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Study Title: ***Clozapine for Cannabis Use Disorder in Schizophrenia (CLOCS)***

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Attachments:

- ☐ *Attachment A: Nonsignificant Risk Devices*
- ☐ *Attachment B: Placebo*
- ☒ *Attachment C: Genetic Research*
- ☐ *Attachment D: Employees and Students*
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1. *Abstract.*

Cannabis use disorder (CUD), which is up to ten times more common in patients with schizophrenia (SCZ) than in the general population, worsens the course of this severe psychiatric disorder. Since SCZ occurs in 1% of the population, the co-occurrence of CUD in 13% to 42% of people with this disorder presents society with an important public health problem. Unfortunately, most antipsychotics available for treatment of patients with SCZ do not appear to limit their cannabis use. Moreover, the one antipsychotic that preliminary data suggest may well limit cannabis use in these patients, clozapine (CLOZ), is not used for this purpose; it is reserved for patients whose psychosis is treatment resistant. The overarching idea behind this proposal, however, is that CLOZ's use is being unreasonably restricted and should be made more widely available for patients with SCZ who have a co-occurring CUD but whose psychosis is not necessarily treatment resistant. This notion is supported by our preliminary clinical and animal data on the effects of CLOZ, as well as our neurobiological model of the basis of cannabis use in patients with SCZ that provides a pharmacologic rationale for this effect of CLOZ. Even given all the arguments favoring the potential benefits of CLOZ in patients with SCZ and CUD, however, its side effect profile will likely limit its use until a fully powered study demonstrates its ability to decrease cannabis use in patients with SCZ. This proposal aims to launch such a study. If, as we hypothesize, this study confirms and extends our previous preliminary data of the effects of CLOZ in patients with SCZ and CUD, it will provide a strong impetus to expand the use of CLOZ in this population. In the proposed

study, 132 patients who are comorbid for both SCZ and CUD will be randomized to a 12-week treatment course with either CLOZ or risperidone (RISP). The primary specific aim of this proposal is: (1) To test the hypothesis that patients treated with CLOZ will have decreased cannabis use as compared to patients treated with RISP. Subsidiary aims will further elucidate the effects of CLOZ in this population: (2) a) To determine whether patients treated with CLOZ will have improvements in (i) psychiatric symptoms; (ii) quality of life; and (iii) neuropsychological functions as compared to those taking RISP; and b) to explore whether patients taking CLOZ will show improved reward responsiveness as compared to those taking RISP; and (3) To explore whether those patients with the val/val genotype at the COMT Val158Met locus are more likely to decrease cannabis use during CLOZ treatment than are those without the val/val COMT genotype. Should this study indicate that CLOZ will lessen cannabis use in patients with SCZ more than RISP, it will provide evidence needed to begin to shift clinical practice toward its use in these patients. Given the increased morbidity associated with CUD in patients with SCZ, doing so could dramatically improve the clinical outcome of these individuals. Lastly, CLOZ's use in this study may also reflect its potential to serve as a prototype of the next generation of medications for treatment of SCZ and co-occurring CUD.

2. Objectives & Hypotheses:

The primary specific aim of this proposal is:

(1) To test the hypothesis that patients treated with clozapine (CLOZ) will have decreased cannabis use (intensity and frequency of use) as compared to patients treated with risperidone (RISP).

Subsidiary aims will further elucidate the effects of CLOZ in this population:
(2) (a) To determine whether patients treated with CLOZ will show improved (i) psychiatric symptoms; (ii) quality of life; and (iii) neuropsychological function, as compared to those taking RISP; and (b) to explore whether patients taking CLOZ will show improved reward responsiveness as compared to those taking RISP.

(3) To explore whether those patients with the val/val genotype at the COMT Val158Met locus are more likely to decrease cannabis use during CLOZ treatment than are those without the val/val genotype.

3. *Introduction:*

Note: This introduction is an abridged version of the grant proposal submitted to NIDA. Reviewers desiring a more detailed background for this study are referred to pages 3-7 of the grant proposal. The reference list can be found in Appendix I.

Cannabis use disorder in schizophrenia (SCZ) is an important public health issue: SCZ is a severe psychiatric disorder occurring in 1% of the population worldwide. Most surveys of substance use disorders (SUDs) in patients with SCZ have reported lifetime prevalence of drug/alcohol use disorder in this population ranging from 10 to 60%[17-21] The most comprehensive of these studies, the large-scale NIMH Epidemiologic Catchment Area (ECA) community-based co-morbidity survey, provided clear evidence that patients with SCZ are much more vulnerable to SUDs than are people in the general population.[22] In the ECA study, 47% of patients with SCZ were noted to have serious problems with substance use during their lifetime compared to 16% of the general population. Cannabis is a very common co-occurring substance use disorder in patients with SCZ[21-25] with lifetime rates ranging from 13 to 42%,[26-32] a three to ten-fold increase over the lifetime prevalence of 4% in the general population.[22]

Substance abuse or dependence worsens the course of SCZ. This is true despite the data suggesting that substance abuse in patients with SCZ is characterized by regular but modest levels of use, and with much greater likelihood of substance abuse than dependence in this population.[33] Nonetheless, co-occurring SUD in patients with SCZ is associated with relapse,[34-36] non-compliance with treatment,[37] poorer overall response to typical neuroleptic medication,[38] more rehospitalizations,[35, 39] and an increased risk for violence.[14, 22, 40] Cannabis use disorder (CUD) in particular has been associated with clinical exacerbations, non-compliance with treatment, poor global functioning, and increased relapse and rehospitalization rates.[27, 29, 41-45] Clearly, CUD adds greatly to the financial costs and emotional toll that SCZ places on patients, families and the entire mental health system. [e.g., 53, 54]

Given the clear negative effects of cannabis use in patients with SCZ, the frequent use and abuse of cannabis in these patients is puzzling – why would they use a drug that worsens the symptoms and course of their underlying disease? One common explanation for the use of cannabis/other substances in patients with SCZ invokes the "self-medication" hypothesis,[84, 85] which suggests that use of drugs, despite their negative effects, "corrects" an underlying "deficit", potentially involving negative symptoms,[55, 85] or the side effects of antipsychotic drugs.[55] Despite the observation by some investigators that cannabis use can decrease negative symptoms, [27, 42] a few studies do not support the causal proposition that use of substances is due to negative symptoms. Moreover, the rationale of cannabis use as a means

of overcoming antipsychotic-induced side effects is also subject to question since cannabis and other substance use is common in first episode patients, even before exposure to antipsychotic medications.[88] Thus, while it may be reasonable to suggest that cannabis and other substances may lessen negative symptoms in some patients and also decrease medication-induced side effects, the "reason" for use of substances in these patients may not be merely an attempt at "self medication" of such negative symptoms or medication induced side effects.

We have proposed an alternative formulation of this self-medication hypothesis,[5] based on neurobiological studies that provide some clues about the reason for the high prevalence of CUDs in patients with SCZ. Studies in animals suggest that many brain areas that are dysfunctional in SCZ are part of the DA-mediated "brain reward circuit".[e.g., 92] While cannabis's neuropharmacological actions are complex, and may involve many other neural systems, including norepinephrine and opioid peptides,[e.g., 93, 94] it appears that cannabis, like alcohol, cocaine and other drugs of abuse (including nicotine), produces its reinforcing effects on animal behavior via midbrain DA neurons projecting into the prefrontal cortex and limbic system.[94-99] In patients with SCZ, cannabis and other substance use may decrease negative symptoms via increase in DA activity in the prefrontal cortex (PFC),[e.g., 97, 98, 99, 102] but may also enhance functioning of the dysfunctional brain reward system by an increase in the neuronally-based "signal detection" of these DA-rich systems.[103, 104] Thus, while the abuse of cannabis and other substances may decrease negative symptoms in patients with SCZ, the "basis" of the use of these substances may be related to the difficulty that these patients have in experiencing "normal" levels of reward from the environment and to the ability of cannabis and other substances of abuse to ameliorate this "reward system" deficit.[5, 92, 105, 106] In this sense, use of cannabis is based on the need for patients to “self-medicate” this deficit.

For most of the past six decades, the treatment of psychotic disorders has involved the use of the standard or typical antipsychotic (i.e., neuroleptic) drugs. However, for "dual diagnosis" psychotic patients who are comorbid for SUDs, it appears that the typical antipsychotics are only partially useful. Although the drugs are effective for the underlying psychosis, the side effects they produce (the feeling of being "snowed", and the extrapyramidal system effects) may lead to the further use of cannabis or other substances in an attempt to override (or "self-medicate") such side effects produced by these agents.[42, 55] Thus, while there may be an increased rate of CUD/SUD in patients with SCZ whether treated or not, the typical antipsychotics appear to be of limited value in controlling cannabis or other substance use.

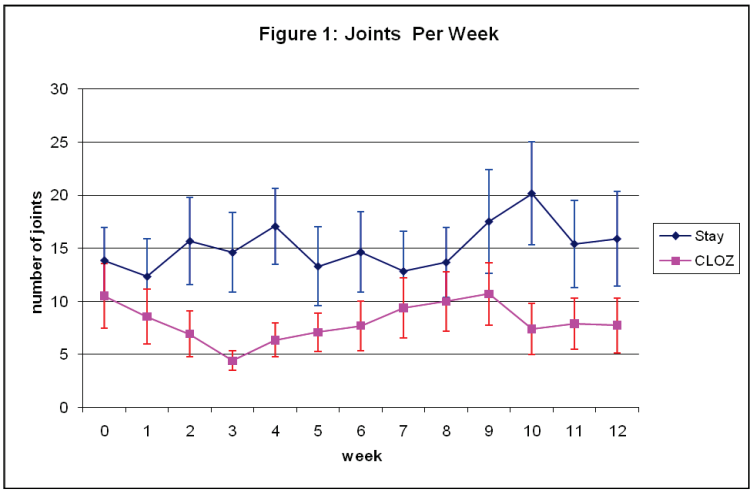
By contrast, a number of reports, including several from the PI's group, suggest that the newer

atypical antipsychotic CLOZ may be helpful in limiting cannabis and other substance abuse in patients with SCZ. In the early 1990s, we described two patients with SCZ who had used alcohol extensively to make them "feel more outgoing", and who dramatically decreased their alcohol use after beginning treatment with CLOZ.[56] Other groups also reported evidence that substance use may decrease during CLOZ treatment.[57-61]

Subsequent studies by our group provided further evidence of the potential role of CLOZ in "dual diagnosis" patients. The first study,[62] a naturalistic, clinical services survey, followed 151 patients who were comorbid for SUD and SCZ or schizoaffective disorder for 3 years. In our analysis of data from this prospective study, we noted that the patients taking CLOZ had higher rates of remission of cannabis abuse (6/9 = 67%) compared to those treated with a typical neuroleptic (12/37 = 32%). Similarly, remission of alcohol abuse was higher in patients taking CLOZ (15/19 = 79%) compared to those treated with typical neuroleptics (29/86 = 34%; Bonferroni corrected p=.003). In a continuing assessment of those patients whose abuse remitted, only 8% of those treated with CLOZ relapsed to abuse in the following 6 months vs. 40% of those treated with other antipsychotics (p=.003).[63]

These findings were further confirmed by our retrospective studies of dual diagnosis patients treated at a separate site, indicating that between 54% and 72% achieved abstinence from cannabis and alcohol during treatment with CLOZ. [64, 65] A report presented by Buckley et al.[66] provided further support for our data (an abstinent rate for all substances of 73% in patients who took CLOZ for 12 weeks), as did another report by Lee et al.[67]

Under support from NIDA, we recently completed a randomized “stay or switch” 12-week trial of CLOZ vs. continued atypical antipsychotics in 35 patients with SCZ and co-occurring CUD. During the study, the patients were not provided extra "dual diagnosis" psychosocial treatment (i.e. beyond clinical care for this population.) Data regarding intensity of cannabis use over the course of the study are indicated in Figure 1. The primary finding from this study[1] is: using longitudinal random effects models, we determined that the intensity of cannabis smoking between the two groups (those randomized to CLOZ and those staying on their original antipsychotic) was systematically different (effect size ~ .6; p<.09), such that, as compared to those staying on



their original antipsychotic, those treated with CLOZ used less cannabis during the 12-week study (with CLOZ, heavy users [≥ 10 joints/week] had a decrease in cannabis use, and most other users [< 10 joints/week] approached abstinence).

Many investigators are currently assessing whether other atypical antipsychotics share with CLOZ an ability to limit co-occurring SUDs in patients with SCZ. Unfortunately, available data are somewhat mixed and not overly promising.[65] Although Smelson et al.[68, 69] reported that risperidone (RISP) reduced craving scores and relapse to cocaine use (as compared to typical antipsychotics) in patients with SCZ and co-occurring cocaine abuse, our retrospective survey of patients with SCZ and co-occurring alcohol or cannabis abuse did not demonstrate an important effect of RISP (on alcohol and/or cannabis use) compared to CLOZ.[70] While there are a few reports of case series suggesting that olanzapine may have a modest effect in limiting substance abuse in these patients,[71, 72] including one from the PI's group,[73] there are two reports[74,75] suggesting that olanzapine may be no more likely to decrease comorbid substance use than are typical antipsychotics. Regarding quetiapine, there are very preliminary reports[76-78] suggesting that this medication may have some beneficial effects in patients with SUD and co-occurring bipolar disorder or SCZ, but further study is needed. And lastly, there have been three open label (small N) reports indicating that aripiprazole, a partial dopamine agonist, may also have some ability to decrease substance use in co-occurring patients.[79-81] Thus, despite the emerging data suggesting that certain of the non-CLOZ atypical medications may have some value in patients with SCZ and co-occurring SUD, CLOZ remains the only one where there is consistent evidence of a substantive decrease in cannabis and other substance use.

