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Short report

Reactivating addiction-related memories under propranolol to reduce craving: A pilot randomized controlled trial

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ABSTRACT

Background: The reconsolidation blocker propranolol abolishes alcohol and drug-seeking behavior in rodents and attenuates conditioned emotional responses to drug-cues in humans in experimental settings. This suggests a role for its use in the treatment of substance dependence. In this translational pilot study, we explored the feasibility and efficacy of this procedure as an adjunct treatment for addiction. We hypothesized that guided addiction-related memory reactivation under propranolol would significantly attenuate tonic craving, a central element in relapse following addiction treatment.
Methods: Seventeen treatment-seeking adults diagnosed with substance dependence were randomized to receive double-blind propranolol ($n = 9$) or placebo ($n = 8$) on six occasions prior to reading a personalized script detailing a drug-using experience. The primary outcome measure was self-reported craving intensity.
Results: After controlling for baseline craving scores, intent-to-treat analysis revealed a time by group interaction, $F(1, 14) = 5.68$, $p = .03$, $\eta^2 = 0.29$; craving was reduced in the propranolol-treated group (Cohen's $d = 1.40$, $p < .05$) but not in the placebo group ($d = 0.06$, n.s.).
Limitations: The usual limitations related to small sample size and the lack of a follow-up apply here.
Conclusion: Drug-related memory reactivation under propranolol can subsequently reduce craving among substance-dependent individuals. Considering the relapse rate among individuals treated for substance dependence, our study highlights the feasibility of, and need for, more comprehensive trials of this treatment approach.

1. Introduction

Substance dependence is a chronically relapsing psychiatric disorder characterized by uncontrollable drug use despite significant adverse physical and psychosocial consequences (Diagnostic and Statistical Manual [DSM], American Psychiatric Association [APA], 2000, 2013). Recent perspectives on the neurobiological pathophysiology of addiction suggest that prolonged use of addictive drugs induces neuroplastic changes and altered neurotransmitter activity in brain regions associated with reward-related learning, effectively usurping normally adaptive associative memory mechanisms (Milton & Everitt, 2010; Torregrossa, Corlett, & Taylor, 2011). Consolidated long-term, drug-related memory cues in drug users can subsequently trigger conditioned responses (i.e., craving) that increase their risk of relapse, even after successful initial treatment and/or protracted abstinence (e.g., Torregrossa et al., 2011). However, reconsolidation theory posits that retrieval induces a transient period of memory lability where additional neurochemical processes are required for memory re-stabilization. Reconsolidation mechanisms putatively serve to enhance, impair, or update existing memories (Agren, 2014; Exton-McGuinness, Lee, & Reichelt, 2015; Sandrini, Censor, Mishoe, & Cohen, 2013). From a treatment-relapse perspective, decreasing the strength of alcohol- and drug-related memories by impairing their reconsolidation would be a highly desirable outcome.

When administered during the time-dependent reconsolidation

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window, the β_2-adrenergic blocker propranolol has been shown to attenuate drug-seeking behavior in alcohol (Schramm, Everitt, & Milton, 2015; Wouda et al., 2010), cocaine (Milton, Lee, & Everitt, 2008), and morphine (Robinson & Franklin, 2007) dependent rodents. These animal paradigms, which model the motivational/rewarding effects of drug-related stimuli, suggest that disrupting the reconsolidation of underlying drug-related memories can reduce drug-seeking behavior akin to the relapse process in humans. In experimental settings, memory retrieval combined with propranolol administration attenuates memory for positive and negative drug-related words in abstinent heroin-dependent patients, as well as subjective craving and conditioned responses to drug-related cues in abstinent cocaine-dependent patients (Saladin et al., 2013; Zhao et al., 2011). These results were not replicated however in a sample of nicotine-dependent participants (Pachas et al., 2015). Nevertheless, impairment of the reconsolidation of drug-related memories with propranolol may facilitate treatment of substance dependence, as has been accomplished for traumatic memories in post-traumatic stress disorder (Brunet et al., 2008; Brunet, Poundja et al., 2011).

