A Randomized Controlled Trial of Quetiapine for the Treatment of Youth With Co-Occurring Substance Use Disorders (SUDs) and Severe Mood Dysregulation (SMD)

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1 List of Abbreviations

Abbreviation	Abbreviation definition
SUD	Substance use disorder
SMD	Severe mood dysregulation
DMDD	Disruptive mood dysregulation disorder
SGA	Second Generation antipsychotic
BD	Bipolar Disorder
M.I.N.I 7.0	Mini-International Neuropsychiatric Interview
KSADS-PL	DMS-V Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime
YMRS	Young Mania Rating Scale
AIMS	Abnormal Involuntary Movement Scale
CGI	Clinical Global Impressions
C-SSRS	Columbia Suicide Severity Rating Scale
GAF	DSM-V Global Assessment of Functioning
ASR	Adult Self-Report
YSR	Youth Self-Report
BRIEF	Behavior Rating Inventory of Executive Function
BDI-II	Beck Depression Inventory-II
PHQ-9	Patient Health Questionnaire-9
TLFB	Timeline Followback of Substance Use
AE	Adverse event
SAE	Serious adverse event

2 Protocol Summary

Title:	A Randomized Controlled Trial of Quetiapine for the Treatment of Youth With Co-Occurring Substance Use Disorders (SUDs) and Severe Mood Dysregulation (SMD)
Population:	We plan to enroll 56 youth, ages 15 to 24, with SUD and SMD.
Intervention:	**Drug name**: Quetiapine **Route of administration**: Oral **Dose**: Quetiapine will be titrated to the maximum achieved dose as tolerated during the first three weeks of the trial. Study medication will be initiated at 50 mg twice daily and will be gradually up-titrated by 100 mg per day (increasing by 50 mg twice daily) to a maximum dose of 150 mg twice daily. Titration of the study medication is flexible, guided by tolerability with the option for slower, lower, or hold titration. If a participant prefers once daily dosing instead of twice daily dosing this will be allowed.
Objectives:	**Specific Aim 1**: To evaluate the effect of quetiapine on SUD in youth with SUD and SMD

	Specific Aim 2: To evaluate the effect of quetiapine on SMD in youth with SUD and SMD. **Specific Aim 3**: To evaluate the effect of quetiapine on engagement in outpatient treatment in youth with SMD and SUD. **Specific Aim 4:** Assess the safety and tolerability of quetiapine in youth with SUD and SMD. **Exploratory Aims:** Evaluate whether substance use and mood symptoms are related and if so, examine the nature of the relationship. Evaluate whether scales that measure emotional regulation, the Emotional Control Subscale for the Behavior Rating Inventory of Executive Function and the Anxiety/Depression, Attention, and Aggression subscales of the Youth Self-Report or Adult Self-Report, predict treatment response and/or what specific components improve with treatment. Evaluate whether the Patient Health Questionnaire-9 is a valid measure of mood symptoms in youth with co-occurring substance use and SMD. Examine the impact of quetiapine (versus placebo) on self-reported and objective measures of non-primary substances of use. Evaluate whether differences exist in medication adherence, high-risk behaviors associated with HIV and Hepatitis C, and global functioning between the active treatment and placebo groups. Examine the impact of common psychiatric co-morbidities for youth with SUD and SMD on outcome and retention in the study. Evaluate whether youth's reasons for substance use, motivation to change, and confidence in their ability to change impact response to treatment. Assess whether level of engagement in self help and therapy impact response to treatment. Evaluate whether peer substance use and exposure to substance use in the subject's living environment impact response to treatment.
Design/Methodology:	To evaluate the effect of quetiapine on substance use, SMD, and engagement in care, we are proposing an 8-week randomized, double blind placebo controlled parallel design study for youth with SUD and SMD who are entering into or currently engaged in behavioral therapy. Please refer to the Schedule of Events in the Appendix for a table of visits and assessments.
Total Study Duration:	Open for Data Analysis until May 2022

Subject Participation Duration: 10 weeks

3 Background/Rationale & Purpose

3.1 Background Information

Substance use disorders (SUDs) in youth commonly co-occur with categorical and dimensional measures of psychopathology [1-4] including prominent dysregulation of mood and emotions found in severe mood dysregulation (SMD). For clarity in this project, SMD includes bipolar spectrum disorders, disruptive mood dysregulation disorder, and mood disorder not otherwise specified. While a growing literature suggests an important link between SMD and SUD [5] the relationship between SMD and SUDs has been best characterized in youth with SMD indicative of bipolar disorder (BD). Specifically, among adolescents with SUD, 8% to 32% have been found to have BD. [1, 6-8] Conversely, clinical samples of adolescents with BD also have elevated rates of SUD, ranging from 9% to 39% when evaluated cross-sectionally and followed prospectively.[9-14]

SUD co-occurring with SMD is particularly concerning due to the morbidity associated with the co-occurrence of both disorders. For example, in BD we found that young people (mean age 21 years) with co-occurring SUD and BD had significantly higher rates of severe SUDs (13% had an opioid use disorder and 9% a cocaine use disorder) compared to similar aged non-mood disordered control peers.[15] Co-occurring SUD and BD in youth has also been associated with increased morbidity when compared to youth with BD alone. Compared to BD alone, youth with SUD and BD have higher rates of lifetime hospitalizations[15], increased lifetime prevalence of suicide attempts, and higher rates of past year legal difficulties, and more frequent unplanned pregnancies and abortions among females.[16] Delbello and colleagues [11] found that none of the adolescents with BD, attention deficit hyperactivity disorder (ADHD), and alcohol use disorder were adherent with medication during the year following hospitalization for a manic episode compared to 38% in similarly affected adolescents without an alcohol use disorder. Medication nonadherence was associated with a longer recovery period after initial hospitalization in this same sample of adolescents with BD.[11]

Although less studied, evidence exists that SMD, such as observed in BD, may be driving SUD in some youth.[5, 17-19] For example, in a case controlled sample of BD, we reported that emotional dysregulation was significantly linked with an increased risk for SUD.[5] Lorberg and colleagues found that adolescents with BD and SUD were more likely than controls with SUD to start using their drug of choice to change their mood[18] Additionally, Goldstein and colleagues in a longitudinal sample of BD spectrum youth found a strong relationship between mood symptoms and substance use.[17] In adolescents with BD greater hypo/mania symptom severity was observed in the 12 weeks before they developed a SUD compared to other 12 week periods over four year follow up and compared to adolescents with BD who did not develop a SUD. Since SMD may be associated with substance use it follows that treatments developed for SMD may be effective in reducing substance use in youth with co-

occurring SUD and SMD.

Despite the high prevalence and morbidity associated with SUDs and SMD in youth, there is a dearth of studies on the treatment of this comorbidity. Only one small randomized control trial (RCT) of lithium in SUD adolescents with or at high risk for BD (e.g. SMD) has been published. [20] In this study twenty-five adolescents were randomized to lithium with mean blood levels 0.9 mEq/L versus placebo and followed twice weekly during the six week trial. Adolescents treated with lithium had significant improvement in their SUD and overall improved functioning compared to controls.[20] Interestingly, no change in mood scores was observed, and despite a strong signal in a relatively small sample that treatment with a mood stabilizer leads to a reduction in substance use in adolescents with co-occurring SUD and SMD, no other medication RCTs have been published in this high-risk group.

Lithium's usefulness for the treatment of youth with SUDs and SMD has been limited due to lithium's narrow therapeutic index and concern regarding toxicity in patients with active substance use due to associated shifts in hydration and adherence to monitoring.[21, 22] Since Geller's publication a new class of mood stabilizers, second generation antipsychotic (SGAs) medication, have been developed that appear to have less risk for acute toxicity. A significant literature supports the effectiveness of SGAs for the treatment of SMD, specifically adolescent manic symptoms and DMDD.[23-26] A recent meta-analysis suggested superior efficacy of SGAs for mania in adolescents compared to traditional mood stabilizers.[24] Several SGAs have FDA approval for use in adolescents with manic episodes associated with BD including: risperidone, olanzapine, quetiapine, and aripiprazole.[27] Furthermore, adolescent versus adult-onset manic symptoms appear more responsive to SGAs than traditional mood stabilizers.[28] Less information exists on the effectiveness of SGAs for the treatment of depressive symptoms in youth with BD. [29] Given the efficacy associated with SGAs for SMD it is no surprise that SGAs are increasingly used in the treatment of SMD.[30, 31]

Since excess dopamine is thought to mediate the reinforcing effect of substances of abuse in the reward circuitry system of the brain[32] dopamine antagonists and SGAs in particular have been investigated as a treatment for SUDs in adults. Positive findings have been found for olanzapine, aripiprazole and quetiapine for various measures associated with substance use in adults with SUDs. Both one dose of olanzapine and five days of daily olanzapine were shown to be effective in decreasing alcohol cravings when subjects were exposed to alcohol.[33, 34] Further work by Hutchinson et al in a 12-week RCT demonstrated olanzapine to be effective for decreasing cravings for alcohol and alcohol consumption in subjects with alcohol dependence who had a particular genetic polymorphism.[35] Aripiprazole was evaluated as a treatment for adults with alcohol dependence in a 12-week RCT.[36] While there was no difference between aripriprazole and placebo in percent days abstinent, the aripiprazole group reported significantly fewer drinks per drinking day and subjective improvement in their alcohol dependence.[36] In contrast, several RCTs of both olanzapine and risperidone did not show superior efficacy to placebo in decreasing cravings for cocaine[37-39] or cocaine use[37, 38, 40] in adults with cocaine use disorders. Open label treatment with quetiapine however was shown to be effective in decreasing cravings for

cocaine and days of cocaine use.[41] A retrospective review of males with alcohol dependence who were treated or not treated with quetiapine demonstrated treatment with quetiapine was associated with increased number of days abstinent and decreased number of hospitalizations.[42] Another retrospective review of patients with opioid use disorders engaged in outpatient opioid detoxification found that quetiapine was associated with decreased opioid cravings in 74% of patients.[43] Hence, the preponderance of data seems to suggest a role for SGAs in SUD; however, little is known about this treatment in youth with SUD.