Our neurobiological formulation also suggests that CLOZ's unique pharmacological profile may help explain its unusual clinical profile in patients with SCZ and co-occurring cannabis (and other substance) use disorder. We have proposed, based on animal studies, that CLOZ's unusual clinical effects may relate to its varied pharmacologic actions, including those on dopaminergic and, particularly, noradrenergic systems. Work of a number of groups has suggested that some of CLOZ's clinical effects may result from release of DA in the PFC,[e.g., 107-109] which, through regulation of the mesolimbic DA pathway, may contribute to its antipsychotic potential.[e.g., 89, 90] However, CLOZ's unusual actions on noradrenergic neurons may be of paramount importance in understanding its clinical effects.[5, 110] Specifically, we have proposed that CLOZ's activation of the norepinephrine (NE) system (including its antagonistic effects at the NE α_2 receptor and its ability to release NE)[e.g., 111-120] may potentiate functioning of (and ameliorate dysfunction in) the DA-mediated "reward system" through

increase of signal detection in DA subcortical neurons.[5] Within our proposed study (in Aim 2b), we will begin to explore, through study of reward responsiveness,[e.g., 4] whether CLOZ, but not RISP, modulates this aspect of reward circuit functioning in patients with SCZ and CUD, and thus improves their response to reward cues.

Following our neurobiologic formulation, the lack of effect on alcohol/substance use of other antipsychotics may indicate that these antipsychotics are less likely than CLOZ to ameliorate a reward system deficit. We are assessing, under funding from NIAAA and industry, the action of antipsychotic medications in alcohol-preferring rodents with an eye toward creation of a CLOZ-like agent that could decrease alcohol and other substance use in patients with SCZ. Our animal studies have provided considerable support for our neurobiologic formulation of the action of CLOZ. They have suggested that increasing the DA D_2 receptor potency of CLOZ (by the addition of raclopride to CLOZ) will diminish the ability of CLOZ to suppress alcohol drinking; and adding the NE reuptake inhibitor desipramine (DMI) to RISP will allow RISP, which does not decrease alcohol drinking when given alone, to suppress alcohol drinking.

Given our formulation of the mechanism of action of CLOZ in patients with SCZ and CUD or other SUD, we are interested in beginning to investigate whether patients with the val/val genotype at the COMT (catechol-o-methyl transferase) Val158Met locus are more likely to decrease cannabis use with CLOZ than are those with (particularly) the met/met genotype and (possibly) the val/met genotype. We base our hypothesis about this on the action of COMT, which breaks down DA (and NE) particularly in the frontal cortex (given the relative lack of DA reuptake capacity in this brain region).[124, 125] The val/val genotype subjects (25 – 30% of the population) would have a “high output” form of COMT, thus increasing the metabolism of DA in their PFC (where DA-ergic activity is deficient in patients with SCZ).[126] Moreover, the COMT val allele has been reported to predict the development of psychosis following adolescent cannabis use in a longitudinal study of a birth cohort followed through adulthood.[16] Given our formulation of the action of CLOZ, we would expect that those individuals whose cannabis use occurs in the presence of the COMT val/val genotype would be more likely to respond to CLOZ (with a decrease in cannabis use, and potentially a decrease in symptoms) than will individuals who have the met/met (and possibly the val/met) COMT genotype.

The preliminary data from our group and others, including our recent NIDA – funded pilot study of CLOZ vs. other atypical antipsychotics in SCZ and CUD, suggest that CLOZ, despite its side-effect burden, should be considered as a routine treatment option for patients with SCZ and CUD, even for those patients who are not classically “treatment resistant” (i.e., regarding their psychosis). With CLOZ, however, increasing use is an uphill battle – given its potential

side effects (e.g., rare seizures, and very rare agranulocytosis or myocarditis, as well as weight gain, and glucose and lipid increases),[82, 83] requiring regular blood monitoring, and the resulting "medicalization" of treatment, which may be uncomfortable for psychiatrists working in mental health centers. With CLOZ, the evidence in favor of its use needs to be very solid before its use will become routine for treatment of co-occurring CUD. As noted by the Schizophrenia PORT Treatment Recommendations group,[13] the studies generating the existing data regarding the beneficial effects of CLOZ in this population all have limitations. It is the special nature of this drug that indicates to us that the field needs a well-powered trial of CLOZ vs. another (preferably atypical) antipsychotic that will provide the base for change in practice. We are proposing such a trial.

In addition, we will explore whether the val/val COMT genotype may identify those subjects with SCZ most likely to respond to CLOZ with a decrease in cannabis use. Given the side effects of CLOZ, it will be important to be able to exclude from CLOZ treatment any patient in whom CLOZ is not likely to be effective.

4. Design, procedures, materials and methods:

This a longitudinal, randomized, double-blind 12-week study of CLOZ and RISP in a group of 132 participants diagnosed with SCZ and co-occurring CUD, cannabis abuse or dependence. To reach 132 randomized participants we believe we will need to consent and screen approximately 300 participants due to the high screenfail and drop out rate in this population.

Individuals who appear eligible will meet with the study physician to review and, if appropriate, sign the consent document.

Participants will be screened for medications, diagnosis, substance abuse history and health status. If participants appear eligible at the end of the screening, then the next phase of the study will begin.

If an individual is on a medication that is exclusionary, but appears otherwise eligible and expresses a desire to be in the study, our procedure will be to have the medication regimen and proposed change reviewed by the Medication Adjustment Group (MAG), consisting of all study physicians that serve in an advisory capacity on the study and patient care, and led by Dr. Brunette, to ensure that medication decisions are made in a similar fashion across all sites.

The procedure for considering and making such a medication change as deemed appropriate will be as follows:

o Assess whether a change in or elimination of the agent is likely to worsen the clinical condition of the patient. If the MAG determines the risk to be too great, then the person may not enter the study.

o If there is no reason to assume that elimination of the exclusionary medication or use of an alternate medication would worsen the patient's condition and the patient wants to be in the study, he/she will be consented to the study at that time (if not already consented), and the change in medication will be made in consultation with the person's regular physician.

o The MAG will determine the length of time the person must be off of the exclusionary medication before beginning the study and set an interval at which the study doctor is to meet with the person to supervise his or her medication change. Participants will be paid for their time and travel up to $25 per visit for these additional visits.

At the end of the period set by the MAG, if the patient appears to be likely to continue to meet study entry criteria, he or she will continue the screening visit. If not, the person will continue to be transitioned back to the regular treating physician.

At baseline, subjects will be randomly assigned to one of 2 groups of approximately 66 subjects: taking (blinded) RISP or CLOZ. The blinded CLOZ will be titrated on a recommended standard schedule, supervised by a study physician (or other prescriber) who can make the necessary adjustments to account for symptom control and tolerability. The titration is recommended to begin at 12.5 mg and then increase while the open-label base antipsychotic is tapered with a recommended goal of decreasing the base antipsychotic by 25% each week. If clinically tolerated, the target dose of CLOZ is 400 mg/day. The blinded RISP will also be titrated with a target dose of 4 mg/day, while the open label base antipsychotic is tapered in a similar fashion. Participants, treatment providers and study staff will be blinded to study condition by having study medications prepared to look the same.

After the initial 4 week cross-titration period, the prescribing psychiatrist will conduct a formal medication review and, after consulting with the MAG, may elect to increase or lower the dose of blinded medication to achieve optimal response or to accommodate side effects. Study physicians may change doses to address symptom control or tolerability at any time. The principle to be followed is that CLOZ and RISP should be maintained at an optimal dose for psychiatric symptoms. To keep RISP in the dosage range thought to be "atypical" and to

minimize the seizure potential of CLOZ, we will employ a maximum dose of 6 mg of RISP and 550 mg of CLOZ per day – doses likely to be sufficient for most patients. Compliance with study medication will be monitored by packaging the pills into some form of blister-pack or planner, conducting pill counts, and paying participants $5 per week for returning their blister-pack or planner.

The question of concurrent psychotropic medication is a complex issue for this study. Although completely restricting non-study medications in the protocol would make for a methodologically pure design, we are concerned that such a protocol restriction would limit study feasibility and severely curtail the generalizability of our findings. Nonetheless, providing no restrictions on concurrent medications during the trial would confound the experimental design. Therefore, we have decided on the following guidelines: (1) Where clinically appropriate, patients will be taking only RISP or CLOZ during the course of the study; (2) enrolled patients will have concurrent psychotropic medications reduced prior to randomization unless (a) the "MAG" indicates the medication is necessary for their treatment and should not be removed; and (b) the concurrent medication is neither specifically prohibited in the study nor contraindicated in combination with CLOZ or RISP. Wherever possible, concurrent medications will be held stable during the trial. Prospective participants requiring benzotropine and propanolol (or other similar side-effect medications) will be allowed into the study following approval by the MAG. Sedative-hypnotics will be severely restricted (allowed only on an occasional basis, approved by the MAG prior to study entry or for emergencies). The principle to be followed is that concurrent agents may only be used for non-substance-related psychiatric disorders. We believe that this plan will allow us to achieve our specific aims while providing good clinical care.

Participants will be followed for 12 weeks past baseline with weekly study visits. If participants cannot tolerate their assigned study medication after randomization, it will be stopped, though the participant may continue to be followed on another treatment (ideally their pre-study antipsychotic medication) for the remaining weeks of the study.

At the end of an individual's participation (whether as scheduled or earlier if the person leaves the study early), he or she will be asked to have a final study visit. The research physician will work with the participant and his or her treatment team to determine the best course of treatment following the study. If the decision is for the participant to remain on the same antipsychotic as during the study, then the patient and his or her treatment team will be

unblinded to study condition but the research team will remain blinded. If the participant opts to stop the study medication and the clinical team will be responsible for the transition to another medication, the study team will provide for four additional blood draws after clozapine is stopped. They will unblind the participant's treatment provider to the individual's study treatment condition so that the treatment provider can supervise the cross titration of the antipsychotic medications.

Occasionally, after a patient completes the study, a piece of data is missing or that we come to understand that it would be helpful to ask an additional question of all participants. For this reason, participants will be asked as part of the consent process if they are willing to be contacted after their study participation ends.

While our study teams strive to have all participants complete all assessments, this is a population that struggles with the impact of two debilitating disorders. Symptoms of psychosis, including avolition, apathy and cognitive disturbances, commonly lead to behavior that can be inconsistent and result in poor appointment attendance and variable tolerance of assessment batteries. Substance use disorders can similarly contribute to persons having complex lives that can be unpredictable and lead to a variety of difficulties with participation in research activities. Additionally, problems related to symptoms of schizophrenia and substance dependence can cause a number of challenges to carrying out the protocol with a given participant, including: missed appointments, visits outside of the window, inability to complete all study assessments, not taking medication correctly, and not returning medication containers and extra pills. Such events will not be considered protocol deviations unless they impact a participant's safety or the scientific validity of the study.

Pharmacy Problem: In February 2014, the pharmacy providing the medications for this study ceased doing business. The study team intends to arrange services with a new pharmacy, but this may take weeks or months. During this time, participants will be randomized to open label treatment with either risperidone or clozapine. The only other change in the protocol during this time is that after the baseline visit participants randomized to risperidone, will not need the weekly clozapine blood monitoring. A new consent form is being created for this period of time. Any participants consented using the existing consent form with be reconsented. Once arrangements are made with a new pharmacy, participants who were randomized to open label study medication will remain on open label medication. New individuals entering the study after a new pharmacy begins to provide services will be consented using the currently

approved consent describing the use of double-blind study medication and double-blind randomization will re-commence. We will notify the CPHS when this occurs.

Transition Back to Double-Blind: As the various study sites receive all necessary approvals to transition back into the double-blind design, screening will continue and some patients who screen positive may not be randomized immediately so that they can be randomized when the double-blind design is operating again. This delay may be as short as a few days or as long as a few weeks, and may potentially involve one or more extra study visits and possibly one more blood test for blood cell count.

Taping: We hope to audio or video record research interviews for training and reliability purposes. Recording will be done on digital equipment when possible, and on traditional analog equipment when necessary. We plan to transfer digital recordings either directly from the digital recorder to the supervisor's computer or through email as password-protected attachments. When transmitting analog recordings, research interviewers will either hand-carry the tapes back to the supervisor or mail the tapes via registered mail

5. Inclusion/Exclusion Criteria:

Inclusion Criteria:

1. Ages 18-55

2. Meets the DSM-IV TR criteria for diagnoses of schizophrenia or schizoaffective disorder and a cannabis use disorder (abuse or dependence) based on the Structured Interview for the DSM-IV TR [SCID].

3. Has used cannabis on 8 or more days over the 28 days prior to randomization (assessed by the Timeline Followback [TLFB] interview)

4. Stable outpatients as determined by the MAG (e.g. no psychiatric hospitalization for increased psychosis within the past 4 weeks)

5. Stable on antipsychotic medication as determined by the MAG (i.e. no substantial change in dose/type of antipsychotic in the past 4 weeks.)

6. Treated with an antipsychotic drug other than CLOZ at the time of study entry and willing to be treated with either CLOZ or RISP

7. Is willing and able to provide informed consent

Exclusion Criteria

1. Current diagnosis of a substance use disorder other than a CUD or an Alcohol Use Disorder. Caffeine and nicotine (tobacco smoking) use will be allowed, but monitored. Note: Persons using synthetic cannabinoids will be allowed in the study assuming they also have a CUD.

