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Memory reconsolidation blockade for treating substance dependence:

A feasibility study

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CONTRIBUTION OF AUTHORS

This work is part of a clinical trial examining the feasibility and efficacy of propranolol to interfere with drug-cue memory reconsolidation in treatment-seeking individuals with substance dependence disorder. Dr. Alain Brunet, Dr. Daniel Saumier, Dr. Jacques Tremblay, and Dr. Thomas Brown originally designed the study, of which I was assigned as research assistant. My role consisted of coordinating the study in collaboration with the staff from Sobriety Home Drug and Alcohol Treatment Center in Huntingdon, QC and CRD Foster outpatient facility in Montreal, QC. I aided the principle investigators and research coordinators with ethics and grant applications; I recruited participants, performed the eligibility evaluation, administered psychometric assessments to participants, implemented the experimental treatment protocol, followed-up with participants, entered the data, and conducted the statistical analyses. Dr. Alain Brunet and Dr. Daniel Saumier agreed that I could use this data for my master's thesis. Thus, I conducted the literature review, interpreted the statistical analyses, and wrote the present thesis, all of which was supervised and reviewed by Drs. Alain Brunet and Daniel Saumier.

Dr. Alain Brunet, Dr. Daniel Saumier, and Daniel Rabouin acted as statistical consultants for the results of the present thesis. Additionally, Dr. Daniel Saumier actively participated in participant recruitment, implemented the treatment protocol, and coordinated research activities with clinical staff. Drs. Jacques Tremblay and Charles Badin were the physicians for the present clinical trial. Dr. Thomas Brown acted as a consultant for the present study.

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ABSTRACT

Background: According to the pathological memory model of addiction, conditioned drug-related memories formed during repeated drug using episodes underlie craving and the long-term propensity for addicted individuals to relapse, posing a formidable barrier to sustained recovery. However, reconsolidation theory suggests that the act of retrieval transiently destabilizes previously consolidate memories, during which time they can be pharmacologically manipulated prior to re-stabilizing back to long-term storage. Previous literature has revealed that the noradrenergic beta-blocker propranolol can reduce drug-seeking behaviour in rodents and craving in humans when administered in conjunction with the retrieval of drug-related memories. Reducing the strength of drug-related memories, and subsequent craving and relapse, would open the door to a novel treatment for addiction. **Objective:** In a feasibility study, we examined whether a memory reconsolidation blockade protocol previously designed by our laboratory for treating posttraumatic stress disorder can be successfully modified and implemented in a sample of treatment-seeking individuals with substance dependence. We further explored preliminary treatment effects. **Methods:** Eligible participants (18-65 years old) were randomized to receive six treatments of memory reconsolidation blockade under propranolol or placebo, or to a treatment as usual only control condition. Memory reactivation was achieved by having participants read aloud to the investigator a personal drug-using narrative. One-week and 4-month post-treatment assessments were also performed. Feasibility outcome measures included evaluating recruitment and retention rates, the eligibility criteria, and protocol adherence. Secondary feasibility outcomes examined preliminary treatment effects, as measured by difference scores on self-report craving severity between the baseline and post-treatment assessments, and rates of relapse. **Data Analysis:** Feasibility outcomes are reported descriptively. Fisher's exact tests for categorical and independent t-tests for continuous baseline demographic and clinical variables were used to examine variables related to study dropout. For analysis of treatment effects, missing data was imputed using multiple imputation procedures, and independent *t*-tests were used to examine between-group differences on craving change between the baseline and post-treatment assessments. Relapse during the trial was dichotomized and compared between treatment groups. All tests were two-tailed with alpha set at .05. **Results:** Although retention rates were comparable to what's currently observed in addiction treatment programs, recruitment remained difficult. However, the eligibility criteria were considered

appropriate, and participants and research staff generally adhered to the protocol. Results from preliminary analyses of treatment effects revealed no significant between-group differences on change in subjective craving or relapse during the trial, despite propranolol treated participants tending to demonstrate slightly greater improvement. **Conclusion:** Despite finding no significant between-group differences, larger-scaled multi-center trials of disrupting memory reconsolidation to treat substance dependence using the described protocol are warranted, provided several procedural changes are implemented. The authors discuss ways to address potential methodological pitfalls in future studies.

ABRÉGÉ

Contexte: Selon le modèle de la mémoire pathologique de la toxicomanie, les souvenirs liés à la drogue sous-tendent le désir de consommation et la tendance à long terme de rechute, posant un obstacle considérable au rétablissement. La théorie de la reconsolidation soutient que la récupération d'un souvenir préalablement consolidé le rend de nouveau labile et vulnérable aux interférences pharmacologiques. La littérature précédente a démontré que le bétabloquant noradrénergique propranolol peut atténuer les conduites toxicophiles chez les animaux et le désire de consommer chez l'humain lorsqu'il est administré parallèlement à la réactivation du souvenir. Cette procédure est appelée le blocage de la reconsolidation mnésique. Si le blocage de la reconsolidation mnésique peut réduire le désir de consommer et la rechute chez les toxicomanes, cela constituerais une nouvelle possibilité thérapeutique. **Objectif :** Dans une étude de faisabilité, nous avons examiné si un protocole de blocage de reconsolidation mnésique, antérieurement conçu par notre laboratoire pour le traitement du trouble de stress post-traumatique, peut être modifié et appliqué avec succès dans une population de toxicomanes suivant un programme de traitement thérapeutique. Nous avons également exploré les effets préliminaires du traitement. **Méthodes** : Les participants admissibles (âgés de 18 à 65 ans) ont été randomisés selon trois conditions : le traitement habituel seulement ou six traitements de blocage de la reconsolidation mnésique soit sous le propranolol ou un placebo. La réactivation des souvenirs a été réalisée en demandant aux participants de lire à haute voix, un récit personnel détaillant leur cycle de consommation de drogues. Le suivi post-traitement s'est fait une semaine et 4 mois suivant la dernière session de traitement. Les mesures de faisabilité incluaient le taux de recrutement, ainsi que l'évaluation des critères d'admissibilité et l'adhésion au protocole. L'effet du traitement a été mesuré par des questionnaires auto-administrés évaluant le désir de consommer, et le taux de rechute. **Analyse de données :** Les résultats de faisabilité sont présentés de façon descriptive. Des tests de Fisher pour les variables catégorielles, et des tests-*t* indépendant pour les variables continues, ont été utilisés pour examiner si certaines variables démographiques et cliniques de base sont associées à l'abandon de l'étude. Pour l'analyse des effets du traitement, les données manquantes ont été imputées à l'aide de procédures d'imputation multiple, et un test-*t* indépendant a été utilisé pour comparer les groupes propranolol et placebo sur le changement du désir de consommation entre les scores obtenus au

pré-test et au post-test. La rechute pendant l'étude a été dichotomisée et comparée entre le groupe propranolol et placebo. Tous les tests étaient bicodaux avec un seuil de significativité fixé à $p < .05$. **Résultats :** Bien que le taux de rétention obtenu dans cette étude soit comparable à ce qui est actuellement observé dans les programmes de traitement de la toxicomanie, le recrutement a été difficile. Cependant, les critères d'éligibilité ont été jugés appropriés, et les participants et le personnel de recherche ont généralement adhéré au protocole. Les résultats de l'analyse préliminaire des effets du traitement n'ont révélé aucune différence significative entre les deux groupes expérimentaux sur le changement du désir subjective, ni sur le taux de rechute. Malgré ceci, les participants traités avec le propranolol ont montré un peu plus d'amélioration sur le désir que le groupe placebo. **Conclusion :** Des essais cliniques multicentriques à plus grande échelle examinant le blocage de la reconsolidation mnésique pour le traitement de la toxicomanie et utilisant le protocole décrit sont justifiés, à condition que certains changements procéduraux soient mis en œuvre. Les auteurs discutent plusieurs moyens de remédier aux pièges méthodologiques potentiels pour les études futures.

Memory reconsolidation blockade for treating substance dependence: A feasibility study

The recreational use of drugs and alcohol is a prominent part of human culture. Potentially addictive substances[1] (e.g. alcohol, stimulants, cannabis, and opiates among others) are most often used for their pharmacological effects of inducing pleasure and/or relieving psychological and physical distress (Torregrossa, Corlett, & Taylor, 2011). While many individuals who use or abuse addictive drugs may never experience long-term consequences nor require therapeutic attention, a minority will develop a pathological and compulsive motivation to obtain and use addictive substances at the expense of all other life goals and overall well-being (Hyman, 2005; Torregrossa et al., 2011). This is the core manifestation of substance dependence, colloquially referred to as addiction[2].

Substance dependence is a chronically relapsing psychiatric disorder that can include progressive tolerance to the drug's pharmacological effects and negative physiological and psychological withdrawal symptoms when the drug is discontinued. Addicted individuals relentlessly seek any opportunity to use drugs, and experience great difficulty with controlling consumption, despite significant psychosocial and physical adverse consequences (American Psychiatric Association [APA], 2013). Addiction is a costly and devastating public health concern, affecting the individual, their loved ones, and society; in a report from 2002, the cost of substance use disorders on the Canadian economy was estimated at $39 billion dollars (Rhem et al., 2006). According to the 2012 World Drug Report released by the United Nations Office of Drugs and Crime (UNODC), an estimated 6% of the world's population uses illicit drugs, and 10-13% of those qualify for a *Diagnostic and Statistical Manual of Mental Disorders* (4th ed. text rev.; *DSM-IV-TR*; American Psychiatric Association [APA], 2000) dependence or abuse

[1] In the present thesis, the term "drugs" or "substances" refers to all major classes of potentially addictive substances, including alcohol.
[2] Following existing literature, the terms "substance dependence" and "addiction" will be used interchangeably throughout this thesis.

diagnosis. Aside from nicotine, the most common addictive substances tend to be prescription medications (i.e., opiates), cocaine, alcohol, and cannabis. Notably, the same report revealed that approximately 20% of addicted individuals seek and receive treatment (UNODC, 2012).

While conventional psychotherapeutic and pharmacological interventions, such as cognitive behavioural therapy or pharmacotherapy, are effective for some addicted individuals, there exists no intervention that reliably and significantly ameliorates the condition for a majority of treatment-seekers (McLellan, Lewis, O'Brien, & Kleber, 2000; Welberg, 2011). Successful treatment is often precluded by recurrent cravings and relapses, which persist even after extended periods of abstinence (Erickson, 2007; Hyman, 2005). Literature suggests that approximately 50-60% of individuals battling substance dependence relapse within six months of completing treatment (McLellan, McKay, Forman, Cacciola, & Kemp, 2005). Given the substantial social and economic burden of substance dependence, innovative, empirically based, and effective treatments are needed.

Substance dependence has been considered akin to other chronic medical illnesses, such as type 2 diabetes and asthma; without constant commitment to treatment, the risk of symptom relapse remains high throughout the patient's lifetime (Hyman, 2005; McLellan et al., 2000; McLellan et al., 2005). However, recent understandings of the underlying neural circuitry of substance dependence have suggested that its persistently relapsing nature is due, at least in part, to maladaptive drug-related memories formed during repeated drugs using episodes (Everitt & Robbins, 2005; Hyman, 2005; Hyman, Malenka, & Nestler, 2006; Milton & Everitt, 2012; Milton, Lee, & Everitt, 2008). The following thesis rests on that assumption. In the introduction, an overview of the "pathological memory model" of addiction is presented (Hyman, 2005). A treatment congruent with memory reconsolidation theory is proposed, and a number of empirical

hypotheses are introduced. This section is followed by the methods, results, and discussion of a feasibility study examining a new treatment aimed at reducing craving for addictive substances by targeting pathogenic drug-related memories.

Pathophysiology of Substance Dependence: A Role for Learning and Memory

Intense cravings for addictive substances are among the main causes of relapse, and can be induced by exteroceptive (i.e., people, settings, and paraphernalia) and interoceptive (i.e., psychological states, bodily sensations) cues previously associated with drug availability and use through associative learning mechanisms (Fricks-Gleason & Marshall, 2008; Hyman, 2005). Although the definition of craving and its role in relapse to addictive drugs is the subject of continued debate (Rosenberg, 2009), there is a general consensus that it consists of a subjective pathological motivational state (Franken, 2003). It has been argued that craving represents the heightened emotional and physiological arousal (i.e., conditioned response including increased heart rate and blood pressure) produced by the memory of the drug-reward (Franken, 2003; Koob & Le Moal, 2008).

The pathological memory model of substance dependence postulates that after prolonged use, addictive substances seize normal reward-related associative learning mechanisms through their direct (and indirect) action on the mesocorticolimbic dopamine system, leading to the "overconsolidation" of drug-related memories (Everitt & Robbins, 2005; Hyman, 2005; Torregrossa et al., 2011). Memory consolidation refers to the progressive, protein-synthesis dependent, stabilization of new learning to long-term memory storage (McGaugh, 2000). Thus, in individuals with genetic, environmental, and/or psychological vulnerabilities, addictive substances may have a more potent effect on the neural substrates of learning and memory, maintaining their addictive state (Torregrossa et al., 2011).

Enhanced consolidation of drug-related memories. The mesocorticolimbic dopamine system has been theorized to be primarily responsible for attributing motivational significance to rewards and the cues that predict them (Robinson & Berridge, 2008). Natural and drug-related rewards increase levels of midbrain dopamine, particularly in the nucleus accumbens and prefrontal cortex (Kiefer & Dinter, 2011; Torregrossa & Taylor, 2012). The nucleus accumbens is intimately involved in the acquisition and expression of motivation and reward-reinforcement learning; among other functions, the prefrontal cortex is implicated in decision-making, emotional regulation, biasing attention, and directing behaviour towards goal achievement (Di Chiara et al., 1999; Kiefer & Dinter, 2011). Furthermore, dopamine projections to and from the hippocampus facilitate consolidation of the declarative stimulus-reward association, while activation of the amygdala conditions the emotional tone of the associative memory (Everitt & Robbins, 2005; Torregrossa & Taylor, 2012). Emerging evidence suggests that neuroplastic alterations occur in all abovementioned mesocorticolimbic brain regions in the pathogenesis of addiction (Erickson, 2007; Goldstein & Volkow, 2011; Kiefer & Dinter, 2011).

Importantly, noradrenaline, synthesized from dopamine by the enzyme dopamine-β-hydroxylase, is also implicated in learning and memory consolidation, and evidence suggests that noradrenergic signalling is altered in substance dependence (Fitzgerald, 2013; Sofuoglu & Sewell, 2009). A recent hypothesis, put forth by Fitzgerald (2013), suggests that elevated noradrenergic activity may be an important factor underlying the etiology of a variety of substance dependencies, possibly by exacerbating the hedonic effects of addictive drugs in individuals with genetic and environmental predispositions. Emotional arousal, whether positive or negative, activates endogenous stress hormones (i.e., noradrenaline) within the amygdala,

which enhances consolidation, subsequently increasing the salience of the memory (Roozendaal & McGaugh, 2011).

According to Robinson and Berridge's (2008) incentive sensitization theory, repeated drug use sensitizes dopamine transmission in the mesocorticolimbic circuit to some of the drugs' effects and, more crucially, to drug-predictive stimuli. In susceptible individuals, heightened sensitization of mesolimbic circuits creates a pathological motivation for addictive substances, or drug "wanting", which is dissociable from drug "liking" (Robinson & Berridge, 1993, 2000, 2008). In brief, chronic drug use leads to increased attribution of incentive salience to drug-related stimuli, which can trigger emotional and physiological craving responses (i.e., "drug wanting") when exteroceptive or interoceptive cues are confronted in one's environment. Combined with dysfunctional executive control over self-regulatory behaviour, these drug-associated memory cues can initiate drug-seeking and use long after withdrawal symptoms have abated (Robinson & Berridge, 2008).

Relative to natural rewards, the quantity and duration of dopamine release is increased by addictive drugs, an effect that does not habituate over time, producing an enduring enhancement of associative memory formation (Di Chiara et al., 1999; Torregrossa & Taylor, 2012). Over time, drug-conditioned cues acquire the ability to trigger dopamine release and activate mesocorticolimbic structures in their own right, possibly encoding a prediction-error signal, allowing the organism to predict the availability of the drug-reward (Hyman et al., 2006). Neuroimaging studies involving addicted individuals have demonstrated activation of, and increased dopaminergic activity in, the amygdala, hippocampus, nucleus accumbens, and areas of the prefrontal cortex when presented with drug-related cues including autobiographical scripts, drug paraphernalia, and drug-themed videos (Childress et al., 1999; Fotros et al., 2013;

Grüsser et al., 2004). In these studies, the observed activations were positively correlated with craving and relapse.

Chronic drug exposure also facilitates habit learning, deeply ingrained inflexible behaviours that persist despite devaluing the reward (Torregrossa et al., 2011). Several investigators have revealed increased dopamine release in, and activation of, the dorsal striatum, a brain region associated with reward and habit learning, when presented with cocaine-related interoceptive and environmental cues (Garavan et al., 2000; Sinha et al., 2005; Volkow et al., 2006). Interestingly, this activation was positively associated with subjective cocaine craving (Volkow et al., 2006). While some authors argue that habit forming alone is insufficient to fully account for the compulsive nature of substance dependence (Robinson & Berridge, 2008), these findings underscore the importance of drug-related cues in craving.