Research on the efficacy of SGA medication in RCTs for the treatment of adults with co-occurring SUD and a type of SMD, BD, has been mixed. Quetiapine, approved by the FDA for both manic and depressive episodes associated with adult BD, has been the most extensively studied SGA for the treatment of adults with co-occurring SUD and BD. When compared to placebo as adjuvant treatment, quetiapine significantly decreased alcohol use and depressive symptoms in a subgroup of adult patients with heavy baseline levels of alcohol consumption who met criteria for an alcohol use disorder and BD.[44] Both quetiapine and risperidone were equally effective in improving mania, mixed, and depressive symptoms as well as drug cravings when compared in a RCT trial for the treatment of adults with co-occurring stimulant use disorders and BD.[45] An open label study of quetiapine for cocaine dependence and BD showed improvements in cravings for cocaine and measures of mood, with nonsignificant decreases in days per week of cocaine use.[46] Other studies that evaluated quetiapine as adjuvant medication and the primary medication for the treatment of co-occurring alcohol dependence and BD did not find significant differences between placebo.[47, 48] Although treatment trials of adults with co-occurring SUD and BD provide some guidance on effective treatment strategies it is unclear if youth with co-occurring SUD and SMD would respond similarly to adults based on the different phenotypic descriptions of BD and medication treatment responses seen between youth and adults with BD.

To our knowledge there have been no published papers to date specifically examining treatment of co-occurring SUD and SMD in youth with SGAs. Delbello reported on a RCT in adolescents with frequent cannabis use and BD with symptoms of mania (Young Mania Rating Scale (YMRS) score greater than 20) who were treated with quetiapine and randomized to topiramate or placebo.[49] Although quetiapine plus topiramate was more effective than quetiapine alone in reducing substance use, both treatment groups showed overall improvement in substance use and mood. Substance use decreased by 10 joints per week (-72%) in the quetiapine only group and by 10.6 joints per week (-96%) in the quetiapine plus topiramate group. YMRS scores decreased by 16 in the quetiapine only group (ca -53%) and 14 (ca -47%) in the quetiapine plus topiramate group—these data suggest quetiapine could be a highly useful intervention for treatment of SUD co-occurring with BD when adolescents are experiencing symptoms of mania. Further research is warranted to determine if quetiapine would be more efficacious compared to placebo in decreasing both SUD and affective symptoms.

To this end, we aim to study the efficacy of a SGA, quetiapine, as treatment for active SUD, as well as

mood symptoms in youth with SUD and SMD in a naturalistic, outpatient treatment setting. Quetiapine was selected as the SGA to target SUD and SMD since the adolescent and adult literature has suggested possible efficacy for treatment of SUDs and quetiapine is FDA approved for the treatment of adolescent BD.

We propose to use quetiapine as an adjunct treatment to treatment as usual to improve both SUD and mood symptoms in a double blind, parallel design RCT over 8 weeks for youth with SUD and SMD who are in a comprehensive outpatient treatment program utilizing evidence based family and individual behavioral therapies.[50, 51] Our trial will examine a number of important variables including the impact of acute treatment with quetiapine on SUD, mood, and treatment engagement in youth with co-occurring SUD and SMD. Although this study cannot directly evaluate the relationship between substance use and mood symptoms and vice versa, we will closely monitor the trajectory of these symptoms. We will also explore whether scales that measure SMD—the Emotional Control Subscale for the Behavior Rating Inventory of Executive Function (BRIEF)[52] and the Anxiety/Depression, Attention, and Aggression (AAA) subscales of the Youth Self-report (YSR)[53] or Adult Self-Report (ASR)[54], which are self-report versions of Achenbach System of Empirically Based Assessments based on age—predict treatment response in youth with co-occurring SUD and SMD; as well as specific improvement in areas thereof that may be reflective of improved SUD. We will explore the impact of quetiapine (versus placebo) on self-reported and objective measures of non-primary substances of use. We also plan on exploring the impact of pharmacologic treatment on medication adherence, retention in treatment, high-risk behaviors associated with human immunodeficiency virus (HIV) and hepatitis C virus (HCV), and overall global functioning. Furthermore, we will examine the impact of common psychiatric co-morbidities for youth with SUD and SMD, such as conduct disorder, attention deficit hyperactivity disorder (ADHD), and anxiety, on outcome and retention in the study.

As noted earlier, quetiapine is FDA approved for the treatment manic episodes associated with bipolar disorder in adolescents, and the treatment of manic and depressive episodes associated with bipolar disorder in adults. An IND was not requested because this study is not intended to support a new indication for use, change in labeling for the drug, or change in the advertising of quetiapine. Furthermore, this study does not involve a change in route of administration or dosage level, use in a subject population, or other factor that significantly increases the risk associated with the use of quetiapine.

This study was originally approved by the Partners Healthcare IRB on 09/14/2016 and has been taking place at the Massachusetts General Hospital (MGH). To date the study has completed 161 phone screens, scheduled 75 screening visits, consented 39 subjects, and randomized 19 subjects. Since the PI has changed employers from MGH to BMC this study is currently closed to recruitment at MGH and is being closed with the Partners IRB.

This study will be conducted in compliance with the protocol, applicable regulatory requirements, and BMC/BU Medical Campus Human Research Protection policies and procedures.

3.2 Rationale and Purpose

Given the morbidity associated with SUDs and SMD there is a need to continue to evaluate strategies to stabilize SUDs when co-occurring with SMD in youth. It is particularly important to evaluate treatment strategies in youth since delayed treatment of both SUDs and SMD in youth has been associated with a more complicated course of illness. [55, 56] The exclusion of youth with SUDs from treatment trials for BD has been a barrier to progress in this field.

Increasing knowledge on effective ways to stabilize and engage this high-risk population in treatment will be of utility to the field by decreasing the morbidity associated with SUD and SMD in youth. Additionally, once treatments for acute stabilization have been established, the field can begin to evaluate maintenance treatment strategies and improve our understanding of the common relationship between substance use and mood longitudinally in youth with co-occurring SUD and SMD.

4 Objectives

4.1 Study Objectives

Primary Objectives:

Objective 1: Evaluate the effect of quetiapine on SUD on youth with SUD and SMD.

Hypothesis 1A: Treatment with quetiapine will decrease self-reported substance use for primary substance of use (e.g. number of days of use past month, % abstinence past month). Hypothesis 1B: Treatment with quetiapine will increase the number of toxicology specimens negative for primary substance of use Hypothesis 1C: Treatment with quetiapine will decrease drug craving for primary substance of use demonstrated by a reduction in the Weiss cravings scale.

Objective 2: Evaluate the effect of quetiapine on SMD in youth with SUD and SMD.

Hypothesis 2A: Treatment with quetiapine will result in a decrease in symptoms of mania demonstrated by reduction in Young Mania Rating Scale. Hypothesis 2B: Treatment with quetiapine will result in a decrease in symptoms of depression demonstrated by reduction in the Beck Depression Inventory II.

Objective 3: Evaluate the effect of quetiapine on engagement in outpatient treatment in youth with SUD and SMD.

Hypothesis 3A: Treatment with quetiapine will lead to greater engagement in outpatient treatment as demonstrated by greater number of appointments attended in the active treatment group.

Objective 4: Assess the safety and tolerability of quetiapine in youth with SUD and SMD.

Exploratory Objectives:

Evaluate whether substance use and mood symptoms are related and if so, examine the nature of the relationship. Evaluate whether scales that measure SMD, the Emotional Control Subscale for the Behavior Rating Inventory of Executive Function and the Anxiety/Depression, Attention, and Aggression subscales of the Youth Self-Report or Adult Self-Report, predict treatment response and/or what specific components improve with treatment. Evaluate whether the Patient Health Questionnaire-9 is a valid measure of mood symptoms in youth with co-occurring substance use and SMD. Examine the impact of quetiapine (versus placebo) on self-reported and objective measures of non-primary substances of use. Evaluate whether differences exist in medication adherence, high risk behaviors associated with HIV and Hepatitis C, and global functioning between the active treatment and placebo groups. Examine the impact of common psychiatric co-morbidities for youth with SUD and SMD on outcome and retention in the study. Evaluate whether youth's reasons for substance use, motivation to change, and confidence in their ability to change impact response to treatment. Assess whether level of engagement in self-help and therapy impact response to treatment. Evaluate whether peer substance use and exposure to substance use in the subject's living environment impact response to treatment.

4.2 Study Outcome Measures

4.2.1 Primary Outcome Measures

Outcome 1: SUD response to quetiapine for primary substance of use will be assessed by Timeline Followback of Substance Use to assess self-report of substance use, toxicology screens negative for substances for objective measurement of substance use, and the Weiss drug craving scale to assess cravings. The Timeline Followback will be used to compare self-report of substance for the month prior to study entry versus the last month of the study. Toxicology screens and the Weiss drug craving scale will compare values from baseline to endpoint.