2. Is currently pregnant, trying to become pregnant or nursing

3. Has a history of a seizure disorder

4. Is currently treated with CLOZ or RISP

5. Contraindication to treatment with RISP or CLOZ

6. Treatment with two or more antipsychotics, unless the MAG determines that one of the antipsychotics is prescribed at a dose that is less than therapeutic for psychosis (e.g. low doses of quetiapine for sleep.)

7. Receives treatment with a psychotropic agents proposed to curtail substance use (e.g., disulfiram, naltrexone, acamprosate, topiramate, valproate, levetiracetam, varenicline or bupropion) as determined by the MAG.

8. Is at risk of suicide (as determined by the MAG.)

9. Has a medical condition that would increase risk of study participation.

10. Is deemed inappropriate for the study by the study team or MAG (e.g. due to other medical conditions, medication, psychiatric concerns or other circumstances that could cause safety concerns or impair the person's ability to participate in or benefit from the study.

6. *Statistical Methods and Review Statement:*

The primary outcome measures (Aim 1) will be intensity (number of joints) and frequency (days of use) of **cannabis use** (per week) during follow-up. We will also assess global severity of use monthly. Secondary auxiliary measures (Aim 2) will include **symptoms**: the BPRS score (total, positive and negative subscales), the SANS (negative symptoms), and the CGI total score; **quality of life**: QLS (composite, interpersonal relations and instrumental role subscales), QLI (satisfaction score); **neuropsychological functioning**: five subcomponents from the MATRICS battery: attention/vigilance (CPT IP); verbal learning and memory (Letter

Number Span, Hopkins learning and memory trials); nonverbal learning and memory (Spatial Span and BVMT learning and memory trials); reasoning and problem solving (NAB Mazes); and speed of processing (Trail Making A, Category Fluency, Symbol-Coding); and **reward responsiveness**: delta response bias (delta RB) on the Probabilistic Reward Task. The measures for Aim 3 will include: val/val, val/met and met/met COMT genotypes.

Aim 1: For both explanatory and intent-to-treat comparisons, we will first graphically describe treatment differences over time and check for unusual data and patterns. For the LRE models, polynomial time trends (e.g., slopes) will be used to fit the population mean response curve for the RISP (control) group. Group-by-time interactions will be modeled as a function of time to fit between-group effects. Subject-specific parameters will be estimated to model individual subject deviations from the group mean. For efficiency, baseline measures of intensity of cannabis use and clinical symptoms will be included in the model as covariates; history of treatment resistance and indicators of the COMT genotype subgroup will be included to control for possible imbalances between groups. While not a specific aim, secondary analyses of SUD will assess the effects of CLOZ vs. RISP on nicotine and other substance use, using baseline measures as controls.

Aim 2: The analyses for this aim will be carried out as for Aim 1, but using the auxiliary measures described above. Nicotine dependence at baseline will serve as a control for RR comparisons.

Aim 3: The analyses for this aim will be explanatory, using LRE models that include measures of cannabis use and clinical symptoms as baseline covariates. Subjects in the CLOZ group will be stratified into three subgroups according to their COMT genotype (val/val, val/met, met/met). Separate models for each subgroup will also be used to explore differences, as there is likely to be insufficient power for (subgroup x time) interactions. Differences in use over time will be qualitatively assessed using categorical response (50% decrease, based on predicted values from LRE models).

Sample Size: The sample size for this study was chosen to provide statistical power for an effect size (ES) for Aim 1 as small as 0.45, based on results from our preliminary “stay or switch” study for assessing the effects of CLOZ vs. other antipsychotics on cannabis use. That study provided an ES of 0.6, but to be conservative (given uncertainty in estimated effect sizes from small pilot data), we power this study for a smaller ES. For our primary explanatory analyses, assuming 30% of the 132 subjects fail to complete the study on assigned medication, the detectable ES (two-sided tests, alpha = .05, power = .80) for primary analyses

is .30 for small within-subject correlation (r = .2) and .44 for moderate within-subject correlation (r =.5).

7. *Data and Safety Monitoring:*

The Dartmouth Department of Psychiatry has created a Data Safety Monitoring Board (DSMB) to independently oversee clinical trials and other studies. The DSMB for this study will be composed of at least three people and will include (at minimum) a clinician knowledgeable about SCZ and co-occurring substance use disorders, and a biostatistician who will be independent of the study group. The group will follow the NIH policy for data and safety monitoring and guidelines as published on http://www.nimh.nih.gov/research-funding/grants/nimh-policy-on-data-and-safety-monitoring-in-extramural-investigator-initiated-clinical-trials.shtml. Study data regarding subject enrollment, characteristics, symptoms, substance use, adverse events and serious adverse events will be submitted to the DSMB for review and analysis quarterly. The DSMB will review study data quarterly to oversee the safety of study participants and conduct of the study. It will advise the PI (and the Departmental Research Committee) on continuation of the study and provide reports to the IRB regarding recruitment of appropriate subjects and presence of adverse effects.

8. *Instruments:*

Please refer to Appendix II: Schedule of Events for the specific timing of assessments.

Diagnosis: Patients will be assessed at recruitment with the Structured Clinical Interview for DSM-IV (SCID).[176] Information gathered from all sources (e.g., charts, clinicians, patients).

Cannabis and other substance use: Cannabis/other substance use (including nicotine) will be assessed primarily by weekly self-report using the Timeline Followback (TLFB) method,[139, 181] enhanced by procedures to strengthen the reliability and validity of this measure, as well as data from collateral informants, urinary and breath measures.

Participants' urine will be tested weekly for the presence of cannabis and other substances. We will also test for alcohol (using a breathalyzer). At three points in the study, we will obtain a *urinary cotinine level*. Urine screen tests that are positive for cannabis use will be quantified using liq. chromatography/mass spectrometry (LC/MS/MS). In addition, a urine specimen sample each month will be sent for testing of synthetic cannabinoids. The Fagerström Test for Nicotine Dependence will be used to assess smoking status.

Psychiatric symptoms: Level of psychiatric symptoms will be assessed with the modified Brief Psychiatric Rating Scale (BPRS),[190] the Clinical Global Inventory (CGI),[191] and the Schedule for the Assessment of Negative Symptoms (SANS). [192] Suicidality *will be assessed with the Columbia Suicide Severity Rating Scale (C-SSRS).*[9] Extrapyramidal system effects will be assessed with the Simpson-Angus Scale (S-A),[194] the Abnormal Involuntary Movements Scale (AIMS),[195] and the Barnes Akathisia Scale (BAS).[196]

Quality of life (QOL): Quality of life measures can provide a broad assessment of the status of patients, including those with substance use disorders.[174, 197] We will use items from the Quality of Life scale (QLS) scale[199] and the "subjective section" from the Quality of Life interview (QLI)[200] for the proposed study.

Neuropsychological (NP) functions: In this study, to complement the quality of life functional measures, and because cannabis use produces cognitive effects[201] we will utilize a small battery of NP tests to assess the effects of the two treatments on aspects of NP function that have been shown to be impaired in patients with both schizophrenia and CUD (i.e., attention/vigilance, verbal and visual short- and long-term memory, and executive functions). This will include components from the Wechsler Abbreviated Scale of Intelligence,[204] and an abbreviated online cognitive assessment ("Integneuro"), a 20 minute assessment that, includes brief visual memory span, attention switching, processing speed. There is also an additional brief functional capacity assessment using virtual reality (another 10 -20 minutes).

Reward responsiveness (RR): In an exploratory aim, in order to obtain empirical data regarding functioning of brain reward circuitry during treatment with CLOZ and RISP, we will assess reward responsiveness using the computerized Probabilistic Reward Task[4]. This task measures the extent to which a participant biases their responding toward a more rewarded versus less rewarded stimulus, consistent with the view that frequency of responding is increased toward reinforcers.[208] Relevant for the proposed research, impaired RR in this task has been associated with increased levels of nicotine dependence[209] and affective flattening in patients with schizophrenia.[210]

CLOZ/RISP blood levels: We will draw blood samples to measure CLOZ/RISP levels, and to explore for possible effects of the CLOZ/RISP level on cannabis use.

DNA collection and COMT Val158Met genotyping: A venous blood sample (5 ml) will be drawn and sent to Dartmouth for DNA extraction and genotyping. (Note: An extra tube of blood will be drawn [with permission] and frozen for possible subsequent genetic testing.)

Treatment and service utilization: We will monitor treatment for drug/alcohol abuse and psychosis with a modified version of the Treatment Services Review (TSR).[221]

Other assessments: Other assessments that will be done and are mentioned elsewhere in this Study Plan include: a medical history and physical at screening; an EKG at screening and as clinically appropriate; laboratory testing, including CBC with diff (to obtain blood cell counts) and glucose, cholesterol and triglyceride levels, renal and hepatic function tests; monitoring of vital signs (including weight); monitoring medication compliance via pill counts; reviewing current medications and adverse events; pregnancy tests; monitoring for signs of withdrawal from alcohol and cannabis; and assessing for possible cardiac side effects. EKGs and blood cardiac enzymes will be taken as appropriate clinically.

Note: In order to assure a high degree of reliability in the rating for this study, some of the assessments may be conducted via secure video conference using centralized raters.

9. *Risks and Benefits:*

Potential risks and benefits for participants:

(1) Medications:

(a) Safety of CLOZ: Risks of CLOZ include agranulocytosis – occurs in approximately 0.37% of patients, if a weekly blood count monitoring system is in place (as will be done in this study – see below). All subjects in this study will participate in this weekly blood count monitoring system. The study will follow the FDA package insert for monitoring for neutropenia and treatment recommendations. If the package insert recommends interrupting or discontinuing treatment with clozapine, this will be done in consultation with the patient and his/her clinical psychiatrist, another antipsychotic will be started and the patient's care will be transition from the study to the clinical team. Patients and staff will be specifically instructed to recognize and report any evidence of leukopenia or granulocytopenia such as fever, malaise, sore throat, etc. We limit our population under study to patients between ages 18 and 55 primarily because of the slightly increased risk of agranulocytosis in children and the elderly, and to avoid the confounding effects of age for our neuropsychological measures. (Most patients meeting our inclusion criteria, however, will be within this age range).

The second major risk is the development of seizures. In patients who had no seizure history seizures occurred in 0.9% of people at doses less than 600 mg/day, and 1.5% at doses greater than 600 mg/day. Higher rates have been reported in patients with medical comorbidities and history of head injuries. For this reason we will carefully exclude patients with unstable medical conditions and history of previous seizures and we will utilize a target dose of CLOZ of 400 mg/day. We will exclude patients with a history of a seizure disorder, and carefully assess for prodromal signs of seizures, including myoclonus, in patients within

the study. Should a seizure occur, the medication trial will be terminated and the patient will be treated as appropriate clinically. The doses of CLOZ chosen (target of 400 mg/day, with an upper limit of 550 mg/day) will lower the rate of seizures.

CLOZ is associated with a minimally increased risk of myocarditis early in treatment (between 0.015% and 0.188%). Although this is a very rare effect of CLOZ, patients will be carefully assessed at each visit for signs indicative of myocarditis (e.g., chest congestion, syncope, heart failure, etc.). EKGs will be taken as appropriate clinically.

CLOZ can also cause cardiometabolic side effects such as weight gain, increased glucose levels (with increased rate of diabetes), as well as increased levels of triglycerides and cholesterol. Potential cardiometabolic side effects will be carefully monitored. Patients will be weighed at each visit, vital signs will be taken and patients will be provided brief advice for exercise and nutrition. Patients will be tested for glucose, triglycerides and cholesterol at screening, 6 and 12 weeks. Patients who have elevations in triglycerides or cholesterol will be managed clinically. Patients with clinically significant elevations in glucose will be switched back to pre-study medication or another medication mutually agreed upon by the study physician, the patient, and the patient's clinical physician.

Lastly, CLOZ can also cause hypotension, tachycardia, fever, sedation and sialorrhea. Study physicians will ask participants about side effects each week and will instruct them to call the study team at any time between study visits should adverse events occur. Management of side effects will be discussed with participants. Any moderate to severe side effect will trigger the study physician to consider taking measures to minimize the side effect burden. Lowering the dose of study medication or discontinuing the study medication will be considered and discussed with the MAG and with the participant.

(b) Safety of RISP: Neurologic side effects associated with the short term use of RISP include, in order of frequency: rigidity and stiffness (30%), restlessness (20%), tardive dyskinesia (<3%), and, rarely, neuroleptic malignant syndrome (<1%) -- although the rates of these neurologic side effects are lower than with standard (typical) antipsychotic drugs. We will monitor patients for these effects weekly. In our previous studies of these patients, the rates of neurologic effects have been quite low. If a participant experiences significant side effects, dose adjustment will be attempted or an anticholinergic medication (or propranolol) will be added.

RISP is often associated with elevations in serum prolactin, which is usually asymptomatic but can lead to breast discharge and menstrual difficulties. Participants will be monitored for these potential side effects weekly.

RISP may also cause cardiometabolic side effects (although at rates significantly lower than CLOZ), including weight gain, increased glucose and diabetes, and increased triglycerides and cholesterol. All participants will also be monitored for cardiometabolic side effects as described above.

