EVALUATION OF AN INTEGRATED RISK REDUCTION INTERVENTION'S EFFECTS ON SUBSTANCE USE SPECTRUM MEASURES IN PATIENTS WITH BIPOLAR I DISORDER

by

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ABSTRACT

Background: Substance use is common among people with bipolar I disorder, a mental illness marked by periods of mania and depression. Although substance use affects people with bipolar I disorder more than the general population, and psychotherapy-inclusive treatments show promise in treating comorbid substance use and bipolar I disorders, no studies to our knowledge have applied these treatments to bipolar I disorder people with sub-threshold substance use. The public health importance of minimizing substance use in people with bipolar I disorder is to minimize impacts such as hospitalization costs, lost compensation, and early mortality, through control of symptoms.

We conducted secondary analyses to determine whether one such treatment, integrated risk reduction intervention (IRRI), decreased substance use spectrum measures more than standard care, psychiatric care with medical monitoring (PCMM). The primary study was a randomized controlled trial conducted to reduce medical risks and minimize morbidity and mortality in bipolar I disorder participants. In our current secondary analyses, we hypothesized that 1) all participants would have decreased substance use spectrum measures after 6 months of either treatment, 2) IRRI participants would have a greater decrease than PCMM participants,

and 3) the change in substance use spectrum measures would decrease more among those with a prior alcohol use disorder than those with no prior alcohol use disorder.

Methods: Participants were recruited in Pittsburgh, PA and randomly assigned to IRRI (n=58) or PCMM (n=56). Four substance use spectrum measures from the Self-Report Last Month Substance Use Spectrum assessment (SUBS-SR – Last Month) were evaluated, if completed at both study entry and 6 months. Wilcoxon signed rank tests, Wilcoxon rank sum tests, and multiple linear regression were used for analyses.

Results: There were no significant changes in substance use spectrum measures from study entry to 6 months among all participants. There were no clinically meaningful differences in substance use measures between IRRI and PCMM participants or between participants with versus without a lifetime alcohol use disorder.

Conclusions: The current format of IRRI does not appear to have an effect on substance use spectrum measures after 6 months of treatment. The public health implications of this study are that further study is needed to identify the effectiveness of psychotherapy-related treatment of sub-threshold substance use in bipolar I disorder patients.

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PREFACE

Authors for this project include Felicia R. Bixler, BS, Gale A. Richardson, PhD, Ellen Frank, PhD, Maria Brooks, PhD, and Nancy W. Glynn, PhD. We thank National Institute of Mental Health grant MH081003 (David J. Kupfer), National Heart, Lung, and Blood Institute grant HL082610 (Daniel J. Buysse) and the Jan Mueller Trust Fund for supporting this research.

1.0 INTRODUCTION

1.1 BIPOLAR I DISORDER

Worldwide, 60 million people are affected with the mental illness bipolar disorder ("WHO | Mental disorders | Fact sheet N°396," October 2014). About 2.6% of the United States' (U.S.) adult population (5.4 million adults) has bipolar disorder ("Gender: 2000 | Census 2000 brief," September 2001; Kessler, Chiu, Demler, Merikangas, & Walters, 2005), which is characterized by episodes of mania and depression. One type, bipolar I disorder, makes up about 42% of all bipolar cases (Kroon et al., 2013). Thus, bipolar I disorder is present in about 2.3 million U.S. adults. In 1991, U.S. costs for bipolar disorder amounted to $45 billion, of which $17 billion accounted for lost compensation (Wyatt & Henter, 1995). By 2009, bipolar-related costs were estimated at $151 billion in the U.S. (Dilsaver, 2011).

Bipolar I disorder is defined by having at least one lifetime episode of mania, marked by an abnormal and persistent elevated mood and, usually, episodes of major depression (American Psychiatric Association. & American Psychiatric Association. Task Force on DSM-IV., 2000). Although bipolar I disorder typically onsets around 18 years of age, with a first manic episode in the early 20's (Kennedy et al., 2005), it can onset anytime from childhood to 60+ years of age (American Psychiatric & American Psychiatric Association, 2013). Kroon et al. (2013) found that the month and season of onset of bipolar I disorder are, interestingly, unrelated to the month

and season of birth. Bipolar disorder is also unrelated to race, ethnicity, and family income and is inversely related to education level (Merikangas et al., 2007). The relationship between bipolar I disorder and marital status shows higher rates in those who are separated, divorced, or widowed than in those who are married or have never been married (American Psychiatric & American Psychiatric Association, 2013). When viewing bipolar I disorder incidence rates by urban classification, no difference was found between urban and non-urban areas (Kroon et al., 2013). However, there is a high incidence of bipolar I disorder in deprived areas (~0.9 per 10,000 person years) compared with non-deprived areas (~0.4 per 10,000 person years) (Kroon et al., 2013). (Deprivation assessment was based on a combination of factors such as number of people per area, average income, and number of people receiving social security.) This chronic illness often impacts work, social life, and finances and can lead to disability or suicide.

Patients with bipolar disorder die about 9 years earlier than people in the general population (Crump, Sundquist, Winkleby, & Sundquist, 2013). The majority of excess deaths in bipolar disorder are secondary to medical conditions such as obesity and substance use (Roshanaei-Moghaddam & Katon, 2009). Medical illnesses such as cardiovascular disease and diabetes mellitus create increased mortality for patients with bipolar disorder compared with the general population (Crump et al., 2013). Medications used to treat bipolar disorder, such as mood stabilizers and antipsychotics, cause obesity and type 2 diabetes, among other illnesses (Roshanaei-Moghaddam & Katon, 2009). Most patients with bipolar disorder are overweight or obese (Fagiolini et al., 2002; Wang et al., 2006). It is important to stabilize the symptoms of bipolar disorder to avoid the disturbing impacts on life, work, and monetary resources.

To stabilize the symptoms of bipolar disorder would mean to prevent manic and depressive episodes and to alleviate the manifestations (i.e. sleeplessness, grandiosity, fatigue,

indecisiveness, etc.) of episodes that do occur. Bipolar disorder symptom stabilization is often impeded by physical and psychiatric comorbidities such as diabetes mellitus, migraines, cardiovascular disease, anxiety, attention deficit hyperactivity disorder, and substance use disorder (Merikangas et al., 2007; Sagman & Tohen, 2012). The majority of patients with bipolar I disorder (86.2%) have at least three psychiatric comorbidities (Merikangas et al., 2007). One that is highly prevalent and potentially problematic in stabilization of bipolar disorder symptoms is substance use disorder, as shown in the next section.

1.2 SUBSTANCE USE

1.2.1 SUBSTANCE USE IN BIPOLAR I DISORDER

The National Institute of Mental Health (NIMH) Epidemiologic Catchment Area study showed that 60.7% of people with bipolar I disorder have a substance abuse diagnosis, 46.2% have an alcohol abuse/dependence diagnosis, and 40.7% have a drug abuse/dependence diagnosis (Regier et al., 1990). Substance use disorders include dependence and abuse of alcohol, amphetamines, caffeine, cannabis, cocaine, hallucinogens, inhalants, nicotine, opioids, phencyclidine (PCP), and sedatives/hypnotics/anxiolytics (American Psychiatric Association. & American Psychiatric Association. Task Force on DSM-IV., 2000).

People with comorbid bipolar and substance use disorders have greater health risks than bipolar people without substance use disorders. For example, people with comorbid bipolar and substance use disorders have worse social functioning (Mazza et al., 2009), conceptual reasoning skills, and visual memory (Marshall et al., 2012) and are more likely to be suicide attempters

(Carrà, Bartoli, Crocamo, Brady, & Clerici, 2014; Dalton, Cate-Carter, Mundo, Parikh, & Kennedy, 2003) than bipolar patients without a substance use disorder. Bipolar disorder patients who use tobacco are also at a greater risk of coronary heart disease than bipolar patients who do not use tobacco (Garcia-Portilla et al., 2010). Interestingly, a study conducted among veterans with bipolar disorder showed that those who use substances, versus those who do not, are about three times more likely to have psychiatric hospitalizations (Hoblyn, Balt, Woodard, & Brooks, 2009). As such, even without crossing the threshold of being a disorder, substance use has particularly adverse consequences in people with bipolar disorder.

Sub-threshold substance use disorder is when a person has symptoms of the disorder, but not enough symptoms to meet criteria for a diagnosis (Sbrana et al., 2005). In 2005, Sbrana et al. discussed the idea that substance use disorders are best approached as a spectrum, to include threshold and sub-threshold use. Although this thought was not in line with the DSM-IV (in use at that time), it is consistent with the current DSM-5 approach, published in 2013. The DSM-IV separates substance use disorders into two categories, substance abuse and substance dependence. The DSM-5 combines these into one category, substance use disorders, and includes the categories of mild, moderate, and severe. This spectrum approach allows for diagnosis of sub-threshold substance use. Due to the negative effects on patients with substance use disorder at any point in the disorder's spectrum, it is imperative that substance use be minimized among people with bipolar I disorder, even if it has not reached the level of a substance use disorder.

1.2.2 SUBSTANCE USE TREATMENT IN BIPOLAR I DISORDER

Studies on treatment for comorbid bipolar and substance use disorders have historically focused on pharmacotherapy (Brown, Nejtek, Perantie, & Bobadilla, 2002; Brown, Nejtek, Perantie, Orsulak, & Bobadilla, 2003; Chengappa, Gershon, & Levine, 2001) and have shown mixed results of the pharmacologic effects on these comorbid disorders. Some of the pharmacotherapy treatments used include mood stabilizers, antidepressants, and atypical antipsychotics (Matson et al., 2006). The mixed effects include weight gain, sedation, and tremors (Mago, Borra, & Mahajan, 2014). Psychotherapy has been a successful treatment for bipolar disorder, but few studies have used it to treat comorbid bipolar and substance use disorders.

Weiss et al. (2000) conducted a pilot study, which incorporated psychotherapy as a treatment for comorbid bipolar and substance use disorders. The study used hour-long integrated group therapy sessions among 45 participants for up to 20 weeks. This therapy was designed to incorporate recovery and relapse processes that are found in both bipolar disorder treatments and substance use disorder treatments and included psychoeducation and group psychotherapy. The integrated group therapy sessions consisted of a "check-in" on patients' progress over the prior week, a review of the major points from the prior week's session, a didactic session and discussion of the current session topic, and 2-page session summary handouts (Weiss, Najavits, & Greenfield, 1999). The sessions had an "open" format, rather than building upon the prior topics, so that people can start the therapy at any point. The control group received 6 monthly therapy sessions (Weiss et al., 2000). Participants in the integrated group therapy had significantly lower drug and alcohol scores on the Addiction Severity Index (ASI) fifth edition (McLellan et al., 1992) and had improved mood compared with those in the control group. Weiss et al. (2000) also found that participants in the 20-week versus 12-week integrated group

therapy did better with decreasing drug and alcohol use. In 2007, Weiss, et al. published on a randomized controlled trial among 62 participants comparing 20 weeks of integrated group therapy with 20 weeks of group drug counseling. Integrated group therapy still focused on both mood and substance use related issues, while group drug counseling focused only on substance use related issues. They found that participants in the integrated group therapy had decreased drug and alcohol use compared with the control group. After separating substance use into drugs and alcohol, they found that the decrease applied to alcohol use, but not to drug use. There were no differences in mood found between the groups. Weiss et al. (2009) have since created a "community-friendly" version of the integrated group therapy. In this version, adjusted to be more adaptable in community treatment programs, the integrated group therapy was altered to be shorter (12 weeks) and administrable by substance use disorder counselors who had no formal training in counseling on mood disorders. Results showed that the 31 integrated group therapy participants did better in decreasing drug and alcohol use than the 30 participants in the control group (group drug counseling). During treatment, the integrated group therapy participants also had more improved mood than the control group.

To our knowledge, the only other psychotherapy-inclusive treatment focused on comorbid bipolar and substance use disorders was conducted by Jones et al. (2011). They reported on a preliminary, uncontrolled intervention in five participants with comorbid bipolar and substance use disorders. The intervention used motivational interviewing to identify a patient's concerns and life goals, followed by identification of how bipolar disorder and substance use affected these. Cognitive behavioral therapy strategies were then used to guide patients into making related changes that could help them address their concerns and goals.

They found that the intervention helped reduce substance use in four of the five participants, but did not find clear indications of mood improvement.

These studies have shown that incorporating a psychotherapy component into treatment for people with comorbid bipolar and substance use disorders can have a positive impact on substance use and, possibly, mood symptoms. The optimal situation would be to give patients tools to regulate their substance use so they can avoid substance abuse and dependence. The current secondary analyses aim to determine whether substance use was reduced in participants with bipolar I disorder, who were not abusing or dependent on substances at study entry, after participation in an integrated risk reduction intervention (IRRI).

