6 month change scores (post-pre) were compared by treatment and severity level using analysis of variance (ANOVA) and multivariate analysis of variance (MANOVA). A p-value <0.05 was considered significant. Plasma thiamine levels were assessed for a subset of participants (n=26) randomized to the active benfotiamine arm who completed the entire 6 month study protocol with the average baseline and 6 month thiamine levels calculated. The expected normal range for plasma thiamine is 8 to 30 nmol/l as established by the commercial laboratory (ARUP).

3. RESULTS

3.1 Baseline Psychiatric Characteristics

Eighty-five alcohol dependent males were randomized to the treatment protocol and 50 subjects completed the entire 6 month study (Manzardo et al., 2013). Study subjects consisted of predominantly African-Americans (71%; n=60) and the majority reported a family history of alcoholism (82%; n=70) among first degree relatives and/or grandparents. Subjects reported drinking alcohol for a mean duration of 33 ± 8.6 years (8 to 46 years) and their mean AS score was 23 ± 5 (11 to 32). Baseline SCL-90R and BIS scores were significantly higher than normative ranges for the general population suggesting significant pathology.

The examination of baseline psychometric measures showed significantly greater mean raw scores for SCL-90-R subscales by alcoholism severity level indicating increased psychiatric symptomatology among the high versus low severity groups [obsessive-compulsive (1.8±0.8 vs 1.3±0.9, $F=5.7$, $p<0.05$); depression (1.7±0.8 vs 1.2±0.7, $F=7.8$, $p<0.01$); anxiety (1.4±0.8 vs 0.9±0.8, $F=6.0$, $p<0.05$); and phobic anxiety symptoms (0.9±0.8 vs 0.5±0.7, $F=5.6$, $p<0.05$) [Figure 1]. The mean global severity index (GSI) was 90 for the HAS group and 74 for the LAS group ($F=6.21$, $p<0.05$). No differences were observed among AS subgroups for BIS measures including mean raw scores for total impulsivity at baseline (Figure 2).

3.2 Plasma Thiamine Levels

Mean baseline thiamine level for the subset of participants studied was 14.7 (±5.9) nmol/l [range 6 to 32, n=18] which is within the expected normal range of 8 to 30 nmol/l. The mean thiamine level for participants randomized to the active benfotiamine arm who completed the entire 6 month protocol was 591 (±763) [range 5 to 2000, n=26]. Fifty-four percent (n=14) of these subjects exhibited thiamine levels above the normal range at the 6 month follow-up.

3.3 Response to Benfotiamine Treatment

Examination of study data showed a significant decrease in SCL-90R and BIS subscale scores among all completed subjects (N=50) but no effect of treatment assignment. Measured thiamine levels at month 6 were not associated with baseline SCL-90R scores, alcoholism severity classification or changes in most SCL-90R outcomes. The change in SCL-90R depression score at month 6 was significantly greater among participants with measured plasma thiamine levels above the normal range (>30 nmol/l; mean change= −1.8±0.9) than for those within or below the normal range (mean= −1.3±0.6) indicating a significant reduction in depression symptoms with above normal plasma thiamine levels ($F=4.8$, $p< 0.04$). A significant trend toward reduced phobic anxiety symptoms was also observed with higher (mean change = −0.1±0.9) compared to lower (mean change = −0.93±0.94) plasma thiamine levels at month 6 ($F=3.2$, $p<0.09$).

When the HAS subgroup was considered separately from the LAS subgroup for all completed subjects, BF treatment assignment was associated with a selective reduction in

psychiatric symptomatology compared with PL measured using the SCL-90-R instrument (Table 1). A statistically significant reduction in change scores was observed with BF treatment for obsessive-compulsive symptoms with a mean change of 1 for BF versus 0.26 for placebo ($F=6.1$, $p<0.02$) and phobic anxiety with mean reduction of 0.98 with BF versus 0.12 for placebo ($F=8.2$, $p<0.01$, Figure 3). No significant treatment response (BF vs. PL) was observed for BIS measures among the HAS group. Participants in the LAS subject group also showed significant reductions in SCL-90-R scores after 6 months of participation however change scores for PL treated LAS subjects showed greater decreases than BF treated LAS subjects for several subscales (Table 1). LAS subjects given placebo showed significantly greater reductions in obsessive-compulsive, anxiety and hostility symptoms compared to BF treated subjects (Figure 4). Global MANOVA modeling of SCL-90R scores for all participants showed a main effect of treatment and identified a significant interaction effect between treatment group and alcoholism severity level which was significant for each of the 10 independent subscales ($F=2.5$, $df_{num}=10$, $df_{den}=30$, $p<0.03$; Table2).