Other side effects of RISP may include anxiety, stomach upset, and rhinitis. Study physicians will ask patients about side effects weekly and address them by adjusting the dose of the medication or using other strategies. If medication side effects are problematic, the medication may be discontinued.

(2) Relapse of psychosis: Although patients will be under treatment for their psychosis during the study, and both RISP and CLOZ are very effective antipsychotics, patients who switch antipsychotic medication may not do as well on either RISP or CLOZ as on their previous antipsychotic medication. Patients who experience an exacerbation are vulnerable to a number of dangerous behaviors, including self-harm or harm toward others. Symptoms will be assessed weekly. Interviewers will consult with the study psychiatrist if there is any evidence of exacerbation of psychosis or dangerous behavior. Research staff will be on call at all times and available for after hours consultation if needed. If, in the opinion of the study staff, further intervention is needed, the team will coordinate with the participant's clinical treatment team to ensure that the participant gets appropriate care, including emergency care and/or hospitalization. In addition, if necessary, study medication will be terminated and the patient placed on the most appropriate medication for clinical management.

(3) Confidentiality: This research involves monitoring and treatment of patients who may use a variety of illegal substances in addition to cannabis. Participants may engage in other illegal activities. Maintaining confidentiality is an area of utmost importance for this population. See Section 27 for details on how the study team will maintain participant's confidentiality.

(4) Research assessments (cannabis/substance use measures, symptom and side effect measures, breath and urine testing): Answering the questions asked by the interviewers may cause some discomfort, boredom, embarrassment, anxiety or fatigue. It is also possible, but not likely, that the patients may experience an increase in their underlying symptoms due to the process of research assessments. Participants will be advised that they can take a break, refuse to answer question(s), or end the interview if they become uncomfortable in any way.

Research staff will involve the study psychiatrist (on-call) to provide consultation if a patient becomes more symptomatic during a study procedure. In addition, each study site provides emergency services that can be accessed at any time if the study psychiatrist is unavailable. Additionally, either our co-investigator, Dr. Brunette, or her coverage, Dr. Noordsy, both of whom are experienced psychiatrists, will be available via pager for emergency consultation.

(5) Cannabis (or alcohol) withdrawal: Although participants will be using cannabis (and possibly some alcohol as well) mostly in a moderate fashion, heavy cannabis users who drastically reduce or discontinue use during the study may experience withdrawal symptoms. Such symptoms, although not medically dangerous, may consist of mood disturbance such as anxiety or irritability, sleep disturbance, loss of appetite, diarrhea, tremors, and night sweats. While alcohol withdrawal can be more of a serious issue, given the exclusion of patients with alcohol dependence, we do not expect to see alcohol withdrawal symptoms. (In our previous studies of patients with SCZ and CUD [as well as alcohol use disorder], we have not seen withdrawal symptoms in our patients.) Patients will be educated about cannabis (and alcohol) withdrawal with a fact sheet that includes a brief list of coping strategies. Participants will be monitored with weekly vital signs and questions to assess withdrawal symptoms (following symptoms with the Cannabis Withdrawal Scale[172] [CWS] and the Clinical Institute Withdrawal Assessment for Alcohol Scale [CIWA][171]). If patients experience severe cannabis or alcohol withdrawal symptoms, research staff will link the patient with clinical support from their treatment team or other resources as necessary for appropriate medical treatment.

(6) Suicidality: Suicidality is increased in patients with SCZ, especially those with substance use disorders. Since CLOZ is known to limit suicidality more than other antipsychotic medications, patients on CLOZ may be less likely than those on RISP to have suicidality. Nonetheless, all patients will be monitored with the Columbia Suicide Severity Rating Scale (C-SSRS) weekly. Interviewers will consult immediately with the study psychiatrist if the C-SSRS indicates any evidence of suicidal ideation or suicide attempts. Should the patient be deemed to be at risk, the study team will ensure appropriate emergency care, and if necessary, termination from study medication, use of a different medication, and/or hospitalization.

(7) Genetic testing: The major risks of genetic testing are related to maintaining confidentiality of results. The confidentiality of genetic data will be closely guarded. The DNA samples will be securely stored in a locked freezer, and labeled with study number and date of sample. Participants will be assigned a study code number used to cross-link participant data sets. No identifying data will be contained in these data sets. Study records will be maintained in a locked file cabinet with controlled access. Following the Dartmouth guidelines for protection of

human subjects, we will not inform participants of the results of the genetic testing used here, because they do not, at this time, have any clinical relevance and would potentially be confusing to participants.

(8) Venipuncture: There is risk of discomfort and a slight risk of infection due to venipunctures. Standard high quality clinical practice will be used to draw blood in order to avoid discomfort and infection.

(9) Risk to pregnant or nursing women: Since the risk of these medications to developing fetuses and pregnant women is unknown, we will exclude women who are pregnant, nursing, or who wish to become pregnant from study participation. Female participants will be tested for pregnancy at screening, 6 weeks and 12 weeks, and they will be required to use birth control. Should pregnancy occur during the study, the patient will be discontinued from the study, and will be referred to appropriate aftercare treatment. It should be noted that there are currently no data suggesting that either CLOZ or RISP is teratogenic for animals or humans.

Managing risks

We will take a variety of precautions to protect participants from these risks. The first step in protecting against risks is informed consent. As described above, only patients who give informed consent will participate in any study procedure. Moreover, the informed consent process will continue throughout the study.

The PI and the DSMB will monitor safety of participants throughout the study. Confidentiality will be maintained with the standard procedures described below. A participant's clinical status will be monitored throughout the protocol and care will be coordinated with each person's clinical treatment team. Patients may discontinue a study procedure at any time if they are uncomfortable or the study procedures appear to be causing exacerbation of illness.

Potential Benefits: Participants may not benefit from participation in the study. Participants with SCZ and CUD may benefit from the treatment with CLOZ by experiencing a reduction in cannabis use. All study participants will be monitored closely, which may be beneficial to them.

Risk/Benefit Analysis: Although the study medications have multiple potential risks, they are both effective treatments for psychosis. All study patients will have diagnoses of schizophrenia and will already be taking an antipsychotic medication for it. Thus, they are already being exposed to potential medication side effects. Since there are preliminary data suggesting that clozapine may be effective in decreasing cannabis use in this population, those who receive CLOZ may benefit from the effect of the drug, although the

risks related to clozapine are somewhat higher than for risperidone. However, benefits of participation in the study may occur whether or not a subject receives clozapine within the study. In addition, significant knowledge will likely accrue from the study, which may be of help in the treatment of the patients recruited or other patients with similar problems.

Though the medications and treatment offered in this study are available for use outside the study, involvement in the study offers benefits not otherwise available. Clients with schizophrenia and cannabis use disorder may not have access to the following: the opportunity to have a comprehensive assessment done, to meet with a doctor weekly for 13-14 weeks (usual community mental health care involves doctor visits once in 3 months), and to have an accurate longitudinal assessment of symptoms and substance use with standardized measures to understand whether medication and treatment are helping or not (standard care doesn't involve the multiple standardized measures used in this study). At the end of the study, the client will have experienced a comprehensive assessment of symptoms and function, and of the response of symptoms, function, and substance use to medication. These assessments are more comprehensive than would have been possible without involvement in the study protocol.

Study participants will be carefully informed of all potential risks and will not participate if they have concerns about these risks. We will monitor study participants carefully and will address all side effects immediately as they occur. The other potential risks of study participation are minimal. We will use our standard procedures to maintain the highest level of confidentiality and to minimize all potential risks related to the study. Overall we believe the potential benefits outweigh the risks.

10. *Adequacy of Resources to Protect Subjects:*

Describe availability of psychological, social, or medical services, which include counseling or social support services, that may be required as a consequence of research participation.

All study participants will be engaged in treatment and have access to their usual case manager and psychiatrist as well as psychological and medical services available in their communities. The medications being prescribed in this study have been FDA-approved and typically prescribed for many years. While in the study, participants will be monitored very closely. If need for increased assessment or treatment arises, the study doctor will access any and all services needed, including inpatient hospitalization.

Describe psychological, social, or medical monitoring, ancillary care, equipment needed to

protect participants (e.g. close proximity to resuscitation equipment or a plan for monitoring of emotional state during study procedures).

Investigators and site personnel, trained and experienced at conducting assessments in persons with schizophrenia, will assess for deteriorating mental status and/or suicidal ideation. Participants will meet with a study physician at each visit and have routine monitoring of psychiatric symptoms. As described above staff have a number of means of addressing psychiatric symptoms. Staff will also monitor participants through schedule weekly assessments for changes in vital signs, withdrawal from alcohol, and medication side effects. Changes in status will be referred to the treating study physician for follow-up. Each site will have access to medical care in the unlikely event that a participant should develop severe side effects.

Describe other resources needed for the protection of subjects in the conduct of this research (e.g. language translation services).
None

11. *Pregnant Women:*
Are pregnant women eligible for enrollment into this study? ☐ *Yes* ☒ *No*

Although women of childbearing capacity, pregnant women, and nursing women who have SCZ and co-occurring CUD can benefit from treatment with RISP and CLOZ, the risks for pregnant or nursing mothers, and for fetuses and nursing babies are not clear. Thus, pregnant and nursing mothers will not be included in the study. Women with childbearing capacity will be required to use birth control and pregnancy tests will be conducted at baseline, week 6, and week 12 (cost covered by the study).

12. *Fetuses and Neonates:*
Are fetuses and neonates participants in the research?
☐ *Yes* ☒ *No*

13. *Women of Child-Bearing Capability*
Are women of child-bearing capability eligible for enrollment into this study?
☒ *Yes* ☐ *No*

Although women of childbearing capacity who have SCZ and co-occurring CUD can benefit from treatment with RISP and CLOZ, the risks for pregnant or nursing mothers, and for fetuses and nursing babies are not clear. Women with childbearing capacity will be required to use

birth control and pregnancy tests will be conducted at baseline, week 6, and week 12 (cost covered by the study).

14. *Individuals With Impaired Decision-Making Capacity:*

Will participants potentially lacking capacity to provide informed consent be eligible to enroll in this study? ☒ *Yes* ☐ *No*

Is it likely study participants may lose their capacity to provide informed consent during the conduct of the study? ☐ *Yes* ☒ *No*

If yes to a or b, respond to ***Research Involving Individuals with Impaired Decision-Making Capacity: Attachment G***

15. *Recruitment:*

Individuals who are interested in learning about the study will be invited to meet with the study coordinator to review the consent and their possible eligibility. They will be given information about the protocol as well as the opportunity to ask questions. Because these individuals are often coming in for a special appointment to meet with study staff, they will be compensated with a $25 voucher for attending this session.

16. *Consent Process:*

Our group has a procedure for the consent of participants into medication studies. It allows for only physicians and ARNPs to consent participants to be in studies. Other staff may present a consent form to participants and review it with them, but a physician or ARNP must meet with the person (face-to-face or via telephone) to answer questions, and assess understanding and voluntariness prior to the participant signing the consent form. The physician or ARNP will also assess the competency to consent of each potential participant. If an individual's capacity to consent is in doubt and the person does not have a guardian, the consent process will stop. The physician or ARNP will consult with the individual's primary psychiatrist. If in the opinion of the psychiatrist, the person cannot consent and the person lacks a guardian, the person will not be recruited. If the treating psychiatrist believes that the diminished capacity is more of a transitory state, then the consent process will be tried again on another day. Potential participants are encouraged to read the consent form and ask questions. They are further encouraged to solicit input from significant others and/or care providers, if appropriate. To minimize coercion, the consent form has language that clearly spells out that participation in

the study is voluntary and refusal to participate will not affect a person's health/mental health care.

Because we do not have foreign language version of all of the assessments, we do not anticipate consenting persons who do not speak English. We do not intend to recruit persons who are illiterate, but if illiteracy is a problem, our group follows the Dartmouth Committee for the Protection of Human Subjects procedure for consenting persons who cannot read or cannot read well. Finally, our group makes a concerted effort to make the language in consent forms understandable to participants.

17*. Privacy and Confidentiality*:

From the moment that a subject is approached to participate in the study, every effort to protect his/her confidentiality will be maintained. To minimize risk of divulging confidential information regarding substance use or other illegal activities as well as other study information, strict attention to confidentiality will be maintained throughout every aspect of this research with standard policies and procedures. Unless contraindicated by recent interpretations of the governing law, a Certificate of Confidentiality (provided by NIDA) will be obtained. All members of the research team, including investigators and research staff, will follow the procedures to protect confidentiality adhered to by research groups at Dartmouth.

Each patient will be assigned a unique identification number. The list of subject names and identification numbers will be kept separate from the database. This list will be maintained in a locked file cabinet. All hard copies of research records will be kept in separate locked files. Access to the computerized data system is carefully protected by a secured password entry system. Ratings done by video conference will be conducted using a secure system (e.g. WebEx) Subjects will be made aware of the various parties who will have access to their data in the informed consent document, including research personnel, IRBs and the DSMB. Access to participants' data will be restricted to project investigators on a need to know basis. Patient information, if reported, will be reported as group data or anonymously in case reports. No patients will be individually identified.

18. *Responsibility for costs of injury or illness related to research:*

Will the sponsor or other funding agency be responsible for costs of injury or illness related to the research?

☐ *Yes* ☒ *No*

NIDA funding is unable to bear the cost of a hospitalization. If a participant requires hospitalization, it will be billed to their insurance.

19. *Participant Remuneration:*

Participants will receive a $50 gift card for each of the 14 scheduled research visits listed in Appendix II (14 x $50= $700). Participants will also receive $5 cash each week if they return their medication packs to monitor medication compliance (12 X $5 = $60). This is a total of $760.