Outcome 2: SMD response to quetiapine will be assessed by the YMRS and BDI-II comparing values from baseline to endpoint.

Outcome 3: The impact of treatment with quetiapine on outpatient treatment engagement will be monitored by collateral from the outpatient program regarding the percentage of scheduled appointments attended after randomization.

Outcome 4: An EKG will be administered at study screening to screen for cardiac risk factors that would exclude subjects from participation. A blood draw will be completed at screening and completion; approximately 30 ccs of blood will be drawn from each subject over the course of the study. Safety and tolerability of quetiapine monotherapy will be monitored by a battery of blood tests, weight measurements (to calculate Body Mass Index (BMI)), and the AIMS at baseline and endpoint to monitor for extrapyramidal symptoms. Weight, the AIMS, and urine HCG test will also be completed at midpoint. Adverse events, suicidality (C-SSRS), the CGI-S and CGI-I for SUD and SMD will be monitored at every study visit. Vital signs will be monitored at screening, midpoint and endpoint.

4.2.2 Secondary Outcome Measures

Exploratory Outcome Measures: Evaluate whether scales that measure emotional regulation, the Emotional Control Subscale for the BRIEF and the AAA subscales of the YSR or ASR predict treatment response and/or what specific components improve with treatment in youth with co-occurring SUD and SMD. The validity of the PHQ-9 as a measure of mood symptoms in youth with co-occurring substance use and SMD will be evaluated by administering the instrument in conjunction with the BDI-II at Week 0 and every 2 weeks thereafter. The impact of treatment with quetiapine on medication adherence will be assessed with weekly pill counts, a medication diary, and the medication adherence rating scale. Non-primary substances of use will be evaluated by Timeline Followback of substance use, toxicology screens, urine THC levels, and a questionnaire on nicotine use. Changes in high risk behaviors associated with HIV and HCV due to treatment with quetiapine will be assessed with the Risk Behavior Survey. The effect of treatment with quetiapine on functioning will be assessed by the GAF. Psychiatric co-morbidities will be assessed at baseline with specific, predetermined modules from the M.I.N.I. 7.0. For an objective measure of adherence, approximately 4 ccs of blood will be drawn to assess quetiapine levels. This blood will be frozen and analyzed for subjects randomized to Quetiapine at the completion of the study. Changes in the subject's motivation and confidence in their ability to change will be assessed with two questions about subjects' confidence in staying sober and the importance of abstaining from their primary substance of use.

5 Study Design

To evaluate the effect of quetiapine on substance use, SMD, and engagement in care, we are proposing an 8-week randomized, double blind placebo controlled parallel design study for youth with SUD and SMD who are entering into or currently engaged in behavioral therapy. Youth with active substance use who meet criteria for a SUD with the exclusion of current methamphetamine use disorders and unstable opioid use disorders and have symptoms of SMD as quantified by the aggregate score from the Anxiety/Depression, Attention, and Aggression (AAA) of the Youth Self Report or Adult Self Report will be randomized to adjunct treatment with quetiapine or placebo. We define an unstable opioid use disorder as less than three months on medication assisted treatment, i.e. naltrexone extended release, buprenorphine, or methadone. We will be studying use of quetiapine up to 300 mg/day administered in daily or twice-daily dosing. Subjects will be continued on existing medication if indicated (e.g. buspirone for anxiety). Subjects will be asked not to change their existing psychiatric medications while taking the study medication. Subjects will be excluded if they plan on modifying their psychiatric and/or non-psychiatric medications during the study such that they would be increasing the dose of an existing medication that may prolong QTc interval and/or adding a new medication that may prolong QTc interval.

See the Appendix for the Schedule of Events.

5.1 Virtual Visits in the Context of COVID-19

Due to public health concerns regarding the COVID-19 pandemic, we would like to minimize in person interaction as much as possible. Thus, study procedures may take place either in person at Boston Medical Center or remotely through BMC Zoom videoconferencing software. Zoom Video Communications is a remote conferencing services company that provides remote conferencing services, which combines video conferencing, screen sharing services, online meetings, chat, and mobile collaboration, with both audio and video communication options. We will use a BMC Zoom account which is HIPAA compliant. Participants can use zoom via their phone, computer, or tablet/iPad. Both the study clinician and study coordinator will be present during the virtual study visits and conduct the visit in a private and professional setting.

Screening, midpoint and final visits (Weeks 99, 4 and 8) will always be held in person. All other study visits may take place virtually due to patient preference or health and safety concerns. During the consent process, participants will be informed that in person study visits may not be permitted and that remote study visits may be a possibility if they choose to enroll or continue.

In the event that a subject is unable to make it to the office for an in-person visit, or is unable to join a Zoom videoconference, clinician and patient rated scales may be completed over the phone with a focus on safety, medication efficacy and tolerability.

6 Potential Risks and Benefits

6.1 Risks

Confidentiality: There is a risk of loss of confidentiality in research. However, precautions will be taken to uphold subject privacy and confidentiality. A notation that the subject is taking part in the research study may be made in the subject's electronic medical record. Subjects will be identified by code names and numbers and all research related records that reveal the subject's identity will remain confidential except as may be required by law. We have a federal certificate of confidentiality. Information from the research that relates to the subject's general medical care may be included in the record (for example, results of standard safety and monitoring blood labs done at the hospital laboratory).

Structured Interview: Answering detailed questionnaires may create a mild degree of inconvenience or emotional upset for the subjects. We aim to minimize this risk by reminding subjects that they can choose to not answer questions that make them feel uncomfortable or upset.

Blood draw: Some subjects may experience mild discomfort associated with blood draws and in rare cases a small arm bruise, clot, or infection may occur at the site of the blood drawing. We aim to minimize this risk by having blood draws done by trained phlebotomists.

EKG: Some subjects may have a skin reaction to the adhesive used to apply the electrode on your skin. We aim to minimize this risk by cleaning the skin areas where the electrode was attached after the removal of the electrode.

Risk/Discomforts of Study Medication: Consistent with good clinical practice, safety will be monitored by the Principal Investigator, and will reflect the oversight of study investigators. Adverse events will be recorded and reported according to institutional policies.

Subjects will be given quetiapine throughout the study. The most frequently observed adverse reactions (incidence ≥ 5% and twice placebo) associated with the use of quetiapine include: somnolence, dry mouth, dizziness, pharyngitis, weight gain, constipation, lethargy, ALT increase, postural hypotension, hypertension, dyspepsia, fatigue, increased appetite, tachycardia, vomiting and asthenia. Serious adverse reactions associated with the use of quetiapine include: hyperglycemia, lipid elevations, hypothyroidism, neuroleptic malignant syndrome, seizures, diabetes mellitus, cataracts, QTc prolongation, and tardive dyskinesia. Tardive dyskinesia causes repetitive involuntary movements. The movements most commonly appear in the eyes, lips, tongue, and jaw. Although tardive dyskinesia is rare it can be irreversible.

To minimize adverse reactions a baseline EKG will be completed to assess QTc length, and subject's past medical history will be assessed for thyroid dysfunction, seizures, diabetes mellitus, and cataracts. Adverse reactions will be monitored during the study by assessing for adverse events, as well as vital signs including blood pressure, heart rate, and weight, blood testing (lipids, glucose, AST, ALT), and extrapyramidal symptoms including tardive dyskinesia (AIMS).

Problems and side effects not listed above and not known at this time could occur. Subjects will be told of any changes in the way the study will be done and any newly discovered risks to which they may be exposed.

Quetiapine has a black box warning for increased suicidality risk in adolescents and young adults largely due to co-administration in patients with major depressive disorder who are on antidepressants.

Suicide risk is assessed at every study visit by the study physician (psychiatrist) during the mental status exam. After the first baseline screening visit (week 98) the Columbia Suicide Severity Rating Scale is formally administered by the study physician at each study visit. When the subject completes self-report scales that include questions regarding suicidality the study coordinator will review the subject's responses before the subjects leaves the study visit. If the subject endorses suicidality on the self-report scales this will be reviewed with the study physician before the subject leaves the study visit. The study physician will assess acute risk for suicide and will use clinical judgement to guide next steps. If the study physician feels the subject is at risk to acutely harm themselves by suicide, and the subject requires

further evaluation, a section 12 will be completed and the subject will be transported to the emergency room by hospital security.

There are no medications with specific FDA approval for the treatment of co-occurring SUD and SMD in youth. There are other medications approved for the treatment of mania associated with SMD such as second generation antipsychotics, specifically risperidone, olanzapine, and aripiprazole.

As with any drug, an allergic reaction to Quetiapine could occur. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat, or trouble breathing. Subjects will be informed to call 911 immediately if they are having trouble breathing.

The effects of the study drug on an embryo or fetus, or on a breastfeeding infant, is unknown and may be harmful. Because of these unknown risks, the subject cannot take part in the study if she is pregnant. Furthermore, to participate in the study subjects must agree to use birth control and pregnancy tests are scheduled for weeks 99, 4, and 8. If the subject becomes pregnant during the study, she will be instructed to stop taking the study medication.

Treatment with quetiapine may add to the hypotensive effects of antihypertensive agents. Alternately, quetiapine may antagonize the effect of levodopa and dopamine agents. Caution should be used when quetiapine is used concomitantly with drugs known to cause electrolyte imbalance, increase QT interval, or centrally acting drugs, and P450 3A inhibitors may decrease the clearance of quetiapine.

Subjects will be given the contact information to reach the study investigator 24 hours a day, 7 days a week. The PI or designee will review any and all reports of adverse events. Subjects are repeatedly advised that they can discontinue participation in the study at any time.