The study on which the current secondary analyses were run was expected to reduce several modifiable medical risks. It is important to educate people with bipolar disorder about how to lead a healthy lifestyle and the potential consequences of not doing so. If patients are able to manage their substance use, they will be less likely to abuse or become dependent on substances. The secondary analyses of the current study, which was built on a strong healthy lifestyle psychoeducation program, are expected to show a positive impact of IRRI on participants' substance use and related factors.

The current study has a larger sample size than those conducted by Jones et al. (2011) and Weiss et al. (2000, 2007, 2009). These prior studies focused on patients with comorbid bipolar disorder and substance use disorder, whereas the current analyses focus on bipolar disorder patients who use substances and are not currently abusing or dependent on substances. Due to the many harmful effects of substances on bipolar disorder patients, as noted above in section 1.2 (e.g., problems with conceptual reasoning and increased risk of coronary heart disease, suicide attempts, and psychiatric hospitalizations), it is imperative that treatments help

patients manage their substance use. In addition, if a patient has previously abused or been dependent on substances and has remitted, it is critical to treat this patient to avoid relapse. The current study will add a sizeable sample to the literature addressing substance use in patients with bipolar I disorder who are not currently abusing or dependent on substances. The study treatment, IRRI, addresses substance use through education, guidance in maneuvering an individual's personal barriers, and reinforcement of progress and goals (Frank et al., 2014).

A randomized clinical intervention trial in treatment-seeking, adult participants with bipolar I disorder was conducted to determine the effectiveness of IRRI in reducing modifiable risks. The current secondary analyses focus on determining whether IRRI reduced substance use and related factors. We hypothesize that the successful psychiatric treatment (IRRI or psychiatric care with medical monitoring (PCMM)) of bipolar I disorder participants will reduce substance use and related factors after 6 months of treatment because there will be regular attention and monitoring of the patient's medical status. In addition, participants treated with IRRI compared with PCMM will have a greater reduction of substance use and related factors because IRRI includes a healthy lifestyle behaviors program, intended to help participants achieve a balanced lifestyle through education. The gap in current knowledge, which these analyses intend to address, is psychotherapy-inclusive treatment for patients with bipolar I disorder who use substances but are not currently abusing or dependent on substances.

1.3 SUMMARY

The population of interest is a subset of people with bipolar disorder. They have bipolar I disorder – in remission, are overweight with a body mass index of >25, and do not currently have

a substance use disorder, although they made have had one in the past and could currently be using substances.

1.3.1 SPECIFIC AIMS AND HYPOTHESES

The specific aims and hypotheses of this study are:

1. Aim: To determine whether substance use, use of substances or drugs as self-medication, symptoms of substance use disorder, and total substance use spectrum scores from the Self-Report Last Month Substance Use Spectrum assessment (SUBS-SR – Last Month) decrease in participants with bipolar I disorder who are overweight or obese, after undergoing 6 months of psychiatric treatment (IRRI or PCMM).
    1.1. Hypothesis: In participants with bipolar I disorder who are overweight or obese, substance use, use of substances or drugs as self-medication, symptoms of substance use disorder, and total substance use spectrum SUBS-SR – Last Month scores will decrease after 6 months of psychiatric treatment (IRRI or PCMM).
2. Aim: To determine whether there is a greater decrease of substance use, use of substances or drugs as self-medication, symptoms of substance use disorder, and total substance use spectrum SUBS-SR – Last Month scores in participants with bipolar I disorder who are overweight or obese, after undergoing 6 months of IRRI treatment compared with PCMM treatment.
    2.1. Hypothesis: In participants with bipolar I disorder who are overweight or obese, there will be a greater decrease of substance use, use of substances or drugs as self-medication, symptoms of substance use disorder, and total substance use spectrum

SUBS-SR – Last Month scores after undergoing 6 months of IRRI treatment compared with PCMM treatment.

3. Aim: Among participants with bipolar I disorder who are overweight or obese, to determine whether there is a difference between participants with a prior alcohol use disorder compared with participants who do not have a prior alcohol use disorder in the change of substance use, use of substances or drugs as self-medication, symptoms of substance use disorder, and total substance use spectrum SUBS-SR – Last Month scores after undergoing 6 months of psychiatric treatment (IRRI or PCMM) and to determine whether having a prior alcohol use disorder modifies the relative effect of IRRI treatment versus PCMM treatment.

    3.1. Hypothesis: Among participants with bipolar I disorder who are overweight or obese, participants with a prior alcohol use disorder will have a larger change of substance use, use of substances or drugs as self-medication, symptoms of substance use disorder, and total substance use spectrum SUBS-SR – Last Month scores compared with participants who do not have a prior alcohol use disorder after undergoing 6 months of psychiatric treatment (IRRI or PCMM). In addition, having a prior alcohol use disorder will amplify the relative effect of IRRI treatment versus PCMM treatment.

2.0 METHODS

This thesis involves a secondary analysis of data collected from a randomized clinical trial. Sections 2.1-2.3 below focus on the main trial and sections 2.4-2.5 address elements of the current secondary analyses of these data.

2.1 STUDY DESIGN

Treatment-seeking participants were recruited from Western Psychiatric Institute and Clinic outpatient and research facilities, University of Pittsburgh Medical Center general public and employees, and University of Pittsburgh students and staff. Participants received a verbal explanation of the prospective randomized intervention before giving written informed consent. The study was approved by the University of Pittsburgh Institutional Review Board (NCT00746343).

The aims of the main trial were to determine whether IRRI was a superior treatment to PCMM in reducing medical risks and minimizing morbidity and mortality associated with bipolar I disorder, the results of which were published by Frank et al. in 2014. In order to address these aims, patients with bipolar I disorder and a body mass index (BMI) of ≥ 25 kg/m^2, who were otherwise healthy, were selected to participate. Noteworthy to the current secondary analyses of data from that main trial, participants could not have a current substance use

disorder, but may have had a remitted substance use disorder at study screening. Bipolar I disorder and substance use disorder (past, current, or never) were identified via the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), a semi-structured, clinician administered, diagnostic interview based on criteria from the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) (First, Spitzer, Gibbon, & Williams, 1995).

Participants had to be 18 to 55 years of age, with their bipolar I disorder remitted for at least four consecutive weeks prior to study entry. Remission was defined as a score of ≤7 on both the Hamilton Rating Scale for Depression (17-item; HRSD-17) (Hamilton, 1960) and the Young Mania Rating Scale (YMRS) (Young, Biggs, Ziegler, & Meyer, 1978) and a score of <3 on the Clinical Global Impressions for Bipolar Disorder Scale (CGI-BP-S) (Spearing, Post, Leverich, Brandt, & Nolen, 1997). Participants were assessed for remission by these clinician-administered scales at least twice during the four weeks prior to study entry. Those with ultra-rapid cycling bipolar I disorder (>4 episodes in 6 months), pervasive developmental disorder, antisocial personality disorder, schizophrenia, or organic mental disorder as identified by the SCID-I were ineligible to participate. Unstable, severe medical illness requiring immediate, intense treatment as identified by the patient or the patient's medical record, unwillingness or inability to comply with study requirements, and inability to provide informed consent were all study exclusions. The last participation criterion for the main trial was that women planning to become or currently pregnant or breast-feeding were excluded. This was based on self-report, except when there was reason to suspect pregnancy in women not using reliable birth control, in which case a pregnancy test was performed.

To ensure balance between treatment groups, a stratified permuted block design was utilized. The strata were low risk and high risk and the blocks were a size of four. The strata

risk level was based on an algorithm that indicated the stability and complexity of the participant's medication regimen. After random allocation to either IRRI or PCMM, participants remained in their assigned group for the entire 24-month study period.

The study duration was divided into two phases: phase 1 constituted the first 6 months and phase 2 the remaining 18 months. During phase 1, treatment took place up to weekly and consisted of 15-17 structured psychoeducation modules for IRRI participants (Table 1). In phase 2, participants attended 5-7 monthly sessions during study months 7 through 12 and 4-5 quarterly sessions during study months 13 through 24. The timing and number of the phase 2 sessions depended on when the phase 1 sessions ended. The purpose of the phase 2 sessions was to follow-up and to assess the progress of the IRRI participants' healthy lifestyle changes. Included in the phase 2 IRRI sessions were: i) assessments of sleep/wake and social rhythm patterns, weight, nutrition, and physical activity; ii) assessments of progress toward participants' individual goals; iii) adherence emphasis; and iv) assistance with progress barriers including addressing relapses.

2.2 INTERVENTIONS

IRRI consisted of three components and PCMM consisted of two, also described in Frank et al., 2014. Both interventions included psychopharmacologic treatment and medical monitoring, although in PCMM, medical monitoring was less intensive than in IRRI. The third component in IRRI was the healthy lifestyle behaviors program.

Psychopharmacologic treatment (IRRI and PCMM)

An attempt was made to limit participants to one or two of the following medications: lithium, divalproex, aripiprazole, and quetiapine. This was done to minimize the variance associated with an extensive regimen of different psychiatric medications. However, some participants remained on already stable medication regimens. The study psychiatrist made efforts to balance the participants' mood symptoms with medication side effects, such as weight gain. The Bipolar Disorder Visit Form (BDVF) was used to guide the psychiatrist in monitoring the participants' medications as related to all states of bipolar disorder (remitted, manic, hypomanic, and depressed). The BDVF was adapted from the Clinical Monitoring Form (CMF) used in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) (Sachs, Guille, & McMurrich, 2002; Sachs et al., 2003).

Medical monitoring (IRRI and PCMM)

Participants saw the nurse monthly except when symptomatic; then they visited twice a month. Similarly, they saw the psychiatrist every two months except when symptomatic at which time they went monthly. Visits with the nurse or psychiatrist lasted about 30 minutes. The nurse assessed and monitored the participants' psychiatric symptoms, psychiatric medications, and medication side effects, and conducted safety evaluations. Between visits, the nurses took phone calls from participants and notified psychiatrists of any psychiatric related issues. Labs were taken at study entry, every six months, and as needed for medical issues. For abnormal lab values, participants were referred to their PCP or medical specialist. The medical team (psychiatrist, nurse, and, when applicable, lifestyle coach) met weekly to discuss the participants' status including labs and recommendations.

IRRI participants only: The nurse worked to make sure IRRI participants adhered to medical and psychiatric treatments, including pharmacotherapy and the healthy lifestyle behaviors program and notified the psychiatrist and lifestyle coach of the participants' adherence. Additionally, the nurse coordinated and assisted with communications among the participant, psychiatrist, lifestyle coach, primary care physician (PCP) or medical specialist, and study endocrinologist or cardiologist (when needed).

Healthy lifestyle behaviors program (IRRI only)

During one hour sessions, the lifestyle coach administered the healthy lifestyle behaviors program using the Social Rhythm Metric-5 (SRM-5) (Monk, Flaherty, Frank, Hoskinson, & Kupfer, 1990). The program was based on the thought that stabilizing social rhythms and sleep/wake cycles helps minimize medical risk factors. It consisted of structured modules designed to educate participants about healthy lifestyle behaviors and risk reduction, promote quality of life, and help participants establish a healthy routine, adhere to treatments and medications, increase physical activity, lose or maintain weight, and if applicable, cease smoking. Substance use is an important modifiable medical risk, which was discussed in all pertinent modules.

In the healthy lifestyle behaviors program, the participants identified goals most important to them and the coach tried to incorporate some aspect of these goals in the modules early on, without changing the order of the modules. This helped build a bond with the participants and give them early gratification for making progress toward their goals. Participants set goals weekly and discussed the prior week's behavioral change goals with the coach. Together, they adjusted the behavior modification as needed (advanced or adjusted the modification). The coach also provided encouragement to help participants accomplish goals

and adhere to medication and treatment. Other tools used in the study were daily diet records, calorie counter books, and pedometers.

2.3 STUDY STAFF

Staff experienced in treating bipolar disorder included psychiatrists, psychologists, social workers, and Bachelor's or Master's level psychiatric nurses. Lifestyle coaching was conducted by a health education specialist educated in nutrition and exercise physiology or, when she was unavailable, by a psychiatric social worker trained in behavioral modification techniques such as interpersonal and social rhythm therapy. The lifestyle coaches were trained over two days in motivational interviewing techniques, sleep medicine, behavioral weight control, and nutrition by experts in each of these fields. Dr. Ellen Frank supervised the health education specialist biweekly to ensure program adherence.

Nurses worked with either IRRI participants or PCMM participants and were blind to the other intervention's participants' progress. An additional nurse who was blind to all participants' treatment assignments conducted weekly chart reviews to ensure that the treatment algorithms were being administered correctly and that they were consistent across both treatment groups.