In addition, participants will "win" between $15-$20 for completing the Rewards Responsiveness Task. Because many vendors only provide gift cards in $5 increments, the first $15 at each session will be paid in the form of a gift card and the remainder in cash. Over the three sessions, this would not total more than $50. We do not state the exact amount in the consent because it invalidates the testing.

Individuals who attend appointments to learn about the study will be compensated with a $25 voucher for their time and travel (see p. 33 for details.)

Finally, if additional in-clinic visits are required (e.g. due to switching medications to be eligible for the study or post-study blood tests conducted by the research team), then participants will receive a $25 gift card for these visits.

20. *Use of Drug or Biological Agent:*

List the drugs and biologic agents to be used in this study:

The drugs used in this study are clozapine and risperidone. The FDA has determined that an IND is not required for this study. Dartmouth will provide a copy of the FDA's determination to any site requiring this.

21. *Conflict of Interest:*

☒ *No: The Principal Investigator or other key personnel **do not** have any financial interests listed in a. - g. above.*

☐ *Yes: The Principal Investigator or other key personnel **do** have financial interests listed in items a. - g. above.*

***Only if you have answered yes to the question above** about study-specific financial interests for a member of the research team, please provide the following additional information.*

Name of each individual with a listed financial interest: _____

Attachment C
Genetic Research

For research studies involving genetic testing the CPHS describes below two categories of studies to assist its further review. The researcher should determine if the research falls into category A or B as described below. If the research falls into category A. indicate by checking below and add comments as appropriate to this research project.
If the research falls into category B. please respond to questions that follow.

Respond to A or B:

☒ *A. The study is looking for an association between a genotype or a biomarker and a specific disease or condition, but at this point it is not clear if the genetic marker has predictive value. The uncertainty regarding the predictive value of the genetic marker is such that studies in this category will not involve referral of participants to genetic counseling.*

Comment:

This trial will allow us to begin to explore whether the val/val COMT genotype may identify those subjects with SCZ most likely to respond to CLOZ with a decrease in cannabis use. Given the side effects of CLOZ, it would be an important advance to be able to exclude from CLOZ treatment any patient in whom CLOZ is not likely to be effective. Following the Dartmouth guidelines for protection of human subjects, we will not inform participants of the results of the genetic testing used here, because they do not, at this time, have any clinical relevance and would potentially be confusing to participants. We will also be asking for an extra tube of blood to be be drawn [with permission] and frozen for possible subsequent genetic testing.

☐ *B. The study is based on the premise that a link between a genotype or a biomarker and a specific disease or condition is clinically useful in predicting the development of that specific disease or condition.*

Attachment G
Research Involving Individuals With Impaired Decision-Making Capacity

Please indicate the option(s) requested to allow for consent if a subject is incompetent to provide consent:

Durable power of attorney for health care (DPAHC)	☐ *YES*	☒ *NO*
Court appointed legal guardian	☒ *YES*	☐ *NO*
Next-of-kin.	☐ *YES*	☒ *NO*

Even with the permission of a DPAHC, or court appointed legal guardian, the federal regulations will not permit a subject who lacks capacity to give informed consent to participate in a research study that offers little chance of DIRECT BENEFIT to the research subject over what they could receive outside the research setting and involves a meaningful increase in the risk of harm or discomfort, regardless of the potential gain to future subjects or society in general.

Please complete a) and b):

a) *Does participating in this study offer the subject a chance of direct benefit over what they could receive outside the research setting?*

While both medications are FDA approved for the treatment of schizophrenia and available to prospective study participants, the level of care offered in this study (e.g. weekly physician visits, level of symptom and medical assessment) is not possible in standard care.

b) *Is there an increase in the risk of harm or discomfort for the subject over what they would experience outside the research setting?*

No - Both of these medications are reasonable treatments for this population of patients. If anything, the added care described above lessens the medical risks to participants because if they chose one of these medications in a purely treatment setting, they could not get this level of monitoring. The only increase in risk is fatigue or stress due to the level of assessments being greater than what is offered in standard care.

GLOSSARY OF ACRONYMS

AIMS = Abnormal Involuntary Movements Scale
AUS = alcohol use disorder
BAS = Barnes Akathisia Scale
BPRS = Brief Psychiatric Rating Scale
BVMT = Brief Visuospatial Memory Test
CBC = complete blood count
CGI = Clinical Global Inventory
CIWA = Clinical Institute Withdrawal Assessment for Alcohol Scale
CLOZ = clozapine
COMT = catechol-o-methyl transferase
CPT IP = Continuous Performance Test – Identical Pairs
C-SSRS = Columbia Suicide Severity Rating Scale
CUD = cannabis use disorder
CWS = Cannabis Withdrawal Scale
DA = dopamine
DMI = desipramine
DSM-IV TR
ECA = Epidemiologic Catchment Area
EKG = electrocardiogram
ES = effect size
LC/MS/MS = liquid chromatography/mass spectrometry
LRE = longitudinal random effects
MAG = medication adjustment group
NE = norepinephrine
NIAAA = National Institute on Alcohol Abuse and Alcoholism
NIDA = National Institute on Drug Abuse
NP = neuropsychological
PORT = Patient Outcomes Research Team
QLI = Quality of Life interview
QLS = Quality of Life scale
RISP = risperidone
RR = reward responsiveness
S-A = Simpson-Angus Scale
SANS = Schedule for the Assessment of Negative Symptoms
SCID = Structured Clinical Interview for DSM-IV
SCZ = schizophrenia
SUD = substance use disorder
TLFB = Timeline Followback
TSR = Treatment Services Review
WRAT-4 = Wide Range Achievement Test Revision 4, Word Reading Subtest

APPENDIX I: REFERENCES

Clozaril for Cannabis Use Disorder in Schizophrenia (Alan I. Greem, PI)

1. Brunette MF, Dawson R, O'Keefe CD, Narasimhan M, Noordsy DL, Wojcik J, Green AI. A randomized trial of clozapine vs. other antipsychotics for cannabis use disorder in patients with schizophrenia. Journal of Dual Diagnosis. 2011;7(1):50-63.
2. Noordsy DL, Smith JN, Green AI. Clozapine vs. Risperidone for People with First Episode Schizophrenia and Co-Occurring Cannabis Use Disorder. 2nd Biennial Schizophrenia International Research Conference. Schizophrenia Research. 2010;117:165-6.
3. Tiihonen J, Lonnqvist J, Wahlbeck K, Klaukka T, Niskanen L, Tanskanen A, Haukka J. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). Lancet. 2009;374(9690):620-7.
4. Pizzagalli DA, Jahn AL, O'Shea JP. Toward an objective characterization of an anhedonic phenotype: a signal-detection approach. Biol Psychiatry. 2005;57(4):319-27.
5. Green AI, Zimmet SV, Strous RD, Schildkraut JJ. Clozapine for comorbid substance use disorder and schizophrenia: do patients with schizophrenia have a reward-deficiency syndrome that can be ameliorated by clozapine? Harv Rev Psychiatry. 1999;6(6):287-96.
6. Huestis MA, Cone EJ. Differentiating new marijuana use from residual drug excretion in occasional marijuana users. Journal of Analytical Toxicology. 1998;22:445-54.
7. Schwilke EW, Gullberg RG, Darwin WD, Chiang CN, Cadet JL, Gorelick DA, Pope HG, Huestis MA. Differentiating new cannabis use from residual urinary cannabinoid excretion in chronic, daily cannabis users. Addiction. 2010;106(3):499-506.
8. Smith ML, Barnes AJ, Huestis MA. Identifying new cannabis use with urine creatinine-normalized THCCOOH concentrations and time intervals between specimen collections. J Anal Toxicol. 2009;33(4):185-9. PMCID: PMC3159564
9. Posner K, Brent D, Lucas C, Gould M, Stanley B, Brown G, Fisher P, Zelazny J, Burke A, Oquendo M, Mann J. Columbia-Suicide Severity Rating Scale (C-SSRS). The Reserach Foundation for Mental Hygiene, Inc. 2008.
10. Volavka J. The effects of clozapine on aggression and substance abuse in schizophrenic patients. Journal of Clinical Psychiatry. 1999;60(Suppl 12):43-6.
11. Spivak B, Roitman S, Vered Y, Mester R, Graff E, Talmon Y, Guy N, Gonen N, Weizman A. Diminished suicidal and aggressive behavior, high plasma norepinephrine levels, and serum triglyceride levels in chronic neuroleptic-resistant schizophrenic patients maintained on clozapine. Clin Neuropharmacol. 1998;21(4):245-50.
12. Meltzer HY, Alphs L, Green AI, Altamura AC, Anand R, Bertoldi A, Bourgeois M, Chouinard G, Islam MZ, Kane J, Krishnan R, Lindenmayer JP, Potkin S. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). Arch Gen Psychiatry. 2003;60(1):82-91.
13. Buchanan RW, Kreyenbuhl J, Kelly DL, Noel JM, Boggs DL, Fischer BA, Himelhoch S, Fang B, Peterson E, Aquino PR, Keller W. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. Schizophr Bull. 2010;36(1):71-93 PMCID 2800144. PMCID: PMC2800144.
14. Swanson JW, Holzer CE, 3rd, Ganju VK, Jono RT. Violence and psychiatric disorder in the community: evidence from the Epidemiologic Catchment Area surveys. Hosp Community Psychiatry. 1990;41(7):761-70.
15. Potkin SG, Alphs L, Hsu C, Krishnan KR, Anand R, Young FK, Meltzer H, Green A. Predicting suicidal risk in schizophrenic and schizoaffective patients in a prospective two-year trial. Biol Psychiatry. 2003;54(4):444-52.
16. Caspi A, Moffitt TE, Cannon M, McClay J, Murray R, Harrington H, Taylor A, Arseneault L, Williams B, Braithwaite A, Poulton R, Craig IW. Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-

methyltransferase gene: longitudinal evidence of a gene X environment interaction. Biol Psychiatry. 2005;57(10):1117-27.
17. Alterman AI, Erdlen FR, Murphy E. Alcohol abuse in the psychiatric hospital population. Addict Behav. 1981;6(1):69-73.
18. Ananth J, Vandewater S, Kamal M, Brodsky A, Gamal R, Miller M. Missed diagnosis of substance abuse in psychiatric patients. Hosp Community Psychiatry. 1989;40(3):297-9.
19. Freed EX. Alcoholism and schizophrenia: the search for perspectives. A review. J Stud Alcohol. 1975;36(7):853-81.
20. Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry. 1994;51(1):8-19.
21. Mueser KT, Yarnold PR, Levinson DF, Singh H, Bellack AS, Kee K, Morrison RL, Yadalam KG. Prevalence of substance abuse in schizophrenia: demographic and clinical correlates. Schizophr Bull. 1990;16(1):31-56.
22. Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, Goodwin FK. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. Jama. 1990;264(19):2511-8.
23. Degenhardt L, Hall W. The association between psychosis and problematical drug use among Australian adults: findings from the National Survey of Mental Health and Well-Being. Psychol Med. 2001;31(4):659-68.
24. Koskinen J, Lohonen J, Koponen H, Isohanni M, Miettunen J. Rate of cannabis use disorders in clinical samples of patients with schizophrenia: a meta-analysis. Schizophr Bull. 2010;36(6):1115-30. PMCID: PMC2963055.
25. Ringen PA, Lagerberg TV, Birkenaes AB, Engn J, Faerden A, Jonsdottir H, Nesvag R, Friis S, Opjordsmoen S, Larsen F, Melle I, Andreassen OA. Differences in prevalence and patterns of substance use in schizophrenia and bipolar disorder. Psychol Med. 2008;38(9):1241-9.
26. Dixon L, Haas G, Weiden PJ, Sweeney J, Frances AJ. Drug abuse in schizophrenic patients: clinical correlates and reasons for use. Am J Psychiatry. 1991;148(2):224-30.
27. Peralta V, Cuesta MJ. Influence of cannabis abuse on schizophrenic psychopathology. Acta Psychiatr Scand. 1992;85(2):127-30.
28. Mueser KT, Nishith P, Tracy JI, DeGirolamo J, Molinaro M. Expectations and motives for substance use in schizophrenia. Schizophr Bull. 1995;21(3):367-78.
29. DeQuardo JR, Carpenter CF, Tandon R. Patterns of substance abuse in schizophrenia: nature and significance. J Psychiatr Res. 1994;28(3):267-75.
30. Hambrecht M, Hafner H. Substance abuse and the onset of schizophrenia. Biol Psychiatry. 1996;40(11):1155-63.
31. Karam EG, Yabroudi PF, Melhem NM. Comorbidity of substance abuse and other psychiatric disorders in acute general psychiatric admissions: a study from Lebanon. Compr Psychiatry. 2002;43(6):463-8.
32. Rabinowitz J, Bromet EJ, Lavelle J, Carlson G, Kovasznay B, Schwartz JE. Prevalence and severity of substance use disorders and onset of psychosis in first-admission psychotic patients. Psychol Med. 1998;28(6):1411-9.
33. Corse SJ, Hirschinger NB, Zanis D. The use of the Addiction Severity Index with people with severe mental illness. Psychiatric Rehabilitation Journal. 1995;19:9-18.
34. Drake RE, Rosenberg SD, Mueser KT. Assessing substance use disorder in persons with severe mental illness. New Dir Ment Health Serv. 1996(70):3-17.
35. Richard ML, Liskow BI, Perry PJ. Recent psychostimulant use in hospitalized schizophrenics. J Clin Psychiatry. 1985;46(3):79-83.
36. Gupta S, Hendricks S, Kenkel AM, Bhatia SC, Haffke EA. Relapse in schizophrenia: is there a relationship to substance abuse? Schizophr Res. 1996;20(1-2):153-6.