Subjects will be monitored for adverse events at each visit and all events will be recorded. After study completion (week 8), or if a subject withdraws early from the study, subjects will be offered up to 3 free clinical follow-up visits. The first follow-up visit will be offered within 2 weeks of the last study visit. If the subject would like to continue medication after the study they will be offered the choice of quetiapine and a prescription will be sent to the pharmacy. If a subject chooses to not continue quetiapine after the study there is no need to taper when the medication is discontinued.

6.2 Potential Benefits

This study will examine the efficacy of quetiapine for treating youth with co-occurring SUD and SMD. Youth with co-occurring SUD and SMD enrolled in this study may benefit from an improvement in their SUD and/or severe mood symptoms if they are randomized to receive quetiapine. Findings from the study could lead to increased knowledge on effective ways to quickly stabilize and engage this high-risk population in treatment that may decrease the morbidity associated with these co-occurring illnesses.

These data may also help elucidate the important mechanistic connection between SMD and SUD in youth.

6.3 Analysis of Risks in Relation to Benefits

All efforts are made to minimize risks to subjects. Risks are minimized by careful subject selection, including only subjects that are appropriate. This protocol is designed to ensure that safety measurements are completed prior to initiation of medications and that the subject's response is closely monitored. All procedures used are consistent with sound research design and do not unnecessarily expose subjects to risk.

7 Study Subject Selection

7.1 Subject Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:
-Male or female age 15 to 24
-Meet DSM-5 criteria for a substance use disorder
-Substance use ≥ 14 days of past 28 days (i.e. use ≥ 50% of days in the past 28 days)
-If subject in restricted setting/care (e.g. detox or residential treatment) for ≤ 2 weeks, then use ≥ 50% of days while outside of restricted setting (e.g. 7 days of substance use out of 14 days in unrestricted setting)
-Subjects need to have been in an unrestricted setting for at least 2 weeks prior to screening
-Meets DSM-5 criteria for bipolar disorder or disruptive mood dysregulation disorder or DSM IV criteria for mood disorder NOS
-Symptoms of SMD: YSR or ASR AAA ≥180
-Stable to be treated in outpatient level of care
-Access to internet and the ability to utilize Zoom videoconferencing software

7.2 Subject Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:
-Current methamphetamine use disorder
-Current unstable opioid use disorder (i.e. < 3 months on medication assisted treatment for an opioid use disorder)
-Pregnant or breastfeeding
-Placement in a restricted setting (e.g. detox or residential treatment) for ≥ 2 weeks out of past 28 days prior to screening visit, or placement in a restricted setting at anytime during study participation
-Unwilling or unable to use effective birth control
-Unwilling or unable to sign release of information for the treatment program providing behavioral treatment to coordinate care (e.g. study visit and treatment attendance and any safety concerns)

-For participants >17 years—unable or unwilling to identify emergency contact
-Medical or psychiatric condition likely to make participation unsafe as judged by the clinical investigator
-EKG shows a QTc>450 or arrhythmia or the subject has a family history of malignant arrhythmia or sudden death
-Current treatment with a CYP3A4 inhibitor (e.g. clarithromycin, fluconazole)
-AST or ALT greater than three times normal
-BMI > 35
-Poor command of the English language
-Current treatment with quetiapine, or an allergy to quetiapine
-No internet access or the inability to utilize Zoom videoconferencing software
- Planning to change any psychiatric and/or non-psychiatric medications during the study such that they would be increasing the dose of an existing medication that may prolong QTc interval and/or adding a new medication that may prolong QTc interval

8 Study Intervention

The study drug will be acquired from, stored by, and distributed by the BMC research pharmacy. After the week 99 visit, a two week supply of medication will be mailed to the participant's preferred address. After the week 1 visit, another two week supply will be mailed to the participant. The rest of the medication will be provided to the participant in person at the Week 4 visit.

Pill counts will be conducted at each visit. During virtual visits, study participants will be asked to count remaining pills with study staff over videoconference call. During in-person visits (week 4 and week 8), study participants will be asked to return any unused study medication. Unused study medication will be counted by study staff and disposed of per the investigational pharmacy's protocol.

Dosage will range from 50 MG to 300 MG as tolerated by the study participant. The study medication is titrated to full dose tolerated by the study participant during the first four weeks of the study. Quetiapine will be administered orally.

Capsules of 50 mg and 100 mg dosages of quetiapine or placebo will be dispensed. Capsules of quetiapine will be created with quetiapine powder.

9 Study Procedures

9.1 Recruitment

We plan to primarily recruit subjects from the referral pool of both new and existing patients from the Center for Addition Treatment for Adolescents/ Young Adults who use Substances (CATALYST), the Child Outpatient Psychiatry clinic, and the Adult Outpatient Psychiatry clinic at Boston Medical Center. The CATALYST program is a multidisciplinary SUD treatment program for young people under 26 years of age

that is based in the adolescent and young adult medical home. Possible study participants from CATALYST will be identified by clinical staff primarily during a weekly meeting that all clinicians attend where new evaluations and current patients in the program are discussed regularly. Clinical staff from CATALYST may also contact study staff outside of this meeting. The Child and Adult Outpatient Psychiatry Clinics are housed at Boston Medical Center as well. Research staff will present the study at clinical meetings for the Child Outpatient team, Adult Outpatient team and Integrated Behavioral Health team. Possible study participants will be identified by clinical staff during these meetings. Clinical staff from outpatient psychiatry departments may also contact study staff outside of this meeting.

We will also use BMC Quest reports to identify potentially eligible participants. We will pull BMC Appointment Reports for visits to Child Outpatient Psychiatry, Adult Outpatient Psychiatry, and Integrated Behavioral Health departments. We will then filter these reports to look for patients aged 15-24 who have a diagnosis of Bipolar Disorder or Mood Disorder not otherwise specified. We will use information from the report, such as patient name, date of birth, age, MRN, provider, and clinic, to reach out to the patient's clinician.

The medical record for patients identified by clinical staff at CATALYST or Outpatient Psychiatry Clinics with symptoms of SMD, or patients identified by pulled Quest Reports, will be reviewed by study staff, with a focus on encounter notes, problem lists, medications, and allergies. If the patient appears to meet eligibility criteria the patient's name, the name of the provider the patient is scheduled to see, and the date of the patient's next appointment will be recorded. Study staff will discuss with the clinician who the patient will see at the next appointment and the best strategy to connect the patient with study staff for more information about the study (e.g. IRB-approved flyer provided to the patient, verbal permission obtained for study staff to call patient, and/or meet briefly with study staff after the appointment to discuss the study). If study staff meet/are introduced to the patient in-person the phone screen would be done in person instead of over the phone.

In addition to the BMC psychiatry clinics, we will also contact participants who are referred from another study on which PI Dr. Amy Yule is an investigator. This study, H-40668: *Does Treating Young Persons Psychopathology Prevent the Onset of Opioid and other Substance Use Disorders?*, is a multisite study that takes place at Mass General Brigham and Boston Medical Center. Participants who indicate interest in being contacted for other studies during informed consent for study H-40668 will be referred to our study staff after a brief introduction by their research assistants. Our study staff will then contact the potential participant for a phone screen.

We may also recruit in the community with IRB-approved flyers. We may advertise at therapeutic high schools in the area, but only in the event that the school administrator provides written authorization to do so beforehand. We will provide the school administrator with information about the study and a document for him/her to sign if he/she wishes to provide the written authorization. We will also contact colleges and universities in the area to ask if they would be willing to advertise our study to their

students. This will entail the distribution of our study flyer in digital settings such as the school website or student newsletters. Schools may also decide to include a short summary of our study when they distribute the flyer. Flyers will include a study phone number and email address which potential participants may call, text, or email if interested in the study.

In addition to flyers in the community, we will work closely with the BMC Communications team to advertise our study on Facebook and Instagram. Potential participants can click on the advertisement to learn more about the study. Clicking the ad will take them to a REDCap page where they can read about the study in more detail. If they are interested, they can call, text or email us with the provided contact information. They also have the option to fill out a short form to indicate their interest in which we will contact the participant to discuss the study in more detail and complete a phone screen. The contact information collected by the REDCap webpage will be deleted if the participant is not eligible after the phone screen. If the participant seems eligible after the phone screen, their name and phone number provided on the REDCap webpage will be saved in the phone screen log.

Texting and email are offered so that the young target population may contact us more easily with their preferred means of communication. Texting and email are to be used solely for assessing interest in the study and for scheduling the initial screening over the phone. Thus, once contacted, study staff will then work with potential participants to schedule a time for a phone screening. In our responses, we will acknowledge that texting/email might not be the most secure form of communication and thus we would prefer to speak by phone. A response to a text or email from potential participant will look similar to the following message: “Thank you for being in touch! To protect your privacy, we would like to continue communication over the phone. Could you provide a good time for us to reach you for a phone screen?” Responses will not include research staff’s personal or contact information except for a first name.

Potential participants will be first screened by phone to ensure that basic inclusion/exclusion criteria are met. Specifically, we will ask questions regarding primary substance of use, and frequency of use. We will also query for past psychiatric diagnoses, current mood status, and psychiatric or substance related hospitalizations within the past month. We will also ask potential participants to self-report their height and weight so that we can calculate BMI. If potential subjects are not taking quetiapine at the time of the phone interview, are not allergic to quetiapine, have a BMI less than or equal to 35, and have a sufficient level of substance use and mood symptoms, they will be invited to meet with a study doctor.