Although it does not provide a complete explanation of the complex development of addiction, substantial evidence has accumulated to support the pathogenic memory model (Di Chiara et al., 1999; Everitt & Robbins, 2005; Hyman, 2005; Hyman et al., 2006; Kiefer & Dinter, 2011; Milton & Everitt, 2012; Robbins, Ersche, & Everitt, 2008). Addictive substances can usurp normally adaptive associative learning mechanisms in subcortical and cortical brain regions, leading to the disproportionate attribution of motivational salience to drug-related cues and dysfunctions in prefrontal attentional and self-regulation capacities (Hyman, 2005; Hyman et al., 2006). The altered neurotransmitter activity produced by addictive drugs enhances the consolidation of drug-related predictive cues, creating powerful memories that are difficult to extinguish (Torregrossa & Taylor, 2012). These persistent maladaptive memories are hypothesized to underlie craving and the long-term propensity of addicted individuals to relapse, posing a formidable barrier to sustained recovery.

Current Treatments for Substance Dependence

Treatments for substance dependence traditionally consist of behavioural and pharmacological approaches, either as stand-alone interventions or in combination. Cognitive behavioural therapy has become one of the most widely used and empirically supported interventions for substance dependence (Dutra et al., 2008; McHugh, Hearon, & Otto, 2010). Rooted in learning theory, this therapy consists of identifying environmental, affective, and cognitive elements that trigger uncontrolled drug use and developing more adaptive thought processes, behavioural responses, and coping mechanisms (Dutra et al., 2008). Several psychotherapies are based on the cognitive behavioural model, such as motivational interviewing, coping-skills training, contingency management, relapse prevention, and cue-exposure therapy (Carroll & Onken, 2005; McHugh et al., 2010). The empirical evidence regarding the efficacy of cognitive behavioural therapy for the treatment of dependence is comparable to other psychiatric disorders, with overall Cohen's *d* effect sizes ranging from .15 to .48 (Dutra et al., 2008; Magill & Ray, 2009). According to Dutra et al.'s (2008) meta-analysis, approximately one-third of individuals receiving cognitive behavioural therapy achieved abstinence following treatment, compared to 13% of participants in various control conditions, such as wait list or 12-step programs. While the authors conclude that cognitive behavioural therapy is superior to no treatment, these results suggest that this approach may not be effective for all addicted individuals (Dutra et al., 2008; Magill & Ray, 2009).

With the recognition that discrete and contextual cues can trigger craving and relapse, exposure therapy has been proposed as a viable treatment option for addiction (Drummond & Glautier, 1994; Martin, LaRowe, & Malcolm, 2010). This approach, based on extinction, suggests that exposing patients to drug-conditioned stimuli while preventing access to the drug

eventually reduces craving and subsequent relapse (Conklin & Tiffany, 2002). While the empirical evidence for exposure therapy has been well established in other areas of psychiatry (e.g. posttraumatic stress disorder (PTSD), specific/social phobia, obsessive compulsive disorder), its applicability to substance dependence remains controversial (Conklin & Tiffany, 2002). Extinction training, or exposure therapy, leads to the consolidation of a new "drug-cue no-reward" memory trace, which competes with the previously learned "drug-cue-reward" memory (Bouton, 2004). Since the originally learned association is still intact, maladaptive behavioural responses are suppressed and therefore vulnerable to three phenomena: i) spontaneous recovery (i.e., the return of behaviour over time); ii) renewal (i.e., the return of behaviour in a context other than the one used for extinction); and iii) reinstatement (i.e., the return of behaviour after unexpected presentation of an environmental cue or the drug itself; Bouton, 2004). Recent literature proposes that pharmacological enhancement of extinction mechanisms may improve efficacy of exposure therapy, yet research in this area is still in its early stages (see Kiefer & Dinter, 2011; Milton & Everitt, 2012; Watson et al., 2011).

Pharmacological interventions for addiction range from antidepressant medications often used to alleviate underlying comorbid psychiatric symptoms, to craving and relapse-prevention strategies such as opiate antagonists for alcohol or heroin dependence (Erickson, 2007). Although these treatments have demonstrated success in promoting abstinence, they often require strong commitment and lengthy adherence regimens (McLellan et al., 2000). Moreover, to date, no pharmacological strategy exists for other chemical addictions, such as cocaine dependence (Fricks-Gleason & Marshall, 2008). Finally, investigations into combination pharmacotherapy/cognitive behavioural therapy techniques has received mixed results; while some studies have shown an additive benefit for augmenting psychotherapy with

pharmacotherapy, others have not (see McHugh et al., 2010; Weiss & Kueppenbender, 2006). The points discussed above highlight the need for investigations into novel, empirically based treatment strategies.

Memory Reconsolidation Theory and Substance Dependence

Both addictive drugs and the emotional arousal that accompanies repeated drug use facilitate and enhance the consolidation of drug-related memories, which are arguably powerful, persistent, and presumed to be central in the maintenance of addiction (Tronson & Taylor, 2013). Contrary to traditional beliefs that memories are permanent and inflexible once fully consolidated, reconsolidation theory argues that long-term memories become transiently destabilized following retrieval (i.e., remembering), after which they must undergo additional neurochemical processes of re-stabilization in order to persist (Nader, Schafe, & Le Doux, 2000b). Evidence for memory reconsolidation mechanisms emerged in the 20th century, with studies demonstrating that the same treatments that disrupt memory consolidation when administered within hours of initial learning (i.e., electroconvulsive therapy, protein-synthesis inhibitors, beta-adrenergic blockers) also interfere with the re-stabilization of the trace when administered within hours of retrieval (Misanin, Miller, & Lewis, 1968; Nader, Schafe, & Le Doux, 2000a; Przybyslawski & Sara, 1997). It has been argued that memory reconsolidation serves to preserve, strengthen, weaken, or otherwise update long-term memories (Diergaarde, Schoffelmeer, & De Vries, 2008; Tronson & Taylor, 2013).

Reconsolidation theory offers a new framework for understanding substance dependence. If reconsolidation mechanisms serve to integrate new information within pre-existing memories, it is possible that this mechanism underlies the strengthening of drug-related memories after repeated drug using episodes (Tronson & Taylor, 2013). Alternatively, disrupting the

reconsolidation of these pathological memories, thereby weakening their motivational and emotional potency, may demonstrate important therapeutic benefit (Milton & Everitt, 2012). From a clinical perspective, this treatment is sometimes referred to as memory reconsolidation blockade or disruption of reconsolidation (Besnard, Caboche, & Laroche, 2012; Brunet et al., 2011a; Fricks-Gleason & Marshall, 2008; Saladin et al., 2013). What's more, given that exposure therapy effectively creates a new memory trace, previously learned maladaptive behaviours are suppressed rather than completely extinguished (Bouton, 2004). Disrupting memory reconsolidation, on the other hand, involves directly modifying or updating the original memory trace; therefore, it would unlikely be vulnerable to spontaneous recovery, renewal or reinstatement effects, thereby producing therapeutic benefits which are relatively long-lasting and more generalized (Debiec & Ledoux, 2004).

Mechanisms of memory reconsolidation: Overview of pre-clinical evidence. Memory reconsolidation has been extensively studied using fear conditioning paradigms involving animals, with the goal of translating results to clinical populations with PTSD (Reichelt & Lee, 2013). The typical experimental protocol involves three phases: i) Pavlovian conditioning (i.e., train animals to associate a light or context [conditioned stimulus, CS] with foot-shock or drug availability [unconditioned stimulus, US], ii) administration of a behavioural or pharmacological intervention (i.e., an amnesic treatment) either prior to or immediately after memory retrieval, and iii) a behavioural test phase (see Brunet et al., 2011a; Schiller & Phelps, 2011). Memory reactivation is usually achieved by presenting the CS in the absence of the US; the CS presentation is purposely kept brief in order to minimize extinction effects. If reconsolidation is disrupted, the behavioural response on test day (i.e., after a washout period of at least 24 hours) will be abolished (Figure 1).

Using this paradigm, Nader and colleagues (2000a) revealed that administering anisomycin, a protein-synthesis inhibitor known to disrupt memory consolidation, immediately after reactivating a contextual fear memory abolished the behavioural fear response in rats. In this study, the authors not only demonstrated that memory reconsolidation requires *de novo* protein synthesis, but also that the observed effect was reactivation-dependent; anisomycin infusions in the absence of memory reactivation had no effect on the expression of fear. Since then, researchers have been interested in examining the conditions under which memory reconsolidation occurs, as well as its underlying neurochemical processes. Effectively, reconsolidation has been shown to occur for variety of emotional and non-emotional memory tasks, using a range of amnesic treatments, and in various species including humans (see Besnard et al., 2012).

As mentioned previously, literature suggests that noradrenergic activity, particularly in the limbic system, is implicated in appetitive and aversive emotional memory consolidation (Roozendaal & McGaugh, 2011). Administering adrenergic agonists facilitates emotional memory consolidation, while the centrally acting $beta_2$-adrenergic antagonist (e.g., propranolol) abolishes emotional memory enhancement in rodents and humans (Milton et al., 2008; Roozendaal & McGaugh, 2011). For instance, in a pre-clinical experiment involving human participants, Cahill, Prins, Weber, and McGaugh (1994) demonstrated that, compared to placebo, oral administration of propranolol prior to exposing participants to an emotional slide story impaired, but did not abolish, memory retention only for the emotionally aversive material. Participants in the propranolol condition recalled the emotional mid-section of the story in a similar way as the neutral sections, suggesting that propranolol interfered with memory consolidation by reducing the enhancing effects of emotional arousal. Consequently, experiments

involving propranolol have been extended to memory reconsolidation paradigms in animals and humans, with encouraging results (Debiec & Ledoux, 2004; Diergaarde et al., 2008; Lonergan, Olivera-Figueroa, Pitman, & Brunet, 2012; Przybyslawski & Sara, 1997).

In a fear conditioning paradigm involving human participants, Kindt, Soeter, and Vervliet (2009) examined the effects of propranolol or placebo on memory reconsolidation. Replicating results from animal literature, the authors demonstrated that administering propranolol prior to memory retrieval significantly weakened the startle fear response, and this occurred only when the memory was reactivated by a brief presentation of the feared CS. In a subsequent study by the same team (Soeter & Kindt, 2010), the authors not only replicated their previous findings, but also found that propranolol's effects were maintained at a one-month follow-up test. Notably, participants in both studies retained the declarative knowledge of the fear-association, which was measured using shock-expectancy ratings. While participants preserved the memory that the CS and shock were associated, they no longer experienced the emotional fear response (Kindt et al., 2009, online supplement). These results suggest that disrupting memory reconsolidation using propranolol not only demonstrates lasting effects, but may also selectively dampen the emotional component of the memory trace (Tronson & Taylor, 2013).

Recently, experiments using animal models of addiction have focused on whether similar mechanisms are implicated in appetitive (i.e., drug-related) memory reconsolidation, which has important implications for substance dependence (Reichelt & Lee, 2013). A central characteristic of environmental drug-CSs is their ability to act as conditioned reinforcers capable of not only sustaining extended periods of drug-seeking, but also of supporting the acquisition of new drug-seeking behaviours (Milton & Everitt, 2010). Thus, Lee, DiCiano, Thomas, and Everitt (2005) investigated whether disrupting the reconsolidation of a drug-CS associative memory (i.e., a light

that predicts cocaine availability) would impair the ability of that CS to support learning a new behavioural response (i.e., nosepoke) using rats in a cocaine self-administration protocol. This protocol has been argued to mirror the reinforcing aspects of addictive substances, as well as the persistent, flexible, and compulsive drug-seeking and using behaviours that are idiosyncratic to addicted individuals (Prus, James, & Rosecrans, 2009). In their experiment, Lee et al. (2005) demonstrated that post-reactivation infusions of anisomycin directly into the basolateral amygdala, the brain area responsible for mediating the consolidation and reconsolidation of discrete CS-US appetitive and aversive associations, impaired the ability of the light-CS to act as a conditioned reinforcer; anisomycin treated rats did not acquire the new drug-seeking response. In a subsequent study by the same team using the same experimental paradigm, Milton et al. (2008) demonstrated that systemic propranolol infusions also disrupted the ability of a natural reward-CS (i.e., sucrose) and a drug-CS (i.e., cocaine) to support the acquisition of a novel instrumental response. Similarly to aversive fear memories, these results suggest that protein synthesis and the beta-adrenergic system are implicated in the reconsolidation of discrete natural-reward memories, as well as drug-conditioned memories.

Another frequently used protocol for investigating the motivational and rewarding effects of drug-related contextual stimuli using animal models is conditioned place preference (Prus et al., 2009), where rats are trained to associate a specific context with drug availability. After repeated pairings, animals show preference for the drug-paired context. In this protocol, reactivation is typically achieved by a brief re-exposure to the drug-paired context. Several authors have shown that single or multiple post-reactivation systemic infusions of propranolol disrupts the reconsolidation of contextual memories associated with drug-reward for cocaine and morphine (Bernardi, Lattal, & Berger, 2006; Fricks-Gleason & Marshall, 2008; Robinson &

Franklin, 2007), as well as natural rewards (Diergaarde et al., 2008). These results further suggest that the impact of discrete and contextual drug-related cues can be diminished by disrupting drug-related memory reconsolidation with propranolol.

Depending on the experimental paradigm and amnesic treatment, discrepancies have been found in the pre-clinical literature surrounding the role of beta-adrenergic mechanisms in ethanol-related memory reconsolidation. For instance, a single systemic post-retrieval injection of propranolol had no effect on the reconsolidation of alcohol-related associative memories in a conditioned place preference task (Font & Cunningham, 2012), or in conditioned approach (i.e., sign-tracking) and pavlovian-to-instrumental transfer paradigms (Milton et al., 2012). The pavlovian-to-instrumental transfer protocol measures conditioned motivation (i.e., the capacity of CSs to stimulate instrumental responding), while sign tracking occurs when the organism approaches locations or stimuli previously associated with successful drug use (Milton & Everitt, 2010; Milton et al., 2012). However, in an ethanol self-administration reinstatement paradigm, which arguably models cue-induced relapse in humans, Wouda et al. (2010) revealed that three (but not one) weekly post-retrieval infusions of propranolol disrupted the reconsolidation of a discrete ethanol-CS memory. Although these results appear discrepant with previous literature of other addictive substances, the findings suggest that alcohol-related associative memories can undergo reconsolidation, and this mechanism involves the beta-adrenergic system.

Disrupting memory reconsolidation in humans: Clinical evidence. With the abundance of pre-clinical evidence for appetitive and aversive memory reconsolidation mechanisms, several laboratories have begun investigating whether disrupting memory reconsolidation can be used for treating psychiatric disorders involving pathogenic memories, such as PTSD and substance dependence (see Brunet et al., 2008; Brunet et al., 2011b; Lonergan,

Brunet, Olivera-Figueroa, & Pitman, 2013; Milton & Everitt, 2010; Saladin et al., 2013). The involvement of the beta-adrenergic system in emotional memory consolidation and reconsolidation is especially important for studies involving human clinical populations, as the protein synthesis inhibitor anisomycin is toxic to humans.

In PTSD populations, trauma-memory reactivation under the influence of propranolol has been shown to weaken the emotional tone of the memory, as measured by physiological arousal to traumatic cues, as well as alleviate chronic PTSD symptoms (Brunet et al., 2008; Brunet et al., 2011b). Considering that heightened emotional and physiological reactivity to reminder cues may underlie the persistently relapsing nature of PTSD and substance dependence (Toledano, Tassin, & Gisquet-Verrier, 2013), disrupting the reconsolidation of drug-related memories, in a similar manner to traumatic memories, may also lead to symptomatic improvement among addicted individuals. However, to date, the clinical evidence examining the reconsolidation of drug-related memories that may underlie craving and relapse remains scarce. A literature search revealed two research teams with published results on disruption of drug-related memory reconsolidation using propranolol in human clinical samples with substance dependence (Saladin et al., 2013; Zhao et al., 2011).

The first investigation demonstrated that pre-retrieval oral administration of propranolol disrupted the reconsolidation of heroin-related declarative memories (Zhao et al., 2011). Abstinent heroin-dependent participants were instructed to learn a list of drug-related and neutral words. One day later the memory was reactivated one hour after ingesting propranolol or placebo; the test of memory reconsolidation interference occurred 24 hours later by having participants recall as many words as possible. Results revealed that compared to placebo, propranolol significantly reduced the recall of positive and negative heroin-related words in a

reactivation-dependent manner. No effects of propranolol were observed for neutral words, nor were any effects observed in the absence of reactivation. These findings were the first to demonstrate that drug-related memories can undergo reconsolidation in addicted individuals, and this mechanism involves the beta-adrenergic system (Zhao et al., 2011).

More recently, Saladin et al. (2013) used a cue-reactivity paradigm to examine the effects of propranolol compared to placebo on the reconsolidation of cocaine-related associative memories. Immediately after exposing cocaine-dependent individuals to a 5-minute drug-themed video and *in vivo* drug paraphernalia, participants were orally administered either propranolol or placebo. Results from a subsequent test session one day later revealed that compared to placebo, propranolol significantly reduced subjective craving as well as psychophysiological arousal (i.e., heart rate, blood pressure) to cocaine-related cues. However, the effect of propranolol was not maintained at a 1-week follow-up. Furthermore, exploratory analyses of treatment effects on quantity of cocaine use at follow-up revealed no effect of disrupting memory reconsolidation using propranolol, although the study did not have sufficient power to detect between-group differences. Nevertheless, this study further established the potential for interfering with the reconsolidation of drug-memories as a therapeutic intervention for substance dependence.