37. Owen RR, Fischer EP, Booth BM, Cuffel BJ. Medication noncompliance and substance abuse among patients with schizophrenia. Psychiatr Serv. 1996;47(8):853-8.
38. Bowers MB, Mazure CM, Nelson CJ, Jatlow PI. Psychotogenic drug use and neuroleptic response. Schizophrenia Bulletin. 1990;16:81-5.
39. Brady K, Anton R, Ballenger JC, Lydiard RB, Adinoff B, Selander J. Cocaine abuse among schizophrenic patients. Am J Psychiatry. 1990;147(9):1164-7.
40. Abram KM, Teplin LA. Co-occurring disorders among mentally ill jail detainees. Implications for public policy. Am Psychol. 1991;46(10):1036-45.
41. Treffert DA. Marijuana use in schizophrenia: a clear hazard. Am J Psychiatry. 1978;135(10):1213-5.
42. Knudsen P, Vilmar T. Cannabis and neuroleptic agents in schizophrenia. Acta Psychiatr Scand. 1984;69(2):162-74.
43. Negrete JC, Knapp WP. The effects of cannabis use on the clinical condition of schizophrenics. NIDA Res Monogr. 1986;67:321-7.
44. Linszen DH, Dingemans PM, Lenior ME. Cannabis abuse and the course of recent-onset schizophrenic disorders. Arch Gen Psychiatry. 1994;51(4):273-9.
45. Swendsen J, Ben-Zeev D, Granholm E. Real-time electronic ambulatory monitoring of substance use and symptom expression in schizophrenia. Am J Psychiatry. 2011;168(2):202-9.
46. Green AI, Tohen MF, Hamer RM, Strakowski SM, Lieberman JA, Glick I, Clark WS. First episode schizophrenia-related psychosis and substance use disorders: acute response to olanzapine and haloperidol. Schizophr Res. 2004;66(2-3):125-35.
47. Large M, Sharma S, Compton MT, Slade T, Nielssen O. Cannabis use and earlier onset of psychosis: a systematic meta-analysis. Arch Gen Psychiatry. 2011;68(6):555-61.
48. Schimmelmann BG, Conus P, Cotton SM, Kupferschmid S, Karow A, Schultze-Lutter F, McGorry PD, Lambert M. Cannabis use disorder and age at onset of psychosis--a study in first-episode patients. Schizophr Res. 2011;129(1):52-6.
49. Shapiro GK, Buckley-Hunter L. What every adolescent needs to know: cannabis can cause psychosis. J Psychosom Res. 2010;69(6):533-9.
50. Kovasznay B, Fleischer J, Tanenberg-Karant M, Jandorf L, Miller AD, Bromet E. Substance use disorder and the early course of illness in schizophrenia and affective psychosis. Schizophrenia Bulletin. 1997;23(2):195-201.
51. Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, Lewis G. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. Lancet. 2007;370(9584):319-28.
52. Eggan SM, Hashimoto T, Lewis DA. Reduced cortical cannabinoid 1 receptor messenger RNA and protein expression in schizophrenia. Arch Gen Psychiatry. 2008;65(7):772-84. PMCID: PMC2890225.
53. Kivlahan DR, Heiman JR, Wright RC, Mundt JW, Shupe JA. Treatment cost and rehospitalization rate in schizophrenic outpatients with a history of substance abuse. Hosp Community Psychiatry. 1991;42(6):609-14.
54. Dickey B, Azeni H. Persons with dual diagnoses of substance abuse and major mental illness: their excess costs of psychiatric care. Am J Public Health. 1996;86(7):973-7.
55. Siris SG. Pharmacological treatment of substance-abusing schizophrenic patients. Schizophr Bull. 1990;16(1):111-22.
56. Albanese MJ, Khantzian EJ, Murphy SL, Green AI. Decreased substance use in chronically psychotic patients treated with clozapine. Am J Psychiatry. 1994;151(5):780-1.
57. Buckley P, Thompson P, Way L, Meltzer HY. Substance abuse among patients with treatment-resistant schizophrenia: characteristics and implications for clozapine therapy. Am J Psychiatry. 1994;151(3):385-9.
58. Marcus P, Snyder R. Reduction of comorbid substance abuse with clozapine. Am J Psychiatry. 1995;152(6):959.

59. Yovell Y, Opler LA. Clozapine reverses cocaine craving in a treatment-resistant mentally ill chemical abuser: a case report and a hypothesis. J Nerv Ment Dis. 1994;182:591-2.
60. McEvoy JP, Freudenreich O, McGee M, VanderZwaag C, Levin E, Rose J. Clozapine decreases smoking in patients with chronic schizophrenia. Biological Psychiatry. 1995;37:550-2.
61. George TP, Sernyak MJ, Ziedonis DM, Woods SW. Effects of clozapine on smoking in chronic schizophrenic outpatients. J Clin Psychiatry. 1995;56(8):344-6.
62. Drake RE, Xie H, McHugo GJ, Green AI. The effects of clozapine on alcohol and drug use disorders among patients with schizophrenia. Schizophr Bull. 2000;26(2):441-9.
63. Brunette MF, Drake RE, Xie H, McHugo GJ, Green AI. Clozapine use and relapses of substance use disorder among patients with co-occurring schizophrenia and substance use disorders. Schizophr Bull. 2006;32(4):637-43.
64. Zimmet SV, Strous RD, Burgess ES, Kohnstamm S, Green AI. Effects of clozapine on substance use in patients with schizophrenia and schizoaffective disorder: a retrospective survey. J Clin Psychopharmacol. 2000;20(1):94-8.
65. Green AI, Noordsy DL, Brunette MF, O'Keefe C. Substance abuse and schizophrenia: pharmacotherapeutic intervention. J Subst Abuse Treat. 2008;34(1):61-71.
66. Buckley P, McCarthy M, Chapman P, Richman C, Yamamoto B. Clozapine treatment of comorbid substance abuse in patients with schizophrenia. Schizophr Res. 1999;36::272.
67. Lee ML, Dickson RA, Campbell M, Oliphant J, Gretton H, Dalby JT. Clozapine and substance abuse in patients with schizophrenia. Can J Psychiatry. 1998;43(8):855-6.
68. Smelson DA, Williams J, Ziedonis D, Sussner BD, Losonczy MF, Engelhart C, Kaune M. A double-blind placebo-controlled pilot study of risperidone for decreasing cue-elicited craving in recently withdrawn cocaine dependent patients. J Subst Abuse Treat. 2004;27(1):45-9.
69. Smelson DA, Losonczy MF, Davis CW, Kaune M, Williams J, Ziedonis D. Risperidone decreases craving and relapses in individuals with schizophrenia and cocaine dependence. Canadian Journal of Psychiatry. 2002;47(7):671-5.
70. Green AI, Burgess ES, Dawson R, Zimmet SV, Strous RD. Alcohol and cannabis use in schizophrenia: effects of clozapine vs. risperidone. Schizophr Res. 2003;60(1):81-5.
71. Smelson DA, Ziedonis D, Williams J, Losonczy MF, Williams J, Steinberg ML, Kaune M. The efficacy of olanzapine for decreasing cue-elicited craving in individuals with schizophrenia and cocaine dependence: a preliminary report. J Clin Psychopharmacol. 2006;26(1):9-12.
72. Akerele E, Levin FR. Comparison of olanzapine to risperidone in substance-abusing individuals with schizophrenia. Am J Addict. 2007;16(4):260-8.
73. Brunette MF, O'Keefe C, Zimmet SV, Wojcik JD, Dawson R, Green AI. Clozapine, Olanzapine, or Typical Antipsychotics for Alcohol Use Disorder in Patients with Schizophrenia. Journal of Dual Diagnosis. 2008;4(4):344-54.
74. Petrakis IL, Leslie D, Finney JW, Rosenheck R. Atypical antipsychotic medication and substance use-related outcomes in the treatment of schizophrenia. Am J Addict. 2006;15(1):44-9.
75. Noordsy DL, O'Keefe C, Mueser KT, Xie H. Six-month outcomes for patients who switched to olanzapine treatment. Psychiatric Services. 2001;52(4):501-7.
76. Potvin S, Stip E, Lipp O, Elie R, Mancini-Marie A, Demers MF, Roy MA, Bouchard RH, Gendron A. Quetiapine in patients with comorbid schizophrenia-spectrum and substance use disorders: an open-label trial. Curr Med Res Opin. 2006;22(7):1277-85.
77. Brunette MF, O'Keefe C, Dawson R, Buckley P, Green AI. An open label study of quetiapine in patients with schizophrenia and alcohol disorders. Journal of Mental Health and Substance Use Disorders. 2009;2(3):203-11.

78. Brown ES, Nejtec VA, Perantine DC, editors. Quetiapine in psychiatric illness with comorbid stimulant abuse. 40th Annual Meeting of the American College of Neuropsychopharmacology; 2001 Dec 9-13; Waikoloa, HI.
79. Beresford TP, Clapp L, Martin B, Wiberg JL, Alfers J, Beresford HF. Aripiprazole in schizophrenia with cocaine dependence: a pilot study. J Clin Psychopharmacol. 2005;25(4):363-6.
80. Brown ES, Jeffress J, Liggin JD, Garza M, Beard L. Switching outpatients with bipolar or schizoaffective disorders and substance abuse from their current antipsychotic to aripiprazole. J Clin Psychiatry. 2005;66(6):756-60.
81. Warsi M, Sattar SP, Bhatia SC, Petty F. Aripiprazole reduces alcohol use. Canadian Journal of Psychiatry. 2005;50(4):244.
82. Baldessarini RJ, Frankenburg FR. Clozapine. A novel antipsychotic agent. N Engl J Med. 1991;324(11):746-54.
83. Marder SR, Wirshing DA. Clozapine. In: Schatzberg AF, Nemeroff CB, editors. Textbook of psychopharmacology. Washington, D.C.: American Psychiatric Publishing, Inc.; 2004.
84. Siris SG. Suicide and schizophrenia. J Psychopharmacol. 2001;15(2):127-35.
85. Khantzian EJ. The self-medication hypothesis of substance use disorders: a reconsideration and recent applications. Harv Rev Psychiatry. 1997;4(5):231-44.
86. Lysaker PH, Bell MD, Beam-Goulet J, Milstein R. Relationship of positive and negative symptoms to cocaine abuse in schizophrenia. Journal of Nervous and Mental Disease. 1994;182:109-12.
87. Buchanan RW, Strauss ME, Breier A, Kirkpatrick B, Carpenter WT, Jr. Attentional impairments in deficit and nondeficit forms of schizophrenia. Am J Psychiatry. 1997;154(3):363-70.
88. Hambrecht M, Hafner H. Cannabis, vulnerability, and the onset of schizophrenia: an epidemiological perspective. Aust N Z J Psychiatry. 2000;34(3):468-75.
89. Weinberger DR. A connectionist approach to the prefrontal cortex. J Neuropsychiatry. 1993;5(3):241-53.
90. Moghadamm B, Sesack SR. Cellular interactions in the prefrontal cortex: a major focus of schizophrenia research. In: Dickstein L, Riba M, Oldham J, editors. American Psychiatric Press Review of Psychiatry. Washington, D.C.: American Psychiatric Association; 1996. p. 351-72.
91. Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry. 1987;44(7):660-9.
92. Gardner EL. Brain Reward Mechanisms. In: JH L, P R, RB M, JG. L, editors. Substance Abuse: A comprehensive textbook. 3 ed. Baltimore: Williams & Wilkins; 1997.
93. Jentsch JD, Andrusiak E, Tran A, Bowers MB, Jr., Roth RH. Delta 9-tetrahydrocannabinol increases prefrontal cortical catecholaminergic utilization and impairs spatial working memory in the rat: blockade of dopaminergic effects with HA966. Neuropsychopharmacology. 1997;16(6):426-32.
94. Tanda G, Pontieri FE, Di Chiara G. Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common mu1 opioid receptor mechanism. Science. 1997;276(5321):2048-50.
95. Gardner EL. Cannabinoid interaction with brain reward systems. In: GG. N, editor. Marijuana and Medicine. Totowa, NJ: Humana Press; 1998.
96. Gessa GL, Melis M, Muntoni AL, Diana M. Cannabinoids activate mesolimbic dopamine neurons by an action on cannabinoid CB1 receptors. Eur J Pharmacol. 1998;341(1):39-44.
97. Diana M, Melis M, Gessa GL. Increase in meso-prefrontal dopaminergic activity after stimulation of CB1 receptors by cannabinoids. Eur J Neurosci. 1998;10(9):2825-30.
98. Fadda F, Mosca E, Colombo G, Gessa GL. Effect of spontaneous ingestion of ethanol on brain dopamine metabolism. Life Sci. 1989;44(4):281-7.