9.2 Informed Consent

IRB-approved informed consent will be obtained from each subject prior to initiation of any study procedures. Parents will provide written, informed consent for their adolescent. All adolescents will be provided with an age-appropriate explanation of the purpose, nature, risks and benefits of the study and will provide written assent to study procedures. Youth over age 17 will provide written informed consent. Informed consent may also be obtained over Zoom videoconference call, in which case an

electronic signature will be obtained through DocuSign. Informed consent documents will be provided to the potential subject prior to the informed consent discussion.

The informed consent document will be used to explain, in simple terms, the purpose, procedures, risks and benefits of study participation to the subject and his or her parent (if applicable). Per IRB guidelines, the informed consent document includes a section on receiving unencrypted text messages detailing the possible associated security risks and fees. Consent will be obtained by a licensed MD investigator on study staff in a private office or over Zoom videoconference. The subject and his or her parent will be encouraged to ask questions pertaining to participation in the study and the subject and his or her family may take as much time as they feel is necessary to consider participation in the study as well as consult with family members and/or the subject's physician. Some subjects may be recruited from the investigators' own patients. Under no circumstances will the physician investigator complete informed consent with her own, ongoing patients. Interested and eligible patients will be consented by a colleague physician who is on study staff. The investigator will reinforce that participation is voluntary, that they do not have to participate, and the decision not to participate will not affect their care, now or in the future. Participation in this study is voluntary and the subject may withdraw at any time. The IRB-approved consent document will be signed, physically or electronically, and dated by the subject (and parent if applicable) and the investigator obtaining consent. Signed consent forms will be saved to a password-encrypted folder on the BMC secure network. A copy of the signed consent form will be given to the subject and the parent/guardian. As part of the consent process, all participants will be aware of HIPAA policies as they apply to research data collected. Participants will also be informed that in person study visits may not be permitted and that remote study visits may be a possibility if they choose to enroll or continue.

After consent has been obtained, all subjects will complete a clinical diagnostic interview with a study clinician to assess medical, psychiatric and substance use history, and potential eligibility.

9.3 Screening and Study Visits

Clinical characterization at the screening visit will consist of a thorough psychiatric and medical evaluation, and the completion of participant rated questionnaires and scales. A clinical interview will be conducted supplemented by modules from the M.I.N.I. 7.0 and the KSADS-PL where applicable. The Timeline Followback of Substance Use over the past month and the YSR or ASR will also be completed at screening to assess eligibility. Additional information regarding participants' past psychiatric /psychotropic history, past/current suicidal ideation, suicide attempts, and past/current delusions will be gathered through clinical interview and the Columbia Suicide Severity Rating Scale (C-SSRS). The Weiss adherence interview will be completed at the screening visit to assess baseline patterns of adherence and past reasons for nonadherence. Participants will also complete the Emotional Control Subscale of the BRIEF to assess emotional regulation. The risk behavior survey will be completed to assess high-risk behaviors associated with HIV/HCV. Participants will also answer questions about reasons for their alcohol/substance use, reasons for coming to treatment, family opinions on their alcohol/substance use, and friends drinking/drug use behaviors.

All participants will be required to complete a breathalyzer test and give a urine sample to screen for certain types of drugs. This includes prescription drugs, illegal drugs (street drugs), and controlled substances (substances that may be habit forming) that may affect behavior and that may be regulated by law. The breathalyzer test and urine sample will be collected by study staff during screening, midpoint, and final visits (in-person visits). Results of the drug screen will be conveyed to the participant by the study clinician. For all other virtual visits, the participant will self-administer the urine drug test before the virtual study visit. These drug tests will be given to the participant at the previous in-person visit. The participants will then share and discuss their results with the clinician over Zoom videoconference call. In addition, female subjects of childbearing potential will complete a urine pregnancy test at the screening, midpoint, and final study visits. If a participant has a positive urine pregnancy test, she will not be able to take part in the study. The study doctor will inform the participant of any positive test results. The decision whether to inform the subject's parent/guardian of these results will be made by the study doctor based on the participant's age, risk level associated with substance use, administration route of substance use, and maturity level.

The medical evaluation at screening will include a clinical interview, vital signs, and laboratory tests focused on assessing for medical conditions that would be contraindications for a trial with quetiapine and for assessing changes at endpoint. Subjects will complete physical assessment measures (height, weight, BMI, heart rate, blood pressure), and a 15 cc blood draw for blood tests measuring both AST/ALT levels, and the presence of Hepatitis C or HIV. If the participant has a BMI between 30 and 35 at screening, we will monitor their weight at every visit instead of just midpoint and endpoint visits. We will ask participants to self-report their weight, and provide a scale if they do not own one at home. If their weight increases such that their BMI increases by ≥1, the participant will be withdrawn from the study. An EKG at the screening visit will be administered to screen for cardiac risk factors that would exclude subjects from participation. The screening process may take place over multiple days, as necessary.

Before receiving study medication, the healthy lifestyle behavior recommendations developed by Correll and Carlson to prevent and minimize weight gain on SGAs will be reviewed with all eligible subjects. Participating youth with active SUD and SMD will be randomized to treatment or placebo in a 1:1 ratio. Randomization lists will be generated by the investigational pharmacy for each age block (e.g. 15-17; 18-24 years). Throughout the 10-week study participants will be encouraged to engage in treatment as usual which includes evidence based behavioral therapies through the Center for Addition Treatment for Adolescents/ Young Adults who use Substances (CATALYST) at Boston Medical Center.

Subjects will be sent appointment reminders via text before their study visits. Reminders will be sent from a cell phone designated for this study's purposes and will only contain the date, time, and location of the appointment. No personal/health information will be shared over text.

The collection of certain scales and study procedures will occur at all 11 visits, and include the following:

Clinician rated assessments:

- Mini-International Neuropsychiatric Interview (M.I.N.I. 7.0)[57]: The M.I.N.I is a short, structured, diagnostic interview with an administration time of approximately 15 minutes that is the structured interview of choice for psychiatric outcome tracking in clinical psychopharmacology trials. Specific, predetermined modules will be completed to assess for DSM-V mood disorders, disruptive disorders, SUDs and anxiety disorders (will be administered at screening). The suicidality, lifetime panic disorder and optional assessment measures to track changes over time including cross cutting measures and disability/functional impairment will not be utilized in the study. The M.I.N.I KID will be administered in subjects under the age of 18. In these interviews the suicidality, separation anxiety disorder, Tourette's disorder, adjustment disorder and autism spectrum disorder modules will also not be utilized in the study.
- DMS-V Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime (KSADS-PL) module for DMDD[58]: The KSADS-PL is a semi-structured assessment of current and lifetime psychopathology in children under 18. The DMDD module has been selected to supplement clinician assessment of children under 18 who have not been diagnosed with bipolar disorder. The assessment is composed of 2 items, rated using a 0 – 3 point scale, and will take approximately 10 minutes to administer.
- Weiss Adherence Interview[59]: will be completed at the screening visit to assess patterns of medication adherence and past reason for nonadherence prior to subject enrollment (will be collected at screening).
- Adverse Experiences and Concomitant Medications: (will be collected at all study visits).
- Young Mania Rating Scale (YMRS)[60]: The YMRS is composed of 11 items, and each question is rated with a likert rating scale. It is designed to capture symptoms over the prior 48 hours, with total scores ranging from 0 to 60: (will be completed at screening, baseline, and every 2 weeks thereafter).
- Abnormal Involuntary Movement Scale (AIMS)[61]: The AIMS is used to record the occurrence of tardive dyskinesia (TD) in patients receiving neuroleptic medications. It is a 12-item anchored scale that requires raters to assess for movement in the face, lips, jaw, tongue, upper extremities, lower extremities, and trunk (it will be administered at screening, midpoint and final study visit).
- Clinical Global Impressions (CGI)[62] scale for SUD and SMD. The CGI is a measure of illness severity, improvement, and efficacy of treatment (will be collected at all study visits).
- Columbia Suicide Severity Rating Scale (C-SSRS)[63]: The C-SSRS is a suicidal ideation rating scale used to evaluate and monitor suicidality. It rates an individual's degree of suicidality on a continuum ranging from passive suicidal ideation to active suicidal ideation with specific intent and plan (will be administered at all study visits).
- DSM-V Global Assessment of Functioning (GAF) scale: The GAF will assess global functioning using a scale from 1 (worst) to 100 (best); (this will take place at the baseline, midpoint, and the final study visits).

- Reproductive Potential Form is used to assess whether or not the patient is able to reproduce. If the patient is female and of childbearing years, a urine pregnancy test is applicable (pregnancy screening will occur at the screening, midpoint, and final study visits if applicable).

Subject/Parent rated scales:

- Socioeconomic Status/Background: A brief demographic interview will be conducted after subjects have signed consent, as part of the screening procedures. This interview will be used to estimate socioeconomic status, as well as collect information about any educational accommodations, and past head injuries and trauma. For youths aged 15-17, this interview will be conducted with the parent.