2.4 MEASURES

The outcomes of interest for the current secondary analyses were the changes in SUBS-SR – Last Month substance use spectrum measure scores from study entry to 6 months. The SUBS-

SR – Last Month was adapted from the Structured Clinical Interview for Substance Use Spectrum (SCI-SUBS), a validated tool that identifies one's substance-related experiences, symptoms, and behaviors (Sbrana et al., 2003). The SUBS assessments consist of 131 questions each covering six domains: I) substance use (medications and recreational drugs), II) substance sensitivity (mood changes, anxiety attacks, and strong sensations), III) use of substances or drugs as self-medication (mood/anxiety, improving performance, social distribution, weight control, body image, and other conditions), IV) sensation seeking (strong emotions), V) attention deficit/hyperactivity symptoms, and VI) symptoms of substance use disorder (abuse, addiction, tolerance, withdrawal, and intoxication) (Bizzarri et al., 2007). The SUBS-SR – Last Month was completed at study entry and 6, 12, 18, and 24 months of treatment. The total score of the assessment was used as an indication of where a person lies on the spectrum of substance use. As a measure of severity of the prior month's substance use, the scores of domain I (substance use; 22 questions), domain III (use of substances or drugs as self-medication; 55 questions), and domain VI (symptoms of substance use disorder; 23 questions) were used. All four of these scores were determined at both study entry and month 6, when the SUBS-SR – Last Month was completed. The outcomes were the difference in score from study entry to the follow-up assessment at 6 months of the substance use, use of substances or drugs as self-medication, symptoms of substance use disorder, and total SUBS-SR – Last Month measures.

2.5 STATISTICAL ANALYSES

The baseline characteristics of the total sample, of each treatment group individually, and by prior alcohol use disorder group are described. These characteristics are age at onset of first

manic episode, age at study screening, gender, race, ethnicity, marital status, education, employment status, depression level from the HRSD-25, mania level from the YMRS, SUBS-SR – Last Month question 3 "In the past month, have you had periods in which you drank a lot of alcohol?," and prior substance use disorders from the SCID-I. Had there been any significant baseline differences between the IRRI and PCMM groups, they would have been adjusted for in subsequent analyses.

To test the first hypothesis, the paired (study entry and 6 months) continuous outcomes (substance use score, self-medication score, substance use disorder symptoms score, and overall substance use spectrum score from the SUBS-SR – Last Month) for all participants were compared. Due to the 'absence of current substance use disorders' enrollment criteria, the outcomes were non-normally distributed and positively skewed (i.e., to the right) among participants. Thus, the data were log-transformed. This did not normalize the data, so a one-sided Wilcoxon signed rank test was used to analyze the non-transformed data. There was 80% power to detect a medium effect size of 0.272 between the paired (study entry and 6 months) substance use, self-medication, substance use disorder symptoms, and overall substance use spectrum scores from the SUBS-SR – Last Month, with α=0.05 based on a one-sided paired t-test using all participants who completed at least one outcome at both time points (Table 2).

The continuous outcomes for the second and third hypotheses were the differences from study entry to 6 months of the SUBS-SR – Last Month total and domain I, III, and VI scores. To test the second hypothesis, the change-score outcomes of the IRRI group were compared with those of the PCMM group (i.e., two independent samples). As the data were non-normally distributed, they were log-transformed. This did not normalize the data, so a one-sided Wilcoxon rank sum test was used to analyze the non-transformed data. There was 80% power to

detect a large effect size of 0.544 between the two treatment groups for the differences from study entry to 6 months of the SUBS-SR – Last Month total and domain I, III, and VI scores, with α=0.05 based on a one-sided two-sample t-test (Table 3).

To test the third hypothesis, the outcomes were analyzed by treatment and prior alcohol use disorder groups. Two multiple linear regression models were developed for the third hypothesis. Model 1 included the parameters treatment group and prior alcohol use disorder group (equation: $y = \beta_0 + \beta_{treatment} + \beta_{alcohol} + \varepsilon$). Model 2 added onto Model 1 with an additional parameter of the interaction between treatment and prior alcohol use disorder groups (equation: $y = \beta_0 + \beta_{treatment} + \beta_{alcohol} + \beta_{treatment}*\beta_{alcohol} + \varepsilon$). As these analyses for the third hypothesis were exploratory, no power calculations are provided.

SAS software, Version 9.4 14w47 for Windows was used for all statistical analyses.

3.0 RESULTS

Figure 1 shows the flow of participants screened, accepted into the study, and included in the current secondary analyses (previously described).

3.1 AIM 1

3.1.1 AIM 1 SAMPLE CHARACTERISTICS

As shown in Table 4, the sample as a whole had a first manic episode onset at 22 years of age and was about 42 years of age at screening. As a whole, the sample was primarily female, White, non-Hispanic, and never married. The majority of participants had at least some college education and was either unemployed or disabled. The HRSD-25 and YMRS scores indicate that the participants were not depressed or manic at study screening. Although very few participants self-reported drinking a lot of alcohol in the month prior to study entry, nearly 40% had a prior alcohol use disorder (Table 4).

3.1.2 AIM 1 FINDINGS

There were no significant changes in substance use, use of substances or drugs as self-medication, symptoms of substance use disorder, or total substance use spectrum SUBS-SR – Last Month scores from study entry to 6 months among all study participants (Table 5).

3.2 AIM 2

3.2.1 AIM 2 CHARACTERISTICS BY TREATMENT GROUP

There were no differences at screening between the treatment groups with respect to first manic episode onset age, age at study screening, gender, race, ethnicity, marital status, education, employment status, depression and mania levels, drank a lot of alcohol in the last month indicator, or prior substance use disorder rates (Table 4).

3.2.2 AIM 2 FINDINGS

There were no differences within either treatment group in substance use related score changes from study entry to 6 months, with one exception. Within the PCMM group, there was a significant decrease in the use of substances or drugs as self-medication scores (domain III) (Table 5). Within the IRRI group, there were no significant changes in the use of substances or drugs as self-medication scores (domain III) (Table 5). When comparing results between groups, the change in use of substances or drugs as self-medication scores from study entry to 6 months

was greater in the PCMM group than the IRRI group (Table 5 footnote). For example, Figure 2 shows that 29% of the PCMM group improved versus 19% of the IRRI group. There were no other significant differences in substance use related score changes from study entry to 6 months between treatment groups (Table 5).

3.3 AIM 3

3.3.1 AIM 3 CHARACTERISTICS BY PRIOR ALCOHOL USE DISORDER

As shown in Table 6, the participants who had a prior alcohol use disorder were significantly less likely to be female and more likely to have additional prior substance use disorders than those with no prior alcohol use disorder. There were no differences between the prior alcohol use disorder and no prior alcohol use disorder groups with respect to first manic episode onset age, age at study screening, race, ethnicity, marital status, education, employment status, or depression and mania levels (Table 6).

In the group with no prior alcohol use disorder, as well as in the group with a prior alcohol use disorder, there were no differences between the treatment groups with respect to first manic episode onset age, age at study screening, gender, race, ethnicity, marital status, education, employment status, depression and mania levels, or prior substance use disorders (Table 7).

3.3.2 AIM 3 FINDINGS

There were no changes in substance use related scores from study entry to 6 months within either of the prior alcohol use disorder groups with the exception of a decrease in self-medication (domain III) score changes in the prior alcohol use disorder group (Table 8). The overall substance use spectrum scores decreased to a greater extent from study entry to 6 months in the prior alcohol use disorder group compared with the no prior alcohol use disorder group (Table 8 footnote). Figure 3 shows this relationship with more participants in the prior alcohol use disorder group improving and fewer worsening than in the no prior alcohol use disorder group. There were no other significant differences in substance use related score changes from study entry to 6 months between the prior alcohol use disorder groups (Table 8 footnote).

There were no significant substance use related score changes from study entry to 6 months within either of the treatment groups among those with no prior alcohol use disorder or those with a prior alcohol use disorder, except for a significant decrease in total spectrum scores in the IRRI-no prior alcohol use disorder group (Table 9).

When factoring in treatment assignment and prior alcohol use disorder status, a multiple linear regression model showed that the PCMM group had significantly decreased self-medication (domain III) change scores from study entry to 6 months compared with the IRRI group (Table 10). Additionally, the prior alcohol use disorder group had significantly decreased self-medication (domain III) and total substance use spectrum change scores from study entry to 6 months compared with the no prior alcohol use disorder group (Table 10). There were no other significant predictors of the independent variables prior alcohol use disorder and treatment assignment (Model 1) (Table 10). There were no significant interactions between treatment

group and prior alcohol use disorder group in Model 2, which also included the independent variables treatment group and prior alcohol use disorder group.

4.0 DISCUSSION

The main trial from which the current analyses were conducted was a randomized, controlled trial comparing outcomes after IRRI treatment versus PCMM treatment. IRRI consisted of psychiatric treatment, nursing management with medical monitoring, and a healthy lifestyle behaviors program. PCMM consisted of psychiatric treatment and medical monitoring (less involved than in IRRI). The aims of the main trial were to determine whether IRRI was superior to PCMM in reducing or stabilizing medical risks (such as cardiometabolic disease) and minimizing morbidity and mortality associated with bipolar I disorder (Frank et al., 2014). As such, selected participants had remitted bipolar I disorder and a BMI of $\geq$ 25 kg/m^2, but were otherwise healthy.

The current secondary analyses of that main trial had three hypotheses. They were that among overweight or obese participants with bipolar I disorder, SUBS-SR – Last Month scores of substance use, use of substances or drugs as self-medication, symptoms of substance use disorder, and total substance use spectrum would 1) decrease after undergoing 6 months of psychiatric treatment (IRRI or PCMM), 2) decrease more after undergoing 6 months of IRRI compared with PCMM, and 3) change differently among participants with a prior alcohol use disorder compared with participants who did not have a prior alcohol use disorder, after undergoing 6 months of psychiatric treatment (IRRI or PCMM), and having a prior alcohol use

disorder would modify the relative effect of IRRI treatment versus PCMM treatment. These hypotheses were not fully supported by our findings.

With respect to the first hypothesis, where our findings showed that there was no change in scores after undergoing 6 months of IRRI or PCMM treatment, the lack of hypothesis support could be due to combining the intervention and control groups. If there had been an extremely strong difference in score changes between the treatment groups, the analysis might have shown significant findings. However, as shown in Table 5, all scores remained relatively low with a median high of 5 points at each time point.

The second hypothesis analyses showed similar results with the exception that, between treatment groups, the PCMM group had significantly decreased use of substances or drugs as self-medication (domain III) scores from study entry to 6 months compared with the IRRI group. Since the possible score for this section was 0-55 and the scores changed from 1 at study entry to 0 at six months, this finding is not clinically meaningful. There were no significant changes in the IRRI group's outcomes. This is not surprising since participants were chosen to be healthy with the exception of a high BMI. All study participants were required to have no current substance use disorders, so it would not have been possible for any of their SUBS-SR – Last Month scores to be very high. Since the participants started with extremely low scores (medians ranging 0-6, Table 5) and their scores could have been as high as 145, it was good to find that they did not significantly worsen with respect to any of the substance use related measures.

This is the first analysis to show the effects of IRRI on substance use related measures. We speculate that PCMM participants were able to make positive changes because they were being treated more regularly than patients not in the study, their psychiatric medications were assuredly stabilized while in the study, and they were not occupied with making healthy lifestyle

changes (as done by IRRI participants), which may account for the significant decrease in use of substances or drugs as self-medication (domain III) scores seen in Table 5.

The third hypothesis analyses added in the factor of having a prior alcohol use disorder. This hypothesis was developed in light of the Weiss et al. (2007) finding that participants who had improved substance use after an integrated group therapy were those who decreased alcohol use as opposed to other substances. The findings in Table 10 indicate that having a prior alcohol use disorder compared with not having a prior alcohol use disorder decreased the SUBS-SR – Last Month outcomes of the entire sample as a whole, but did not affect participants in one treatment differently than the other. This is consistent with results found in prior literature (Weiss et al., 2007). We speculate that people with a prior alcohol substance use disorder may have been attentive to not increasing their use due to coping skills gained through programs such as Alcoholics Anonymous.

The level of change seen in our results is very small and not clinically meaningful. Figure 4 illustrates the frequency of SUBS-SR – Last Month scores of substance use, use of substances or drugs as self-medication, symptoms of substance use disorder, and total substance use spectrum for all participants. The statistically significant changes seen in PCMM may have been due to self-motivation to improve since they were not granted assignment to IRRI. While the intervention did not specifically focus on substance use, the topic was included in pertinent sessions. Therefore, it is possible that greater focus on substance use education may afford a greater result.

Another weakness of these analyses is that selection bias may be present due to the fact that participants with SUBS-SR – Last Month data missing from either screening or 6 months were not included in the analyses. This introduces the possibility of a type II error. A limitation

of the study is that there was not much room for improvement overall because the entire sample was healthy aside from having remitted bipolar I disorder and being overweight or obese. Since the population selected was clinically well, participants with current substance use disorders were naturally selected out at study screening. It is therefore understandable that all scores upon study entry were on the low end of the scales (Figure 4). The SUBS-SR – Last Month assessment does not collect detailed information about which substances were used or amount used. The current version of the SUBS-SR – Last Month has been modified from the originally validated version. Other limitations include the low power of 80% and final sample size of 87. These analyses were limited by the aims of the main study, which focused on reducing modifiable risks such as obesity, as opposed to focusing on decreasing substance use. Although IRRI did not specifically focus on substance use, the topic was included in pertinent sessions.