99. Goeders NE, Smith JE. Reinforcing properties of cocaine in the medical prefrontal cortex: primary action on presynaptic dopaminergic terminals. Pharmacol Biochem Behav. 1986;25(1):191-9.
100. Lupica CR, Riegel AC, Hoffman AF. Marijuana and cannabinoid regulation of brain reward circuits. Br J Pharmacol. 2004;143(2):227-34.
101. Gardner EL. Endocannabinoid signaling system and brain reward: emphasis on dopamine. Pharmacol Biochem Behav. 2005;81(2):263-84.
102. Chen J, Paredes W, Lowinson JH, Gardner EL. Delta 9-tetrahydrocannabinol enhances presynaptic dopamine efflux in medial prefrontal cortex. Eur J Pharmacol. 1990;190(1-2):259-62.
103. Nissel M, Nomikos GG, Svensson TH. Nicotine dependence, midbrain dopamine systems and psychiatric disorders. Pharm and Toxicol. 1995;76:157-62.
104. Tung CS, Grenhoff J, Svensson TH. Nicotine counteracts midbrain dopamine cell dysfunction induced by prefrontal cortex inactivation. Acta Physiol Scand. 1990;138(3):427-8.
105. Blum K, Sheridan PJ, Wood RC, Braverman ER, Chen TJ, Cull JG, Comings DE. The D2 dopamine receptor gene as a determinant of reward deficiency syndrome. Journal of the Royal Society of Medicine. 1996;89(7):396-400.
106. Chambers RA, Krystal JH, Self DW. A neurobiological basis for substance abuse comorbidity in schizophrenia. Biological Psychiatry. 2001;50(2):71-83.
107. Gardner EL, Chen J, Paredes W. Clozapine produces potent antidopaminergic effects anatomically specific to the mesolimbic system. J Clin Psychiatry. 1994;55 Suppl B:15-22.
108. Imperato A, Angelucci L. The effects of clozapine and fluperlapine on the in vivo release and metabolism of dopamine in the striatum and in the prefrontal cortex of freely moving rats. Psychopharmacol Bull. 1989;25(3):383-9.
109. Molina Rodriguez V, Montz Andree R, Perez Castejon MJ, Capdevila Garcia E, Carreras Delgado JL, Rubia Vila FJ. SPECT study of regional cerebral perfusion in neuroleptic-resistant schizophrenic patients who responded or did not respond to clozapine. American Journal of Psychiatry. 1996;153(10):1343-6.
110. Baldessarini RJ, Houston-Lyons D, Campell A, Marsh E, Cohen. Do central antiadrenergic actions contribute to the atypical properties of clozapine? Br J Psychiatry. 1992;17 - suppl.:12-6.
111. Antelman SM, Caggiula AR. Norepinephrine-dopamine interactions and behavior. Science. 1977;195:646-53.
112. Breier A, Buchanan RW, Waltrip RW, Listwak S, Holems C, Goldstein DS. The effect of clozapine on plasma norepinephrine: relationship to clinical efficacy. Neuropsychopharm. 1994;10:1-7.
113. Green AI, Alam MY, Sobieraj JT, Pappalardo KM, Waternaux C, Salzman C, Schatzberg AF, Schildkraut JJ. Clozapine response and plasma catecholamines and their metabolites. Psychiatry Res. 1993;46(2):139-49.
114. Horneykiewicz O. Brain catecholamines in schizophrenia -- A good case for noradrenaline. Nature. 1982;299:484-6.
115. Lieberman J, Johns C, Pollack S, Masiar S, Bookstein P, Cooper T, Iadorola M, Kane J. Biochemical effects of clozapine in cerebrospinal fluid of patients with schizophrenia. In: Tamminga C, Schulz S, editors. Advances in neuropsychiatry and psychopharmacology vol 1: Schizophrenia research. New York: Raven Press; 1991. p. 341-9.
116. Rice HE, Smith CB, Silk KR, Rosen J. Platelet alpha 2-adrenergic receptors in schizophrenic patients before and after phenothiazine treatment. Psychiatry Res. 1984;12:62-77.
117. Sarafoff M, Davis L, Ruther E. Clozapine-induced increase of human plasma norepinephrine. J Neural Transmission. 1979;46:175-80.

118. Svensson TH, Mathe JM, Andersson JL, Nomikos GG, Hildebrand BE, Marcus M. Mode of action of atypical neuroleptics in relation to the phencyclidine model of schizophrenia: role of 5-HT2 receptor and alpha 1-adrenoceptor antagonism. J Clin Psychopharmacol. 1995;15(1 Suppl 1):11S-8S.
119. Thierry AM, Godbout R, Mantz J, Glowinski J. Influence of the ascending monoaminergic systems on the activity of the rat prefrontal cortex. Prog Brain Res. 1990;85:357-64; discussion 64-5.
120. Van Kammen DP, Peters JL, Van Kammen WB, Neylan T, Yao JK, Shaw D, Doherty G. Noradrenaline, state dependency and relapse prediction in schizophrenia. In: Weller M, editor. International Perspectives in Schizophrenia. London: John Libbey; 1990. p. 253-68.
121. Grace AA. Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. Neuroscience. 1991;41(1):1-24.
122. Elman I, Goldstein DS, Green AI, Eisenhofer G, Folio CJ, Holmes CS, Pickar D, Breier A. Effects of risperidone on the peripheral noradrenegic system in patients with schizophrenia: a comparison with clozapine and placebo. Neuropsychopharmacology. 2002;27(2):293-300.
123. See RE, Fido AA, Maurice M, Ibrahim MM, Salama GM. Risperidone-induced increase of plasma norepinephrine is not correlated with symptom improvement in chronic schizophrenia. Biol Psychiatry. 1999;45(12):1653-6.
124. Weinberger DR, Egan MF, Bertolino A, Callicott JH, Mattay VS, Lipska BK, Berman KF, Goldberg TE. Prefrontal neurons and the genetics of schizophrenia. Biol Psychiatry. 2001;50(11):825-44.
125. Funke B, Malhotra AK, Finn CT, Plocik AM, Lake SL, Lencz T, DeRosse P, Kane JM, Kucherlapati R. COMT genetic variation confers risk for psychotic and affective disorders: a case control study. Behav Brain Funct. 2005;1:19.
126. Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE, Goldman D, Weinberger DR. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. Proc Natl Acad Sci U S A. 2001;98(12):6917-22.
127. Myers RD. New drugs for the treatment of experimental alcoholism. Alcohol. 1994;11(6):439-51.
128. McBride WJ, Li TK. Animal models of alcoholism: neurobiology of high alcohol-drinking behavior in rodents. Crit Rev Neurobiol. 1998;12(4):339-69.
129. Piercy KT, Myers RD. Female Syrian golden hamster: drinking of high concentrations of ethanol aversive to other mammals. Alcohol. 1995;12(3):207-11.
130. McCoy GD, Haisley AD, Powchik P, Tambone PC. Ethanol consumption by Syrian golden hamsters. Food intake and blood ethanol levels. J Stud Alcohol. 1981;42(5):508-13.
131. Kulkosky PJ, Cornell NW. Free-choice ethanol intake and ethanol metabolism in the hamster and rat. Pharmacol Biochem Behav. 1979;11(4):439-44.
132. Keung WM, Kunze L, Li DJ, Lazo O. Volitional ethanol consumption affects overall serotonin metabolism in Syrian golden hamsters (Mesocricetus auratus). Biochem Biophys Res Commun. 2000;271(3):823-30.
133. Arvola A, Forsander O. Comparison between water and alcohol consumption in six animal species infree choice experiments. Nature. 1961;191:819-20.
134. Arvola A, Forsander A. Hamsters in Experiments of Free Choice between Alcohol and Water. Q J Stud Alcohol. 1963;24:591-7.
135. Green AI, Chau DT, Keung WM, Dawson R, Mesholam RI, Schildkraut JJ. Clozapine reduces alcohol drinking in Syrian golden hamsters. Psychiatry Res. 2004;128(1):9-20.
136. Chau DT, Gulick D, Xie H, Dawson R, Green AI. Clozapine chronically suppresses alcohol drinking in Syrian golden hamsters. Neuropharmacology. 2010;58(2):351-6.

137. Chau DT, Ahmed J, Wang TT, Xie H, Dawson R, Green AI. Raclopride lessens the ability of clozapine to suppress alcohol drinking in Syrian golden hamsters. Neuropharmacology. 2011;61(4):646-52.
138. Kalkman HO, Loetscher E. alpha2C-Adrenoceptor blockade by clozapine and other antipsychotic drugs. European Journal of Pharmacology. 2003;462(1-3):33-40.
139. Sobell LC, Sobell MB. Timeline Follow-Back Users Guide: Timeline followback instruction and materials for alcohol, cigarettes, marijuana and other drugs and SCQ and DTCQ feedback programs. 1996.
140. Alvir JMJ, Lieberman JA, Safferman AZ, Schwimmer JL, Schaaf JA. Clozapine-induced agranulocytosis: Incidence and risk factors in the United States. N Engl J Med. 1993;329:162-7.
141. Cuffel BJ, Heithoff KA, Lawson W. Correlates of patterns of substance abuse among patients with schizophrenia. Hospital & Community Psychiatry. 1993;44(3):247-51.
142. Morrato EH, Dodd S, Oderda G, Haxby DG, Allen R, Valuck RJ. Prevalence, utilization patterns, and predictors of antipsychotic polypharmacy: experience in a multistate Medicaid population, 1998-2003. Clin Ther. 2007;29(1):183-95.
143. Sankaranarayanan J, Puumala SE. Antipsychotic use at adult ambulatory care visits by patients with mental health disorders in the United States, 1996-2003: national estimates and associated factors. Clin Ther. 2007;29(4):723-41.
144. Chengappa KN, Gopalani A, Haught MK, McChesney K, Baker RW, Schooler NR. The treatment of clozapine-associated agranulocytosis with granulocyte colony-stimulating factor (G-CSF). Psychopharmacology Bulletin. 1996;32(1):111-21.
145. Sperner-Unterweger B, Czeipek I, Gaggl S, Geissler D, Spiel G, Fleischhacker WW. Treatment of severe clozapine-induced neutropenia with granulocyte colony-stimulating factor (G-CSF): Remission despite continuous treatment with clozapine. British Journal of Psychiatry. 1998;172:82-4.
146. Chengappa KN, Vasile J, Levine J, Ulrich R, Baker R, Gopalani A, Schooler N. Clozapine: its impact on aggressive behavior among patients in a state psychiatric hospital. Schizophr Res. 2002;53(1-2):1-6.
147. Gut-Fayand A, Dervaux A, Olie JP, Loo H, Poirier MF, Krebs MO. Substance abuse and suicidality in schizophrenia: a common risk factor linked to impulsivity. Psychiatry Res. 2001;102(1):65-72.
148. Drake RE, Wallach MA. Substance abuse among the chronic mentally ill. Hosp Community Psychiatry. 1989;40(10):1041-6.
149. Erkiran M, Ozunalan H, Evren C, Aytaclar S, Kirisci L, Tarter R. Substance abuse amplifies the risk for violence in schizophrenia spectrum disorder. Addict Behav. 2006;31(10):1797-805.
150. Soyka M. Substance abuse as a risk factor for violence in major mental disorders. Arch Gen Psychiatry. 1999;56(6):582.
151. Cuffel BJ, Shumway M, Chouljian TL, MacDonald T. A longitudinal study of substance use and community violence in schizophrenia. J Nerv Ment Dis. 1994;182(12):704-8.
152. Stroup TS, Lieberman JA, McEvoy JP, Swartz MS, Davis SM, Rosenheck RA, Perkins DO, Keefe RS, Davis CE, Severe J, Hsiao JK. Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. Am J Psychiatry. 2006;163(4):611-22.
153. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med. 2005;353(12):1209-23.
154. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. Am J Psychiatry. 1994;151:825-35.

155. Jibson MD, Tandon R. New atypical antipsychotic medications. Journal of Psychiatric Research. 1998;32(3-4):215-28.
156. Breier AF, Malhotra AK, Su TP, Pinals DA, Elman I, Adler CM, Lafargue RT, Clifton A, Pickar D. Clozapine and risperidone in chronic schizophrenia: effects on symptoms, parkinsonian side effects, and neuroendocrine response. Am J Psychiatry. 1999;156(2):294-8.
157. Meyer RE. Some issues in the pharmacotherapy of alcoholism. In: Naranjo CA, Sellers EM, editors. Novel Pharmacological Interventions for Alcoholism. New York: Springer-Verlag; 1992. p. 40-55.
158. Drake RE, Brunette MF. Complications of severe mental illness related to alcohol and other drug use disorders. In: Galanter M, editor. Recent Developments in Alcoholism: Consequences of Alcoholism. New York: Plenum Publishing Company; 1998. p. 285-99.
159. Greenberg RN. Overview of patients compliance with medication dosing: A literature reveiw. Clin Ther. 1984;6:592-9.
160. Pullar T, Jumar S, Tindall H, Feely M. Time to stop counting the tablets? Clin Pharmacol Ther. 1989;46:163-8.
161. Rudd P, Byyny RL, Zachary V, LoVerde ME, Titus C, Mitchell W, Marshall G. The natural history of medication compliance in a drug trial: Limitations of pill counts. Clin Pharmacol Ther. 1989;46:169-76.
162. Cheung R, Dickins J, Nicholson PW, Thomas AS, Smith H, Larson HE, Deshmulch AA, Dobbs SM. Compliance with anti-tuberculous therapy: a field trial of a pill-box with a concealed electronic recording device. Eur J Clin, Pharmacol. 1988;35:401-7.
163. Cramer JA, Mattson RH, Prevey ML, Scheyer RD, Ovellette VL. How often is medication taken as prescribed? A novel assessment technique. Jama. 1989;261:3273-7.
164. Rudd P, Marshall G, Taylor CB, Agras WS. Medication monitor dispenser for pharmaceutical and clozapine research. Clin Pharmacol Ther. 1981;29:278.
165. Lee JY, Kusek JW, Greene PG, Bernhard S, Norris K, Smith D, Wilkening B, Wright JT, Jr. Assessing medication adherence by pill count and electronic monitoring in the African American Study of Kidney Disease and Hypertension (AASK) Pilot Study. Am J Hypertens. 1996;9(8):719-25.
166. Cramer JA. Feedback on medication dosing enhances patient compliance. Chest. 1993;104(2):333-4.
167. Assanangkornchai S, Srisurapanont M. The treatment of alcohol dependence. Curr Opin Psychiatry. 2007;20(3):222-7.
168. Miller WR, Rollnick SR. Motivational Interviewing. New York: Guilford Press; 1993.
169. Monti PM, Abrams DB, Kadden RM, Cooney NL. Treating Alcohol Dependence. New York: Guilford Press; 1989.
170. Mueser KT, Noordsy DL. Group Interventions. In: Drake RE MK, editor. Dual Diagnosis of Major Mental Illness and Substance Abuse Disorder II: Recent Research and Clinical Implications. San Francisco: Jossy-Bass; 1996.
171. Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM. Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). Br J Addict. 1989;84(11):1353-7.
172. Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. Abstinence symptoms following oral THC administration to humans. Psychopharmacology (Berl). 1999;141(4):385-94.
173. Babor TF, Longabaugh R, Zweben A, Fuller RK, Stout RL, Anton RF, Randall CL. Issues in the definition and measurement of drinking outcomes in alcoholism treatment research. J Stud Alcohol Suppl. 1994;12:101-11.
174. Teitelbaum LM, Carey KB. Alcohol assessment in psychiatric patients. Clin Psychol Sci Prac. 1996;3:323-38.