Low ecological validity limits existing studies by (i) a focus on addiction to a single drug, which is rather uncommon in clinical settings, and (ii) by use of a single memory retrieval session (iii) performed in a non-clinical experimental setting, following which the results were not sustained (Pachas et al., 2015; Saladin et al., 2013). No study to date has evaluated multiple sessions of reconsolidation impairment with personalized drug-use narratives as retrieval cues in individuals in treatment for various drug dependencies. This pilot, double-blind, randomized placebo-controlled trial tested the hypothesis that drug-related memory retrieval under propranolol is safe, tolerable, and produces a significant decrease in tonic (i.e., basal) craving.

2. Materials and method

2.1. Inclusion/exclusion criteria

Participants were recruited from a private residential (05/2011–06/2012) and a community outpatient (10/2012–05/2013) addiction treatment programs. Candidate participants were adults (18–65 years old) with a DSM-IV-TR (APA, 2000) diagnosis of substance dependence and enrolled in an addiction rehabilitation program. Participants with a past or current diagnosis of bipolar or psychotic disorder, actively suicidal, pregnant or breast-feeding women, with asthma, cardiovascular disease, diabetes, low blood pressure (<100 systolic), a resting heart rate of 55 bmp or lower, or with any other medical condition contraindicating the use of propranolol (i.e., use of other beta-blockers, insulin, antiarrythmics, clonidine, calcium channel blockers) were excluded. Participants taking selective serotonin reuptake inhibitors or selective norepinephrine reuptake inhibitors were not excluded if they had medical clearance to skip/postpone their dose on their treatment day (Kinzl, 2009).

2.2. Outcome measures

Primary efficacy outcomes were severity of alcohol/drug craving as measured by reliable and valid self-report questionnaires. Feasibility of the treatment and study protocols was assessed by a participant retention rate around 60%. Participants were assessed for their main substance of abuse. The Cocaine Craving Questionnaire (Tiffany, Singleton, Haertzen, & Henningfield, 1993) and Heroin Craving Questionnaire (Tiffany, Fields, Singleton, Haertzen, & Henningfield, in preparation) each contain 45 items that assess five dimensions of craving (desire, intent, positive/negative anticipation, and lack of control). The Marijuana Craving Questionnaire (Heishman, Singleton, & Liguori, 2001) contains 47 items assessing the same five dimensions, while the Alcohol Craving Questionnaire-revised (Singleton, Tiffany, & Henningfield, 2003) contains 30 items assessing two dimensions (urge/intention and reinforcement). All questionnaires measure current craving severity using a 7-point agree/disagree Likert scale, with statements such as “I crave (…) right now”. Averaging all items provides a general craving index, with higher scores indicative of stronger craving.

2.3. Procedure

The protocol was approved by McGill University's ethics committee and Health Canada. After obtaining signed informed consent, sociodemographic and clinical history information was obtained. The Mini International Neuropsychiatric Interview (Sheehan et al., 1998) was used to assess substance dependence and comorbid psychiatric disorders, and the number of days in the previous month that substance use interfered with the ability to fulfill home, work, or school obligations was used as an additional measure of the level of substance involvement. Participants then prepared a one-page narrative detailing a personal drug-using experience. In order to reactivate drug–cue associations that precipitate craving, participants were instructed to include as many details as possible of a typical drug-using episode including people, places, and environmental cues present during the anticipation, (over)use, and withdrawal stages. Prior to the first treatment visit, interviewers transcribed the script ensuring it was in the first person, present tense. All participants then underwent a medical examination to confirm study eligibility.

Included participants who returned for the first treatment visit (i.e., baseline) were randomized in a double-blind fashion to receive either propranolol hydrochloride or look-alike placebo for the whole duration of the study using an allocation ratio of 1:1. Due to variability in body mass, the medication dose was set to 1 mg/kg, as done in prior research (see Brunet, Poundja et al., 2011). This dosing strategy also reduces drug overexposure in low weight patients often seen in the addiction population. Propranolol hydrochloride is a synthetic noradrenergic beta-blocker that crosses the blood–brain barrier (Dey et al., 1986) and exerts central as well as peripheral effects (O'Carroll, Drysdale, Cahill, Shajahan, & Ebmeier, 1999). The randomization list was created by a third party unrelated to the study who used a randomized block design (Fleiss, 1986) with a block size of six. The list was achieved using a random number generator and was stratified according to type of addictive substance. The placebo and propranolol capsules were manufactured and coded by the Douglas Institute pharmacy to ensure blinding.