While encouraging and informative, these studies are limited in several ways. First, the authors employed common drug-related stimuli to elicit memory reactivation (i.e., word list, drug themed videos, or paraphernalia). Arguably, addicted individuals have unique patterns of substance use, which vary widely from one individual to the next. Therefore, in order to capture personal drug-related cues, we opted to use an autobiographical script to reactivate drug-related memories, as done in previous clinical studies (Brunet et al., 2008; Kilts, Schweitzer, Quinn, & et al., 2001). Second, both studies consisted of only one reactivation and propranolol

administration session. In a recent open-label trial of propranolol induced reconsolidation blockade for the treatment for PTSD, Brunet et al. (2011b) demonstrated that six sessions of pre-reactivation propranolol significantly reduced symptoms of posttraumatic stress, and treatment effects persisted at a six-month follow-up. This, which is in line with animal literature indicating that multiple sessions may lead to stronger effects of propranolol (see Wouda et al., 2010), suggests that a series of treatment sessions may have a cumulative effect, leading to greater therapeutic benefits in clinical populations (Brunet et al., 2011b). Third, previous studies in clinical populations have generally focused on one type of addictive substance (e.g., cocaine, heroin). Although this may introduce additional sources of variability, it would nonetheless be informative to perform a study assessing the feasibility and efficacy of disrupting reconsolidation using propranolol for a variety of substance dependencies. Finally, these previous studies have used fixed medication doses (e.g., 40mg), which limits how informative they are to the effects of individual differences in body mass, sex, or other factors (see Lonergan et al., 2012). Thus, the following study aims to address some of these limitations by examining the feasibility of using a personalized script-based reactivation, increasing the number of treatment sessions, individualizing the dosage of propranolol based on body mass, and including a variety of substance addictions.

Current Study

Objectives and Hypotheses

The primary objective of the current study was to assess the feasibility of conducting memory reconsolidation blockade using propranolol as an adjunct treatment for reducing cravings for addictive drugs. We were interested in determining whether a therapeutic protocol previously designed by our laboratory for treating PTSD (Brunet et al., 2008; Brunet et al.,

2011b) could be successfully modified and implemented in a treatment-seeking population with substance dependence. Thus, we assessed whether the methods and procedures could be easily implemented and adequate for determining efficacy in a larger trial. The second objective was to examine scientific feasibility through preliminary results of treatment effects. Although this study was not adequately powered to provide firm conclusions of treatment efficacy, the main hypothesis of the larger trial predicts that compared to placebo, six sessions of memory reactivation under the influence of propranolol will reduce the emotional and motivational strength of subjective cravings, presumably by disrupting the reconsolidation of pathogenic drug-related memories.

Findings from this study will primarily serve to inform the probability of success for larger and similarly designed clinical trials. Establishing feasibility through piloting allows the investigators to decide if the hypotheses, outcome measures, methodology, and procedures are adequate prior to committing to expensive, large scale clinical trials (Leon, Davis, & Kraemer, 2011; Thabane et al., 2010). Furthermore, evaluating feasibility provides researchers with an opportunity to implement methodological changes that may increase the likelihood of success in larger trials. Finally, our results may provide insights on whether retrieving drug-related memories under the influence of propranolol demonstrates therapeutic potential. Larger clinical trials of memory reconsolidation blockade to treat substance dependence can address some of the limitations of current treatment approaches, while paving the way for the development of brief, cost-effective, empirically supported novel interventions. This pilot study represents an important step in this direction.

Study Design

The trial was a randomized double-blind placebo controlled mixed design and included a 1-week screening phase, a 3 to 6 week treatment phase, and a 4-month post-treatment follow up evaluation (Tables 1 & 2). Participants were randomized to receive six weekly or biweekly treatments of either short-acting propranolol or look-alike placebo capsules in conjunction with memory reactivation and treatment-as-usual, or to a treatment-as-usual only control condition. Drug-related memory reactivation was achieved using a personalized script describing a typical drug using experience (Appendix A.). The Sobriety Home Addiction Treatment Center and the Centre de Réadaptation en Dépendence (CRD) Foster Addiction Rehabilitation Center consented to collaborate with Dr. Brunet's research team by allowing access to clients for recruitment. The study began in May 2011, after obtaining a No Objection Letter from Health Canada and approval from McGill University's Institutional Review Board (IRB). After amending the protocol (see Procedures) and adding CRD Pavilion Foster's as a study site in 2012, ethics approval was sought and obtained from the Comité d'Ethique de la Recherche en Toxicomanie, in addition to McGill University's IRB and Health Canada.

Methods

Participants

Participant candidates were recruited from the private residential Sobriety Home drug and alcohol treatment center (Huntingdon, QC), the public outpatient program at CRD Foster addiction treatment center (Montreal, QC), as well as through local media. All participants were required to be currently enrolled in a drug and alcohol treatment program. Additionally, due to the lack of research on propranolol's possible interactions with addictive drugs, all participants were required to agree to remain abstinent during their participation in the clinical trial.

However, once enrolled, participants were not excluded on the basis of isolated relapse events. Rather, excluding participants for failure to remain abstinent only occurred if the individual was unable or unwilling to stop using the substance regularly, as is the procedure at the outpatient CRD Foster treatment center.

Eligible participants were adults (18-65 years old) with a diagnosis of substance dependence disorder as determined by *DSM-IV-TR* (APA, 2000) criteria within a 1-month period prior to screening. Multiple types of drug addictions were included such as alcohol, heroin/opiates, cocaine, marijuana, benzodiazepine, and amphetamine addiction. Exclusion criteria included past or current *DSM-IV-TR* diagnosis of bipolar disorder or psychotic disorder, women who were pregnant or breast-feeding, individuals with chronic asthma, cardiovascular disease, diabetes, low blood pressure (< 100 systolic), resting heart rate of 55bmp or lower, or any other medical condition that would contraindicate the use of propranolol (i.e., bradycardia, Reynaud's disease, arterial hypotension). Participants who were actively suicidal or deemed at risk to harm themselves or others were excluded, and the appropriate measures were put in place to ensure safety. No individual was considered an active risk of harming themselves or others.

Individuals taking contra-indicated medications (i.e., other beta-blockers, insulin, antiarrythmics, clonidine, imipramine or tricyclic antidepressants, sulfonylureas, lidocaine, iodine contrast agents for medical imaging, and calcium channel blockers) were also excluded. If participants were prescribed and using selective serotonin reuptake inhibitors (SSRIs) or serotonin and norepinephrine reuptake inhibitors (SNRIs), they were included provided they consented to skip their antidepressants on the days they receive treatment, as is sometimes done in other contexts (Kinzl, 2009). All participants provided written informed consent prior to trial enrollment.

Outcome Measures

Evaluating the feasibility of the study processes/operations. All study feasibility outcomes were derived from suggestions put forth in Thabane et al., 2010. For the primary objective, feasibility outcomes related to the study operations included evaluation of recruitment and retention rates, the eligibility criteria, and protocol adherence. Recruitment was considered feasible if an average of 4 participants (2 per recruitment site) were consented and included in the trial per month over a 24-month period. Considering that each recruitment site enrols an average of 7 to 8 new patients per month, this objective was deemed reasonable from the outset. Furthermore, based on previous literature suggesting a treatment drop-out rate of 20-60% among addicted individuals (Brorson, Ajo Arnevik, Rand-Hendriksen, & Duckert, 2013), the study needed to meet the following retention criteria: i) if at least 60% of included participants completed the experimental treatment protocol within the treatment period time-frame; and ii) if at least 60% of randomized intent-to-treat (ITT) participants complete the 1-week post-treatment evaluation and 4-month follow-up. The ITT sample consisted of participants who returned after consent for the first visit to be randomized, treated (for the placebo and propranolol groups), or assessed (treatment-as-usual group). Finally, the eligibility criteria were considered adequate and sufficient if less than 35% of consented participants were deemed ineligible to be randomized (i.e., screen failed).

Protocol adherence was defined in terms of the extent to which the participants and clinical/research staff followed and completed the procedures outlined in the protocol. Thus, the retention criteria outlined above were considered to reflect participant protocol/treatment adherence. To examine whether the protocol procedures were adequately implemented by the research and clinical teams; all of the following criteria were to be met: i) less than 35% of

clinician collected data was missing or incomplete; ii) at least 80% of medical evaluations were completed and conducted within one week of signing consent; iii) at least 65% of ITT participants had to receive all doses of study medication in a blinded manner by a qualified nurse; iv) at least 80% of the personalized scripts were required to be approximately one-page, typed in the first person-present tense, and reflect the details of a typical substance using cycle. We also explored whether the randomization process adequately balanced participants across conditions, as well as whether any baseline demographic or clinical variables were related to study withdrawal.

Evaluating scientific feasibility: Preliminary treatment effects. For the second objective, outcome measures intended to explore scientific feasibility and test the main scientific hypothesis included changes in severity of drug and alcohol craving as measured by self-report craving questionnaires, as well as daily recordings of the frequency and intensity of cravings. Moreover, we explored the effects of treatment on relapse during the trial. Adverse effects of treatment were recorded and defined any untoward medical occurrence reported by participants. Participants were sought from outpatient and inpatient substance dependence treatment programs in order to examine feasibility across different settings and the practicality of administering the experimental treatment protocol at various treatment centers.

Psychometric Instruments for Screening and Scientific Outcomes

Table 2 provides details on the assessment procedures at each trial visit. The Mini International Neuropsychiatric Interview, Plus v. 5.0 (M.I.N.I; Sheehan et al., 1998) was administered by trained research staff to evaluate the diagnosis of alcohol and drug dependence, as well as the presence of any comorbid disorders, during the screening phase. Comorbid disorders which were assessed at screening included the following: major depression,

(hypo)manic episode, panic disorder, agoraphobia, social phobia, obsessive-compulsive disorder, psychotic disorder, anorexia nervosa, bulimia, generalized anxiety disorder, and posttraumatic stress disorder. The M.I.N.I is a reliable, valid, and brief structured diagnostic interview designed to assess the presence or absence of the major Axis I mental disorders according to the *DSM-IV-TR* criteria (Sheehan et al., 1998).

Subjective craving was primarily measured using the self-report questionnaire according to the participants' substance of main dependence: the Cocaine Craving Questionnaire-Now version (CCQ; Tiffany, Singleton, Haertzen, & Henningfield, 1993), the Alcohol Craving Questionnaire Revised-Now version (ACQ-R; Raabe, Grusser, Wessa, Podschus, & Flor, 2005), the Heroin Craving Questionnaire-Now version (HCQ; Tiffany, Fields, Singleton, Haertzen, & Henningfield, in preparation), and the Marijuana Craving Questionnaire-Now version (MCQ; Heishman, Singleton, & Liguori, 2001); Appendix B.). Each questionnaire is scored on a 7-point likert scale, where participants indicate how strongly they disagree (1) or agree (7) with statements such as "I crave cocaine right now" or "I would feel less sick right now if I used heroin". Raw craving scores are obtained by averaging all items of the questionnaire, providing a general craving index between 1 and 7. Higher scores are indicative of greater craving severity. Secondary measures of craving included the use of a self-report diary, in which participants recorded the frequency and intensity (1 = high, 2 = moderate, 3 = low) of their substance cravings on a daily basis throughout the trial (Appendix C.).

The CCQ and HCQ are 45-item questionnaires which assess five dimensions of craving at the moment of assessment: i) desire to use, ii) intention and planning to use, iii) anticipation of positive outcome, iv) anticipation of relief from withdrawal or dysphoria, and v) lack of control over use. The MCQ is a 47-item questionnaire which assesses the same five theoretical

dimensions of craving. The ACQ-R, adapted from the Alcohol Craving Questionnaire (Singleton, Tiffany, & Henningfield, 2003), is a 30-item questionnaire which assesses two dimensions of alcohol craving at the moment of assessment: i) urge and intention to drink, and ii) reinforcement (positive and negative). All craving questionnaires obtained high reliability indices within previous respective validation studies, with internal consistency (coefficient alpha) scores of approximately .95 (Heishman et al., 2001; Raabe et al., 2005; Tiffany et al., in preparation; Tiffany et al., 1993). Internal consistency coefficients in the present sample ranged from .63 for the ACQ-R to .96 for the CCQ and .98 for the HCQ. Despite the small sample size, these values are within the range of those obtained in previous validation studies, with the exception of the ACQ-R for which it was lower in the present sample (Raabe et al., 2005).

The Addiction Severity Index, 5th edition (ASI-5th; McLellan, Luborsky, Woody, & O'Brien, 1980) was used as a secondary efficacy outcome measure to assess the severity of the participant's substance dependence at baseline and follow-up. The ASI is a widely used 200-item semi-structured interview which evaluates seven areas that can be negatively affected by substance dependence (drug use history, alcohol use history, and medical, employment/support, legal, psychiatric, and social/family statuses). For research purposes, each module produces a composite severity score ranging from 0 to 1, which can be compared to produce an index of change over time. Higher composite scores are indicative of greater severity in a given area. The ASI is a reliable, valid, and considered a useful tool for the assessment of addiction severity, especially in a clinical setting for treatment planning (Mäkelä, 2004; McLellan, Cacciola, Alterman, Rikoon, & Carise, 2006). However, the reliability and validity of the composite scores have varied between psychometric studies (see Mäkelä, 2004).

Finally, suicidality and psychiatric symptoms were monitored with the Columbia Suicide Severity Rating Scale (C-SSRS; Posner et al., 2011) and the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962), respectively, throughout the duration of the trial. The C-SSRS is designed to assess four dimensions of suicidality: i) severity and i) intensity of suicidal ideation, iii) suicidal behaviour and iv) the lethality of suicide attempts. The BPRS is an 18-item semi-structured interview designed to screen for psychiatric symptoms such as depression, anxiety, and psychotic behaviour (Overall & Gorham, 1962). The C-SSRS was used to monitor suicidal ideation and behaviour throughout the trial, while the BPRS was used to evaluate participants' mood stability. Thus, neither suicidality nor psychiatric symptoms were outcome measures per se in the present study.

Treatment Programs

Sobriety Home Addiction Treatment center. The privately owned residential Sobriety Home takes an eclectic and individualized approach to inpatient treatment, primarily encompassing cognitive-behavioural and psychodynamic approaches in group and individual therapy. Clients are required to commit to at least one month of treatment. The treatment center is highly structured, with workshops and therapy sessions beginning at 9:00 a.m. and continuing throughout the day. All new clients undergo a psychiatric and medical intake evaluation. All clients are required to participate in the day's therapeutic activities. Following treatment, the center helps their clients reintegrate back into their regular life, find employment, go back to school, or find housing, and encourages them to participate in the aftercare program. Since their clients come from all parts of north-America, therapists provide weekly telephone calls and chat-room group therapy sessions as part of their aftercare program (http://www.sobriety.ca/).

CRD Foster Addiction Rehabilitation center. The CRD Foster outpatient addiction rehabilitation program uses a stepped-care approach to individualized treatment. Through group and individual therapy, this addiction treatment center develops treatment plans aimed at maximizing their clients' chances of recovery. Following the outcome of an intake assessment, clients are either referred to the six-week semi-intensive outpatient program, or their intensive residential program. To examine the feasibility of implementing our treatment in an outpatient setting, we recruited from the semi-intensive outpatient program, specifically the morning cohort. Group therapy sessions occur twice per week from 9:00 a.m. to 11:00 a.m., and each client is assigned a case manager for individual therapy sessions once per week.

Therapeutic approaches include psychoeducation on the development and maintenance of substance dependence, cognitive-behavioural therapy, dialectical behaviour therapy, skills training (i.e., stress coping, anger management, etc.), and psychodynamic therapy. Abstinence from all addictive substances, except nicotine, is required and considered grounds for expulsion if the client is unable to comply. A thirteen week recovery management program concludes treatment, and consists of group therapy once per week. Additionally, CRD Foster provides their clients with tools for reintegration back into daily life, such as help finding employment, building a resume, finding a home, and/or going back to school (http://www.CRDfoster.org).

Other addiction therapy. Participants who chose not to enroll in one of the above two treatment programs were required to enroll in any other type of individualized or group psychosocial treatment, with a specific focus on their substance disorder. Description of the type of treatment received was obtained from each participant, and ranged from private psychotherapy to group programs from various hospitals (i.e., McGill University Health Center: Griffith Edwards Addictions Unit). These participants were required to inform their private

counselor of their participation in the trial and complete a disclaimer identifying the program they pursued and attending therapist. They were not enrolled in the trial until the attestation was received and complete.