4. DISCUSSION

The present study results show a relationship between alcoholism severity level measured over the lifetime and levels of psychiatric distress but not impulsiveness which may have been saturated in this extreme group of current, actively abusing, alcohol dependent males. Baseline severity difference impacted treatment response for the high potency thiamine analogue, benfotiamine, which selectively reduced psychiatric distress among the most severely ill participants but may have attenuated the placebo response in the lower severity group. The severity of alcoholism illness can be predicted to correlate with the degree of thiamine deficiency and may account for the significant reduction in psychiatric symptoms associated with BF treatment. Baseline plasma thiamine levels for a subset of tested participants were in the low normal range (<15 nmol/l) but did not directly correlate with alcoholism severity measures. However, acute high plasma thiamine levels at month 6 were associated with a significant reduction in depression symptoms. The results suggest that thiamine deficiency contributes significantly to psychiatric distress in severe alcoholism and supports a possible benefit of thiamine supplementation for the alleviation of acute and/or chronic thiamine deficiency and psychiatric symptomatology in alcoholism. This result is consistent with previous findings of reduced alcohol consumption with BF treatment in alcohol dependent females in this cohort (Manzardo et al., 2013).

4.1 Thiamine Deficiency, Mood and Behavior

Nutritional factors and deficiencies in alcoholism have been shown to exacerbate neurological damage influencing psychological functioning including mood and the expression of psychological symptoms that may moderate alcohol use and abuse (Abou-Saleh and Coppen, 1986; 2006; Benton et al., 1995a; 1995b; Botez et al., 1977; Brozek, 1957; Heseker et al., 1995; Smidt et al., 1991; Sterner and Price, 1973) Allostatic changes in stress response and reward pathways within the ventral striatum, frontal cortex, and extended amygdala are believed to result from the dysregulation of neurochemical signaling associated with repeated cycling between substance intoxication and withdrawal which may be synergistically impacted by chronic thiamine deficiency (He et al., 2007; Koob, 2013;

Koob et al., 2014; Vetreno et al., 2011) The resulting elevation of corticotropin-releasing factor and dynorphin- κ opioids may induce anxiety-like states and compulsive behaviors (Koob, 2013; Koob et al., 2014). Systematic studies examining the association between thiamine status and mood have reported a rapid onset of irritability and depression symptoms in response to acute thiamine deprivation that markedly deteriorated with time but was readily reversible with thiamine supplementation (Brozek, 1957). Numerous randomized trials have reported improved mood, increased feelings of well-being and decreased fatigue in response to thiamine supplementation of adults with and without defined deficiency (Bell et al., 1992; Benton et al., 1995a; 1995b; 1997; 1999; Heseker et al., 1995; Linton et al., 2002; Smidt et al., 1991). Zhang et al., (2013) also found an inverse correlation between blood thiamine levels and depression symptoms in older, Chinese men and women (50–70 yrs) from the general population. These overlapping influences of alcohol exposure and thiamine deficiency may exacerbate psychiatric symptomatology impacting alcohol recovery.

4.2 Limitations and Future Directions

The present study is limited by the small sample size and high rate of attrition and non-compliance which preclude systematic evaluation of psychosocial and behavioral confounds. However, the stratified and randomized study design should reduce their impact on study findings. Benfotiamine treatment appears to be less efficacious in the LAS group, which may be related to the small sample size or reduced level of deficiency and thus need for supplementation in less severe illness. These differences warrant further investigation and characterization of thiamine blood levels and parameters of benfotiamine use in less severe cases as well as responsivity in acute versus chronic thiamine deficiency states. The present study did not evaluate thiamine levels for all participants thus the degree of deficiency is not known and treatment compliance could not be confirmed at all time points. Plasma thiamine levels measured at study conclusion do not necessarily reflect compliance for the study as a whole. Future studies should address dosage and duration for optimization of treatment parameters with monitoring of thiamine levels.