175. Alterman AI. Methodological issues and prevalence estimates of substance abuse in schizophrenia. J of Nerv and Ment Disease. 1992;180(9):593-6.
176. First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I/P). Washington, D.C.: American Psychiatric Publishing, Inc.; 2002.
177. Drake RE, Osher FC, Noordsy DL, Hurlbut SC, Teague GB, Beaudett MS. Diagnosis of alcohol use disorders in schizophrenia. Schizophrenia Bulletin. 1990;16:57-67.
178. Kranzler HR, Kadden RM, Babor TF, Rounsavill BJ. Longitudinal, expert, all data procedure for psychiatric diagnosis in patients with psychoactive substance use disorders. Journ of Nerv and Ment Disorders. 1994;182:277-83.
179. Meltzer HY. Treatment-resistant schizophrenia--the role of clozapine. Curr Med Res Opin. 1997;14(1):1-20.
180. Fagerstrom KO. Measuring degree of physical dependence to tobacco smoking with reference to individualization of treatment. Addict Behav. 1978;3(3-4):235-41.
181. Sobell MB, Maisto SA, Sobell LC, Cooper AM, Sanders B. Developing a prototype for evaluating alcohol treatment effectiveness. In: Sobell LC, Sobell MB, Ward E, editors. Evaluating Alcohol Drug Treatment Effectiveness. New York: Pergamon; 1980. p. 129-50.
182. Carey KB. Challenges in assessing substance use patterns in persons with comorbid mental and addictive disorders. NIDA Res Monogr. 1997;172:16-32.
183. Wolford GL, Rosenberg SD, Drake RE, Mueser KT, Oxman TE, Hoffman D, Vidaver RM, Luckoor R, Carrieri KL. Evaluation of methods for detecting substance use disorder in persons with severe mental illness. Psychology of Addictive Behaviors. 1999;13:313-26.
184. Sobell LC, Agrawal S, Sobell MB. Factors affecting agreement between alcohol abusers' and their collaterals' reports. J Stud Alcohol. 1997;58(4):405-13.
185. Moyer TP, Palman MA, Johnson P, Charlson JR, Ellefson PJ. Marijuana testing - how good is it? Mayo Clin Proc. 1987;62:413-7.
186. Lowe RH, Abraham TT, Darwin WD, Herning R, Cadet JL, Huestis MA. Extended urinary Delta9-tetrahydrocannabinol excretion in chronic cannabis users precludes use as a biomarker of new drug exposure. Drug Alcohol Depend. 2009;105(1-2):24-32. PMCID: PMC2763020.
187. Carey KB, Cocco KM, Simons JS. Concurrent validity of clinicians' ratings of substance abuse among psychiatric outpatients. Psychiatric Services. 1996;47(8):842-7.
188. Osher FC, Kofoed LL. Treatment of patients with psychiatric and psychoactive substance abuse disorders. Hospital & Community Psychiatry. 1989;40(10):1025-30.
189. Drake RE, Mueser K, McHugo GJ. Using clinical rating scales to assess substance abuse among persons with severe mental illness. In: Sederer LI, Dickey B, editors. Outcome Assessment in Clinical Practice. Baltimore: Williams and Wilkins; 1995.
190. Lukoff D, Nuechterlein KH, Ventura J. Manual for the Expanded Brief Psychiatric Rating Scale (BPRS). Schizophrenia Bulletin. 1986;12:594-602.
191. Guy W. CGI. ECDEU: NIMH; 1976. p. 217-22.
192. Andreasen NC. Scale for the Assessment of Negative Symptoms (SANS). Iowa City: College of Medicine, University of Iowa; 1984.
193. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. Psychological Reports. 1962;10:799-812.
194. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl. 1970;212:11-9.
195. Guy W. AIMS. ECDEU Assessment Manual for Psychopharm: NIMH; 1976. p. 534-7.
196. Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry. 1989;154:672-6.
197. Malm U, May PRA, Dencker SJ. Evaluation of the quality of life of schizophrenic outpatient: A checklist. Schizophr Bull. 1981;7:477-87.
198. Hargreaves WA. Clozapine Cost-effectives Research Design Manual. unpublished. 1992.

199. Heinrichs DW, Hanlon TE, Carpenter WTJ. The Quality of Life Scale: An instrument for rating the schizophrenia deficit syndrome. Schizophrenia Bulletin. 1984;10:388-96.
200. Lehman AF. A quality of life interview for the chronically mentally ill. Evaluation and Program Planning. 1988;11:51-2.
201. Solowij N, Stephens RS, Roffman RA, Babor T, Kadden R, Miller M, Christiansen K, McRee B, Vendetti J. Cognitive functioning of long-term heavy cannabis users seeking treatment. Jama. 2002;287(9):1123-31.
202. Wilkinson G, Robertson G. Wide Range Achievement Test 4 Professional Manual. Lutz, FL: Psychological Assessment Resources; 2006.
203. Harvey PD, Moriarty PJ, Friedman JI, White L, Parrella M, Mohs RC, Davis KL. Differential preservation of cognitive functions in geriatric patients with lifelong chronic schizophrenia: less impairment in reading compared with other skill areas. Biol Psychiatry. 2000;47(11):962-8.
204. Wechsler D. Wechsler Abbreviated Scale of Intelligence. San Antonio, TX: The Psychological Corporation; 1999.
205. Green MF, Nuechterlein KH. The MATRICS initiative: developing a consensus cognitive battery for clinical trials. Schizophr Res. 2004;72(1):1-3.
206. Benedict RHB. The Brief Visuospatial Memory Test – Revised: Professional Manual. Odessa, FL: Psychological Assessment Resources; 1997.
207. Santesso DL, Dillon DG, Birk JL, Holmes AJ, Goetz E, Bogdan R, Pizzagalli DA. Individual differences in reinforcement learning: behavioral, electrophysiological, and neuroimaging correlates. Neuroimage. 2008;42(2):807-16. PMCID: PMC2548326
208. Barr RS, Pizzagalli DA, Culhane MA, Goff DC, Evins AE. A single dose of nicotine enhances reward responsiveness in nonsmokers: implications for development of dependence. Biol Psychiatry. 2008;63(11):1061-5. PMCID: PMC2441863.
209. AhnAllen CG, Liverant GI, Gregor KL, Kamholz BW, Levitt JJ, Gulliver SB, Pizzagalli DA, Koneru VK, Kaplan GB. The relationship between reward-based learning and nicotine dependence in smokers with schizophrenia. Psychiatry Research. In Press.
210. Dutra SJ, Stoeckel LE, Carlini SV, Pizzagalli DA, Evins AE. Varenicline as a smoking cessation aid in schizophrenia: effects on smoking behavior and reward sensitivity. Psychopharmacology (Berl). In Press.
211. Pizzagalli DA, Evins AE, Schetter EC, Frank MJ, Pajtas PE, Santesso DL, Culhane M. Single dose of a dopamine agonist impairs reinforcement learning in humans: behavioral evidence from a laboratory-based measure of reward responsiveness. Psychopharmacology (Berl). 2008;196(2):221-32. PMCID: PMC2268635
212. Heerey EA, Bell-Warren KR, Gold JM. Decision-making impairments in the context of intact reward sensitivity in schizophrenia. Biol Psychiatry. 2008;64(1):62-9. PMCID: PMC2613513
213. Benowitz NL. Nicotine pharmacology and addiction. In: Benowitz NL, editor. Nicotine safety and toxicity. New York: Oxford University Press; 1998. p. 3-16.
214. Ohlsson A, Lindgren JE, Wahlen A, Agurell S, Hollister LE, Gillespie HK. Plasma delta-9 tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. Clin Pharmacol Ther. 1980;28(3):409-16.
215. Bogdan R, Pizzagalli DA. The heritability of hedonic capacity and perceived stress: a twin study evaluation of candidate depressive phenotypes. Psychol Med. 2009;39(2):211-8. PMCID: PMC2628414.
216. Pizzagalli DA, Bogdan R, Ratner KG, Jahn AL. Increased perceived stress is associated with blunted hedonic capacity: potential implications for depression research. Behav Res Ther. 2007;45(11):2742-53. PMCID: PMC2080833.
217. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. Journal of Health and Social Behavior. 1983;24:386-96.

218. Simpson GM, Cooper TA. Clozapine plasma levels and convulsions. Am J Psychiatry. 1978;135:99-100.
219. LeMoing JP, Edouard S, Levron JC. Determination of risperidone and 9-hydroxyrisperidone in human plasma by performance liquid chromatography with electrochemical detection. J Chromatogr. 1993;614:333-9.
220. Lipsky RH, Sparling MB, Ryan LM, Xu K, Salazar AM, Goldman D, Warden DL. Association of COMT Val158Met genotype with executive functioning following traumatic brain injury. J Neuropsychiatry Clin Neurosci. 2005;17(4):465-71.
221. Clark RE, Teague GB, Ricketts SK, Bush PW, Keller AM, Zubkoff M, Drake RE. Measuring resource use in economic evaluations: determining the social costs of mental illness. J Ment Health Adm. 1994;21(1):32-41.
222. Laird NM, Ware JH. Random effects models for longitudinal data. Biometrics. 1982;38:963-74.
223. Waternaux C, Laird NM, Ware J. Methods for the analysis of longitudinal data: Blood concentrations and cognitive development. J Am Stat Assoc. 1989;84:33-41.
224. Rotnitzky A, Robins JM. Semi-parametric regression estimation in the presence of dependent censoring. Biometrika. 1995;82(4):805-20.
225. Honigfeld G, Arellano F, Sethi J, Bianchini A, Schein J. Reducing clozapine-related morbidity and mortality: 5 years of experience with the Clozaril National Registry. J Clin Psychiatry. 1998;59 Suppl 3:3-7.
226. Pacia SV, Devinsky O. Clozapine-related seizures: experience with 5,629 patients. Neurology. 1994;44(12):2247-9.
227. Wilson WH, Claussen AM. Seizures associated with clozapine treatment in a state hospital. J Clin Psychiatry. 1994;55(5):184-8.
228. Merrill DB, Dec GW, Goff DC. Adverse cardiac effects associated with clozapine. J Clin Psychopharmacol. 2005;25(1):32-41.
229. Krakowski M, Czobor P, Citrome L. Weight gain, metabolic parameters, and the impact of race in aggressive inpatients randomized to double-blind clozapine, olanzapine or haloperidol. Schizophr Res. 2009;110(1-3):95-102.
230. Russell JM, Mackell JA. Bodyweight gain associated with atypical antipsychotics: epidemiology and therapeutic implications. CNS Drugs. 2001;15(7):537-51.
231. Miller DD. Review and management of clozapine side effects. J Clin Psychiatry. 2000;61 Suppl 8:14-7; discussion 8-9.
232. Conley RR. Risperidone side effects. J Clin Psychiatry. 2000;61 Suppl 8:20-3; discussion 4-5.
233. Miller DD, Caroff SN, Davis SM, Rosenheck RA, McEvoy JP, Saltz BL, Riggio S, Chakos MH, Swartz MS, Keefe RS, Stroup TS, Lieberman JA. Extrapyramidal side-effects of antipsychotics in a randomised trial. Br J Psychiatry. 2008;193(4):279-88 PMCID 2801816
234. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. CNS Drugs. 2005;19 Suppl 1:1-93.
235. Konarzewska B, Wolczynski S, Szulc A, Galinska B, Poplawska R, Waszkiewicz N. Effect of risperidone and olanzapine on reproductive hormones, psychopathology and sexual functioning in male patients with schizophrenia. Psychoneuroendocrinology. 2009;34(1):129-39.
236. Budney AJ, Hughes JR, Moore BA, Novy PL. Marijuana abstinence effects in marijuana smokers maintained in their home environment. Arch Gen Psychiatry. 2001;58(10):917-24.