- Youth Self-Report (YSR)[53] and Adult Self-Report (ASR)[54]: Several self-report, parent-report, and informant-report scales have been developed by the Achenbach System of Empirically Based Assessment (ASEBA)[64]. Due to the age range of our study population (ages 15-24), we will administer different versions depending on the subject's age. For 15-17 year olds, we will administer the YSR to the subject, and parents may fill out the Child Behavior Checklist (CBCL)[65] if they are present and willing, although it will not be required. Similarly, for 18-24 year olds, we will administer the ASR to the subject, and an informant may fill out the Adult Behavior Checklist (ABCL)[54] if they are present and willing, although it will not be required. All versions of the above scales contain questions to address problematic areas in an individual's functioning scored on a Likert scale (0=Not True, 1=Sometimes True, 2 = Often True). We will be primarily concerned with cumulative scores on the Anxiety/Depression, Attention, and Aggression (AAA) subscales (completed at the screening and final study visits). For this reason, we will only ask subjects/parents/informants to complete pages 3 and 4 of the aforementioned scales. If parents/informants are unable to complete the CBCL/ABCL at screening, they may complete it at the subject's baseline visit.

- Behavior Rating Inventory of Executive Function (BRIEF)[52]: Several self-report, parent-report, and informant-report versions of the BRIEF exist. Due to the age range of our study population (ages 15-24), we will administer different versions of the 10-item emotional control subscale depending on the subject's age. For 15-17 year olds, we will administer the BRIEF-Self Report to the subject, and parents may fill out the BRIEF-Parent if they are present and willing, although it will not be required. Similarly, for 18-24 year olds, we will administer the self-report BRIEF-Adult to the subject, and an informant may fill out the BRIEF-Informant if they are present and willing, although it will not be required. The BRIEF emotional control subscale will be completed at screening and final study visit. If parents/informants are unable to complete the BRIEF-Parent/BRIEF-Informant at screening, they may complete it at the subject's baseline visit.

- Beck Depression Inventory-II (BDI-II)[66]: The BDI-II assesses depressive symptomatology over the 2 weeks prior to administration. It is a 21-item scale with each question rated with a likert rating scale from 0 to 3, and the total score representing a summation of all responses ranging from 0 to 63 (will be administered at baseline and every 2 weeks thereafter). The scale will be administered by the research coordinator who will review question 9 (regarding suicidality) prior

to visit completion. If the subject answers question 2 or 3 on question 9 or makes any spontaneous remarks expressing suicidality the research coordinator will immediately inform the licensed study clinician.

- Patient Health Questionnaire-9 (PHQ-9)[67]: A 9-item instrument with each item rated with a likert scale from 0 (not at all) to 3 (nearly every day) used to assess symptoms of depression upon which the diagnosis of DSM-IV depressive disorders is based. The total score represents a summation of all responses ranging from 0 to 27 (will be administered at baseline and every 2 weeks thereafter). The scale will be administered by the research coordinator who will review question 9 (regarding suicidality) prior to visit completion. If the subject answers question 2 or 3 on question 9 or makes any spontaneous remarks expressing suicidality the research coordinator will immediately inform the licensed study clinician.

- Weiss Craving Scale[68]: A 3-item scale with each question rated with a likert scale from 0 (no desire/likelihood of use) to 9 (strong desire/likelihood of use), and the total score representing the summation of all responses ranging from 0 to 27. Subjects will be asked to rate cravings for their drug of choice (will be administered at baseline and every 2 weeks thereafter).

- Fagerström Tolerance Questionnaire for Adolescents: A 7-item scale used to determine dependence on nicotine. Calculating the total points determines whether a patient is dependent on nicotine. Two additional questions about electronic cigarette use ("vaping") and frequency of use will also be added that will not be factored into the total score. This scale will be completed at baseline, week 4, and final study visit.

- Timeline Followback of Substance Use (TLFB)[69]: Measure used to quantify self-reported alcohol and drug use. It will be administered at initial screening visit to assess use during the month prior to evaluation, and will also be administered weekly over the course of the study to quantify use in the week between subsequent visits. Although all substance use will be queried, the primary focus will be response to quetiapine assessed by evaluating changes in subjects' use of drug of choice.

- Risk Behavior Survey[70]: Will be used to assess the effect of quetiapine treatment on changes in high risk behaviors associated with HIV and HCV (will be administered at baseline, midpoint and final study visit).

- Supplemental Substance Use Questionnaire: Will be used at screening to assess reasons for alcohol/substance use, reasons for coming to treatment, family opinions on subjects' alcohol/substance use, and friends' drinking/drug use behaviors.

Assessments collected at virtual visits may be administered by study staff or sent to participants via REDCap survey. REDCap surveys will be sent via secure email. If emails are sent to external email addresses, the subject line will contain the word "secure." This creates a secure messaging system where the participant will create a login/password to access the email. Study staff will be with participants to troubleshoot the process if needed.

9.4 Medication Management

Quetiapine will be titrated to the maximum achieved dose as tolerated during the first three weeks of the trial. *Dose titration phase:* Study medication will be initiated at 50 mg twice daily and will be gradually up-titrated by 100 mg per day (increasing by 50 mg twice daily) to a maximum dose of 150 mg twice daily. Titration of the study medication is flexible, guided by tolerability with the option for slower, lower, or hold titration. If a participant prefers once daily dosing instead of twice daily dosing this will be allowed.

As noted earlier, safety and tolerability of quetiapine monotherapy will be monitored by a battery of blood tests (30 cc of blood drawn over the duration of the study for fasting glucose and fasting lipids, AST, ALT, Hepatitis C and HIV testing), urine tests, height and weight measurements (to calculate Body Mass Index (BMI)), and the AIMS at screening and endpoint (completion/drop visit). Weight, the AIMS, and urine HCG test will also be completed at midpoint. As previously described, weight may also be monitored at every visit if the participant's BMI at screening is between 30 and 35. If the participant has a BMI under 30 at screening, but between 30 and 35 at midpoint, we will monitor their weight for the remainder of their visits. We will ask participants to self-report their weight, and provide a scale if they do not own one at home. If their weight increases such that their BMI increases by ≥1 from their midpoint BMI, the participant will be withdrawn from the study. Adverse events, C-SSRS, and the CGI-S and CGI-I for SUD and SMD will be monitored at every study visit. Vital signs will be monitored at screening, midpoint and endpoint visits. During the final study visit an additional 4 ccs of blood will be drawn to test the quetiapine level. The quetiapine level will only be tested for subjects who were randomized to Quetiapine. Hence, blood samples will be frozen and stored until the study is complete and unblinded.

9.5 Participant Cost and Compensation

All study visits are at no cost to the subjects. Participating individuals will receive between $10 and $50 deposited on a ClinCard for each study visit they complete. The remuneration schedule is as follows: Screening (week 98): $25; Screening (week 99): $25; Week 0: $15; Week 1: $10; Week 2: $15; Week 3: $10; Week 4: $15; Week 5: $10; Week 6: $15; Week 7: $10; Week 8: $50. In addition, participants will receive an additional $3.50 at each visit that they bring back their medication in the medication bottle. Participants will also receive payment for transportation to Boston Medical Center if they use public transit or park in the hospital garage during study visits. A participant who uses public transportation to get to and from a study visit will receive an additional $5 deposited on their ClinCard for that visit. A participant who parks in the hospital garage during a study visit will receive a parking coupon.

Please see the Appendix for the Schedule of Events.

9.6 Health and Safety Procedures for In-Person Visits

In addition to reducing the number of in-person visits, health and safety measures will be taken to reduce the risk of spread of COVID-19. Two research staff (PI and research coordinator) will be present for all in person visits. The visits will take place in the Psychiatry Research Center at Boston Medical Center, which will operate at reduced capacity, including study participants and staff. Research teams will coordinate times for their study visits to ensure that the capacity is not exceeded.

All research study areas will be sanitized by research staff at the beginning of the day before the first research participant arrives and sanitized again after each participant. Sanitizing methods will include the use of germicidal cleaning wipes and/or spray. In addition to sanitizing the study areas, research staff and participants must wear a mask at all times. The research team will provide sufficient masks for each participant. Research staff will also take the participants temperature with an infrared thermometer before entering the research area.

Physical distancing will not be possible during certain study procedures including an EKG, blood draw, vital signs (weight, blood pressure, and heart rate), as well as brief assessment of upper extremity muscle tension for the assessment of abnormal involuntary movement exam. However, all other procedures that need to be completed during these visits can be done virtually through zoom with the participant on a computer in one office and research staff in another office.

Finally, screening questions for COVID-19 exposure/illness will be asked will be asked throughout the study, starting at Week 98. Study staff will also contact participants by phone the day prior to any in-person visit to ask these screening questions. The screening questions will always be asked at the beginning of each in person (weeks 99, 4 and 8). Responses to these screening questions will be recorded only at Week 98, 99, 4, and 8. (See attached “COVID-19 Screening Questions” CRF for more details.)

10 Assessment of Safety and Data Safety Monitoring Plan (DSMP)

10.1 Definitions

The following definitions will be used in the assessment of safety:

Adverse Event (AE) is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject’s participation in the research, whether or not considered related to the subject’s participation in the research.

Serious Adverse Event (SAE) is any adverse event that

(1) results in death;
(2) is life-threatening;

(3) results in inpatient hospitalization or prolongation of existing hospitalization;
(4) results in a persistent or significant disability/incapacity;
(5) results in a congenital anomaly/birth defect; or
(6) based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Life-threatening means that the event places the subject at immediate risk of death from the event as it occurred.

Unanticipated Problem is defined as an event, experience or outcome that meets **all three** of the following criteria:

- is unexpected; AND
- is related or possibly related to participation in the research; AND
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research

Unexpected means the nature, severity, or frequency of the event is not consistent with either:

- the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol–related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or
- the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

10.2 Safety Review

Both the risks listed in Section 4.1 and unknown risks will be monitored as follows:

Safety monitoring

The Principal Investigator will be responsible for ensuring that adverse events are reported to the local Institutional Review Board in compliance with requirements. Any changes to the protocol will be made in accordance with local IRB policies. The Principal Investigator will supervise all study activities, including those of the research coordinators and co-investigators, and will be available 24 hours by page. The physician investigators will review all laboratory results and adverse events.