4.3 Conclusions

The findings of the present study suggest that men with higher alcoholism severity are more likely to experience thiamine deficiency and as a result may be more likely to experience psychiatric symptomatology. The results support the hypothesis that BF may facilitate recovery in severely affected males with lifetime alcoholism and should be considered for adjuvant therapy in alcohol rehabilitation. The low alcoholism severity group did not appear to benefit from BF treatment and may respond better to traditional water-soluble thiamine supplements. Future research is needed to support these observations and to characterize and optimize benfotiamine treatment parameters. These preliminary findings serve to stimulate future randomized controlled trials to address the influence of severity state on thiamine response in alcoholism.

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Highlights

1. Our study shows the benefits of thiamine supplementation for men with alcoholism using a high potency thiamine analogue, benfotiamine
2. We examined the relationship between lifetime severity of alcoholism, psychiatric symptomology and response to benfotiamine
3. Benfotiamine treatment reduced symptoms of depression and anxiety in those men with alcoholism having the highest lifetime alcoholism severity scores
4. Benfotiamine treatment may be useful as an adjuvant therapy in alcohol rehabilitation to facilitate recovery in severely affected males with alcoholism

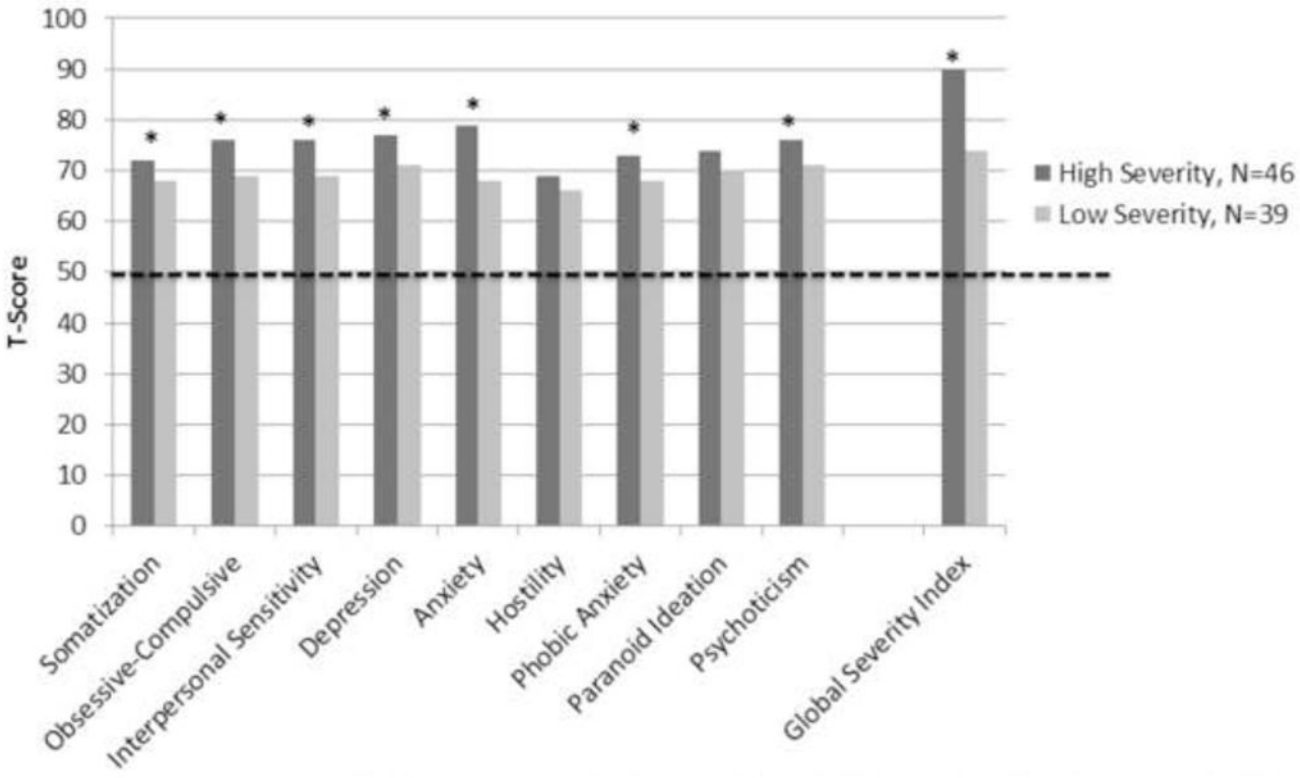

Figure 1.

Symptom Checklist-90-R (SCL-90-R) normative scores for males at baseline by alcoholism severity level relative to non-psychiatric controls.

SCL-90-R normative scores relative to non-psychiatric controls for high (AS ≥ 24) and low (AS < 24) alcoholism severity level. Normative SCL-90-R scores are derived from mean raw scores of 99% non-psychiatric Caucasian male controls. Data are presented as area T scores with a mean=50th centile and a standard deviation=10. Mean values compared using ANOVA.* $p<0.05$.