Experimental treatment protocol. The experimental treatment consisted of administering propranolol or placebo in conjunction with a memory reactivation procedure. Propranolol is a synthetic noradrenergic beta-blocker that readily crosses the blood-brain barrier exerting central as well as peripheral effects (O'Carroll, Drysdale, Cahill, Shajahan, & Ebmeier, 1999; Przybyslawski, Roullet, & Sara, 1999). Medication dose was set at 1mg/kg of body weight. Memory reactivation was achieved by having the participant read aloud a personalized craving script that was written by the participant during the screening phase, and typed by the interviewer prior to the baseline treatment session. In the event that participants were dependent on or used more than one substance, the narrative and craving assessment focused on the most problematic substance (i.e., the primary substance the participant was receiving treatment for).

The purpose of the script reading procedure is to reactivate drug-cue associations that can precipitate craving. Accordingly, participants were instructed to include as many details as possible regarding environmental stimuli (i.e., settings/contexts, people, drug paraphernalia), as well as interoceptive cues (i.e., psychological states and physiological sensations) associated with drug availability, anticipation of drug use, drug consumption, and drug withdrawal, within their scripts. An attempt was made to capture all aspects of the addiction cycle. When necessary, the interviewer probed for further elaboration and clarification of the personal craving script. The role of the interviewer was limited to guiding the participant in reading the narrative aloud; no attempts whatsoever were made to interpret or reframe the meaning of the personalized scripts in a therapeutic manner. The script reading exercise was purposefully kept brief in order to

minimize extinction effects. Participants who experienced distress from the script writing/reading procedure were referred to their individual therapist for further therapeutic support; this occurred for only one participant after one treatment session.

Procedure

Within days of entering the treatment programs, new clients with no major contraindicating medical conditions (such as, diabetes, chronic asthma, history of heart condition, psychosis or bipolar disorder, use of anti-hypertensive medication, or low-blood pressure) were advised of the research study by the clinical staff. Those eligible and who showed interest were referred to the research staff for further information, consent, and eligibility evaluation. Participants recruited through a local advertisement were referred to the collaborating treatment programs prior to consent and eligibility screening if they were not already enrolled in treatment. All participants were advised of the pilot nature of the study. Recruitment at Sobriety Home began in May 2011 and ended in June 2012, and recruitment at CRD Foster was initiated in October 2012 and ended in May 2013.

The medical examination was scheduled within one week after providing informed consent and initial eligibility evaluation. During the medical evaluation, the physicians (J. T. and C. B.) confirmed the substance dependence diagnosis, obtained a detailed medical history from the participant, and conducted a brief physical examination (i.e., heart rate and blood pressure evaluations, weight recording). Within one week of confirming eligibility from the medical evaluation, participants met with the research staff, were randomized by the study physician, who prepared the pill capsules, and underwent their first treatment session. At Sobriety Home, a certified nurse prepared the pill capsules. The randomization list was created by a third party

unrelated to the study, occurred in blocks of six cells (Fleiss, 1986), was stratified according to type of addictive substance, and was achieved using a random number generator.

Placebo and propranolol capsules were identical and coded by the Douglas pharmacy to ensure adequate blinding. To prevent the research staff from deciphering the blind, only the medical doctors (and the nurse at Sobriety Home) had access to the treatment assignment codes. However they did not know which code belonged to which treatment group, with the exception of the treatment as usual (TAU) condition for which it was impossible to maintain the blind. The code was broken only once the study was completed or in case of medical necessity. All treatment sessions occurred on location at the treatment center where the participant was enrolled, or at the Douglas Institute if the participant was enrolled in private therapy. Participants who completed the treatment program before their treatment sessions were complete were permitted to complete the trial at the Douglas Institute, provided they remained in a recovery management program.

Following the baseline treatment visit, five additional treatment sessions were scheduled for each participant. Treatment sessions were separated by at least two days and were planned to occur twice per week for three weeks. The total protocol duration was one month, followed by a 4-month follow-up evaluation over the telephone. Psychometric assessments of subjective craving, mood and anxiety symptoms, and suicidality were administered during each treatment session and at follow-up. Addiction severity was assessed at baseline and follow-up. The daily diary was handed out once per week during the treatment phase. Each treatment session began by recording changes in concomitant medications and administering the psychometric evaluations. Participants then read aloud their personalized craving script to the interviewer. Congruent with reconsolidation theory (Schiller & Phelps, 2011), propranolol or placebo was administered

immediately after the script reading procedure. Tables 1 and 2 describe the study design and assessment procedures throughout the trial.

In January 2012, the following five amendments were made to the protocol (see Table 3). First, the TAU control condition was added in order to compare currently available substance dependence treatment with the experimental treatment; the randomization list was re-done at that time by a third party. Participants in the TAU condition followed the same procedure as the other two conditions; however they did not undergo the experimental treatment. Second, a 1-week post-treatment evaluation was added following the last treatment session in order to explore the more immediate effects of treatment. Third, the timing of the study drug administration changed from immediately after memory reactivation to ninety minutes prior. This change was implemented following experimental evidence suggesting pre-retrieval propranolol may have a more robust effect on memory reconsolidation, due to the time it takes propranolol to reach its peak bioavailability in the brain (i.e., 60-90 minutes; Brunet et al., 2011b; Dey et al., 1986; Lonergan et al., 2012). Fourth, participants dependent on alcohol were included. Fifth, an open-label phase was offered following completion of the double-blind phase for participants in the TAU and placebo conditions. In the open-label phase, participants followed the exact same procedures as the double-blind phase, but all received the propranolol.

In sum, 8 participants were randomized in the first version of the protocol (*n* placebo = 4; *n* propranolol = 4) and received post-reactivation medication. Eleven participants were randomized to the second protocol (*n* placebo = 4; *n* propranolol = 4; *n* TAU = 3) and received pre-reactivation medication. For the purpose of clarity, the original protocol will hereafter be referred to as protocol 1, which was implemented from May 2011 to December 2011 inclusively,

and the modified protocol as protocol 2, which was implemented from January 2012 to May 2013, inclusively.

Statistical Analyses

Evaluating the feasibility of the study processes. Feasibility outcomes related to the study operations (recruitment, retention, eligibility criteria, and protocol adherence) are reported descriptively as counts and percentages. Baseline demographic and clinical variables were compared between treatment groups to evaluate the randomization process. These variables were also used to examine possible factors related to retention and dropping out (Figure 2). Since the TAU only condition contained only 3 participants, we decided to pool both control groups for the purpose of conducting statistical analyses and increasing power. Therefore, the propranolol group consisted of 8 participants, and the control group consisted of 11 participants (Figure 2). To ensure that this process did not create any distortion in the results, sensitivity analyses were performed with and without these participants. Normality of all distributions was assessed with the Shapiro-Wilks test. When variables violated normality assumptions, non-parametric equivalents were performed as sensitivity analyses. In the event of a discrepancy, the results from the non-parametric tests are reported. Additional sensitivity analyses were conducted to examine whether post-reactivation versus pre-reactivation medication influenced any of the results (i.e., differences between protocol 1 and 2, respectively).

For all analyses, Fisher's exact tests for categorical and independent *t*-tests (or equivalent non-parametric Mann-Whitney *U* tests) for continuous variables were conducted. Fisher's exact tests were used to correct for the small sample size and the violation of the expected cell count assumption for chi-square tests (Larntz, 1978). Categorical variables with more than two levels

were dichotomized in order to obtain Fisher's exact test results. All tests used a two-tailed alpha level of .05.

Analysis of preliminary treatment effects: Self-report craving questionnaires. Due to the low response rate at the 4-month follow-up, this data point was dropped from all analyses. For all treatment completers who did not complete the 1-week post-treatment assessment, either because it was not part of the protocol (i.e., protocol 1) or they were lost-to-follow-up, the last-observation carried-forward (LOCF; Streiner, 2010) method was used to impute the 1-week post-treatment time point. Then, using data from the ITT sample, multiple imputation methods were used to impute all other missing data (see Results).

To examine how craving changed over time, a difference score was calculated for each participant by subtracting the post-treatment score from the baseline score. Negative scores indicate that participants' cravings increased in severity between baseline and post-treatment, a score of zero indicates no change, and a positive score indicates a reduction or attenuation of craving. A two-tailed independent *t*-test with alpha set at .05 on the mean change score for each group was conducted to test whether the propranolol and placebo groups were significantly different from one another. Additionally, a paired-samples *t*-test was conducted within each drug group to examine differences between baseline and the 1-week post-treatment follow-up. Finally, with so few follow-up respondents, examining the effects of treatment on dependence severity as measured by the ASI was not possible in the current study.

Analysis of preliminary treatment effects: Daily diary, relapse during the trial, and adverse events. Intensity and frequency of daily cravings as measured with the daily diary were analyzed using a two-way repeated measures ANOVA with treatment group as the between subjects factor and time as the within subjects factor. Significant effects were examined with

post-hoc Bonferroni contrasts. Relapse during the trial was dichotomized into a yes/no categorical variable and compared between drug conditions, protocol type, and whether participants withdrew from the trial, using Fisher's exact tests and relative risk estimates. Adverse effects of treatment reported during the trial were dichotomized into a yes/no categorical variable and compared between the propranolol and placebo group using Fisher's exact test and relative risk estimates. For all tests, the two-tailed alpha was set at .05. All analyses were performed with SPSS v. 22; the missing values module was used for the multiple imputation procedure.

Results

Tables 4 and 5 depict the baseline demographic and clinical characteristics of the randomized sample, by treatment group. In total, 19 participants were randomized; 8 to the propranolol plus memory reactivation and treatment as usual condition, 8 individuals received placebo plus memory reactivation and treatment as usual, and 3 participants were randomized to the TAU control condition. With the exception of psychiatric comorbidity (see below), there were no significant differences between the propranolol and placebo group on any baseline demographic characteristic, suggesting randomization adequately balanced participants. Although three quarters of the randomized sample were men, the sex difference between treatment groups did not reach statistical significance. Comparisons between the two protocols revealed no significant differences on baseline demographic or clinical variable, with two exceptions: i) participants in protocol 1 (M = .34, SE = .06) had significantly higher mean drug use composite scores from the ASI than those in protocol 2 (M = .07, SE = .04), $t(14) = 4.13$, $p < .01$; as well as ii) significantly higher baseline craving scores, (protocol 1: Mdn = 2.60;

protocol 2: *Mdn* = 1.77), $U(8,11) = 20$, $p = .05$. Removing the treatment as usual participants from these analyses did not affect the above results.

Of the randomized participants, 7 were primarily seeking treatment for opiate dependence (i.e., heroin, oxycodone, and hydromorphone), 6 for cocaine dependence, 5 for alcohol dependence, and 1 for marijuana dependence (Table 4). Seven individuals abused or were dependent on more than one substance in their lifetime; 50% of cocaine dependents, 29% of opiate dependents, and the marijuana user qualified for a comorbid lifetime alcohol dependence diagnosis. However, in all cases these participants were primarily seeking treatment for drug rather than alcohol dependence.

Substance dependence often co-occurs with other psychiatric conditions. In this sample, the lifetime prevalence for one or more co-occurring psychiatric disorder was 68.4%, while 37% currently met criteria for one or more psychiatric disorder. The most common comorbid disorder was major depressive disorder with a lifetime prevalence of 53%; at screening, 3 participants were currently experiencing depressive symptoms. Six participants (31.5%) met diagnostic criteria for lifetime generalized anxiety disorder, 4 (21.1%) of which currently met criteria. Five (26.4%) participants met criteria for social phobia, of which 1 was currently experiencing symptoms. Four (21.1%) participants met criteria for lifetime PTSD, with 1 currently experiencing symptoms. Additionally, 3 (15.9%) participants met criteria for lifetime panic disorder; 2 currently met criteria. Finally, 2 (10.5%) participants met current criteria for obsessive compulsive disorder. Compared to the placebo group, the prevalence of lifetime psychiatric comorbidity was significantly higher among propranolol treated participants, Fisher's exact test, $p < .05$, relative risk = 2.2, 95%CI [1.15 – 4.20], as was the lifetime prevalence of depression, Fisher's exact test, $p < .05$, relative risk = 3.21, 95%CI [1.18 – 8.72]; Table 4.

Removing the treatment as usual participants from the analysis resulted in no significant difference in lifetime psychiatric comorbidity between treatment groups. No other discrepancies were revealed. Mann-Whitney *U* tests for continuous variables not normally distributed revealed no differences from parametric tests.

Feasibility of the Study Processes

Recruitment, retention, evaluation of the eligibility criteria, and protocol adherence. The results of the recruitment process are depicted in Figure 2. Thirty-four individuals provided written informed consent; 18 were from Sobriety Home, 10 were from CRD Foster, and 6 were recruited following the local news report released in November 2011. For protocol 1, which was implemented for 8 months, 12 individuals were consented and screened and 9 (75%) were included and eligible for randomization, and 8 (88%) were randomized (Table 1). For protocol 2, which lasted 16 months, 22 individuals were consented and screened, 13 (59%) were eligible for randomization, and 11 (85%) were randomized (Table 3). Additionally, 55% of participants recruited from Sobriety Home were included, 70% of participants recruited from CRD Foster's were included, and 83% of the participants recruited following the local news report were included. In total, 22/34 (65%) of consented participants were included and eligible to be randomized to the trial. Of these, 19 (86%) were randomized, which consisted of the ITT sample; three included participants withdrew prior to being randomized at the baseline treatment visit (Figure 2). Nevertheless, the primary recruitment objective was not met; we could not successfully consent and include an average of 4 participants per month (average 1 participant per month). However, over 80% of included participants returned for the baseline visit and were randomized to the trial.

Two feasibility criteria related to participant retention/adherence were established *a priori*. The first required at least 60% of included participants to complete the experimental treatment within the specified time-frame. In total, 12/22 (55%) included participants completed the treatment phase, but 10/12 (83%) did so within the protocol's time-frame. Among randomized participants (n = 19), reasons for study withdrawal prior to completing the treatment phase included: i) exclusion due to change in medical status requiring medication that contraindicated propranolol use (n placebo = 1); ii) inability/unwillingness to comply with the abstinence inclusion criteria (n placebo = 1; n propranolol = 1); iii) withdrawal from the treatment center (n propranolol = 1); iv) completed the rehabilitation program prior to completing the trial and did not continue participation at the Douglas Institute (n placebo = 1); v) no longer experienced cravings and withdrew (n TAU = 1); and vi) lost-to-follow-up (n placebo = 1). Although 45% of included participants withdrew from the trial, most of those who did complete treatment did so within the allotted time. However, examining only the 19 randomized participants, 7 (37%) withdrew from the study prior to completing treatment.

The second participant adherence/retention criterion required that 60% of ITT participants respond to the 1-week evaluation and 4-month follow-up evaluation. The 1-week post-treatment evaluation was not scheduled for participants in protocol 1; 6/8 (75%) completed the treatment phase and 2/8 (25%) responded to the 4-month follow-up. For participants in protocol 2, 6/11 (55%) completed the treatment phase, 5/11 (45%) completed the 1-week post-treatment assessment, and 2/11 (18%) completed the 4-month follow-up. Of the 19 randomized ITT participants, 1 (5%) from the treatment as only control group and 3 (16%) from the propranolol group completed the 4 month post-treatment follow-up. Only one protocol 2

participant from the treatment as usual condition completed the treatment phase and both follow-up time-points. The second participant adherence criterion was not met.

To examine the suitability of the eligibility criteria, we established *a priori* that less than 35% of consented participants were to be excluded for failing to meet the specified inclusion criteria. This criterion was met: only 6 of the 34 (18%) consented participants endorsed one or more exclusion criteria and could not be included. Two participants had low blood pressure (below 100 systolic), two were asthmatic, one reported a history of bipolar disorder, and one did not meet the abstinence criteria and withdrew from the treatment program (Figure 2). Of the remaining six participants who withdrew consent prior to completing the eligibility assessment, one withdrew from the trial and the treatment center, another participant could not make the commute to CRD Foster in Montreal, QC, and the reason for withdrawal is unknown for four participants. Including the participants who were excluded for endorsing an exclusion criteria after being randomized to the study, a total of 9/34 (26%) participants endorsed one or more exclusion criteria (see reasons for study withdrawal i) and ii) described above).

The first clinician/researcher adherence criterion required that less than 35% of clinician administered data was missing or incomplete. This criterion was met. Less than 10% of sociodemographic and clinical history data collected at screening was missing and in total, 21% of all data planned to be collected by clinicians throughout the trial was missing. The ASI was administered to 16/19 (84%) of participants at baseline. Of the 5 participants who completed protocol 2, 4 (80%) were administered the ASI at the 1-week post-treatment assessment; and of the 4 participants who completed the 4-month follow up, 3 (75%) were administered the ASI. Missing data for the BPRS and suicide assessment was directly due to participant withdrawal.

The second criterion required that at least 80% of participants had to undergo the complete medical evaluation within one week of consent and screening. This criterion was met for 25/28 (89%) of consented participants who completed the medical evaluation. The third research staff adherence criterion specified that at least 65% of participants in the double-blind treatment arms (*n* placebo = 8; *n* propranolol = 8) received all doses of study medication in a blinded manner by a qualified nurse. A certified nurse administered all doses in a blinded fashion and 80% of the total number study medications were dispensed. The reason for not dispensing all study medication was directly related to participant withdrawal, with the exception of one treatment completer from the control condition that refused to take one dose of medication. Finally, the fourth adherence criterion required that at least 80% of personalized scripts were approximately one page, typed in the first person, present-tense, and contain details of a typical cycle of substance use. This was examined in the ITT sample, yet two participants from the treatment as usual control group did not prepare a personalized script. While all scripts consisted of a complete 1-page account of a typical using cycle and were typed in the first person, 14/17 (82%) were written in the present tense.

