Addictive Behaviors 39 (2014) 1057–1061

Contents lists available at ScienceDirect

Addictive Behaviors

Short Communication

Preliminary evidence for normalization of risk taking by modafinil in chronic cocaine users

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HIGHLIGHTS

- We used the Balloon Analogue Risk Task to assess risk taking in cocaine dependence.
- Chronic cocaine users taking modafinil were compared to those taking placebo.
- The modafinil group scored comparably to an age matched healthy comparison group.
- The placebo group scored lower than both the modafinil group and healthy group.
- This suggests an impairment of beneficial risk taking, normalized by modafinil.

ARTICLE INFO

Available online 3 March 2014

Keywords:
Cocaine dependence
Modafinil
Cognition
Risk taking
Balloon Analogue Risk Task

ABSTRACT

Modafinil, a wake-promoting agent used to treat sleep disorders, is thought to enhance cognition. Although modafinil has shown promise as a pharmacotherapy for the treatment of cocaine dependence, it is unknown to what extent cognitive effects may play a role in such treatment. We examined the effect of modafinil on the Balloon Analogue Risk Task (BART), a behavioral measure in which higher scores are purported to reflect a greater propensity for risk-taking. Thirty cocaine dependent individuals, enrolled in a randomized clinical trial of modafinil 400 mg ($n = 12$) versus placebo ($n = 18$), were administered the BART during the second week of inpatient treatment for cocaine dependence. A comparison cohort of healthy participants ($n = 19$) performed the BART under similar conditions. Modafinil treatment was associated with significantly higher BART scores ($p = 0.01$), which were comparable to scores in healthy persons. BART scores in placebo treated participants were much lower than previously reported in healthy participants, and lower than those observed in the comparison cohort. As propensity toward risk taking is typically associated with higher BART scores as well as increased risk for substance use, our findings may reflect a novel aspect of cognitive impairment related to chronic cocaine use. Notably, the low BART scores reflect highly suboptimal performance on the task, and the observed effect of modafinil may indicate a normalization of this impairment and have implications for treatment outcome.

1. Introduction

Chronic cocaine use is associated with long-term neurocognitive impairments (Bolla, Cadet & London, 1998 and Jovanovski, Erb & Zakzanis, 2005) that may predispose individuals to stimulant dependence (Ersche, Turton, Chamberlain, Müller, Bullmore & Robbins, 2012) and could be the result of long-term cocaine use (Beveridge, Gill, Hanlon & Porrino, 2008). Cognitive impairment is associated with lower treatment retention and engagement (Aharonovich, Amrhein, Bisaga, Nunes & Hasin, 2008; Aharonovich, Hasin, Brooks, Liu, Bisaga & Nunes, 2006), so may prove to be an important target for pharmacotherapies developed to treat cocaine use disorders (Sofuoglu, DeVito, Waters & Carroll, 2013).

Modafinil is an agent with pro-cognitive effects (Minzenberg & Carter, 2008), and has shown promise in the treatment of cocaine dependence (Mariani & Levin, 2012) in laboratory self-administration studies (Hart, Haney, Vosburg, Rubin & Foltin, 2008) and in double-blind, placebo-controlled clinical trials (Dackis, Kampman, Lynch, Pettinati & O'Brien, 2005), although positive results have not been universal (Dackis, Kampman, Lynch, Plebani, Pettinati, Sparkman, et al., 2012) and may be limited to sub-populations of cocaine users such as persons without alcohol dependence (Anderson, Reid, Li, Holmes, Shemanski, Slee, et al., 2009). A wake-promoting agent,

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http://dx.doi.org/10.1016/j.addbeh.2014.02.015
0306-4603/

modafinil is FDA approved for the treatment of several sleep disorders including narcolepsy. Modafinil has also been shown to benefit working memory and attention in persons with cocaine dependence who were not alcohol dependent (Kalechstein, Mahoney, Yoon, Bennett & De la Garza, 2013), and when given in the morning has a normalizing effect on sleep architecture in this population (Morgan & Malison, 2007; Morgan, Pace-Schott, Pittman, Stickgold & Malison, 2010). These effects on treatment outcome, cognition and sleep may be interrelated: for instance, changes in sleep architecture during abstinence and laboratory cocaine use correspond with sleep-dependent cognitive performance (Morgan, Pace-Schott, Sahul, Coric, Stickgold & Malison, 2006, 2008). However, the effect of modafinil on risk-taking behavior in cocaine dependent individuals is not known.