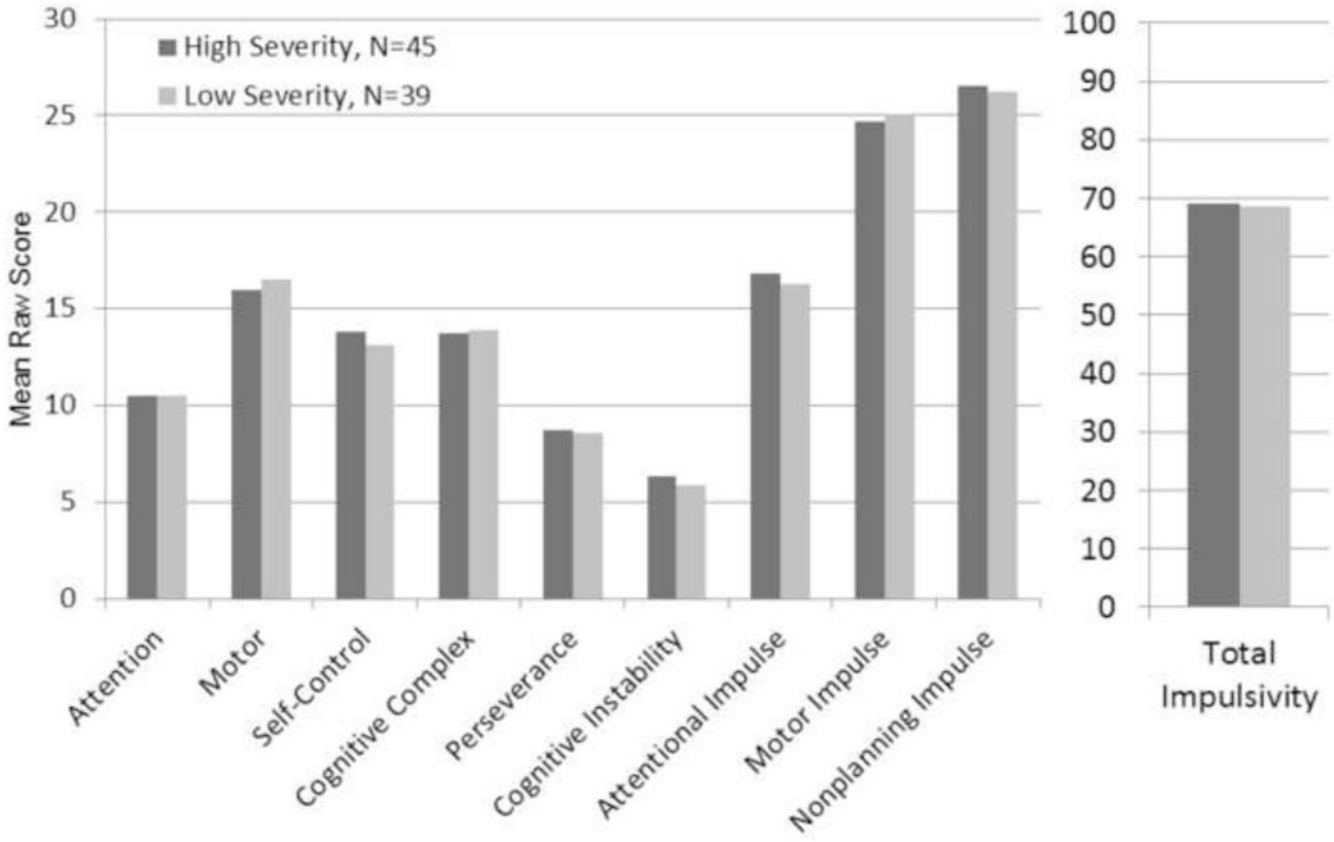

Figure 2.

Barratt Impulsiveness Raw Scores for males at baseline by alcoholism severity level. Barratt Impulsiveness Scale scores for high (AS ≥ 24) and low (AS < 24) alcoholism severity groups. Mean values compared using ANOVA.

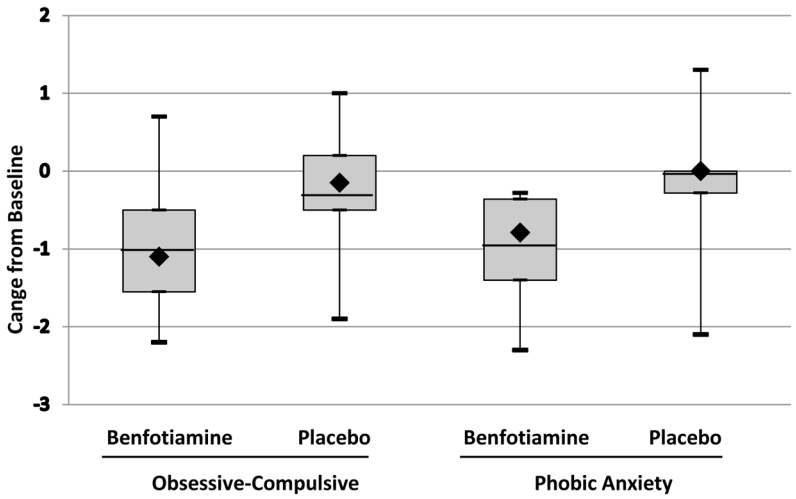

Figure 3.

Sample medians are indicated by black squares and means are indicated by the horizontal lines. Vertical lines show the maximum and minimum