Each treatment session began by administering the psychometric evaluation of craving severity and giving the study drug under medical supervision. One hour after ingesting either propranolol or placebo, participants read aloud their personalized craving script to the interviewer, who probed for further clarification if needed. The interviewer's role was limited to ensuring that participants were emotionally engaged in the script-reading procedure; no attempts were made to interpret or re-structure the meaning of the narrative. If participants required therapeutic support following this procedure, they were to be referred to their case manager. Six bi-weekly sessions (separated by no less than 48 h) were provided over a period of 3 weeks. Treatment sessions took place either at the treatment site or at the Douglas Institute.

2.4. Statistical analyses

Demographic and clinical variables were examined to evaluate the success of the randomization process (Table 1). These variables were also used to explore differences between treatment completers and drop-outs. Fisher's exact tests were used to detect any between-group differences for categorical variables, and independent *t*-tests (or Mann–Whitney *U* tests for non-normal data) were used to compare groups on continuous variables. Categorical variables with more than two levels were transformed into dichotomous variables for comparative purposes. For all tests, alpha was set at 0.05, two-tailed. Patterns of missing data were analyzed using Little's (1988) missing completely at random (MCAR) test. Change in subjective craving over time was examined using mixed 2 × 2 ANCOVA with treatment sessions 2 and 6 as the within factor, drug condition as the between factor, and treatment session 1 craving score as the covariate; this ensured group equivalence at treatment onset. Since the continuous craving data violated the normality and homogeneity of variance assumptions, a log transformation was applied. Analyses were performed with SPSS v.22.

3. Results

Thirty-one individuals were screened for study inclusion. Of these, 19 (61%) were included and 17 (89%) returned to the baseline visit to be randomized. Of the 17 randomized participants, 10 received the full study protocol (6 in the propranolol and 4 in the placebo group) and 7 completed only a portion of the treatment protocol, representing a treatment (and study) completion rate of 59% as depicted in Fig. 1. All participants were concurrently receiving treatment as usual, which consisted of the therapeutic approaches employed by the inpatient and outpatient rehabilitation centers where recruitment was undertaken. There were no significant between-group sociodemographic differences at baseline (see Table 1).

Data were found to be missing at random using Little's (1988) MCAR test, $\chi^2 = 32.45$, $df = 30$, $p = .35$. There were no significant differences on any variable between participants who withdrew and those who completed the trial. Therefore, missing data was imputed using the estimation-maximization algorithm (Gold & Bentler, 2000) in order to analyze data from an intent-to-treat perspective. Results from the ANCOVA revealed a significant group by time interaction ($F[1, 14] = 5.68$, $p = .032$, $\eta^2 = 0.29$) whereby subjective craving was significantly lower by the sixth treatment session in the propranolol group only (see Fig. 2). This represents a moderate (Cohen, 1988) between-group effect size ($d = 0.48$).

Descriptive examination of the mean craving scores over time in a complete case (per protocol) analysis also revealed a between-group treatment advantage in favor of the experimental treatment at the sixth session (placebo $M = 2.87$, $SE = 0.65$ vs. propranolol $M = 1.73$, $SE = 0.45$; $d = 0.97$). Finally, the script-reading procedure did not elicit clinically important distress; no participant requested additional support from their case managers following the experimental treatment. Transient adverse physical effects were reported by nine participants, of which three were from the placebo group and six were from the propranolol group, which consisted of mild nausea and fatigue on treatment days.

Table 1
Demographic and clinical characteristics of the sample by treatment group.

	Propranolol ($n = 9$)	Control ($n = 8$)
	M (SE)	*M (SE)*
Age	44.78 (6.22)	35.63 (5.69)
Years of education	14.11 (0.68)	13.75 (0.70)
Years of drug use	13.50 (4.57)	3.57 (1.13)
Psychosocial impairment due to substance use (# of days in past-month)	23.63 (3.70)	23.25 (6.75)
Previous treatment attempts	3.11 (0.87)	2.71 (1.40)
	n (%)	*n* (%)
Income below $30,000 CAD	4 (44%)	2 (25%)
Male gender	6 (67%)	6 (75%)
In a stable relationship	2 (22%)	2 (25%)
Inpatient	3 (33%)	5 (63%)
Smoking	5 (56%)	6 (75%)
Psychiatric comorbidity	4 (44%)	2 (25%)
Main addiction		
Alcohol	2 (22%)	2 (25%)
Cocaine	4 (44%)	3 (38%)
Opiates/opioids	2 (22%)	3 (38%)
Marijuana	1 (11%)	0