A strength of the study is that the research group that conducted the study is a well-established group with 20 years of experience. This was a new group of patients from those in other studies from the same research group, so there should not be any bias in the results as pertains to prior related research exposure. The measures used in this study are reliable and valid.

The public health relevance of this study is that decreasing substance use among patients with bipolar I disorder will allow for bipolar disorder symptom stabilization and, in turn, will decrease impacts of bipolar I disorder such as hospitalization, lost compensation, suicide, disability, and early mortality. As substance use is common among this population and highly interfering of bipolar disorder symptom stabilization, it proves worthy of time and emphasis to minimize among these patients. While psychotherapy-related treatments have been effective in treating comorbid bipolar and substance use disorders, we studied whether a psychotherapy-

related treatment affected sub-threshold substance use in patients with bipolar I disorder. If patients are able to manage their substance use, they will be less likely to abuse or become dependent on substances, and better able to manage symptoms, which will decrease their risk for devastating impacts.

Future work should focus on decreasing substance use as a primary aim. A future study should only analyze bipolar I disorder patients who are using substances at baseline, but who do not have a substance use disorder. Patients not using substances at study entry should not be included in analyses.

The current format of IRRI does not appear to have an effect on substance use spectrum measures after 6 months of treatment. The level of change seen in our results is very small and, although statistically significant, is not clinically meaningful. A study with greater focus on decreasing substance use among patients with bipolar I disorder should be developed. The public health implications still remain that if patients are able to manage their substance use, they will be less likely to abuse or become dependent on substances, and better able to manage symptoms. Hence, heavy impacts including hospitalization, lost compensation, disability, and suicide may be significantly decreased.

APPENDIX: TABLES AND FIGURES

Table 1. Structured modules of the Healthy Lifestyle Behaviors Program

Component	Topics addressed	Therapeutic goals
Bipolar disorder psychoeducation (3 sessions)	• Overview and rationale of the integrated risk reduction intervention • Bipolar disorder • Importance of a balanced lifestyle • Prevalence and impacts of common health risk behaviors in participants with bipolar disorder: nicotine, alcohol, and drug use	• Increase understanding of the importance of balanced lifestyle • Identify important activities to enhance sleep/wake and social rhythms • Enhance adherence to self-monitoring of sleep/wake and social rhythms and exercise
Healthy sleep/wake and social rhythm practices (4 sessions)	• Sleep/wake disturbances, social rhythms, and mood disorders • Effects of nicotine, alcohol, and drugs on sleep and social rhythmicity • Eating habits and physical activity as cues to enhance sleep/wake and social rhythms • Relapse prevention for sleep/wake and social rhythms	• Continue self-monitoring of exercise and sleep/wake and social rhythms • Behavioral interventions to enhance and consolidate sleep/wake and social rhythm regularity in a gradual manner • Initiate self-monitoring of food intake
Weight loss: nutrition (4 sessions)	• Healthy eating habits and food choices • Exercise and weight loss • Alcohol use in weight management • Relapse prevention for healthy eating and weight loss	• Enhance/maintain adherence to self- monitoring of food intake • Reduce calorie intake by 500 calories per day in a progressive manner • Achieve a modest weight loss (5–7% of initial weight)
Weight loss: physical activity (4 sessions)	• Education about the importance of physical activity and time management strategies to incorporate exercise in a weekly routine • Education about moving more and exercising safely • Identifying ways to add interest and variety to physical activity plan • How to stay motivated; relapse prevention	• Identify and adhere to number of minutes of exercise • Incorporate moderate-intensity exercise for 30 min 3–5 times per week in schedule
Smoking cessation (2 optional sessions)	• Interactions between nicotine and bipolar disorder medication • Stimulus control and smoking • Identify relationship among smoking behaviors, sleep and social rhythms, and eating habits • Education about symptoms of recovery from smoking and available resources	• Self-monitor smoking behaviors and triggers • Identify benefits of and coping skills to quit smoking • Plan smoking cessation

Adapted from Frank, E., Wallace, M. L., Hall, M., Hasler, B., Levenson, J. C., Janney, C. A., . . . Kupfer, D. J. (2014). An Integrated Risk Reduction Intervention can reduce body mass index in individuals being treated for bipolar I disorder: results from a randomized trial. *Bipolar Disord*. doi: 10.1111/bdi.12283

Table 2. Effect sizes at various levels of power for analysis of study hypothesis 1 Self-Report Last Month Substance Use Spectrum assessment (SUBS-SR – Last Month) completed at study entry and 6 months, based on a one-sided paired t-test

N	Power	Alpha	Mean of paired differences	Standard deviation	Effect size
85	80%	0.05	0.272	1	0.272
85	90%	0.05	0.320	1	0.320
85	95%	0.05	0.360	1	0.360
85	99%	0.05	0.434	1	0.434

Note: The boxed figures are those which will be analyzed for study hypothesis 1.

Table 3. Effect sizes at various levels of power for analysis of study hypothesis 2 Self-Report Last Month Substance Use Spectrum assessment (SUBS-SR – Last Month) completed at study entry and 6 months, based on a one-sided two-sample t-test

IRRI (N)	PCMM (N)	Power (1-β)	α	IRRI μ	PCMM μ	IRRI σ	PCMM σ	Effect size
41	44	80%	0.05	0.544	0	1	1	0.544
41	44	90%	0.05	0.640	0	1	1	0.640
41	44	95%	0.05	0.720	0	1	1	0.720
41	44	99%	0.05	0.869	0	1	1	0.869

Note: The boxed figures are those which will be analyzed for study hypothesis 2. Abbreviations: IRRI=integrated risk reduction intervention, PCMM=psychiatric care with medical monitoring

Table 4. Sample characteristics for all participants and by treatment group at study screen

	All Participants (N=114)	IRRI (n=58)	PCMM (n=56)	Between Treatment Groups p-value
Treatment Assignment (% IRRI (n))	50.88 (58)			
Age at Onset of First Mania Episode (median (25%, 75%))	22.0 (17.0, 29.0)	21.0 (16.5, 28.5)	22.0 (18.0, 29.0)	0.40[b]
Age at Study Screening (median (25%, 75%))	42.2 (34.0, 49.0)	42.7 (34.8, 49.0)	41.8 (33.6, 49.6)	0.90[b]
Gender (% female (n))	58.77 (67)	60.34 (35)	57.14 (32)	0.73[c]
Race (% White (n))	85.84 (97)	85.96 (49)	85.71 (48)	0.97[c]
Ethnicity (% non-Hispanic (n))	100.00 (114)	100.00 (58)	100.00 (56)	
Marital Status: Never Married (Never Lived as Married) (% (n))	42.98 (49)	41.38 (24)	44.64 (25)	0.74[d]
Married or Living as Married (% (n))	35.96 (41)	34.48 (20)	37.50 (21)	
Divorced, Widowed, or Separated/No Longer Living as Married (% (n))	21.05 (24)	24.14 (14)	17.86 (10)	
Education: High School or Less (% (n))	11.40 (13)	12.07 (7)	10.71 (6)	0.74[d]
Some College (% (n))	41.23 (47)	36.21 (21)	46.43 (26)	
College Diploma (Bachelor's Degree) (% (n))	28.95 (33)	31.03 (18)	26.79 (15)	
Graduate or Professional Degree (% (n))	18.42 (21)	20.69 (12)	16.07 (9)	
Employment Status: Full-time (35 or More Hours Per Week) for Pay (% (n))	22.81 (26)	24.14 (14)	21.43 (12)	0.64[d]
Part-time for Pay (% (n))	19.30 (22)	15.52 (9)	23.21 (13)	
Homemaker or Unemployed (% (n))	30.70 (35)	29.31 (17)	32.14 (18)	
Disabled or Leave of Absence (% (n))	27.19 (31)	31.03 (18)	23.21 (13)	
Hamilton Rating Scale for Depression (25) Score (median (25%, 75%))	6.0 (4.0, 9.0)	6.0 (3.0, 9.0)	6.0 (4.0, 9.0)	0.93[b]
Young Mania Rating Scale Score (median (25%, 75%))	0.0 (0.0, 2.0)	1.0 (0.0, 3.0)	0.0 (0.0, 2.0)	0.08[b]
Drank a lot of alcohol in the last month at study entry[a] (% yes (n))	7.14 (8)	7.02 (4)	7.27 (4)	1.00[d]
LIFETIME SUBSTANCE USE DISORDERS				
Alcohol (% lifetime threshold (n))	37.72 (43)	41.38 (24)	33.93 (19)	0.41[c]
Cannabis (% lifetime threshold (n))	16.67 (19)	18.97 (11)	14.29 (8)	0.50[c]
Cocaine (% lifetime threshold (n))	10.53 (12)	12.07 (7)	8.93 (5)	0.58[c]
Other or Poly Substance (% lifetime threshold (n))	14.91 (17)	17.24 (10)	12.50 (7)	0.48[c]

IRRI=integrated risk reduction intervention; PCMM=psychiatric care with medical monitoring; [a]SUBS-SR – Last Month question 3 "In the past month, have you had periods in which you drank a lot of alcohol?"; [b]Wilcoxon Rank Sums, [c]Chi-Square, [d]Fisher's Exact Test. All p-values are two-sided.

Table 5. Outcome measures for all participants and by treatment group at study entry, month 6, and change from study entry to month 6

All Participants	N	Study Entry median (25%, 75%)	Month 6 median (25%, 75%)	Change from Study Entry to Month 6 median (25%, 75%)	Change from Study Entry to Month 6 p-value
Domain I: Substance Use Score	85	1.0 (0.0, 2.0)	1.0 (0.0, 3.0)	0.0 (-1.0, 1.0)	0.08
Domain III: Self-Medication Score	79	1.0 (0.0, 3.0)	0.0 (0.0, 2.0)	0.0 (0.0, 1.0)	0.18
Domain VI: Substance Use Disorder Symptoms Score	84	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.0 (0.0, 0.0)	0.39
Substance Use Spectrum Total Score	74	5.0 (3.0, 9.0)	5.0 (2.0, 9.0)	0.0 (-2.0, 3.0)	0.43
IRRI	n				
Domain I: Substance Use Score	42	1.0 (0.0, 2.0)	1.0 (0.0, 3.0)	0.0 (-1.0, 1.0)	0.10
Domain III: Self-Medication Score	39	1.0 (0.0, 3.0)	1.0 (0.0, 4.0)	0.0 (-1.0, 1.0)	0.25
Domain VI: Substance Use Disorder Symptoms Score	40	0.0 (0.0, 2.0)	0.0 (0.0, 2.0)	0.0 (-0.5, 1.0)	0.35
Substance Use Spectrum Total Score	37	4.0 (3.0, 9.0)	4.0 (2.0, 10.0)	0.0 (-4.0, 2.0)	0.28
PCMM	n				
Domain I: Substance Use Score	43	1.0 (0.0, 2.0)	1.0 (0.0, 3.0)	0.0 (-1.0, 1.0)	0.27
Domain III: Self-Medication Score	40	1.0 (0.0, 3.0)	0.0 (0.0, 2.0)	0.0 (0.0, 1.5)	**0.02***
Domain VI: Substance Use Disorder Symptoms Score	44	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.0 (0.0, 0.0)	0.47
Substance Use Spectrum Total Score	37	6.0 (3.0, 9.0)	5.0 (2.0, 8.0)	0.0 (-1.0, 3.0)	0.19

IRRI=integrated risk reduction intervention; PCMM=psychiatric care with medical monitoring; All p-values in the table are from one-sided Wilcoxon Signed Rank tests. Results described below are from Wilcoxon Rank Sum tests.

***Based on a one-sided test, the change in the use of substances or drugs as self-medication scores (domain III) from study entry to 6 months was significantly higher in the PCMM group than the IRRI group (p-value<0.05).** No other substance use related score changes from study entry to 6 months were different (based on one-sided tests) between the treatment groups.