values. Sample medians are indicated by black squares and means are indicated by the horizontal lines. Vertical lines show the maximum and minimum values.

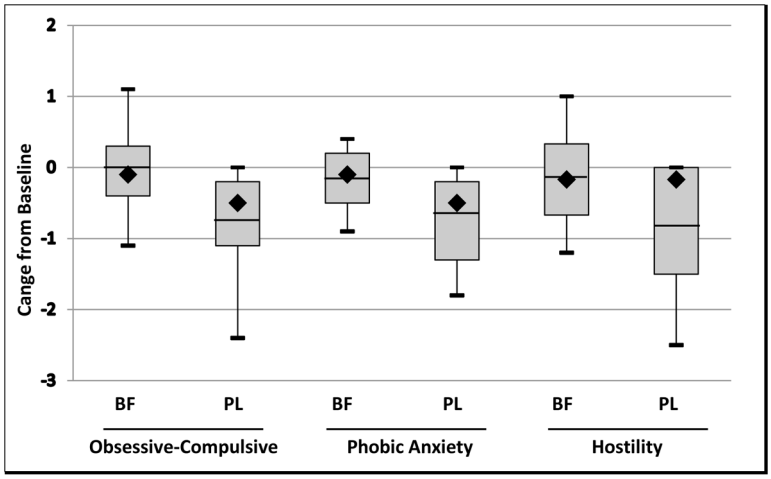

Figure 4.

Change in baseline scl-90-r symptoms for benfotiamine vs placebo treatment for low severity males with alcoholism. Sample medians are indicated by black squares and means are indicated by the horizontal lines. Vertical lines show the maximum and minimum values.