4. Discussion

This study is the first to examine the feasibility of administering propranolol in conjunction with a memory retrieval procedure as an adjunct treatment for substance dependence. We found that this treatment can be feasibly incorporated into human addiction treatment programs, is brief and easy to learn, and was well tolerated. Attrition in this study (41%) was comparable to what is regularly observed among inpatient and outpatient addiction programs (see Brorson, Ajo Arnevik, Rand-Hendriksen, & Duckert, 2013), as well as in large-scale clinical trials (Gertz, 2008). Importantly, the majority of included participants returned for the baseline visit, suggesting that they were not deterred by the extra experimental treatment demands. Attenuation of self-reported craving was observed by the sixth treatment session for propranolol-treated participants only, a finding in both the intent-to-treat and per protocol analyses.

Since the propranolol was administered *prior* to memory reactivation (i.e., retrieval), one could argue that the treatment effects are due -at least in part-to an effect of propranolol on memory retrieval (Schiller & Phelps, 2011) rather than being attributed to *bona fide* reconsolidation impairment. Although this is an important mechanistic question, in practice most clinical studies have given oral propranolol 60–90 min prior to memory reactivation (Brunet, Ashbaugh et al., 2011). This is done in order for the drug to cross the blood–brain barrier and reach optimal bioavailability (Dey et al., 1986) when memory reconsolidation begins within minutes following memory reactivation (Monfils, Cowansage, Klann, & LeDoux, 2009). Moreover, a recent meta-analysis found that post-retrieval propranolol does not result in sustained consolidation/reconsolidation impairment in humans compared to pre-retrieval administration (Lonergan, Olivera-Figueroa, Pitman, & Brunet, 2013).

Future studies will need to determine if our finding of reduced overall (i.e., tonic) craving also extends to cue-elicited (i.e., phasic) craving as reported by Saladin et al. (2013) and persists over a long-term period following treatment. Our study design also lacked a control group receiving propranolol without reactivating drug-related memories. Although this condition could better demonstrate reconsolidation, it is also vulnerable to the white–bear effect (Wegner, Schneider, Carter, & White, 1987) and therefore represents a significant experimental challenge. Further, the predominance of male participants in our study may have underestimated the mean treatment effect. In a study of clinical predictors of outcome of impairing reconsolidation to treat posttraumatic stress disorder, treatment effects were more pronounced among women than men (Poundja, Sanche, Tremblay, & Brunet, 2012). The