Variables related to participant withdrawal. To examine variables that may be related to trial withdrawal, all included participants (*n* = 22), were divided into those who did not complete the six-session treatment phase (*n* = 9) and those who did (*n* = 12). The randomized participant who was excluded due to a change in medical status was not included in the following analyses since that participant did not voluntarily withdraw from the trial (Table 6).

The following variables were examined using Fisher's exact tests: i) the treatment group, ii) whether participants were receiving outpatient or inpatient treatment, iii) sex, iv) any lifetime comorbid psychiatric diagnosis, v) the type of addictive substance the participant was receiving

treatment for, vi) whether participants were in long-term relationships, vii) smoking status, and viii) whether they were in protocol 1 or protocol 2. No variables were significantly related to study withdrawal.

The following continuous variables were analysed using two-tailed independent *t*-tests: i) age, ii) number of years of education, iii) duration of drug use in years, iv) number of previous treatment attempts, v) number of days in the rehabilitation program, vi) baseline craving severity score, and vii) baseline score on depression/anxiety BPRS subscale. No significant differences were found. Non-parametric Mann-Whitney *U* tests for non-normally distributed variables revealed no differences from parametric tests.

Analysis of Preliminary Treatment Effects

As mentioned, the ITT sample consisted of 19 randomized participants who completed at least the first treatment session. Additionally, two randomized participants from the control groups completed the open-label propranolol treatment protocol. Both participants completed the treatment phase; one was unavailable for the 1-week post-assessment following open-label treatment and 4-month follow-up. Open-label data from these two participants were included in the propranolol group in order to increase statistical power. Thus, the total number of ITT participants included in the analyses of subjective craving, relapse during the trial, and adverse events was 21 (*n* = propranolol = 10; *n* placebo = 8; *n* TAU = 3; Figure 2).

Effects of treatment on subjective craving. The following describes specific statistical methods and results for the analysis exploring the effects of treatment on subjective craving as measure with the self-report craving questionnaires. In total, the LOCF method to impute the 1-week post-treatment time-point was used for 8 treatment completers (*n* placebo = 3; *n* propranolol = 5). Almost three-quarters (71.4%) of participants were missing at least one time

point, including participants from protocol 1 for whom the 1-week post-treatment assessment was not part of the study design (n = 6). After implementing the LOCF method, this number dropped to 33%. All missing data points for the craving variable were due to participant drop-out. Results from Shapiro-Wilks tests demonstrated the data with LOCF imputations to be relatively normally distributed.

In order to increase the precision of the multiple imputation model, the plausibility of the missing at random assumption, and to reduce bias, the following variables were included in the imputation model in the following order: 1) protocol type, 2) treatment condition, 3) type of addictive substance, 4) whether the participant relapsed during the trial, 6) whether participants were in residential or outpatient treatment, and 7) mean craving scores from treatment sessions 1 (baseline) through 7 (post-treatment assessment). For the missing at random assumption underlying multiple imputation to be plausibly made, the probability of study drop out may be related to the observed covariates and values, but must be unrelated to the actual missing values (Mackinnon, 2010). Thus, these variables were analyzed with Little's missing completely at random test (MCAR; Little, 1988), which revealed that the data may be considered at least missing at random (MAR) regardless of whether the LOCF values were included in the analysis, LOCF values included: $\chi^2 = 16.78$, df = 10, $p = .08$; LOCF values excluded: $\chi^2 = 23.60$, df = 16, $p = .10$. Accordingly, the fully conditional specification (FCS) imputation approach, which assumes that data are at least missing at random, was used for analysis (van Buuren, 2007).

Forty imputed datasets were created in order to reduce sampling variability and increase the relative efficiency of the pooled imputation model, for a total of 280 imputed values (Sterne et al., 2009). According to several authors, the number of imputed datasets should approximate the percentage of cases with missing data in order for the relative efficiency of the final model to

approximate 100% (Bodner, 2008; Graham, Olchowski, & Gilreath, 2007). The pooled imputation model reached 99% relative efficiency, suggesting that the model was 99% as efficient as using an infinite number of imputed datasets. Inspection of the FCS convergence charts suggested that model convergence was achieved.

In order to directly examine the effects of the experimental treatment, the treatment as usual only participants (n = 3) were removed from the main analysis. Pooled results from the multiply imputed data analysis are shown in Figure 3 and Table 7. There was no significant between-group difference on change in craving severity from baseline to the 1-week post-treatment assessment, as examined by an independent t-test on mean craving difference scores. The between-group effect size was small as per Cohen's standards, d = 0.30 (Cohen, 1988). However, the propranolol group's subjective craving reduced by 37%, while the placebo group's craving reduced by 14%. As shown in Figure 3, the within group contrasts were examined using a two-tailed paired samples t-test, which revealed a significant reduction in craving severity between baseline and post-treatment for the propranolol treated group, $t(787) = 2.13$, $p < .05$, but not the placebo group, $t(309) = .59$, p = ns.

As a sensitivity analysis, these results were compared with the original data (i.e., complete case analysis). In order to examine trends for change in craving severity between baseline and post-treatment, the LOCF data points (n propranolol = 5; n placebo = 3) were kept in the analysis. Figure 4 displays the summary statistics for craving scores at each time point, which demonstrate that mean craving scores in the propranolol treated group steadily declined within the first three treatments, while scores in the placebo group remained relatively stable throughout the trial. Although the between-group difference for mean difference score remained non-significant, the trend was similar; propranolol treated participants' craving reduced by 46%,

while the placebo group demonstrated a 28% reduction in craving between the baseline and 1-week post-treatment assessments.

Effects of treatment on frequency and intensity of daily cravings. One of the two open-label participants completed three weeks of daily diaries, while the other completed none. Including the open-label participant, 13 completed daily diary entries for week 1 (*n* placebo = 5; *n* propranolol = 6; *n* treatment as usual = 2). To examine the effects of the experimental treatment, the treatment as usual only condition was not included in the following analysis. A two-way mixed ANOVA with drug group as the between subjects factor and days (1-7) as the within subjects factor was conducted to examine the effects of treatment on frequency of cravings during week 1. Since data violated the normality and equality of variances assumptions of ANOVA, the square root transformation was applied and corrected the violations. Results revealed a significant main effect of time, $F(6,54) = 2.60$, $p < .05$. No significant between-group differences or interaction were observed. Examining the means, craving frequency decreased between day 1 ($M = 5.10$, $SE = 1.83$) and day 7 ($M = 0.92$, $SE = .46$) of the trial (i.e., after one-two treatment sessions), but the post-hoc Bonferroni contrast was non-significant. Data for intensity of cravings did not violate ANOVA assumptions, was therefore not transformed, and was analysed the same way as craving frequency. Results revealed no significant effects. Data for week 2 was only available for five participants in the propranolol group and three in the placebo group, while data for week 3 was only available for six participants (*n* treatment as usual = 2; *n* propranolol = 4), precluding the possibility of conducting any statistical analyses.

Relapse during trial and adverse effects. Relapse rates during the trial are depicted in Table 7. Including the three individuals randomized to the treatment as usual condition, 8 (*n* TAU = 1; *n* propranolol = 5; *n* placebo = 2) participants relapsed during the trial and 13 did

not. No significant differences between the propranolol and control group on relapse rates emerged; nor were there any significant differences between protocols. Additionally, whether participants withdrew from treatment was not significantly related to relapse. Removing the treatment as usual participants from analysis did not result in any discrepancies in these findings.

Adverse effects of treatment were generally short-lived and reported by 9 participants (*n* propranolol = 6; *n* placebo = 3; Table 7). Although the relative risk for reporting an adverse event was 2.2 times higher for propranolol treated participants, the between group difference was not statistically significant, Fisher's exact test, $p = .20$, 95%CI [.74 – 6.5]. The most commonly reported adverse effect was mild fatigue (*n* propranolol = 4; *n* placebo = 1), followed by nausea and stomach pain (*n* propranolol = 2). Although this may have been linked to the study medication, one participant from the propranolol condition who experienced nausea and stomach pain was concurrently following a methadone maintenance program, and experienced this symptom consistently. Additionally, 2 participants, 1 from the propranolol and 1 from the placebo condition, reported feeling "foggy"; the participant from the placebo condition also reported previous mild depressive symptoms.

As mentioned previously, one participant from the placebo condition experienced hypertension requiring anti-hypertensive medication following the baseline visit, and was therefore excluded from further study participation. For this participant, elevated blood pressure was observed prior to administering the first treatment, and continued to rise by the second visit. No participant experienced any severe adverse effect, and none reported that the reading the personal craving narrative was overwhelmingly distressing; only one participant requested additional therapeutic support following one treatment session due to the script reading process.

Therefore, the experimental treatment was generally well tolerated, with mild to moderate fatigue on treatment days being the most frequent side effect.

Discussion

A major strength of this research is that it is among the first to assess the feasibility of integrating a clinical intervention based on reconsolidation theory within ongoing addiction treatment programs for a variety of dependencies. Disrupting the reconsolidation of drug-related memories to reduce craving and subsequently, treat substance dependence demonstrates several advantages over currently adopted interventions. For instance, traditional psychotherapeutic and pharmacological treatments require a strong commitment for a lengthy period of time (McLellan et al., 2000; McLellan et al., 2005). Reconsolidation blockade, on the other hand, requires individuals to commit to shorter and less frequent treatment sessions. In previous studies from our laboratory, anecdotal observation suggests that treatment effects can be observed as early as the third or fourth treatment session, and each treatment session takes approximately 20 minutes to complete. Furthermore, one of the major issues that plague successful treatment is the persistently relapsing nature of addiction, which is often triggered by drug-related cues that trigger intense cravings (Hyman, 2005; Hyman et al., 2006). Although exposure therapy attempts to address this issue, the initially learned maladaptive behaviours linger, threatening to return when confronted with environmental cues or psychosocial stressors (Torregrossa & Taylor, 2012). Reducing the strength of these drug-related motivational cues by disrupting their reconsolidation directly targets and modifies the underlying conditioned memories, possibly leading to more permanent and longer-lasting treatment effects. Thus, the primary purpose of the current study was to assess the methodological feasibility of disrupting drug-related memory reconsolidation using propranolol as an adjunctive treatment for reducing cravings in treatment-

seeking individuals with substance dependence. The second objective was to examine, in a preliminary way, treatment efficacy.

Based on the results obtained from the evaluation of the current study's operations, it can be concluded that larger multi-center clinical trials are feasible, provided several methodological and procedural modifications be implemented. Importantly, this study demonstrated that disruption of drug-memory reconsolidation using propranolol can be credibly incorporated into ongoing treatment programs. Although the preliminary results from the assessment of scientific feasibility did not reveal any significant effects of propranolol induced disruption of reconsolidation when compared to placebo, results from this and previous studies indicate that the experimental treatment is safe, tolerable, and may lead to symptomatic improvement in larger, more adequately powered trials. The following provides a discussion of several methodological and procedural modifications that may increase the probability of success in larger clinical trials of this nature.

Feasibility of the Study Processes

Recruitment and randomization. The objective of including an average of four participants per month was not met. An average of approximately one participant per month was enrolled during the trial, regardless of which treatment center was the focus of recruitment. Although precise data on how many participants were excluded on the basis of medical contraindications prior to meeting with the research staff and signing informed consent are not available, the recruitment difficulty cannot be readily explained by overly restrictive eligibility criteria, since only 18% of consented participants endorsed one or more exclusion criteria and were therefore, not included. However, some potential participants were not considered due to having low blood pressure upon entering the psychotherapeutic treatment program. This may be

an important factor for future researchers to keep in mind when recruiting participants, as many addicted individuals may present with hypotension. In such a case, it is advisable to closely work with participants and clinical/research staff to monitor blood pressure levels.

The duration of recruitment period (i.e., approximately 24 months) may have contributed to difficulty meeting the objective. However, Saladin et al. (2013) successfully randomized 67 and retained 50 participants over a 28-month period, suggesting that including an average of approximately three participants per month is feasible. With this in mind, Saladin et al. (2013) recruited primarily through local advertisements, suggesting that the criteria requiring participants to be currently enrolled in psychotherapeutic treatment in order to be eligible for trial inclusion may have contributed to a more restrictive recruitment strategy. Therefore, recruiting through local advertisements in addition to treatment centers may have increased the recruitment rates, while still permitting evaluation of whether the treatment can be incorporated into ongoing addiction treatment programs. In sum, the currently proposed recruitment objective may have been met by either recruiting through local advertisements, and/or adding a more treatment centers from which to recruit, which would be feasible in larger multi-center trials.

For participants who are not concurrently in therapeutic treatment, it is worthwhile to have psychotherapists collaborate with the research team in order to provide therapeutic support for any emotional distress or relapse that may be triggered by the memory reactivation procedure. However, it should be noted that although most participants in the present study felt emotional arousal following memory reactivation (i.e., guilt, anger, urge to use), no participant directly relapsed as a result of the experimental treatment, as suggested by no between-group differences in relapse during the trial. Additionally, most included participants returned for the baseline treatment visit, suggesting that they were not deterred by the proposed experimental

procedures. Still, despite only one participant requiring additional intervention following one experimental treatment session, employing qualified therapists to provide additional support is recommended.

Though the randomization method adequately balanced participants across treatment conditions, with the exception of a higher lifetime prevalence of depression and psychiatric comorbidity in the propranolol group, more participants were randomized to the control conditions combined, relative to the active treatment. This may be due to the fact that the treatment as usual only arm added a second non-active control condition. As a result, participants had a 66% chance of being randomized to a control condition, and a 33% chance of being randomized to the active treatment arm. Although the purpose of the treatment as usual condition was to compare the experimental treatment with current substance dependence interventions as provided by the collaborating treatment centers, randomization cells may have been more accurately balanced if the treatment as usual condition was not part of the randomization procedure. Conversely, the present sample size was very small, which may better explain the observed imbalances. For instance, depression and other psychiatric disorders often co-occur with substance dependence (Samet, Waxman, Hatzenbuehler, & Hasin, 2007), rendering it likely that the observed imbalance between groups on lifetime psychiatric comorbidity and depression diagnosis was an artefact of the modest sample size. A larger sample size, as would be the case in larger multi-center trials, would solve these issues.

Participant protocol/treatment adherence. Despite difficulties with recruitment and failing to meet the retention criterion, participant attrition rates of approximately 40% or even higher is common in large scale clinical trials (Gertz, 2008). Only 14% of included participants did not return for the baseline treatment session, and just over 35% of the ITT sample withdrew

prior to completing the treatment phase. However, very few participants were available or responded to the four month follow-up evaluation. Although we ensured that this assessment took place over the telephone and did not require the participant to commute, only four participants responded. Future studies may benefit from shortening the follow-up period to one-month; however this limits investigations into, and clinical follow-up of, the long-term effects of treatment. On the other hand, difficulty with treatment retention may be a characteristic of the population under study (Brorson et al., 2013; Dutra et al., 2008). For instance, some literature has revealed that up to 50% of patients do not complete outpatient treatment, while up to 57% drop out of residential inpatient programs (Brorson et al., 2013). These findings highlight the inherent difficulty of ascertaining remission rates from addiction treatment programs. Unfortunately, in the present study, no common reason for study withdrawal emerged, nor was relapse or any baseline or clinical variable significantly related to trial withdrawal. Consequently, it cannot be ascertained which, if any, factors may have led participants to withdraw from the trial. Finally, with the exception of one individual, participants who withdrew from the trial also did not complete the therapeutic treatment program, suggesting that the observed attrition rate was no different from what is currently observed in addiction treatment programs.

It should be noted that most participants randomized at Sobriety Home completed the study's treatment phase, but were not available for the 4-month follow-up. Furthermore, at CRD Foster's treatment center, no treatment completers were available for the 4-month follow-up. At the Sobriety Home inpatient center, many individuals leave their homes and jobs prior to entering treatment, only to find new ones when treatment is complete. Therefore, it proved difficult to follow-up with participants' four months after completing the trial when telephone numbers and/or home addresses had been changed. It was also common for the clinical staff

from both centers to lose contact with participants four months later. Reducing the follow-up period to one or two months, when participants are still following the aftercare program, may have addressed the lost-to-follow-up problem. Additionally, of the participants who were recruited and randomized through local advertisements (n = 5), 3 completed the 4-month follow-up, further reinforcing the notion that more rigorous recruitment through inpatient settings and local media will improve recruitment and retention rates in larger trials.

Research staff protocol adherence. Overall, the research and clinical staff adhered to the protocol, suggesting that the methods and procedures were easy to learn and adequately implemented. Most participants underwent a complete medical evaluation within one week of signing consent and initial eligibility screening, and all received the study medication in a blinded manner by a qualified professional. Only one participant missed one dose of study medication, and this was at the participant's request. Furthermore, most clinician-administered measures were completely collected throughout the trial. On the other hand, 18% of the personalized narratives were not prepared in the present tense. In order to ensure consistency and adequately reactivate a memory "as if the participant was re-living the event", narratives should be in the first-person, present tense. Future studies of this nature will have to ensure this is systematically accomplished for all participants.