Table 6. Sample characteristics by prior alcohol use disorder group at study screen

	No Prior Alcohol Use Disorder (n=71)	Prior Alcohol Use Disorder (n=43)	Between Prior Alcohol Use Disorder Groups p-value
Treatment Assignment (% IRRI (n))	47.89 (34)	55.81 (24)	0.41[b]
Age at Onset of First Mania Episode (median (25%, 75%))	21.0 (17.0, 26.0)	22.5 (17.0, 31.0)	0.80[a]
Age at Study Screening (median (25%, 75%))	40.6 (33.9, 48.7)	44.5 (34.0, 51.1)	0.40[a]
Gender (% female (n))	69.01 (49)	41.86 (18)	**<0.01**[b]
Race (% White (n))	83.10 (59)	90.48 (38)	0.28[b]
Ethnicity (% non-Hispanic (n))	100.00 (71)	100.00 (43)	
Marital Status: Never Married (Never Lived as Married) (% (n))	40.85 (29)	46.51 (20)	0.83[c]
Married or Living as Married (% (n))	38.03 (27)	32.56 (14)	
Divorced, Widowed, or Separated/No Longer Living as Married (% (n))	21.13 (15)	20.93 (9)	
Education: High School or Less (% (n))	11.27 (8)	11.63 (5)	0.96[c]
Some College (% (n))	42.25 (30)	39.53 (17)	
College Diploma (Bachelor's Degree) (% (n))	29.58 (21)	27.91 (12)	
Graduate or Professional Degree (% (n))	16.90 (12)	20.93 (9)	
Employment Status: Full-time (35 or More Hours Per Week) for Pay (% (n))	22.54 (16)	23.26 (10)	0.76[c]
Part-time for Pay (% (n))	21.13 (15)	16.28 (7)	
Homemaker or Unemployed (% (n))	32.39 (23)	27.91 (12)	
Disabled or Leave of Absence (% (n))	23.94 (17)	32.56 (14)	
Hamilton Rating Scale for Depression (25) Score (median (25%, 75%))	6.0 (4.0, 9.0)	6.0 (4.0, 9.0)	0.79[a]
Young Mania Rating Scale Score (median (25%, 75%))	1.0 (0.0, 3.0)	0.0 (0.0, 2.0)	0.14[a]
LIFETIME SUBSTANCE USE DISORDERS			
Cannabis (% lifetime threshold (n))	9.86 (7)	27.91 (12)	**0.01**[b]
Cocaine (% lifetime threshold (n))	7.04 (5)	16.28 (7)	0.21[c]
Other or Poly Substance (% lifetime threshold (n))	5.63 (4)	30.23 (13)	**<0.01**[b]

[a]Wilcoxon Rank Sums, [b]Chi-Square, [c]Fisher's Exact Test. All p-values are two-sided.

Table 7. Sample characteristics by prior alcohol use disorder group and treatment group at study screen

	No Prior Alcohol Use Disorder			Prior Alcohol Use Disorder		
	IRRI (N=34)	PCMM (N=37)	Between Treatment Groups p-value	IRRI (N=24)	PCMM (N=19)	Between Treatment Groups p-value
Age at Onset of First Mania Episode (median (25%, 75%))	22.0 (17.0, 28.0)	21.0 (18.0, 25.0)	0.90[a]	20.0 (16.0, 30.0)	24.0 (18.0, 31.0)	0.22[a]
Age at Study Screening (median (25%, 75%))	41.2 (36.0, 48.7)	40.6 (33.2, 48.7)	0.73[a]	44.5 (33.7, 49.9)	42.1 (37.7, 52.5)	0.73[a]
Gender (% female (n))	70.59 (24)	67.57 (25)	0.78[b]	45.83 (11)	36.84 (7)	0.55[b]
Race (% White (n))	82.35 (28)	83.78 (31)	0.87[b]	91.30 (21)	89.47 (17)	1.00[c]
Ethnicity (% non-Hispanic (n))	100.00 (34)	100.00 (37)		100.00 (24)	100.00 (19)	
Marital Status: Never Married (Never Lived as Married) (% (n))	32.35 (11)	48.65 (18)		54.17 (13)	36.84 (7)	
Married or Living as Married (% (n))	44.12 (15)	32.43 (12)	0.40[c]	20.83 (5)	47.37 (9)	0.19[c]
Divorced, Widowed, or Separated/No Longer Living as Married (% (n))	23.53 (8)	18.92 (7)		25.00 (6)	15.79 (3)	
Education: High School or Less (% (n))	11.76 (4)	10.81 (4)		12.50 (3)	10.53 (2)	
Some College (% (n))	41.18 (14)	43.24 (16)	1.00[c]	29.17 (7)	52.63 (10)	0.54[c]
College Diploma (Bachelor's Degree) (% (n))	29.41 (10)	29.73 (11)		33.33 (8)	21.05 (4)	
Graduate or Professional Degree (% (n))	17.65 (6)	16.22 (6)		25.00 (6)	15.79 (3)	
Employment Status: Full-time (35 or More Hours Per Week) for Pay (% (n))	26.47 (9)	18.92 (7)		20.83 (5)	26.32 (5)	
Part-time for Pay (% (n))	14.71 (5)	27.03 (10)	0.61[c]	16.67 (4)	15.79 (3)	0.52[c]
Homemaker or Unemployed (% (n))	35.29 (12)	29.73 (11)		20.83 (5)	36.84 (7)	
Disabled or Leave of Absence (% (n))	23.53 (8)	24.32 (9)		41.67 (10)	21.05 (4)	
Hamilton Rating Scale for Depression (25) Score (median (25%, 75%))	6.0 (3.0, 9.0)	6.0 (4.0, 9.0)	0.88[a]	6.0 (3.5, 8.5)	6.0 (4.0, 9.0)	0.79[a]
Young Mania Rating Scale Score (median (25%, 75%))	1.5 (0.0, 3.0)	0.0 (0.0, 2.0)	0.23[a]	1.0 (0.0, 2.0)	0.0 (0.0, 1.0)	0.09[a]
LIFETIME SUBSTANCE USE DISORDERS						
Cannabis (% lifetime threshold (n))	5.88 (2)	13.51 (5)	0.43[c]	37.50 (9)	15.79 (3)	0.12[b]
Cocaine (% lifetime threshold (n))	5.88 (2)	8.11 (3)	1.00[c]	20.83 (5)	10.53 (2)	0.44[c]
Other or Poly Substance (% lifetime threshold (n))	2.94 (1)	8.11 (3)	0.62[c]	37.50 (9)	21.05 (4)	0.24[b]

IRRI=integrated risk reduction intervention; PCMM=psychiatric care with medical monitoring; [a]Wilcoxon Rank Sums, [b]Chi-Square, [c]Fisher's Exact Test. All p-values are two-sided.

Table 8. Outcome measures by prior alcohol use disorder group at study entry, month 6, and change from study entry to month 6

No Prior Alcohol Use Disorder	n	Study Entry median (25%, 75%)	Month 6 median (25%, 75%)	Change from Study Entry to Month 6 median (25%, 75%)	Change from Study Entry to Month 6 p-value
Domain I: Substance Use Score	53	1.0 (0.0, 2.0)	1.0 (0.0, 3.0)	0.0 (-1.0, 1.0)	0.17
Domain III: Self-Medication Score	47	1.0 (0.0, 3.0)	0.0 (0.0, 2.0)	0.0 (-1.0, 1.0)	0.41
Domain VI: Substance Use Disorder Symptoms Score	50	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.0 (0.0, 0.0)	0.26
Substance Use Spectrum Total Score	46	5.0 (2.0, 9.0)	5.0 (2.0, 10.0)	0.0 (-3.0, 2.0)	0.18
Prior Alcohol Use Disorder					
Domain I: Substance Use Score	32	1.0 (0.0, 2.0)	2.0 (0.5, 2.5)	0.0 (-1.0, 0.0)	0.15
Domain III: Self-Medication Score	32	1.0 (0.0, 3.0)	0.0 (0.0, 1.5)	0.0 (0.0, 2.0)	**0.04**
Domain VI: Substance Use Disorder Symptoms Score	34	0.0 (0.0, 2.0)	0.0 (0.0, 1.0)	0.0 (0.0, 0.0)	0.35
Substance Use Spectrum Total Score	28	5.5 (4.0, 10.0)	5.0 (3.0, 8.5)	1.0 (-1.0, 5.5)	0.08*

Notes: All p-values in the table are from one-sided Wilcoxon Signed Rank tests. Results described below are all based on Wilcoxon Rank Sum tests.
***Based on a one-sided test, the change in total substance use spectrum score from study entry to 6 months was significantly higher in the lifetime alcohol use disorder group compared with the no lifetime alcohol use disorder group (p-value=0.02).** There were no other significant differences in substance use related score changes from study entry to 6 months (based on one-sided tests) between the lifetime alcohol use disorder groups.

Table 9. Outcome measures by prior alcohol use disorder group and treatment group at study entry, month 6, and change from study entry to month 6

No Prior Alcohol Use Disorder IRRI	n	Study Entry median (25%, 75%)	Month 6 median (25%, 75%)	Change from Study Entry to Month 6 median (25%, 75%)	Change from Study Entry to Month 6 p-value
Domain I: Substance Use Score	24	1.0 (0.0, 2.0)	1.0 (0.0, 3.0)	0.0 (-1.0, 0.5)	0.14
Domain III: Self Medication Score	22	1.0 (0.0, 2.0)	1.0 (0.0, 8.0)	0.0 (-2.0, 0.0)	0.07
Domain VI: Substance Use Disorder Symptoms Score	22	0.0 (0.0, 1.0)	0.0 (0.0, 3.0)	0.0 (-1.0, 1.0)	0.25
Substance Use Spectrum Total Score	21	3.0 (2.0, 9.0)	5.0 (1.0, 15.0)	-1.0 (-6.0, 2.0)	**0.04**
PCMM					
Domain I: Substance Use Score	29	1.0 (1.0, 2.0)	1.0 (0.0, 2.0)	0.0 (-1.0, 1.0)	0.43
Domain III: Self Medication Score	25	1.0 (0.0, 3.0)	0.0 (0.0, 2.0)	0.0 (0.0, 1.0)	0.09
Domain VI: Substance Use Disorder Symptoms Score	28	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.0 (0.0, 0.0)	0.47
Substance Use Spectrum Total Score	25	6.0 (2.0, 8.0)	5.0 (2.0, 8.0)	0.0 (-1.0, 2.0)	0.30
Prior Alcohol Use Disorder					
IRRI					
Domain I: Substance Use Score	18	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	0.0 (-1.0, 1.0)	0.34
Domain III: Self Medication Score	17	1.0 (0.0, 3.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.19
Domain VI: Substance Use Disorder Symptoms Score	18	1.0 (0.0, 3.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.42
Substance Use Spectrum Total Score	16	5.5 (4.0, 10.0)	4.0 (3.0, 8.0)	1.0 (0.0, 5.0)	0.10
PCMM					
Domain I: Substance Use Score	14	1.5 (0.0, 2.0)	2.0 (0.0, 3.0)	0.0 (-1.0, 0.0)	0.22
Domain III: Self Medication Score	15	0.0 (0.0, 3.0)	0.0 (0.0, 2.0)	0.0 (0.0, 2.0)	0.08
Domain VI: Substance Use Disorder Symptoms Score	16	0.0 (0.0, 0.5)	0.0 (0.0, 0.5)	0.0 (0.0, 0.0)	0.42
Substance Use Spectrum Total Score	12	5.5 (3.5, 10.0)	6.0 (3.0, 11.0)	1.5 (-1.5, 5.5)	0.26

IRRI=integrated risk reduction intervention; PCMM=psychiatric care with medical monitoring; All p-values in the table are from one-sided Wilcoxon Signed Rank tests.