General safeguards will be in place for all subjects enrolled in the study. All subjects will have access to 24 hours a day, 7 days a week coverage provided by the PI or designated substitute by pager for emergencies. The PI will be responsible for monitoring the safety of the study and complying with the reporting requirements. Continuous, close monitoring of participant safety will include prompt and frequent reporting of safety data (i.e., adverse/serious adverse events) to the Boston Medical Center Institutional Review Board and/or appropriate study staff with oversight responsibility. Serious adverse events and unanticipated problems will be reviewed by the PI within 24 hours of the study team knowing about the AE/UP. Unanticipated Problems (UPs) will be reported to the Data Safety and Monitoring Board (DSMB) chair within 24 hours of the PI learning of the event and to the IRB within 7 days. Non-serious adverse events will be reviewed by the PI within 7 days of a study visit. A summary of serious adverse events and AEs will be reviewed by the PI every 6 months during progress reports as well as during the written report required by the IRB as part of the annual IRB renewal process.

Data Safety and Monitoring Board (DSMB)

We have established a DSMB board which includes the following members:

-Thomas J. Spencer M.D.; Child Psychiatrist, Researcher; Massachusetts General Hospital

-Gagan Joshi M.D.; Child Psychiatrist, Researcher; Massachusetts General Hospital

-Martha Kane Ph.D.; Child and Addiction Psychologist, Addictionologist, member of the MGH QI/QA committee; Massachusetts General Hospital

-MaryKate Martelon M.P.H.; Statistician; Massachusetts Department of Public Health, and Massachusetts General Hospital

The DSMB will meet once per year during the active study and most recently met on 09/10/2019. The DSMB will be provided with unblinded data from the study so as to examine whether the study should be stopped because the drug interventions are either clearly beneficial or harmful to participants. In addition to the IRB, the K12 PI, and the NIH project officer, the DSMB chair will be informed of any unanticipated problems that occur during the trial. The primary concern of the investigators of this study is the safety of the subjects.

Adverse Event Reporting: Consistent with good clinical practice, safety will be monitored by study staff at each study visit. A study clinician will supervise all study activities including ratings, reported adverse events, lab results and vital signs, and the Principal Investigator, Dr. Amy Yule, will be available for further review. Should any study activities require urgent attention, the PI and study clinicians will be available 24 hours a day by page. All procedures have been designed to minimize subject discomfort, and no subject will be asked to engage in research procedures not outlined in the consent form. Subjects will be monitored for adverse events at each visit. All adverse events (including unexpected and serious AEs) will be recorded and reported in accordance with Boston Medical Center Institutional Review Board guidelines. We will follow and adhere to all guidelines as defined and outlined on the Boston Medical Center Institutional Review Board website:
http://www.bumc.bu.edu/irb/files/2019/06/Reporting_Requirements.pdf

Data Monitoring

The PI will be responsible for ongoing quality control. This includes all aspects of the study related to safety, but also data integrity and protocol compliance. Quality control will include self-audits of data collection and storage as well as compliance with the informed consent procedure. The review of data and procedures may result in early termination of the study, amendment of the protocol or data collection plans, or amendment of study forms. The IRB will be notified and all amendments approved prior to study implementation. In addition, the participants will be notified of any significant new findings that develop during the course of research (e.g., other potential risks) that may affect their wish to continue participation in the study.

The study clinicians, research coordinator, and Principal Investigator will monitor study progress including enrollment, adherence to inclusion/exclusion criteria and study protocol, as well as any adverse events. The Principal Investigator will be responsible for ensuring that adverse events are reported to the local Institutional Review Board in compliance with local and federal requirements. Any changes to the protocol will be made in accordance with local IRB policies. The Principal Investigator will supervise all study activities, including those of the research coordinator and co-investigators, and will be available 24 hours a day by page.

For quality control purposes, audio of clinician-administered measures completed during the visits may be recorded, with subjects' permission. These recordings will be used to monitor quality control and inter-rater reliability in this study by the PI. Each audio file will be coded with subject initials and number to maintain confidentiality. These recordings will be de-identified and stored in a password-protected file.

10.3 Reporting Plans

The Principal Investigator at BMC/BU Medical Campus will report Unanticipated Problems, safety monitors' reports, and Adverse Events to the BMC/BU Medical Center IRB in accordance with IRB policies:

- Unanticipated Problems occurring at BMC/BU Medical Campus will be reported to the IRB within 7 days of the investigator learning of the event.
- Reports from safety monitors with recommended changes will be reported to the IRB within 7 days of the investigator receiving the report.
- Adverse Events (including Serious Adverse Events) will be reported in summary at the time of continuing review, along with a statement that the pattern of adverse events, in total, does not suggest that the research places subjects or others at a greater risk of harm than was previously known.
- Reports from safety monitors with no recommended changes will be reported to the IRB at the time of continuing review.

10.4 Stopping Rules

A subject will be withdrawn from the study if they:

- Develop an adverse event despite dose adjustments that is determined to be intolerable based on clinician judgment. An intolerable event is any side effect or worsening of SMD or SUD symptoms that are determined by the investigator to be excessive in severity or in duration
- Have worsening SMD or SUD symptoms (as determined by clinician judgment indicated through scores ≥5 on the CGI Global Improvement scale on two consecutive weeks) that warrants an early termination
- Have new onset of severe SUD (e.g. intravenous, intentional/unintentional overdose)
- Have unstable mental health (new onset SI/HI with intent and/or plan)
- Become incarcerated
- Demonstrate severe noncompliance with medication dosing or study procedures
- Become pregnant during the study
- Modify their psychiatric and/or non-psychiatric medications such that they would be increasing the dose of an existing medication that may prolong QTc interval
- Add a new medication that may prolong QTc interval
- Gain weight such that their BMI increases by ≥1 point if 1) their starting BMI is between 30-35 or 2) their starting BMI is < 30 but BMI at midpoint is between 30-35

In case of an emergency, the investigator will be able to contact the Boston Medical Center research pharmacy for emergency unblinding 24 hours a day. The blinded information is to be broken only when knowledge of such treatment may have an impact on future treatment decisions or aid in the emergency treatment of the subject. This decision can only be made by Dr. Yule or designee. Any subject for whom the blind is broken will be discontinued from the study. If an SAE occurs, the principal investigator, Dr. Yule or designee, should be informed of the event within 24 hours so appropriate actions may be taken.

11 Data Handling and Record Keeping

11.1 Confidentiality

All research related records initiated as a result of a subject's participation in this study that reveal the subject's identity will remain confidential except as may be required by law. Data obtained from this study will not identify the subjects individually. Subjects will be assigned code names and ID numbers. Biospecimens will be stored securely in a locked room only accessible to study staff. Data obtained from our studies may be published, but published data will not identify individual participants. Original research-related records may be reviewed by the Boston Medical Center Institutional Review Board and regulatory authorities for the purpose of verifying clinical trial procedures and/or data. Information will be held and processed on a computer, but access to these computerized records will be password protected and restricted to study staff. At the onset of an initial clinical encounter, subjects will be informed of Federal privacy guidelines that pertain to them under the Healthcare Insurance Portability and Accountability Act. Results of urine drug or pregnancy testing will not become part of the subject's medical record. Subjects will only be contacted regarding future studies if they indicate that they are

interested in being contacted by initialing in the specific section of the consent form. Information may be held and processed on a computer. Access to these computerized records will be password protected and restricted to study staff.

Data Use Agreements and Material Transfer agreements will be filed with the appropriate offices regarding receiving identified data and biospecimens from Massachusetts General Hospital.

11.2 Source Documents

Structured diagnostic and psychosocial interviews will be collected from youth and parents when available. Biological samples of blood will be collected to measure hepatic function, test for hepatitis C and HIV, and monitor glucose and lipid levels during treatment. Urine samples will be collected to measure drug toxicology and detect pregnancy. For a full list of data records, please see the Schedule of Events in the Appendix.

Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or special research files, one per subjects, which will be identified by an ID number that will not identify the subject in any way. Data may be transcribed legibly on hard copy CRFs supplied for each subject or directly inputted into REDCap—an electronic data management system. Any hard copy material including the names of subjects or other identifying information (consent/assent forms, paper records) will be kept in locked filing cabinets in a locked room or scanned and uploaded to a password-encrypted folder on the BMC secure network. Documentation linking subjects' names and numbers will be kept in a password-protected electronic file on a BMC networked drive only accessible by the project coordinator and primary investigator (PI) on a password-protected computer located behind a secure and maintained firewall. Blood sample collection, analysis and disposal will be managed by the BMC lab. Urine sample collection, analysis, and disposal will be managed by study staff and samples will not contain identifying information. Data will be transmitted only in pooled form, and subjects will be identified by ID numbers. Any publications of study findings will be reported so that no person can be identified individually. These issues will be clearly stated in consent forms and discussed with participants during the informed consent process, prior to any study related procedures.

11.3 Case Report Forms

The study case report forms (CRF) will be the primary data collection instruments for the study. All data requested on the CRFs will be recorded. All missing data will be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, "N/D" will be written. If the item is not applicable to the individual case, "N/A" will be written. All entries will be printed legibly in black ink. If any entry error has been made, to correct such an error, a single straight line will be drawn through the incorrect entry and the correct data will be entered above it. All such changes will be

initialed and dated. There will be no erasures or white-out on CRFs. For clarification of illegible or uncertain entries, the clarification will be printed above the item, then initialed and dated.