The Addiction Severity Index, 5th ed., was among the most frequently missing clinician administered assessment tool; it was not administered to 16% of participants at baseline. This may be due to the length of time it takes to administer the ASI depending on the interviewers' skill level (i.e., approximately 1 hour) and the limited time participants may have for completing this assessment. The ASI was chosen to measure change in dependence severity since it is a reliable and valid semi-structured interview widely used in clinical and research settings to

evaluate the effects of treatment on various life domains that are often affected by substance dependence and can be administered by trained lay interviewers (Samet et al., 2007). However, the reliability and validity of the composite scores as a measure of treatment outcome have been questioned in cases where interviewer training is more limited (Mäkelä, 2004; Samet et al., 2007). Considering the length of time and skill level required for adequately administering the ASI, other standardized diagnostic measures, such as the Leeds Dependence Questionnaire (LDQ; Raistrick et al., 1994)) or the substance dependence module of the Composite International Diagnostic Interview, 2nd edition (CIDI-2; Forman, Svikis, Montoya, & Blaine, 2004; Kessler et al., 1998), may be viable options to measure of change in dependence severity. While the LDQ is a self-report questionnaire predominantly validated for assessing opiate and alcohol dependence, the substance dependence module of the CIDI-2 is a structured diagnostic interview that requires 20-30 minutes to complete and can be administered by interviewers with various backgrounds after brief training (Forman et al., 2004; Raistrick et al., 1994).

However, the choice of which instrument is most appropriate as a measure of change in dependence severity will depend on several practicality issues, such as the level of training of the interviewers, the amount of time researchers are willing to commit to training interviewers, the amount of time researchers and participants are willing to spend on each evaluation, and the type of addictive substance under study. Nevertheless, administering diagnostic based instruments at baseline, 1-week post-assessment, and follow-up in an adequately sized sample would permit further exploration of treatment effects on severity of participant's substance dependence diagnosis. If disrupting reconsolidation using propranolol can effectively reduce subjective craving thereby improving treatment outcome, an interesting hypothesis for future studies to test would be that the treatment would also reduce diagnostic dependence severity.

Scientific Feasibility and Preliminary Treatment Effects

The primary scientific hypothesis of the larger trial predicts that, compared to placebo, six sessions memory reactivation under propranolol will significantly reduce craving severity in substance dependent participants. Although there were no between-group effects for craving intensity during week 1 (i.e., after two treatment visits), frequency of daily cravings decreased significantly for the whole sample during the first week of treatment. Furthermore, despite finding no significant between-group differences on change in craving severity or relapse during the trial, propranolol treated participants' tended to demonstrate significantly greater reduction in craving severity between baseline and post-treatment, as assessed by validated self-report craving questionnaires. Although this finding was not statistically meaningful, as reflected by the small between-group effect size, the trend was apparent when examining the summary statistics of the complete case data, with LOCF imputations, as well as the data analysed following multiple imputation. However, since participants were concurrently following a therapeutic treatment program, it cannot be ascertained if preliminary effects are due to the experimental treatment. Furthermore, the study was not adequately powered to detect significant between-group differences for the primary scientific outcomes. Consequently, these results should be interpreted with caution, and the main scientific hypothesis was not supported. The following outlines several factors that may have contributed to the observed null findings.

The floor effect and the measurement of craving. Subjective craving, as measured with the self-report craving questionnaires, was relatively low at baseline in the present sample, suggesting a potential floor effect ($M = 2.72$, $SE = 0.34$, $N = 19$). It is possible that the measures of craving did not fully capture the construct in the present sample. For instance, the ACQ-R received the lowest reliability score in the present sample, and alcohol dependent participants

largely contributed to the floor effect. However, it was not possible to conduct analyses without these participants, as this would have substantially reduced the sample size. In addition, the literature has revealed mixed result regarding the prognostic ability of craving to predict relapse in substance dependence (Tiffany & Wray, 2012), rendering it likely that treatment effects were not observed by measuring subjective craving alone. In the current study, participants who relapsed reported lower mean craving scores at baseline, a finding which appears counterintuitive under the notion that craving can trigger relapse. It is possible that participants with stronger tendencies to relapse may underestimate self-report cravings, suggesting that the use of additional interviewer administered measures of craving may be desirable in future studies. Complementing self-report questionnaires with more objective measurements of craving would have permitted further analyses of treatment effects and may have helped address the floor effect observed from self-report questionnaires. For instance, cue-induced physiological reactivity (i.e., increased heart rate, blood pressure, and skin conductance) has been observed to positively correlate with subjective craving, and may be considered its subconscious expression (Reynolds & Monti, 2013). As demonstrated by Saladin et al. (2013), a single administration of post-retrieval propranolol, compared to placebo, significantly reduced physiological arousal and subjective craving to cocaine-related cues. While self-report questionnaires should not be completely discounted, future studies would greatly benefit from complementing these measures with psychophysiological measurements of craving.

Furthermore, one of the two recruitment centers consisted of a residential inpatient facility and roughly half of the sample was recruited from this center, possibly influencing the floor effect. If drug-related memories and the environmental cues that trigger their recall do underlie craving and subsequent relapse, it is likely that for participants in residential treatment,

who were entirely removed from previous drug-using environments, did not experience cravings as severely whilst in treatment. However, in the present sample, participants receiving residential treatment obtained higher baseline craving scores than outpatient participants. Although this was not statistically significant, this observation further highlights the complexities of measuring craving and the debate surrounding its role in relapse. While numerous experts agree that craving severity should be included as an outcome in addiction treatment research, further measuring treatment efficacy by examining dependence severity should be included in future studies, as mentioned above (Tiffany & Wray, 2012).

Likewise, several participants, notably those with substance use triggers related to the time of day, commented that their responses to craving items would have been higher had they been administered the questionnaire in conjunction with their "time of day" trigger. The versions of the self-report questionnaires employed in the current study evaluate the intensity of craving at the moment of assessment, which may have contributed to the floor effect. However, there are other versions of these questionnaires which assess the intensity of craving over the previous week, or days, such as the Cocaine Craving Questionnaire – General (Tiffany et al., 1993). Evaluating instead participant's general craving intensity over the preceding days may have addressed the floor effect observed in the present study. Although this was the goal for using the daily diary as a secondary outcome, in which frequency and intensity of daily cravings were recorded by participants as "homework", most participants either lost or forgot to return the diaries. Thus, the use of additional objective interviewer administered craving assessment tools and an outcome measure of dependence severity in future studies is recommended.

Effects of the personal narrative. Although attempts were made to capture all reminder cues associated with the phases of the addiction cycle (i.e., anticipation, binge, withdrawal)

within the individual narratives, it is possible that the personal scripts did not sufficiently elicit emotional craving in the present sample. In line with the observed floor effect, it is also possible that many participants simply did not experience substantial craving. Examining the baseline composite scores from the addiction severity index suggests that dependence severity was also relatively low in the present sample (Table 5). However, pre-clinical literature of aversive emotional memory reconsolidation suggests that if the stimuli do not elicit ample emotional arousal, propranolol may not exert its blocking effects on reconsolidation mechanisms (Kroes, Strange, & Dolan, 2010; Lonergan et al., 2012). Yet without measures of cue-elicited emotional or physiological arousal taken at the time of, or ideally immediately following, the script-reading procedure, it was not possible to examine this hypothesis. Nevertheless, it may be that the preliminary treatment effects were driven by a sub-group of participants who experienced substantial craving and emotional arousal from the memory reactivation procedure.

The approach used to create personalized craving narratives in the current study was adapted from previous work using script-driven imagery in trauma-exposed participants (Brunet et al., 2008), which has also been successfully modified and implemented in a sample of cocaine dependent participants (Kilts et al., 2001). However, a difference between the present study and that of Kilts et al. (2001) pertains to the focus of the narratives. While we aimed to obtain a complete picture of the addiction cycle, Kilts et al. (2001) targeted only the anticipatory phase of drug use, which may provide a better reflection of the motivational effects of conditioned stimuli. In Kilts et al.'s (2001) study, activation of mesolimbic structures was observed during script-driven imagery of cocaine-related personalized memories. Thus, future studies may benefit from restructuring the personal narratives in order to effectively elicit emotional and physiological craving. In addition, psychophysiological recordings taken during the script-

imagery procedure will confirm the extent to which the narratives elicit craving-related arousal. Finally, implementing the personal narratives with *in vivo* cues, as done by Saladin et al. (2013) and other exposure based treatment approaches, may elicit more powerful cravings and therefore, a stronger effect of treatment.

Timing of the study drug administration. It is also likely that post-retrieval propranolol, as was done in the first segment of the study (i.e., protocol 1), decreased the strength of the findings. Based on the reconsolidation theory, the amnesic treatment should be administered immediately after reactivation in order to control for non-specific effects on memory retrieval (Schiller & Phelps, 2011). Although some studies have found an effect of immediate post-retrieval propranolol on memory reconsolidation in both PTSD and substance dependent populations (Brunet et al., 2008; Saladin et al., 2013), the effect is not always observed or sustained (Lonergan et al., 2012; Saladin et al., 2013).

Notably, participants in protocol 1 had significantly higher drug use composite scores, as measured with the ASI, as well as significantly higher severity of craving at baseline. Therefore, it could be argued that compared to participants from protocol 2, who received pre-retrieval medication, those receiving post-retrieval medication represented a more treatment-resistant population, obscuring any possibility of observing an effect of treatment. Alternatively, a more plausible explanation lies in other procedural changes that were implemented simultaneously with the shift from post- to pre-retrieval drug administration, such as the inclusion of alcohol dependence. Given that alcohol dependent participants were only included in the trial when protocol 2 was implemented, and as mentioned, largely contributed to the floor effect, the direction of the significant between-protocol differences are not surprising. As a result of this,

and due to the modest sample sizes, it was not possible to fully examine the extent to which pre- versus post-reactivation medication influenced the results in the present study.

However, in a recent meta-analysis examining propranolol's capacity to disrupt emotional memory consolidation and reconsolidation (Lonergan et al., 2012), administering the beta-blocker either immediately before or after reactivation resulted in no 'treatment' effect. Furthermore, an investigation of the neural correlates of pre-reactivation propranolol found no effect of the beta-blocker on memory retrieval, suggesting that the procedure is not likely to affect this process (Schwabe, Nader, Wolf, Beaudry, & Pruessner, 2011). Given the time it takes propranolol to reach its peak bioavailability in the brain and previous results, propranolol administered prior to memory reactivation would presumably lead to stronger treatment effects (Brunet et al., 2011a; Dey et al., 1986). The large proportion of participants (42%) receiving immediate post-reactivation propranolol may have contributed to the null findings. From a clinical perspective, future studies should utilize pre-retrieval propranolol to maximize treatment effect.

Gender differences. Finally, the disproportionate amount of males in the present sample may have underestimated treatment effects. Although Saladin et al. (2013) and Zhao et al. (2011) were able to observe an effect of propranolol on drug-memory reconsolidation in samples comprised of mostly men, other studies suggest that treatment effects may be more pronounced among women (Poundja, Sanche, Tremblay, & Brunet, 2012). In a recent open-label investigation of predictors of treatment outcome of a propranolol induced reconsolidation blockade protocol with PTSD patients, women improved significantly more than men on a number of PTSD diagnostic measures (Poundja et al., 2012). The authors suggested that observed sex differences in emotional memory processing and differences in the metabolism of

propranolol between sexes may influence the efficacy of the experimental treatment. For instance, recent literature suggests that the effects of propranolol on emotional memory processing may be moderated by sex, and more specifically, sex hormones (Nielsen, Ertman, Lakhani, & Cahill, 2011). Although sex differences in drug-related memory reconsolidation have yet to be explored, it would be useful and important for future studies to explore whether sex moderates treatment efficacy. Unfortunately, with only two women in the propranolol and placebo groups, respectively, it was not possible to explore this question in the current study.

Statistical power and sample size. As mentioned, the present study was not powered to detect significant between-group differences on craving change scores or relapse outcomes. The observed power for the between-group effect of craving severity was approximately 9%, and that for relapse outcomes was approximately 11%. An *a priori* power analysis using a medium between-group effect size of $d = .50$ for craving change score suggests that a sample size of 128 ($n = 64$ per group) would be adequate to obtain an effect of treatment with the two-tailed alpha set at .05 and 80% power. This may realistically be accomplished in larger multi-site trials by implementing the recruitment recommendations highlighted above (see Recruitment sub-section). Although the multiple imputation procedure arguably preserves statistical power, with so few participants per treatment arm power was nevertheless, sufficiently lacking. Still, the preliminary results from the imputed data suggesting slightly greater improvement for propranolol treated participants support further investigations of disrupting reconsolidation to treat substance dependence using larger samples drawn from multiple sites.

In line with this, the aim of the study was to explore preliminary treatment effects for a wide variety of substance addictions in order to shed light on particular feasibility challenges which may be inherent in specific addicted populations. However, adequately investigating

treatment effects in various sub-groups of addicted individuals would have required a substantially larger sample size. Moreover, the bulk of the pre-clinical and clinical literature of disrupting the reconsolidation of drug-related memories has focused on cocaine and opiate dependence, with a few studies only beginning to investigate alcohol or other types of addictions. For instance, a search on clinicaltrials.gov revealed that one research team is investigating this approach for treating nicotine addiction, while the literature examining alcohol-related memory reconsolidation is more limited to pre-clinical studies.

The literature on alcohol-related memory reconsolidation indicates that this process may be less influenced by propranolol and the beta-adrenergic system than other types of substance addictions (Font & Cunningham, 2012; Milton et al., 2012; Wouda et al., 2010), suggesting that it may be more complex to treat alcohol dependence with reconsolidation blockade using propranolol. Considering the variable neurobiological mechanisms of differing substances, it is possible that the observed preliminary effects may have been driven by one of the subgroups of drug dependent participants; however it was not possible to explore this question in the current study. Although some hypothesize that enhanced noradrenergic signalling may underlie dependence on a wide variety of substances, including alcohol, the literature investigating this question is still in its early stages (Fitzgerald, 2013). Nevertheless, the current study remains the first to explore the feasibility of using propranolol induced reconsolidation blockade to treat a variety of addictions. Based on these and previous findings, future studies should carefully consider the implications of including individuals with alcohol dependence, or amalgamating a variety of dependencies, until further pre-clinical progress has been accomplished, or unless sufficient sample sizes are obtained.

Drawbacks of multiple imputation procedures. Due to the large fraction of missing outcome data and correspondingly large fraction of imputed data, unknown sources of bias may have been present in the multiple imputation model used for analysis. For instance, the post-treatment time point consisted of data collected at the 1-week follow-up for 6 participants (including one open-label propranolol participant) and was imputed using the conservative LOCF method for 8 participants, which may have confounded the results. An alternative explanation may be the presence of patterns in the missing data, reducing the likelihood that the data were in fact missing at random. The assumption that data was missing at random in the present study was based on two observations: 1) there were no significant differences on any variable, including craving severity, between participants who withdrew and those who didn't, and 2) results from Little's MCAR test using the variables that were included in the imputation model suggested the data were missing at random. Despite this, it was not computationally possible to include all variables that may be related to missingness in the imputation model for the present analysis. This is likely due to the large fraction of missing data within a rather small sample size, and unfortunately, it is not possible to distinguish between missing at random and missing not at random based on observed data (Sterne et al., 2009). Finally, the modest sample size and respectively low power may have precluded the possibility of finding significant differences between participants who withdrew and those who did not.

However, it should be noted that complete case analysis (i.e., analysis of the original non-imputed data) works under the assumption that missing data are completely at random (Mackinnon, 2010). Although results from Little's MCAR test suggested that this was the case for the present data, not all variables were included in the analysis of missing values and randomness. Therefore, assuming that the pattern of missingness in the present study was

completely at random should not be made lightly. Several authors have noted that assuming data are missing completely at random is a conservative and rather rare phenomenon (Long, Hsu, & Li, 2012). Moreover, differences may exist between treatment completers and dropouts that were not captured by the collected data, rendering it possible that individuals who completed the study did not represent the larger sample, which can introduce substantial bias (Mackinnon, 2010). Considering that descriptive results of the complete case data, with LOCF imputations, revealed a similar trend as the multiple imputation analysis, pooled results from the imputed data should be considered as reasonable preliminary estimates of treatment effects. Yet, caution is warranted for interpreting the impact of the final results due to the heavy reliance on simple (i.e., LOCF) and multiple imputation methods.

In the current study, proportionally more participants responded to the 1-week post-treatment assessment than the 4-month follow-up. Therefore, future researchers should consider planning two post-treatment evaluations of treatment outcome, as done in the second half of this study, in order to maximize participant retention and minimize missing post-treatment data. Furthermore, in the event that larger trials have substantial fractions of missing data, the larger sample size would permit the addition of more variables to the imputation model, thereby increasing the plausibility of the assumptions underlying multiple imputation and subsequently, the accuracy of the results. Fortunately for future researchers, there is a growing number of statistical packages and literature allowing non-statisticians the opportunity to implement multiple imputation techniques with precision, which are increasingly becoming the preferred method of handling missing data (Graham et al., 2007; Horton & Lipsitz, 2001; Long et al., 2012; Mackinnon, 2010; Sterne et al., 2009; van Buuren, 2007).