Table 10. Multiple linear regression Model 1 (predictors=treatment and prior alcohol use disorder) for each substance use related score change outcome

Change in Domain I: Substance Use Score (n=85, R2<0.01)	**Estimated Beta**	**Standard Error of Beta**	**p-value**
Intercept	-0.14	0.23	0.54
IRRI (vs. PCMM)	-0.19	0.29	0.51
Prior Alcohol Use Disorder (vs. No Prior Alcohol Use Disorder)	< 0.00	0.30	0.99
Change in Domain III: Use of Substances or Drugs as Self-Medication Score (n=79, R^2=0.10)			
Intercept	0.28	0.47	0.56
IRRI (vs. PCMM)	-1.36	0.59	**0.02**
Prior Alcohol Use Disorder (vs. No Prior Alcohol Use Disorder)	1.20	0.60	**0.05**
Change in Domain VI: Symptoms of Substance Use Disorder Score (n=84, R^2=0.02)			
Intercept	-0.46	0.47	0.33
IRRI (vs. PCMM)	-0.28	0.60	0.64
Prior Alcohol Use Disorder (vs. No Prior Alcohol Use Disorder)	0.75	0.61	0.22
Change in Total Substance Use Spectrum Score (n=74, R2=0.08)			
Intercept	-0.98	1.24	0.43
IRRI (vs. PCMM)	-2.15	1.59	0.18
Prior Alcohol Use Disorder (vs. No Prior Alcohol Use Disorder)	3.60	1.64	**0.03**

IRRI=integrated risk reduction intervention; PCMM=psychiatric care with medical monitoring

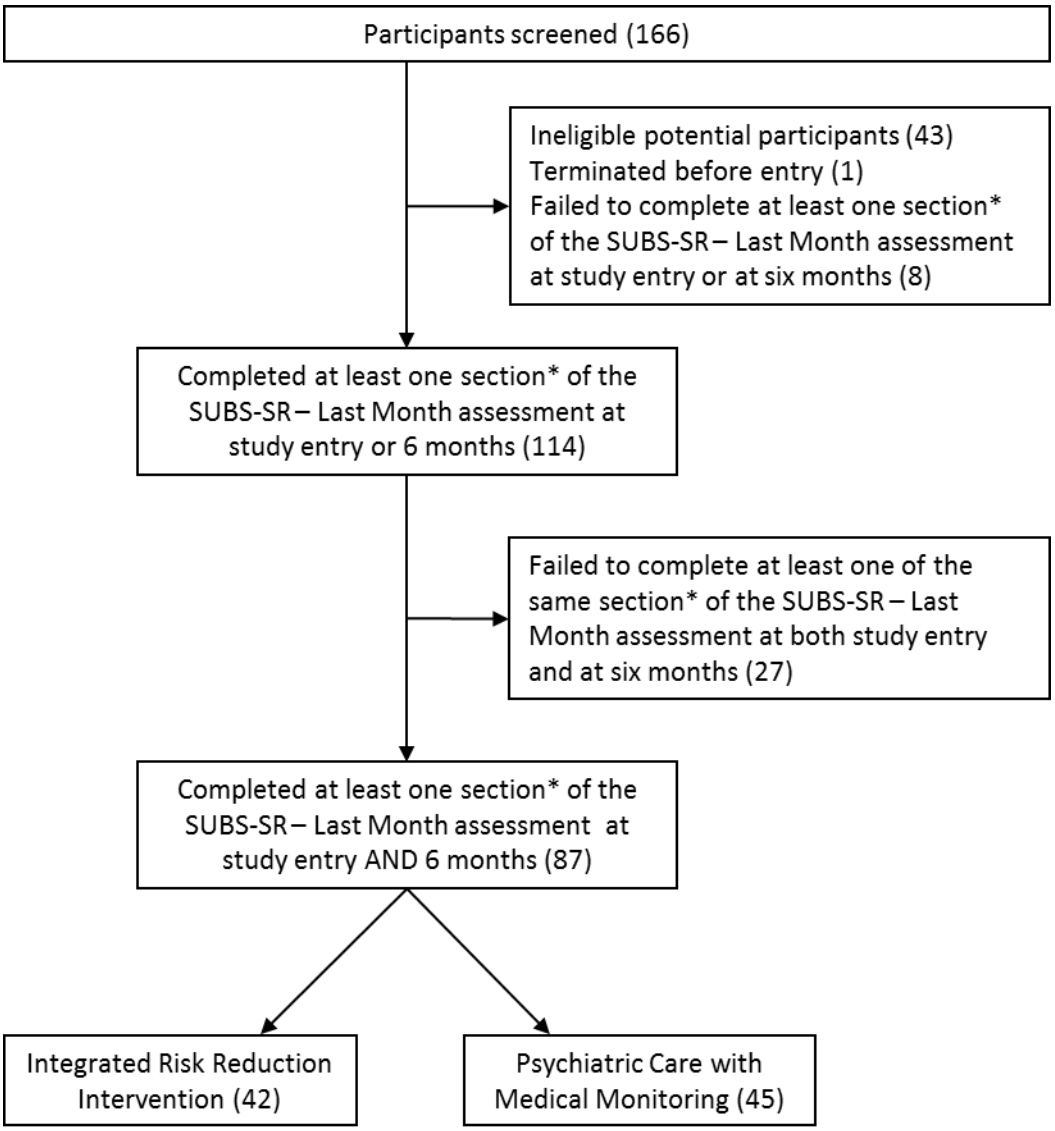
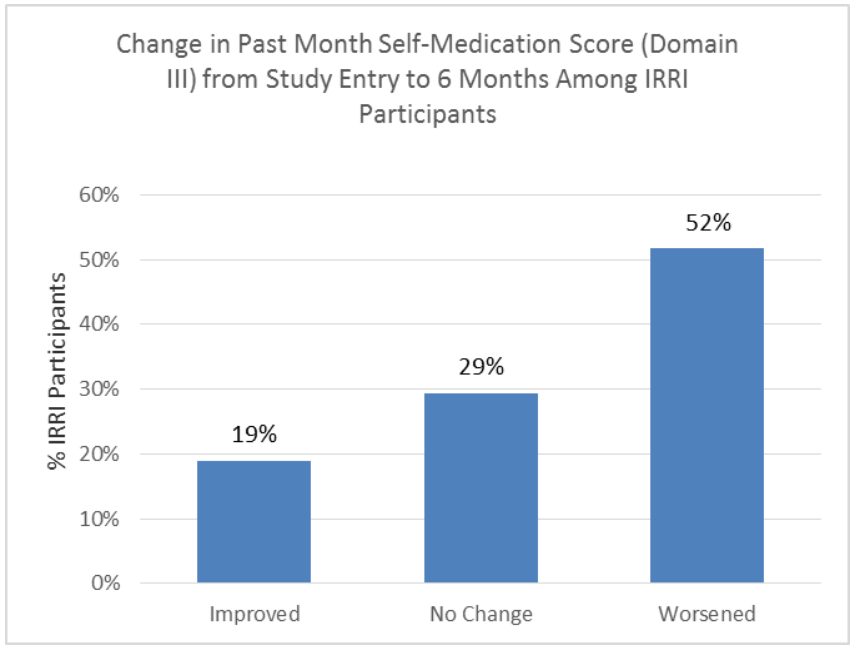


Figure 1. Flow chart of participants in substance use spectrum analyses

*Section: Domain I (substance use, questions 1-22), domain III (self-medication, questions 42-96), domain VI (substance use disorder symptoms, questions 109-131), or total substance use spectrum (all questions: 1-131) from the Self-Report Last Month Substance Use Spectrum assessment (SUBS-SR – Last Month).



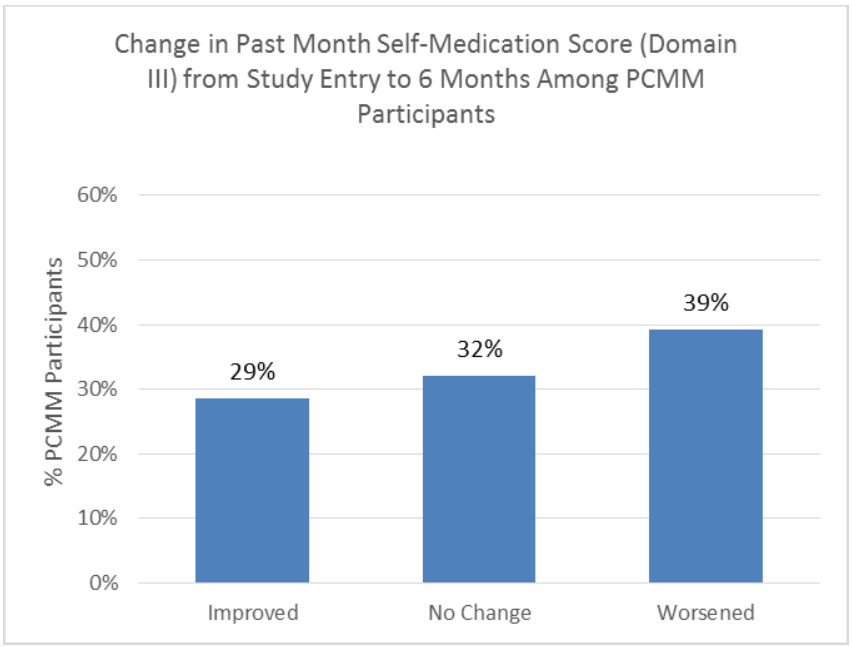
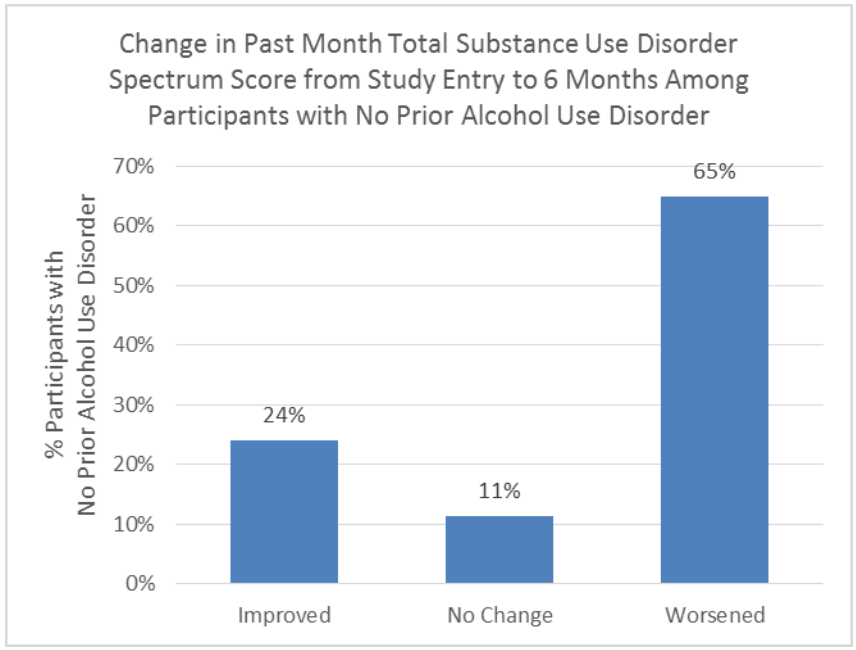


Figure 2. Comparison between treatment groups of change in past month self-medication (domain III) Self-Report Last Month Substance Use Spectrum assessment (SUBS-SR – Last Month) scores from study entry to six months

IRRI=integrated risk reduction intervention; PCMM=psychiatric care with medical monitoring