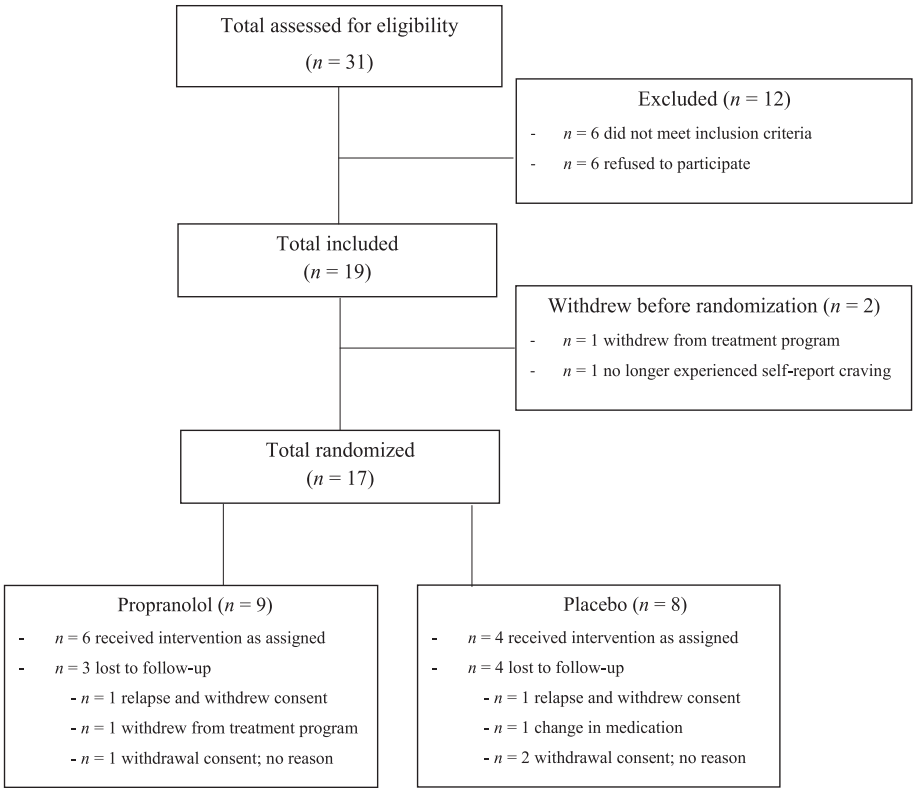

Fig. 1. Recruitment and retention flow-chart.

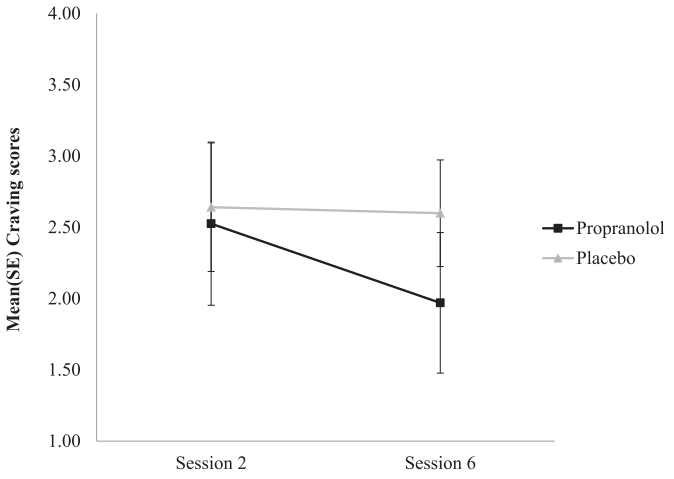

Fig. 2. Subjective Craving Scores Over Time in an Intent-to-treat Analysis. Treatment session 1 (baseline) is controlled. Propranolol group (n = 9): M session 2 = 2.53, SE = 0.57, M session 6 = 1.97, SE = 0.49, p = .005, paired effect size of d = 1.40. Placebo group (n = 8): M session 2 = 2.64, SE = 0.45; M session 6 = 2.60, SE = 0.37, p = .89, paired effect size of d = 0.06.

impairing effects of propranolol on memory reconsolidation may be influenced by sex differences in emotional memory processing and/or the metabolism of propranolol (Lonergan et al., 2013; Nielsen, Ertman, Lakhani, & Cahill, 2011).

Worthy of note, the current study used a naturalistic sample exhibiting a mix of dependencies, and was not designed to disentangle whether propranolol works best for one addictive substance or the other. Pre-clinical substance-specific research attempting to impair alcohol-related dependency is still in its infancy (see Milton & Everitt, 2010; Wouda et al., 2010). Propranolol may be more effective with certain types of substances than others (see for instance the negative results of Pachas et al., 2015). However, our decision to treat a mixed naturalistic sample makes sense from a treatment implementation perspective, considering that dependence to different substances usually receive equivalent psychosocial treatment, and enhanced noradrenergic signaling represents a common factor underlying the etiology of a range of chemical dependencies (Fitzgerald, 2013). Future large scale clinical trials of this procedure could allow subgroup analyses that would clarify what specific substance dependency is best treated using this approach. In addition, the primary outcome in the present study was the effects of the treatment on self-report craving, which is arguably the behavioral manifestation of drug-related memories. Future studies should include a quantitative outcome measure in order to evaluate the effects of treatment on various facets of substance dependence.

5. Conclusion

In this report, we examined the clinical feasibility and preliminary efficacy of impairing drug-related memory reconsolidation using propranolol as an adjunct to treat substance dependence. This study extends previous findings to the realm of clinical populations and demonstrates an impairing effect of propranolol on tonic craving in addition to the previously-found phasic (cue-elicited) craving (see Saladin et al., 2013). Our results highlight the feasibility of, and demand for, larger randomized controlled trials

using this procedure, and the need to examine whether this treatment strategy can reduce craving for a range of substances.

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