Conclusion

Substance dependence is a chronically relapsing psychiatric disorder, where sustained recovery is difficult to achieve for many addicted individuals. The pathological memory model of addiction suggests that chronic drug use usurps normally adaptive learning and memory mechanisms, leading to the overconsolidation of drug-related memories, which can trigger craving and subsequent relapse when memory cues are encountered. This theory attempts to provide a neurobiological account of the maintenance of addiction on a range of substances, as well as explain the tendency for addicted individuals to relapse after protracted abstinence. Despite ongoing debate about the definition of craving and its role in relapse, the recognition that the construct plays a large role in the persistence of addiction is reflected in the recently released *DSM-V,* in which craving has been added as a new diagnostic criterion (APA, 2013).

Reconsolidation theory argues that retrieving previously consolidated long-term memories render them labile, requiring another time-dependent neurochemical process of restabilization to persist. This process is suggested to serve as a memory updating mechanism, allowing organisms to adapt to changes in their environments (Tronson & Taylor, 2013). Growing pre-clinical and clinical literature suggests that disrupting the reconsolidation of drug-related memories by administering propranolol in conjunction with memory retrieval can reduce drug-seeking behaviour in animals and cravings in humans, which opens the door for innovative treatments for substance dependence. Thus, the motivation for the current study was to assess whether this approach can be feasibly implemented as part of ongoing addiction treatment programs, and whether any preliminary treatment effects can be observed for a variety of substance dependencies.

Notwithstanding several methodological issues, predominantly with recruitment and establishing an appropriate outcome measure, the current study demonstrated that disrupting memory reconsolidation to reduce craving in treatment-seeking substance dependent individuals can be feasibly incorporated into current addiction treatment programs. Furthermore, preliminary results suggest that participants in the active treatment condition may have improved somewhat more than those receiving placebo when examining within group change scores in craving severity. However, this conclusion is to be interpreted with caution, as no significant between-group difference on change in craving severity, frequency and intensity of daily cravings, or relapse was observed.

In this study, recruitment remained difficult, and the authors suggest strategies for improving enrollment rates. Participant attrition was high, yet these rates were similar to the norm observed in current treatment programs. Most participants who dropped out of the study also withdrew from the treatment program, stressing the need for more rigorous recruitment strategies with this population. Although self-report craving severity was the primary outcome in the current study, future studies should utilize additional outcome measures to examine treatment efficacy, such as measures of psychophysiological reactivity to drug-conditioned cues and clinician assessed severity of substance dependence diagnosis. In sum, findings from this study will provide future researchers with important guidelines to maximize participant recruitment and fully investigate the potential for memory reconsolidation blockade as a novel treatment for substance dependence in larger multi-center clinical trials.

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Figure 1. Schematic representation of the typical experimental reconsolidation protocol

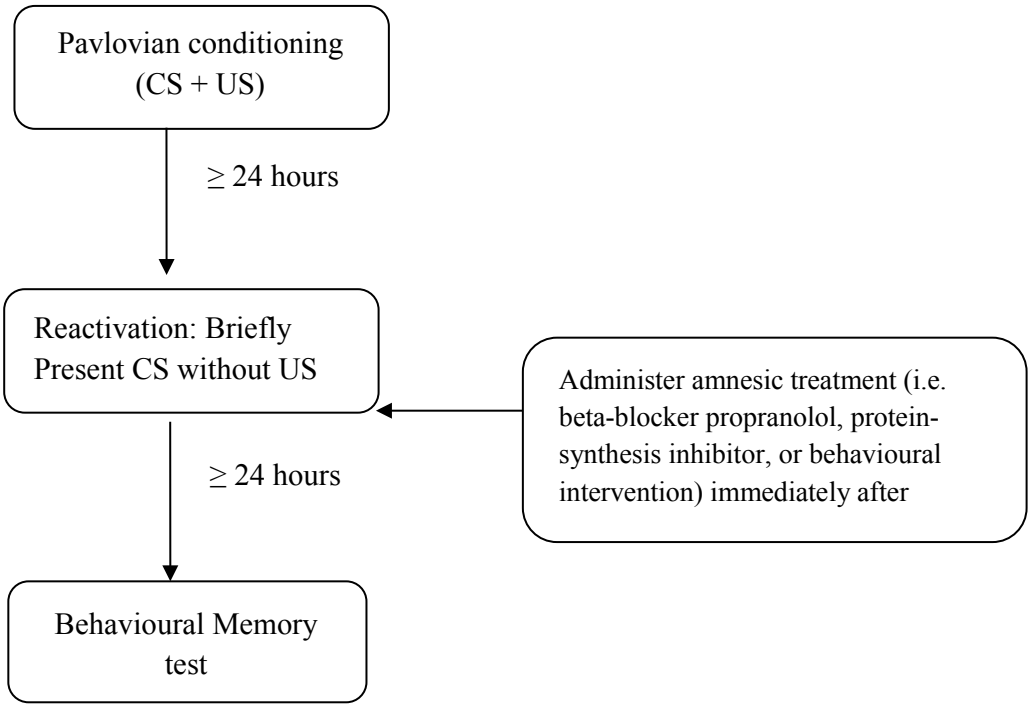


Table 1. Protocol 1: Original study design (*n* = 8)

Visit	**T0**	**T1**	**T2-T6**	**T7**
	Week 1	**Week 2 – 4**		**4 months post-treatment**
Procedure	Screening and eligibility evaluation	Randomization + Intervention + Baseline symptom assessment	Intervention + Symptom assessment	Symptom Assessment
Group 1 **Propranolol** **(*n* = 4)**	Consent Screening assessments Medical Evaluation Craving script production	Symptom Measures Craving script reading + Propranolol administration	Symptom Measures Craving script reading + Propranolol administration	Symptom Measures
Group 2 **Placebo** **(*n* = 4)**		Symptom Measures Craving script reading + Placebo administration	Symptom Measures Craving script reading + Placebo administration	Symptom Measures

Table 2. Assessment procedures throughout the trial[a]

Visit	T0	T1	T2	T3	T4	T5	T6	T7[b]	T14
	Screening (1 week)	Randomization + Baseline						Follow-up	
Consent form & Medical Exam	X								
Craving script writing	X								
Sociodemographic and clinical history	X								
MINI (15-20 min)	X								
Craving script reading[c]		X	X	X	X	X	X		
Medication administration[c]		X	X	X	X	X	X		
Craving Scales (15 min)		X	X	X	X	X	X	X	X
ASI (20-30 min)		X						X	X
BPRS (10 min)		X	X	X	X	X	X	X	X
Suicide assessment (5-15 min)	X	X	X	X	X	X	X	X	X
Distribution of daily diary		X		X		X			

[a] Assessment procedures from T1 – T7 are identical for the open label phase (T7-T14 in Table 3)

[b] 1-week follow-up evaluation added in January 2012.

[c] Not applicable to participants randomized to the treatment as usual group.

Table 3. Protocol 2: Study design following changes made in January 2012 (*n* = 11).

<table>
<tr><th>Visit</th><th>T0</th><th>T1</th><th>T2-T6</th><th>T7</th><th>T8 – T12</th><th>T13</th><th>T14</th></tr>
<tr><td>Procedure</td><td>Screening & Medical evaluation (week 1)</td><td>Randomization + Intervention + Baseline symptom assessment (week 2)</td><td>Intervention + symptom assessment (week 2 – 4)</td><td>Symptom Assessment (Week 5)</td><td>Intervention + Symptom assessment (week 5- 7)</td><td>Symptom Assessment (week 8)</td><td>Symptom assessment (4 months)</td></tr>
<tr><td>Group 1

Propranolol (n = 4)</td><td rowspan="3">Consent

Screening assessments

Medical Evaluation

Craving script production</td><td>Propranolol administration

Symptom Measures (during 90 min wait)

Craving script reading after 90 minute</td><td>Propranolol administration

Symptom Measures (during 90 min wait)

Craving script reading after 90 minutes</td><td>Symptom Measures</td><td colspan="3">Not applicable</td><td rowspan="3">Symptom Measures</td></tr>
<tr><td>Group 2

Placebo (n = 4)</td><td>Placebo administration

Symptom Measures (during 90 min wait)

Craving script reading after 90 minutes</td><td>Placebo administration

Symptom Measures (during 90 min wait)

Craving script reading after 90 minutes</td><td colspan="2" rowspan="2">Open-label Treatment* (n = 2)

Propranolol administration
+
Symptom Measures (during 90 min wait)
+
Craving script reading after 90 minutes</td><td rowspan="2">Symptom Measures</td></tr>
<tr><td>Group 3

Treatment as usual (n = 3)</td><td>Symptom measures</td><td>Symptom measures</td></tr>
</table>

Table 4. Baseline demographic and clinical characteristics of the randomized sample.

	Propranolol (n = 8)	Control[a] (n = 11)	p – value[b]
Demographic characteristics			
Age (M±SE)	42.25(6.44)	41.36(5.13)	.92[c]
Sex (n(%) male)	6(75%)	8(73%)	1.0[d]
Ethnicity (% Caucasian)	100%	100%	N/A
Civil Status (n(%) relationship)	2(25%)	4(36%)	1.0[d]
Years of education (M±SE)	14.25(.75)	13.36(.70)	.35[c]
Individual income			
(n(%) earning < $30,000)	3(37.5%)	4(40%)	1.0[d]
Clinical characteristics			
Treatment program (n(%) inpatient)	3(37.5%)	6(55%)	.65[d]
Smoking status (n(%) current smokers)	4(50%)	6(60%)	1.0[d]
Substance of choice			1.0[d]
n alcohol	2	3	
n opiates	2	5	
n cocaine	3	3	
n marijuana	1	0	
Polysubstance users (n(%) yes)	4(50%)	3(27%)	.38[d]
Duration of drug use (years; M±SE)	13(5.2)	7.67(3.03)	.40[c]
Number of previous treatment			
attempts (M±SE)	3 (.93)	2.4(.99)	.67[c]

Table 4. Baseline demographic and clinical characteristics (continued).

Number of days in treatment (M±SE)	52.3(12.02)	121.78(76.13)	.41[c]
Lifetime psychiatric comorbidity (n(%) yes)	8(100%)	5(45.5%)	.02[d]
Lifetime depression	7(87.5%)	3(27.3%)	.02[d]
Lifetime anxiety disorder (any)	7(87.5%)	4(36.4%)	.06[d]
Current psychiatric comorbidity	4(50%)	3(27%)	.38[d]
Baseline craving severity (M±SE)	2.66(.58)	2.77(.44)	.88[c]
Baseline depression/anxiety scores (M±SE)	11(1.44)	8.55(1.2)	.21[c]

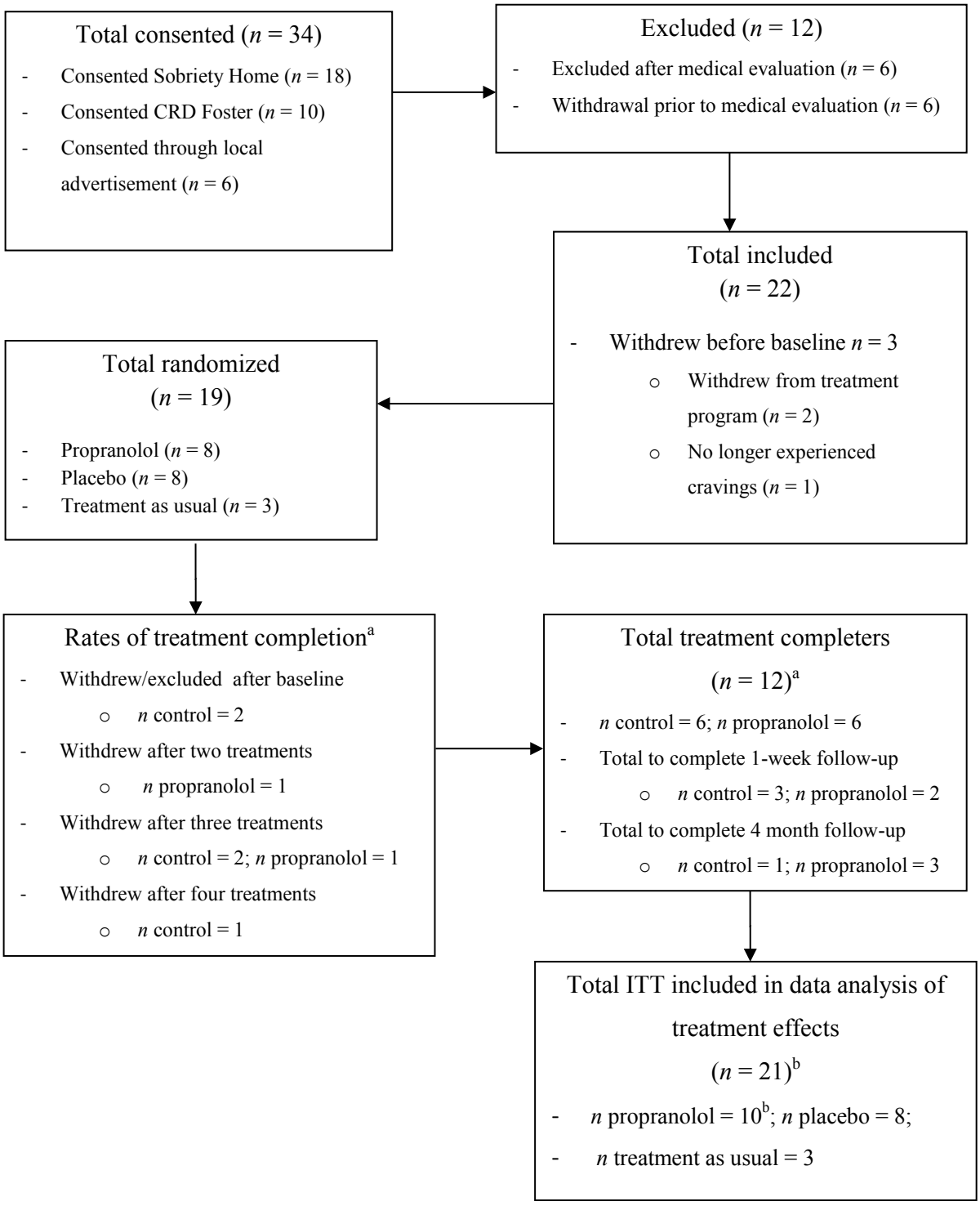
[a] Control group: $n = 8$ participants placebo + memory reactivation; $n = 3$ participants treatment as usual.
[b] Treatment as usual group pooled with placebo participants. Sensitivity analyses were conducted on all variables to confirm that pooling groups created no distortion in the results. No distortions revealed.
[c] Independent *t*-tests with two-tailed alpha set at .05. Non-parametric Mann-Whitney *U* tests were used for sensitivity analysis for variables not normally distributed and revealed no discrepancy in results.
[d] Fisher's exact test for dichotomous 2 X 2 contingency table with two-tailed alpha set at .05. Categorical variables with more than two levels were transformed into dichotomous variables (i.e., Substance of choice = alcohol vs. other drugs; Treatment program = inpatient vs. outpatient; civil status = long-term relationship vs. single).

Table 5. Baseline Addiction Severity Index, 5th ed. composite scores by treatment group

	Propranolol (n = 7)	Control (n = 9)[a]	p –value[b]
ASI Medical composite (M±SE)	.27(.10)	.20(.09)	.63
ASI Employment composite (M±SE)	.46(.13)	.46(.10)	.97
ASI Alcohol use composite (M±SE)	.33(.09)	.25(.12)	.63
ASI Drug use composite (M±SE)	.22(.08)	.20(.06)	.79
ASI Legal composite (M±SE)	.06(.06)	.08(.05)	.78
ASI Family/Social composite (M±SE)	.24(.05)	.38(.08)	.16
ASI Psychological composite (M±SE)	.43(.06)	.22(.08)	.07

[a]Includes n = 2 treatment as usual participants. Removing these participants did not affect the results.
[b]Results from two-tailed independent *t*-tests with alpha set at .05. Non-parametric Mann-Whitney *U* tests conducted for variables not normally distributed; no discrepancy in results.

Figure 2. Recruitment and retention flow-chart



[a] Control group: Placebo and treatment as usual participants ($n = 3$) pooled together.
[b] Includes data from 2 propranolol open-label participants. Both completed the six-session treatment phase. One completed the 1-week post-assessment and 4-month follow-up, one did not complete 1-week post assessment or follow-up.

Table 6. Variables related to retention/dropping out in the included sample ($n = 21$)[*].

	Drop-out ($n = 9$)	Retained ($n = 12$)	p - value
Categorical variables[a]			
Treatment group[**]			
n propranolol	2	6	.64
n control	4	6	
Rehabilitation program			
n inpatient	4	6	1.0
n outpatient	5	6	
Gender			
n male	7	8	.66
n female	2	4	
Any lifetime comorbid disorder			
n yes	4	10	.16
n no	5	2	
Substance of choice			
n alcohol	2	2	1.0
n drugs	7	10	
Civil Status			
n single	7	8	.66
n relationship	2	4	
Individual income			
$n \leq$ \$30,000	3	4	1.0
$n >$ \$30,000	6	8	
Smoking status			
n smokers	7	6	.16
n non-smokers	1	6	
Protocol			
n protocol 1	3	6	.66
n protocol 2	6	6	

Table 6. Variables related to retention/dropping out (continued).