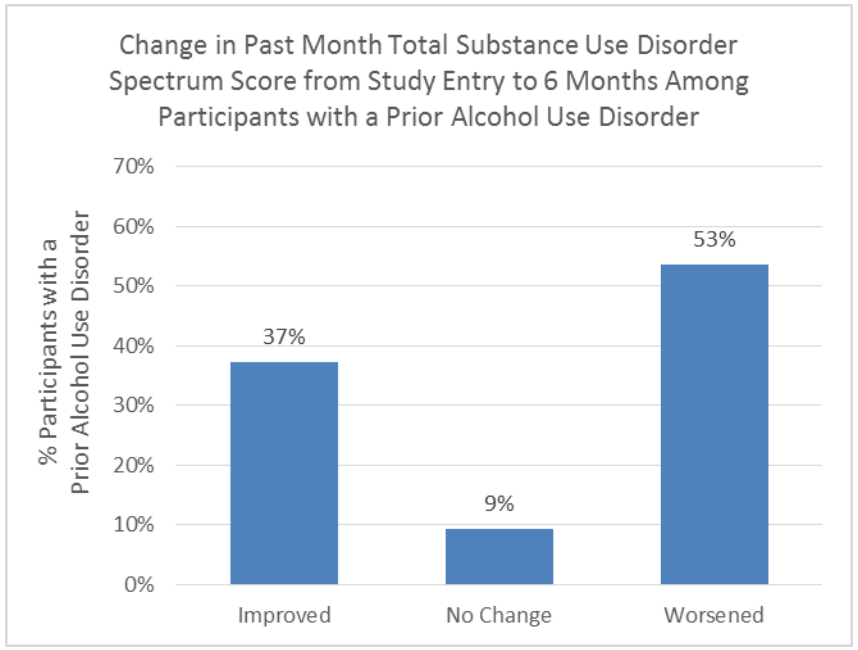
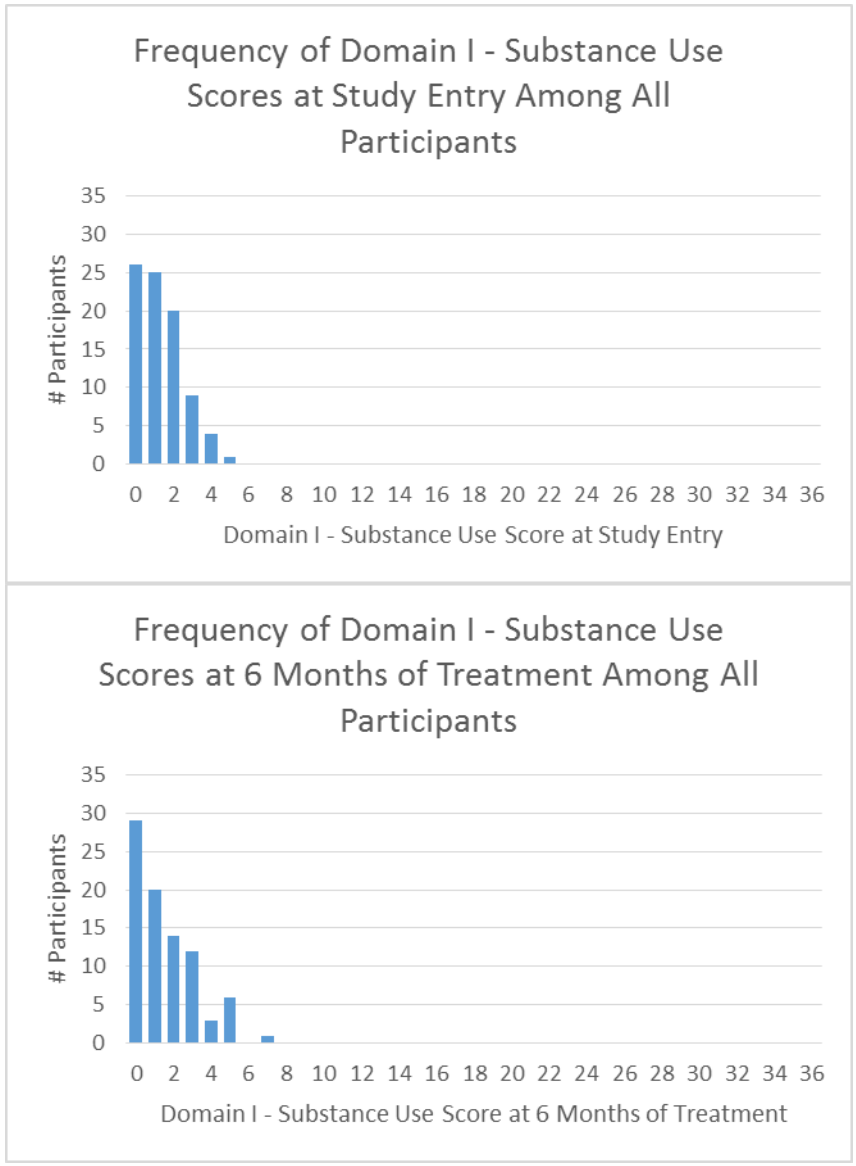
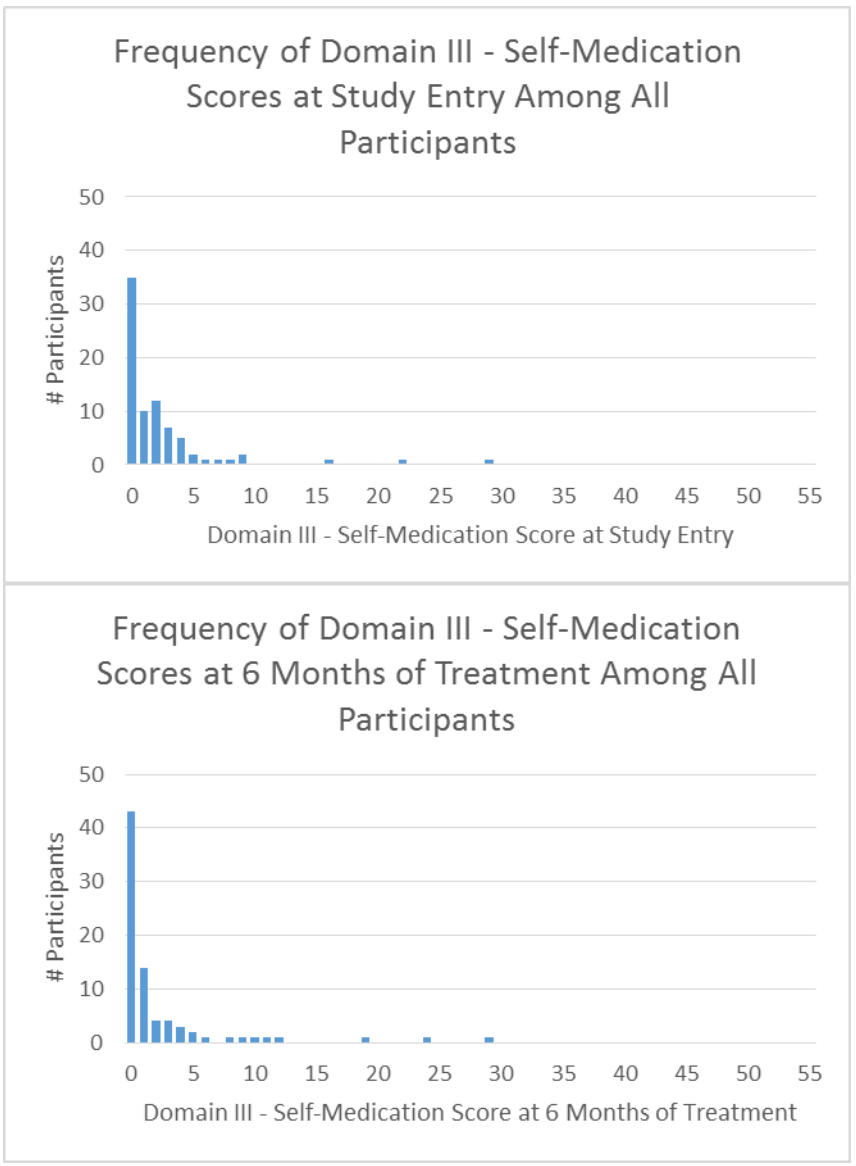


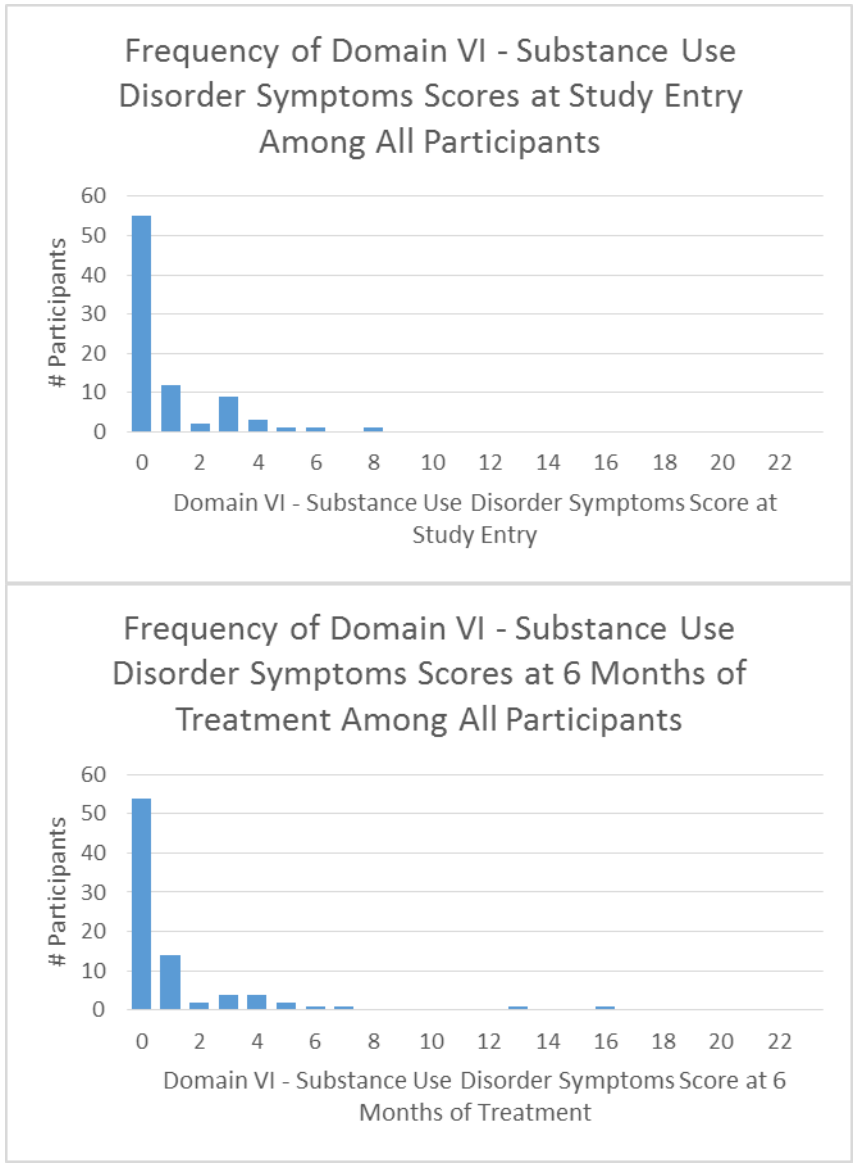
Figure 3. Comparison between prior alcohol use disorder groups of change in past month total Self-Report Last Month Substance Use Spectrum assessment (SUBS-SR – Last Month) scores from study entry to six months


Frequency of Domain I - Substance Use Scores at Study Entry Among All Participants
Participants
0 5 10 15 20 25 30 35
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36
Domain I - Substance Use Score at Study Entry
Frequency of Domain I - Substance Use Scores at 6 Months of Treatment Among All Participants
Participants
0 5 10 15 20 25 30 35
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36
Domain I - Substance Use Score at 6 Months of Treatment

A.

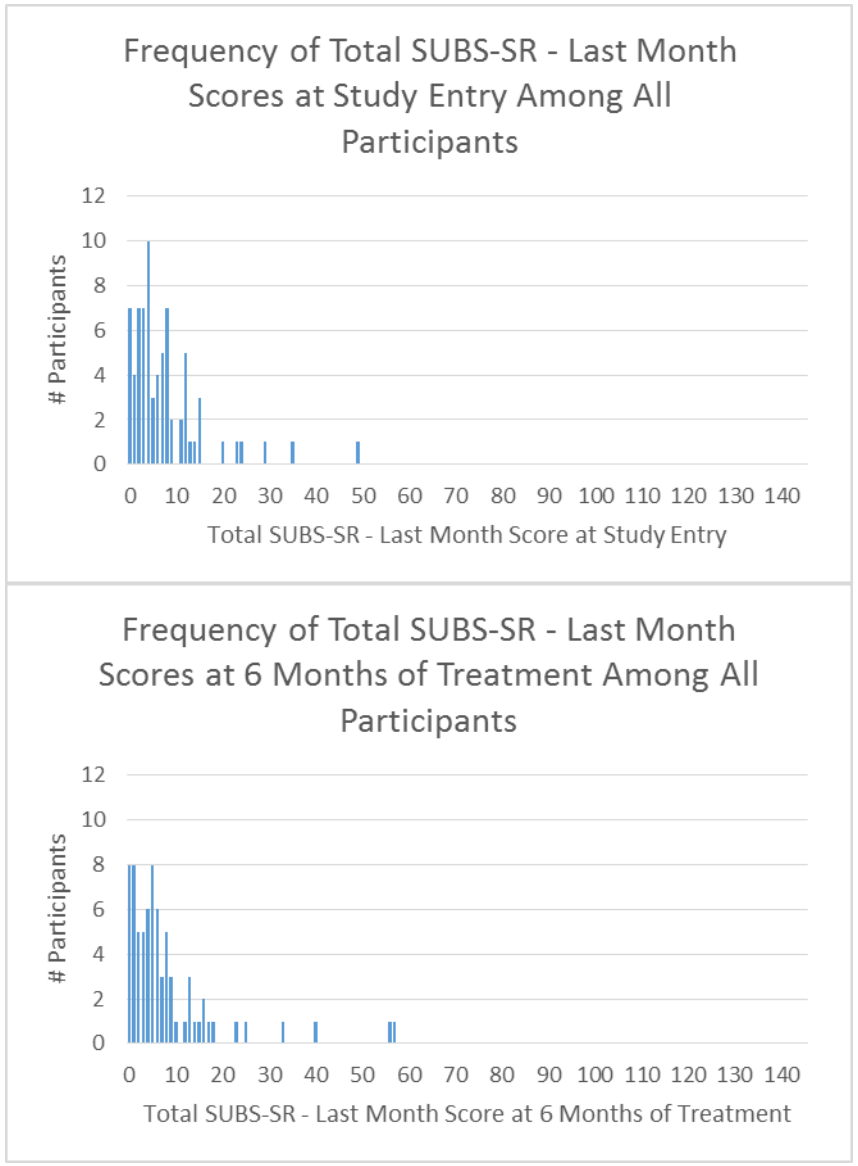

Frequency of Domain III - Self-Medication Scores at Study Entry Among All Participants
Participants
0 10 20 30 40 50
0 5 10 15 20 25 30 35 40 45 50 55
Domain III - Self-Medication Score at Study Entry
Frequency of Domain III - Self-Medication Scores at 6 Months of Treatment Among All Participants
Participants
0 10 20 30 40 50
0 5 10 15 20 25 30 35 40 45 50 55
Domain III - Self-Medication Score at 6 Months of Treatment

B.


Frequency of Domain VI - Substance Use Disorder Symptoms Scores at Study Entry Among All Participants
Participants
0
10
20
30
40
50
60
0 2 4 6 8 10 12 14 16 18 20 22
Domain VI - Substance Use Disorder Symptoms Score at Study Entry

C.