The Balloon Analogue Risk Task (BART) is a task developed to assess risk-taking tendency (Lejuez, Read, Kahler, Richards, Ramsey, Stuart, et al., 2002). Previous studies in healthy populations have consistently associated higher BART scores with greater self-reported risk taking, including social drinking and experimentation with illicit substances (Aklin, Lejuez, Zvolensky, Kahler & Gwadz, 2005; Lejuez, Aklin, Daughters, Zvolensky, Kahler & Gwadz, 2007, and Lejuez et al., 2002). However, fewer studies have examined BART performance in chronic substance users (e.g. Hopko, Lejuez, Daughters, Aklin, Osborne, Simmons, et al., 2006; Lejuez, Simmons, Aklin, Daughters & Dvir, 2004; Tull, Trotman, Duplinsky, Reynolds, Daughters, Potenza, et al., 2009), and it is not clear whether BART score differences are associated with chronic substance use. An early study found that smokers scored higher than nonsmokers (Lejuez, Aklin, Jones, Richards, Strong, Kahler, et al., 2003), but other work has found no differences between non-substance-users and either smokers (Dean, Sugar, Hellemann & London, 2011), cannabis users (Gonzalez, Schuster, Mermelstein, Vassileva, Martin & Diviak, 2012), or recreational stimulant users (Bishara, Pleskac, Fridberg, Yechiam, Lucas, Busemeyer, et al., 2009).

Given the potential effects of modafinil on both cognition and clinical outcomes in substance users, we sought to examine differences in BART performance in cocaine dependent individuals who were administered either modafinil or placebo in the context of a randomized clinical trial.

2. Methods

2.1. Cocaine dependent participants

Participants were recruited as part of an ongoing clinical trial on the use of modafinil to treat cocaine dependence. The first 30 participants who completed the at least 10 days of the initial 2-week inpatient portion of this trial were administered the BART (18 placebo, 12 modafinil).

Participants were chronic cocaine users who met DSM-IV criteria and were seeking treatment for cocaine dependence. Potential participants were excluded if they reported lifetime dependence on substances other than cocaine and nicotine, or current alcohol use in excess of 350 grams (25 standard drinks) per week for the past month (to approximate the population that appears to respond best to modafinil; Anderson et al., 2009); if they had a medical condition that would render study participation unsafe, a known hypersensitivity to modafinil, or any non-substance related Axis I disorder; if they currently used any psychiatric medications, medications that affect sleep, or medications not safe to take with modafinil; or, if female and of childbearing potential, if they were pregnant, lactating, or unwilling to use contraceptives for the duration of the study.

Urn randomization was used to balance age, gender, and recent quantity of cocaine used between groups. All participants reviewed and signed a consent form, approved by the local institutional review board, before entering the study.

2.2. Healthy comparison participants

Nineteen healthy volunteers were recruited as a reference group for BART data and did not receive study medication or placebo. Eligibility criteria were similar to those used for cocaine dependent individuals, except these individuals were excluded if they had any current illicit substance use, or any history of substance abuse or dependence other than nicotine.

Healthy participants were screened by phone, and then reported to the laboratory for a single 1–2 h session. Healthy participants were given a series of questionnaires including the Shipley Institute of Living Scale (Shipley, 1940 and Zachary, 1986) and the Southern Oaks Gambling Scale (SOGS) (Lesieur & Blume, 1987).

2.3. Study design

Cocaine dependent participants were admitted to an inpatient research unit for 12 days prior to 6 weeks of outpatient treatment. Placebo treatment for all participants began on Day 2 (at 7:30 AM), and modafinil up-titration began on Day 5 at 100 mg, and increased by 100 mg per day until 400 mg daily was achieved on Day 8. No participant complained of side-effects that resulted in a change in the up-titration schedule.

2.4. Questionnaires

Demographic information was collected during the telephone screen. During the subsequent in-person screen, cocaine dependent participants completed the Shipley Institute of Living Scale, SOGS, Addiction Severity Index (ASI) (McLellan, Kushner, Metzger, Peters, Smith, Grissom, et al., 1992; McLellan, Luborsky, Woody & O'Brien, 1980), and a 30-day timeline follow back of all substance use (Miller & Del Boca, 1994 and Sobell & Sobell, 1980).

2.5. Balloon Analogue Risk Task (BART)

A standard 30-trial form of the BART (Lejuez et al., 2002) was administered on Day 10 for cocaine dependent participants, and was administered to healthy participants during the single session. During this task, a balloon is displayed on the screen, along with a button that will pump up the balloon. Each pump inflates the balloon and deposits 5 cents in a temporary bank. At any point, the participant may cease pumping and click another button to collect the money accrued, transfer it into a permanent bank, and continue to the next balloon. However, if a balloon pops, no money is collected on that trial. At all times, the amount in the permanent bank and the number of pumps made on the current balloon are displayed on-screen.

The probability of the balloon popping was 1/128 on the first pump and increased with successive pumps such that the probability of a pop was 1/(129 − pump number). The maximum times a balloon could be inflated therefore was 128, and the optimal number of pumps (to maximize earnings) was 64 (Lejuez et al., 2002).

Participants were instructed on how to select the pump and collect buttons, and were told that the objective was to win as much money as possible, that there were 30 balloons, and that the balloons could pop at any point between the first pump to the time that it filled up the entire screen. Participants were not given additional compensation based on task performance.

2.6. Statistical analyses

Potential differences in demographics, other baseline information, and outcomes between modafinil and placebo groups were compared using unpaired two-tailed *t*-tests and Fisher's exact tests. The main BART outcome measure was average adjusted pump count (i.e. including only trials in which the balloon did not pop; Lejuez et al., 2002;