Table 1

Change from Baseline SCL-90R Scale Scores for High and Low Alcoholism Severity Groups

High Severity Males

Subscale	Benfotiamine, N=12 Mean (SD)	Placebo, N=14 Mean (SD)	F value	p-value
Somatization	−0.65 (0.64)	−0.33 (0.87)	1.1	0.30
Obsessive-Compulsive	**−1.0 (0.80)**	**−0.26 (0.73)**	**6.1**	**0.02**
Interpersonal Sensitivity	−0.83 (0.68)	−0.44 (0.84)	1.6	0.21
Depression	−0.84 (0.68)	−0.55 (0.93)	0.77	0.39
Anxiety	−0.69 (0.73)	−0.36 (0.82)	1.2	0.28
Hostility	−0.64 (0.82)	−0.38 (1.1)	0.48	0.50
Phobic Anxiety	**−0.98 (0.72)**	**−0.12 (0.79)**	**8.2**	**0.01**
Paranoid Ideation	−0.86 (0.76)	−0.32 (0.99)	2.3	0.14
Psychoticism	−0.77 (0.59)	−0.36 (0.77)	2.2	0.15
Global Severity Index	−0.78 (0.59)	−0.38 (0.77)	2.1	0.15

Low Severity Males

Subscale	Benfotiamine, N=15 Mean (SD)	Placebo, N=9 Mean (SD)	F value	p-value
Somatization	−0.35 (0.58)	−0.71 (0.59)	2.1	0.16
Obsessive-Compulsive	**−0.07 (0.61)**	**−0.74 (0.79)**	**5.5**	**0.03**
Interpersonal Sensitivity	−0.30 (0.80)	−0.52 (0.69)	0.48	0.50
Depression	−0.25 (0.56)	−0.62 (0.79)	1.8	0.19
Anxiety	**−0.13 (0.40)**	**−0.70 (0.69)**	**6.8**	**0.02**
Hostility	**−0.17 (0.58)**	**−0.87 (1.0)**	**4.8**	**0.04**
Phobic Anxiety	−0.04 (0.23)	−0.40 (0.67)	3.5	0.07
Paranoid Ideation	−0.31 (0.56)	−0.54 (0.83)	0.64	0.43
Psychoticism	−0.19 (0.53	−0.54 (0.63	2.2	0.15
Global Severity Index	−0.21 (0.45)	−0.65 (0.64)	3.9	0.06

Mean values compared using Analysis of Variance.

Table 2

Multivariate Analysis of Variance Model of Change from Baseline SCL-90R Scores

Main Effects	F Value	Degrees of Freedom	p-value
Alcohol Severity	1.1	10	0.42
Treatment	2.5	10	**0.03**
Treatment x Severity	2.5	Num 10 (Den 30)	**0.03**

Subscale Effects	Alcohol Severity	Treatment	Treatment x Severity
Somatization	F=0.29; p=0.59	F=0.05; p=0.83	**F=4.9; p<0.03**
Obsessive-Compulsive	F=1.0; p=0.32	F=0.88; p=0.35	**F=14.5; p<0.001**
Interpersonal Sensitivity	F=0.20; p=0.65	F=1.3; p=0.25	**F=4.0; p<0.05**
Depression	F=0.65; p=0.42	F=0.41; p=0.53	**F=4.2; p<0.05**
Anxiety	F=0.14; p=0.71	F=0; p=0.96	**F=7.8; p<0.01**
Hostility	F=0.49; p=0.49	F=0.02; p=0.89	**F=8.5; p<0.01**
Phobic Anxiety	F=2.6; p=0.11	**F=5.1; p<0.03**	**F=18.5; p<0.0001**
Paranoid Ideation	F=0.03; p=0.86	F=3.1, p=0.09	**F=6.8; p<0.01**
Psychoticism	F=0.56; p=0.46	F=0.47; p=0.5	**F=5.9; p<0.02**
Global Severity Index	F=0.25; p=0.62	F=0.47; p=0.5	**F=9.0; p<0.005**

Multivariate Analysis of Variance (MANOVA) model of the effects of treatment group and severity level on SCL-90-R subscale scores.