Frequency of Domain VI - Substance Use Disorder Symptoms Scores at 6 Months of Treatment Among All Participants
Participants
0
10
20
30
40
50
60
0 2 4 6 8 10 12 14 16 18 20 22
Domain VI - Substance Use Disorder Symptoms Score at 6 Months of Treatment


Frequency of Total SUBS-SR - Last Month Scores at Study Entry Among All Participants
Participants
0
2
4
6
8
10
12
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140
Total SUBS-SR - Last Month Score at Study Entry

D.

Frequency of Total SUBS-SR - Last Month Scores at 6 Months of Treatment Among All Participants
Participants
0
2
4
6
8
10
12
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140
Total SUBS-SR - Last Month Score at 6 Months of Treatment

Figure 4. Comparison of past month total Self-Report Last Month Substance Use Spectrum assessment (SUBS-SR – Last Month) scores from study entry and six months
A. Domain I of the SUBS-SR – Last Month – Substance use
B. Domain III of the SUBS-SR – Last Month - Use of substances or drugs as self-medication
C. Domain VI of the SUBS-SR – Last Month – Symptoms of substance use disorder
D. Total score of the SUBS-SR – Last Month

BIBLIOGRAPHY

American Psychiatric, A., & American Psychiatric Association, D. S. M. T. F. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5*. Arlington, VA: American Psychiatric Association.

American Psychiatric Association., & American Psychiatric Association. Task Force on DSM-IV. (2000). *Diagnostic and statistical manual of mental disorders : DSM-IV-TR* (4th ed.). Washington, DC: American Psychiatric Association.

Bizzarri, J., Benedetti, A., Rucci, P., Scarpellini, P., Dilani, F., Milanti, M., . . . Cassano, G. (2009). Comorbidity with anxiety and substance use disorders in patients with schizophrenia. *Giornale Italiano di Psicopatologia / Italian Journal of Psychopathology, 15*(2), 120-125.

Bizzarri, J. V., Sbrana, A., Rucci, P., Ravani, L., Massei, G. J., Gonnelli, C., . . . Cassano, G. B. (2007). The spectrum of substance abuse in bipolar disorder: reasons for use, sensation seeking and substance sensitivity. *Bipolar Disorders, 9*(3), 213-220. doi: 10.1111/j.1399-5618.2007.00383.x

Brown, E. S., Nejtek, V. A., Perantie, D. C., & Bobadilla, L. (2002). Quetiapine in bipolar disorder and cocaine dependence. *Bipolar Disord, 4*(6), 406-411.

Brown, E. S., Nejtek, V. A., Perantie, D. C., Orsulak, P. J., & Bobadilla, L. (2003). Lamotrigine in patients with bipolar disorder and cocaine dependence. *J Clin Psychiatry, 64*(2), 197-201.

Carrà, G., Bartoli, F., Crocamo, C., Brady, K. T., & Clerici, M. (2014). Attempted suicide in people with co-occurring bipolar and substance use disorders: systematic review and meta-analysis. *Journal of Affective Disorders, 167*, 125-135. doi: 10.1016/j.jad.2014.05.066

Chengappa, K. N., Gershon, S., & Levine, J. (2001). The evolving role of topiramate among other mood stabilizers in the management of bipolar disorder. *Bipolar Disord, 3*(5), 215-232.

Crump, C., Sundquist, K., Winkleby, M. A., & Sundquist, J. (2013). Comorbidities and mortality in bipolar disorder: A Swedish national cohort study. *JAMA Psychiatry, 70*(9), 931-939. doi: 10.1001/jamapsychiatry.2013.1394

Dalton, E. J., Cate-Carter, T. D., Mundo, E., Parikh, S. V., & Kennedy, J. L. (2003). Suicide risk in bipolar patients: the role of co-morbid substance use disorders. *Bipolar Disord, 5*(1), 58-61.

Dilsaver, S. C. (2011). An estimate of the minimum economic burden of bipolar I and II disorders in the United States: 2009. *J Affect Disord, 129*(1-3), 79-83. doi: 10.1016/j.jad.2010.08.030

Fagiolini, A., Frank, E., Houck, P. R., Mallinger, A. G., Swartz, H. A., Buysse, D. J., . . . Kupfer, D. J. (2002). Prevalence of obesity and weight change during treatment in patients with bipolar I disorder. *J Clin Psychiatry, 63*(6), 528-533.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (1995). *Structured Clinical Interview for DSM-IV Axis I Disorders - Patient Edition (SCID-I/P, Version 2.0)*. New York: Biometrics Research, New York State Psychiatric Institute.

Frank, E., Wallace, M. L., Hall, M., Hasler, B., Levenson, J. C., Janney, C. A., . . . Kupfer, D. J. (2014). An Integrated Risk Reduction Intervention can reduce body mass index in individuals being treated for bipolar I disorder: results from a randomized trial. *Bipolar Disord*. doi: 10.1111/bdi.12283

Garcia-Portilla, M. P., Saiz, P. A., Benabarre, A., Florez, G., Bascaran, M. T., Díaz, E. M., . . . Bobes, J. (2010). Impact of substance use on the physical health of patients with bipolar disorder. *Acta Psychiatrica Scandinavica, 121*(6), 437-445. doi: 10.1111/j.1600-0447.2009.01498.x

Gender: 2000 | Census 2000 brief. (September 2001). from http://www.census.gov/prod/2001pubs/c2kbr01-9.pdf

Hamilton, M. (1960). A rating scale for depression. *J Neurol Neurosurg Psychiatry, 23*, 56-62.

Hoblyn, J. C., Balt, S. L., Woodard, S. A., & Brooks, J. O., III. (2009). Substance use disorders as risk factors for psychiatric hospitalization in bipolar disorder. *Psychiatric Services, 60*(1), 50-55. doi: 10.1176/appi.ps.60.1.50

Jones, S. H., Barrowclough, C., Allott, R., Day, C., Earnshaw, P., & Wilson, I. (2011). Integrated motivational interviewing and cognitive–behavioural therapy for bipolar disorder with comorbid substance use. *Clinical Psychology & Psychotherapy, 18*(5), 426-437.

Kennedy, N., Everitt, B., Boydell, J., Van Os, J., Jones, P. B., & Murray, R. M. (2005). Incidence and distribution of first-episode mania by age: results from a 35-year study. *Psychol Med, 35*(6), 855-863.

Kessler, R. C., Chiu, W. T., Demler, O., Merikangas, K. R., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry, 62*(6), 617-627. doi: 10.1001/archpsyc.62.6.617

Kroon, J. S., Wohlfarth, T. D., Dieleman, J., Sutterland, A. L., Storosum, J. G., Denys, D., . . . Sturkenboom, M. C. J. M. (2013). Incidence rates and risk factors of bipolar disorder in the general population: a population-based cohort study. *Bipolar Disorders, 15*(3), 306-313. doi: 10.1111/bdi.12058

Mago, R., Borra, D., & Mahajan, R. (2014). Role of adverse effects in medication nonadherence in bipolar disorder. *Harv Rev Psychiatry, 22*(6), 363-366. doi: 10.1097/HRP.0000000000000017

Marshall, D. F., Walker, S. J., Ryan, K. A., Kamali, M., Saunders, E. F. H., Weldon, A. L., . . . Langenecker, S. A. (2012). Greater executive and visual memory dysfunction in comorbid bipolar disorder and substance use disorder. *Psychiatry Research, 200*(2-3), 252-257. doi: 10.1016/j.psychres.2012.06.013

Matson, J. L., Gonzalez, M. L., Smith, K. R., Terlonge, C., Thorson, R. T., & Dixon, D. R. (2006). Assessing side effects of pharmacotherapy treatment of bipolar disorder: a 20-year review of the literature. *Res Dev Disabil, 27*(5), 467-500. doi: 10.1016/j.ridd.2005.06.002

Mazza, M., Mandelli, L., Di Nicola, M., Harnic, D., Catalano, V., Tedeschi, D., . . . Janiri, L. (2009). Clinical features, response to treatment and functional outcome of bipolar disorder patients with and without co-occurring substance use disorder: 1-year follow-up. *Journal of Affective Disorders, 115*(1-2), 27-35. doi: 10.1016/j.jad.2008.08.019

McLellan, A. T., Kushner, H., Metzger, D., Peters, R., Smith, I., Grissom, G., . . . Argeriou, M. (1992). The Fifth Edition of the Addiction Severity Index. *J Subst Abuse Treat, 9*(3), 199-213.

Merikangas, K. R., Akiskal, H. S., Angst, J., Greenberg, P. E., Hirschfeld, R. M., Petukhova, M., & Kessler, R. C. (2007). Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey Replication. *Arch Gen Psychiatry, 64*(5), 543-552. doi: 10.1001/archpsyc.64.5.543

Monk, T. H., Flaherty, J. F., Frank, E., Hoskinson, K., & Kupfer, D. J. (1990). The Social Rhythm Metric. An instrument to quantify the daily rhythms of life. *J Nerv Ment Dis, 178*(2), 120-126.

Regier, D. A., Farmer, M. E., Rae, D. S., Locke, B. Z., Keith, S. J., Judd, L. L., & Goodwin, F. K. (1990). Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. *JAMA, 264*(19), 2511-2518.

Roshanaei-Moghaddam, B., & Katon, W. (2009). Premature mortality from general medical illnesses among persons with bipolar disorder: a review. *Psychiatr Serv, 60*(2), 147-156. doi: 10.1176/appi.ps.60.2.147

Sachs, G. S., Guille, C., & McMurrich, S. L. (2002). A clinical monitoring form for mood disorders. *Bipolar Disord, 4*(5), 323-327.

Sachs, G. S., Thase, M. E., Otto, M. W., Bauer, M., Miklowitz, D., Wisniewski, S. R., . . . Rosenbaum, J. F. (2003). Rationale, design, and methods of the systematic treatment enhancement program for bipolar disorder (STEP-BD). *Biol Psychiatry, 53*(11), 1028-1042.

Sagman, D., & Tohen, M. (2012). Comorbidity in bipolar disorder. *Psychiatric Times, 29*(6), 30.

Sbrana, A., Bizzarri, J. V., Rucci, P., Gonnelli, C., Doria, M. R., Spagnolli, S., . . . Cassano, G. B. (2005). The spectrum of substance use in mood and anxiety disorders. *Compr Psychiatry, 46*(1), 6-13. doi: 10.1016/j.comppsych.2004.07.017

Sbrana, A., Dell'Osso, L., Gonnelli, C., Impagnatiello, P., Doria, M. R., Spagnolli, S., . . . Endicott, J. (2003). Acceptability, validity and reliability of the Structured Clinical Interview for the Spectrum of Substance Use (SCI-SUBS): a pilot study. *Int J Methods Psychiatr Res, 12*(2), 105-115.

Spearing, M. K., Post, R. M., Leverich, G. S., Brandt, D., & Nolen, W. (1997). Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP. *Psychiatry Res, 73*(3), 159-171.

Wang, P. W., Sachs, G. S., Zarate, C. A., Marangell, L. B., Calabrese, J. R., Goldberg, J. F., . . . Ketter, T. A. (2006). Overweight and obesity in bipolar disorders. *J Psychiatr Res, 40*(8), 762-764. doi: 10.1016/j.jpsychires.2006.01.007

Weiss, R. D., Griffin, M. L., Greenfield, S. F., Najavits, L. M., Wyner, D., Soto, J. A., & Hennen, J. A. (2000). Group therapy for patients with bipolar disorder and substance dependence: results of a pilot study. *J Clin Psychiatry, 61*(5), 361-367.

Weiss, R. D., Griffin, M. L., Jaffee, W. B., Bender, R. E., Graff, F. S., Gallop, R. J., & Fitzmaurice, G. M. (2009). A "community-friendly" version of integrated group therapy for patients with bipolar disorder and substance dependence: A randomized controlled

trial. *Drug and Alcohol Dependence, 104*(3), 212-219. doi: 10.1016/j.drugalcdep.2009.04.018

Weiss, R. D., Griffin, M. L., Kolodziej, M. E., Greenfield, S. F., Najavits, L. M., Daley, D. C., . . . Hennen, J. A. (2007). A randomized trial of integrated group therapy versus group drug counseling for patients with bipolar disorder and substance dependence. *The American Journal of Psychiatry, 164*(1), 100-107. doi: 10.1176/appi.ajp.164.1.100

Weiss, R. D., Najavits, L. M., & Greenfield, S. F. (1999). A relapse prevention group for patients with bipolar and substance use disorders. *J Subst Abuse Treat, 16*(1), 47-54.

WHO | Mental disorders | Fact sheet N°396. (October 2014). from http://www.who.int/mediacentre/factsheets/fs396/en/#.VMvcHHorXfw.mendeley

Wyatt, R. J., & Henter, I. (1995). An economic evaluation of manic-depressive illness--1991. *Soc Psychiatry Psychiatr Epidemiol, 30*(5), 213-219.

Young, R. C., Biggs, J. T., Ziegler, V. E., & Meyer, D. A. (1978). A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry*, *133*, 429-435.