See the Appendix for the following CRFs:

Clinician rated assessments (stored in patient files/ REDCap):

- Mini-International Neuropsychiatric Interview (M.I.N.I. 7.0)
- DMS-V Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime (KSADS-PL) module for DMDD
- Weiss Adherence Interview
- Adverse Experiences and Concomitant Medications
- Young Mania Rating Scale (YMRS)
- Abnormal Involuntary Movement Scale (AIMS)
- Clinical Global Impressions (CGI)[62] scale for SUD and SMD
- Columbia Suicide Severity Rating Scale (C-SSRS)
- DSM-V Global Assessment of Functioning (GAF) scale
- Reproductive Potential Form

Subject/Parent rated scales (stored in patient files/REDCap):

- Socioeconomic Status/Background
- Youth Self-Report (YSR) and Adult Self-Report (ASR)
- Behavior Rating Inventory of Executive Function (BRIEF)
- Beck Depression Inventory-II (BDI-II)
- Patient Health Questionnaire-9 (PHQ-9)
- Weiss Craving Scale
- Fagerström Tolerance Questionnaire for Adolescents
- Timeline Followback of Substance Use (TLFB)
- Risk Behavior Survey
- Supplemental Substance Use Questionnaire

Other CRFs (stored in patient files/REDCap):

- Laboratory tests: Drug screen (urine and breathalyzer), Urine HCG

- Safety/reliability procedures: EKG, Heart Rate, Blood Pressure, Height, Weight
- Chart Note
- Adverse Events Log
- Concomitant Medication Log
- COVID-19 Screening Questions

Other CRFs stored in patient Medical Record and patient files/REDCap

- Laboratory tests: AST/ALT, Hepatitis C, HIV, Fasting Lipids, Fasting Glucose, Urine THC, Creatinine

11.4 Study Records Retention

All study records will be retained for at least seven years after the completion of the study, per Boston Medical Center Research Center requirements. These records include informed consent documents for all subjects.

12 Statistical Plan

12.1 Study Hypotheses

Primary Aim 1: Evaluate the effect of quetiapine on SUD. Hypothesis 1A: Treatment with quetiapine will decrease self-reported substance use for primary substance of use (e.g. number of days of use past month, % abstinence past month). Hypothesis 1B: Treatment with quetiapine will increase number of toxicology specimens negative for primary substance of use Hypothesis 1C: Treatment with quetiapine will decrease drug craving for primary substance of use.

Primary Aim 2: Evaluate the effect of quetiapine on SMD. Hypothesis 2A: Treatment with quetiapine will result in a decrease in symptoms of mania demonstrated by reduction in Young Mania Rating Scale. Hypothesis 2B: Treatment with quetiapine will result in a decrease in symptoms of depression demonstrated by reduction in the Beck Depression Inventory II.

Primary Aim 3: Evaluate the effect of quetiapine on engagement in outpatient treatment. Hypothesis 3A: Treatment with quetiapine will lead to greater engagement in outpatient treatment as demonstrated by greater number of appointments attended in the active treatment group.

12.2 Sample Size Determination

Since there have not been any published studies to date on quetiapine for the treatment of SUD co-

occurring with SMD in young people, we are estimating the effect size of quetiapine for the treatment of youth with co-occurring SUD and SMD based on Delbello and colleagues' preliminary report on a sample of 75 patients with frequent cannabis use and BD who were treated with quetiapine and randomized to topiramate or placebo.[49] The quetiapine plus placebo group had improvements in both substance use and mood. Cannabis use decreased from an average of 14 joints per week to 4 joints per week representing a 72% decrease. In this study, the YMRS decreased by 16 (from approximately 30 to 14) indicating a 53% improvement in mood. These expected improvements in SUD associated with mood are reminiscent of those of Geller et al using lithium for youth with SUD and SMD (effect size of ca 1.0).[20]

Power Analysis: To achieve 90% power using a two-tailed test with 5% significance level to detect a difference in measures of substance use we will need 22 subjects per group. To detect similarly powered differences in measures of mood we will need 10 subjects per group. Clinical trials for quetiapine in adolescents with BD have a 75 to 80% completion rate.[71, 72] We therefore estimate we may have 20% attrition and aim to recruit 28 subjects per group for a total of 56 subjects.

12.3 Statistical Methods

All analyses will be modified intention to treat, which will be defined by completing at least one week of study medication. We will analyze group differences across demographics using Pearson's Chi Squared tests for binary outcomes and student t tests or linear regression models for continuous outcomes. To assess our main outcomes, we will use generalized estimating equations that estimate the main effects of drug and time as well as any interactions (time X drug). We will evaluate our primary outcome measures hierarchically in the following order for SUD: Timeline Followback of substance use, urine drug screen, and Weiss craving scale. For binary outcomes, logistic regression models will be fit with Poisson family and log link, and for normally distributed data, linear regression models will be fit with the Gaussian distribution and the identity link. Exploratory aims will be examined using models similar to the main outcomes. All statistical tests will be performed using STATA 13.0. The statistical significance will be set at 5% and all tests will be two-tailed.

To evaluate hypotheses 1A, 1B and 1C, we will monitor SUD response to quetiapine for primary substance of use by way of the Timeline Followback of Substance Use (TLFB). Specifically, the TLFB will be used to compare self-report of substance for the month prior to study entry versus the last month of the study. We will use weekly toxicology screens negative for primary substance of abuse as an objective measurement of decrease in substance use severity. The Weiss Craving Scale will be used to assess the effect of quetiapine treatment on cravings for primary substance of use. Values for all three measures (TLFB, toxicology screens, and Weiss Craving Scale) will be compared between baseline and endpoint.

To evaluate hypotheses 2A and 2B, we will assess SMD response to quetiapine by way of comparing

values from baseline to endpoint on the YMRS and BDI-II.

To evaluate hypothesis 3A, the impact of treatment with quetiapine on outpatient treatment engagement will be monitored by collateral from the outpatient program regarding the percentage of scheduled appointments attended after randomization.

To evaluate exploratory aims, we plan to administer scales that measure emotional regulation, including the Emotional Control Subscale for the BRIEF (BRIEF-Self-Report, BRIEF-Adult, BRIEF-Parent, BRIEF-Informant) and the AAA subscales of the Achenbach Assessments (Youth Self-Report, Adult Self-Report, Child Behavior Checklist, Adult Behavior Checklist) to determine if they predict treatment response and/or what specific components improve with treatment in youth with co-occurring SUD and SMD. The impact of treatment with quetiapine on medication adherence will be assessed with weekly pill counts, a medication diary, and the medication adherence rating scale. Non-primary substances of use will be evaluated by TLFB and toxicology screens. Changes in high risk behaviors associated with HIV and HCV due to treatment with quetiapine will be assessed with the Risk Behavior Survey. The effect of treatment with quetiapine on functioning will be assessed by the GAF. Psychiatric co-morbidities will be assessed at baseline with specific, predetermined modules from the M.I.N.I. 7.0. Youth's reasons for substance use and peer substance use will be assessed with a supplemental substance use questionnaire at screening. Motivation to change, confidence in their ability to change, level of engagement in therapy, and exposure to substance use in the subject's living environment will be assessed with additional questions added to the Weiss Craving Scale but not factored into the total score. The validity of the PHQ-9 will be evaluated by administering the instrument in conjunction with the BDI-II at Week 0 and every 2 weeks thereafter

13 Ethics/Protection of Human Subjects

This study is to be conducted according to applicable US federal regulations and institutional policies (which are based in federal regulations, guidance, and ICH Good Clinical Practice guidelines).

This protocol and any amendments will be submitted to the Boston Medical Center and Boston University Medical Campus IRB, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The consent form will be submitted with the protocol for review and approval by the IRB. The consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. Consent will be documented as required by the IRB.

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15 Appendix

1. Schedule of Events
2. DSMB Charter
3. Case Report Forms (CRFs)
    a. Urine Drug and Breathalyzer
    b. Adverse Events
    c. CBCL
    d. MARS
    e. AIMS
    f. BDI-II
    g. Craving Scale
    h. ABCL
    i. Concomitant Medications
    j. Reproductive Potential
    k. Fagerstrom Tolerance Questionnaire
    l. Chart Notes (Week 98 & 99, Week 0, Weeks 1-8)
    m. KSADS DMDD Module
    n. Electronic Cigarette Use Questionnaire
    o. GAF
    p. Supplemental Substance Use Questionnaire
    q. BRIEF-Subscale Adult
    r. BRIEF- Subscale Parent
    s. BRIEF- Subscale Informant
    t. BRIEF-Subscale Self-Report
    u. Demographics Facepage
    v. Lifetime Weiss Adherence Interview
    w. ASR
    x. CSSR-S
    y. YSR
    z. CGI SMD
    aa. YMRS
    bb. PHQ9
    cc. Risk Behavior Survey
    dd. MINI Adult 7.0
    ee. MINI Kid 7.0
    ff. CGI SUD
    gg. Timeline Followback Forms (2020, 2021)
    hh. COVID-19 Screening Questions
4. Data Management Plan
5. Informed Consent
6. Recruitment Flyer
7. Medication Diary
8. Deviation Exception Log

9. Healthy Lifestyle Behaviors
10. Dosing Instructions
11. Recruitment Email
12. Telephone Script
13. Quetiapine package insert