Continuous variables[b]			
Age (M±SE)	40.11(4.7)	40.92(4.9)	.91
Number of years of education (M±SE)	13(0.6)	14(.62)	.27
Duration of drug use in years (M±SE)	6.86(2.54)	11.70(4.2)	.40
Number of previous treatments (M±SE)	3.5(1.30)	1.82(.59)	.21
Number of days in treatment (M±SE)	128.57(100.4)	53.92(7.7)	.50
Baseline craving severity (M±SE)	2.96(0.76)	2.78(0.4)	.81
Baseline depression / anxiety score (M±SE)	8.83(2.4)	9.75(1.0)	.67

*One participant (alcohol) excluded from trial due to change in medical status was not included in these analyses

**Excludes non-randomized participants (n = 3).

[a] Results from Fisher's exact tests with two-tailed alpha set at .05.

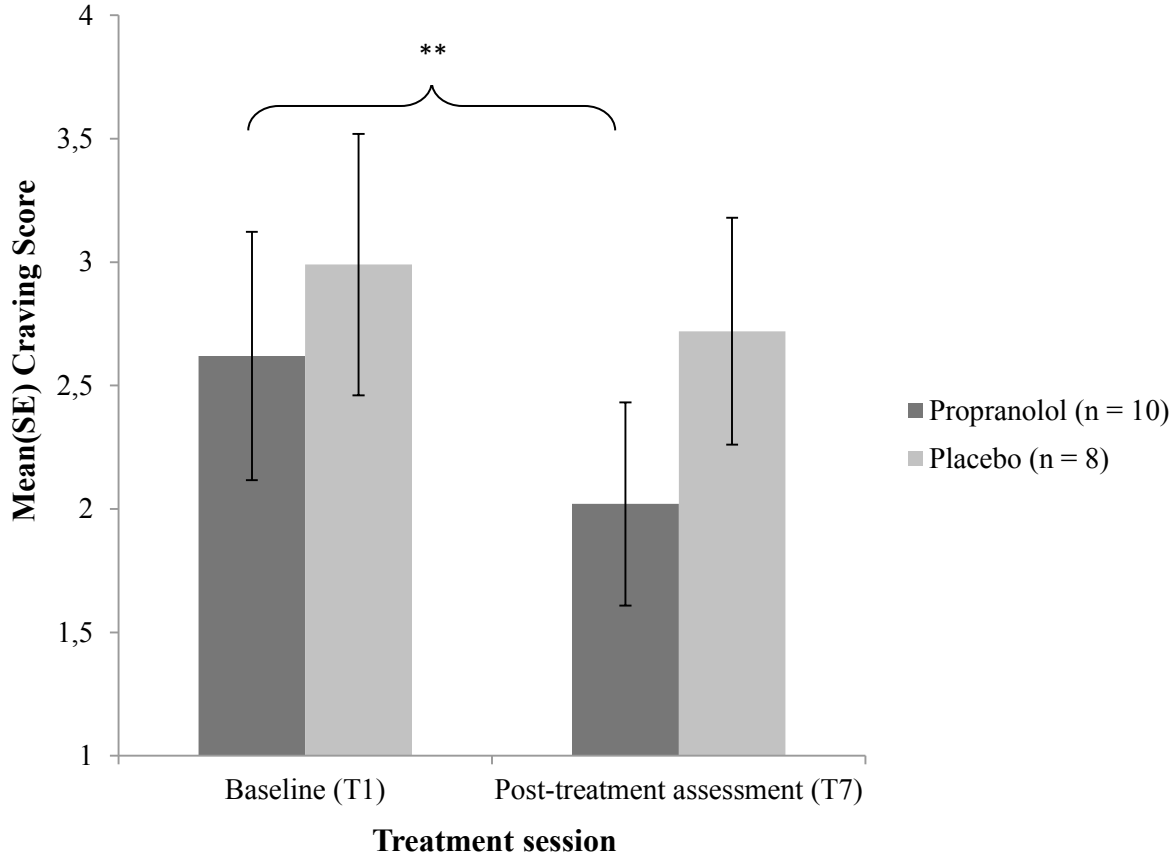
[b] Results from independent t-tests with two-tailed alpha set at ..05. Non-parametric Mann-Whitney U tests were conducted as sensitivity analyses. No discrepancies were revealed.

Table 7. Change in craving severity, relapse during the trial, and adverse events by treatment group in the ITT sample ($n = 21$)[a].

	Propranolol ($n = 10$)[a]	Control ($n = 11$)	p –value
Craving score baseline (M±SE)	2.62(.50)	2.99(.53)[a]	.57[b]
Pooled craving score post treatment (M±SE)	2.02(.41)	2.73(.46)[a]	.25[b]
Pooled craving difference score (M±SE)	.59(.28)	.26(.44)[a]	.50[b]
Relapse during the trial (n(%))	5(50%)	3(27.3%)	.38[c]
Adverse effects (n(%))	6(60%)	3(25%)	.19[c]

[a] Includes 2 propranolol open-label participants; treatment as usual ($n = 3$) removed from control group craving scores.
[b] Independent *t*-test with two-tailed alpha set at .05; non-parametric Mann-Whitney *U* tests as sensitivity analyses.
[c] Fisher's exact test for 2X2 contingency table with two-tailed alpha set at .05

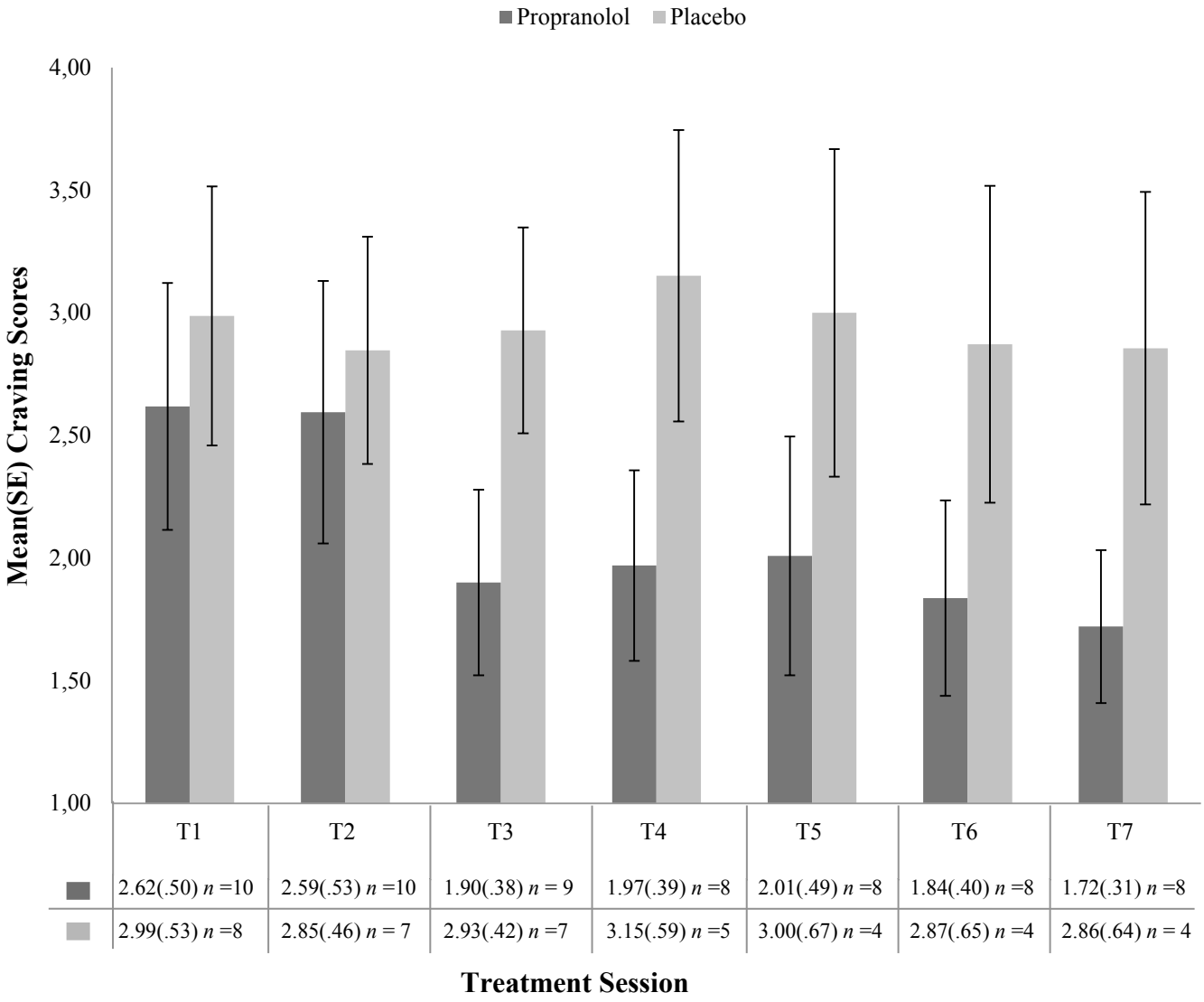
Figure 3. Pooled mean(SE) craving scores by treatment group in the ITT sample (n = 18)*. Results from multiple imputation analysis.



*Treatment as usual participants (n = 3) excluded.

** Propranolol group, paired t-test, $p < .05$.

Figure 4. Mean(SE) craving scores of original complete case data by treatment group (n = 18)*.



*TAU participants (n = 3) removed from analysis; 1-week post-treatment (T7) imputed using LOCF for n = 3 placebo participants and n = 5 propranolol participants.

Appendix A.

Instructions for, and example of, a personalized drug-using script

N.B. The following example is for illustration purposes only. It reflects a typical narrative obtained by participants. The script shown here is fictitious and was not prepared by a participant from the current study.

General Drug-Use Experience -Construction Questionnaire

Event Type: Cocaine use

We would like you to write a description of your typical experience using drugs (as indicated above). Include in your description the bodily sensations you were aware of at the time. We will interview you in more detail about his experience later. You may elect to dictate your script to the interviewer if you chose to do so.

Sometimes it is difficult to think of something to write "on the spot". It may help to close your eyes and imagine yourself back in the situation. Try to generate the same sensations and feelings that you experienced at the time. While the image is vivid in your memory, jot down the details of the scene and the sensations you experienced.

Describe the drug-use situation. Please include such details as who was there, what you were wearing, where you were, how things looked, what you heard, etc. Continue on the reverse side if necessary.

_____ It's Friday morning. I wake up feeling depressed, lethargic, and tense all over. All I can think is "I would feel so much better if I had some coke". I make plans with my friends for drinks after work; an excuse to use. It's all I can think of during my work day. As soon as I get home, I call my dealer, and wait for him to arrive. The anticipation of his arrival is overwhelming. Finally, after what seems like hours, the doorbell rings. I feel anxious and nervous until he leaves, I have butterflies in my stomach, but as soon as I close the door behind him, I am excited for that first line. I run up to my room and lock the door. I don't know why, no one is home. I am alone; my room is dimly lit, my bed still unmade. I open the baggie and bust out that first line on top of my dresser. I'm sweating; I feel it hit me as soon as I snort my first line; my nose is burning, my tongue is numb, my heart is pounding, I feel it dripping down the back of my throat – I think of how much I enjoy that feeling – and all of a sudden I am awake, euphoric. I meet my friends at the bar and have a couple of beers. I feel confident, powerful, and energetic. But these sensations don't last; so I do more. All night while my friends are having a drink at the bar, I keep making bathroom trips. Soon my stash is gone; I'm talking a mile a minute, my mouth feels pasty and I'm gritting my teeth. The night is over, and I start to come down; to crash. The depression and anxiety is unbearable. I feel nauseous and sweaty. My head is pounding. I toss and turn the whole night feeling wired, and I sleep the whole day, wishing for the misery of the crash to go away. All I know is that doing more will make me feel better again. So I make another phone call, wait for my dealer, and do it all over again._____

Listed below are a number of bodily sensations that people may experience in various situations. Circle all of the responses that you experienced in the situation you just described.

Heart stops
Heart beats slower
Heart beats faster
Heart pounds
Feel aroused
Dizzy
Energetic
Ecstasy
Palms are clammy
Beads of perspiration
Sweat pours out
Nauseous
Dry mouth
Butterflies in the stomach
Cramps in the stomach
Body tingles
Body feels heavy

Faster breaths
Slower breaths
Even breathing
Feel tired
Shallow breathing
Laboured breathing
Sense of euphoria
Feel tense all over
Feel relaxed all over
Tension in forehead
Excited
Tension in back
Grit my teeth
Clenched jaw
Numbness
Alert
Hands trembling

Whole body shakes
Eye twitches
Eyes closed
Eyes burn
Eyes wide open
Eyes water
Feel hot all over
Blood rushing to head
Flushed face
Head pounds
Sensitized
Feel restless
Jittery
Calm
Heavy eyelids
Feel powerful
Arms and legs warm and relaxed

Appendix B.

Example of a self-report craving questionnaire: The CCQ-Now.

CCQ-NOW Cocaine Craving Questionnaire

Indicate how much you agree with each of the following statements by placing a single checkmark (like this: ___✓___) along each line between STRONGLY DISAGREE and STRONGLY AGREE. The closer you place your checkmark to one end or the other indicates the strength of your disagreement or agreement. Please complete every item. We are interested in how you are thinking or feeling **right now** as you are filling out the questionnaire.

RIGHT NOW

1. If I were using cocaine, I could think more clearly.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

2. Right now, I am not making plans to use "coke".

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

3. My desire to use cocaine seems overpowering.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

4. I am thinking of ways to get cocaine.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

5. I don't want to use "coke" now.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

6. If I were offered some "coke", I would use it immediately.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

7. Using cocaine would make me feel less depressed.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

8. I could easily control how much cocaine I used right now.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

9. I crave "coke" right now.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

GO TO NEXT PAGE ->

RIGHT NOW

10. Using cocaine now would make me feel powerful.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

11. If there was cocaine right here in front of me, it would be hard not to use it.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

12. Using cocaine would not help me calm down now.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

13. I would feel very alert if I used cocaine now.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

14. If I had the chance to use “coke”, I don’t think I would use it.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

15. I would not enjoy using cocaine right now.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

16. I would do almost anything for cocaine now.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

17. I could control things better right now if I could use cocaine.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

18. Even if it were possible, I probably wouldn’t use cocaine now.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

19. Using “coke” would not be pleasant.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

20. I think that I could resist using “coke” now.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

GO TO NEXT PAGE ->

RIGHT NOW

21. I have an urge for cocaine.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

22. I would not be able to control how much cocaine I used if I had some here.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

23. Starting now, I could go without using cocaine for a long time.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

24. I would be less irritable now if I could use cocaine.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

25. I would feel energetic if I used cocaine.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

26. All I want to use now is cocaine.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

27. Using cocaine would not sharpen my concentration.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

28. I do not need to use cocaine now.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

29. It would be difficult to turn down cocaine this minute.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

30. If I used cocaine right now, I would not feel less restless.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

31. I will use cocaine as soon as I get the chance.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

GO TO NEXT PAGE ->

RIGHT NOW

32. Using cocaine now would make things seem just perfect.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

33. I want cocaine so bad I can almost taste it.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

34. Nothing would be better than using “coke” right now.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

35. If I used cocaine, my anger would not decrease.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

36. It would be easy to pass up the chance to use cocaine.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

37. I am going to use cocaine as soon as possible.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

38. I have no desire for cocaine right now.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

39. I could not stop myself from using cocaine if I had some here now.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

40. Using “coke” right now would make me feel less tired.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

41. Using cocaine would not be very satisfying now.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

42. If I tried a little “coke” now, I would not be able to stop using more of it.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

GO TO NEXT PAGE ->

RIGHT NOW

43. I would not feel less anxious if I use “coke”.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

44. I am not missing using cocaine now.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

45. If I had some “coke” with me right now, I probably wouldn’t use it.

STRONGLY DISAGREE_____:_____:_____:_____:_____:_____:_____: STRONGLY AGREE

Appendix C.

Recording the frequency and intensity of cravings:
The Daily Diary

Daily Diary: Week 4

Please record the time(s) at which you had an intense drug craving or an unpleasant thought or image related to a drug craving experience

Rate the intensity of each thought or image: 1= High; 2=Moderate; 3: Low

BETWEEN START	END	AM/PM	DATE √	Rating	DATE √	Rating	DATE √	Rating	DATE √	Rating	DATE √	Rating	DATE √	Rating	DATE √	Rating
6	7	AM														
7	8	AM														
8	9	AM														
9	10	AM														
10	11:00	AM														
11:00	12:00	AM														
12:00	13:00	PM														
13:00	14:00	PM														
14:00	15:00	PM														
15:00	16:00	PM														
16:00	17:00	PM														
17:00	18:00	PM														
18:00	19:00	PM														
19:00	20:00	PM														
20:00	21:00	PM														
21:00	22:00	PM														
22:00	23:00	PM														
23:00	00:00	PM														

At the end of the 7-day period, please respond to the following statement:
'I have often been unable (or have forgotten) to record my cravings or unpleasant thoughts and images in the tick diary''

0 = Not at all true of me
10 = Extremely true of me

Rating= ☐