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Treatment with modafinil and escitalopram, alone and in combination, on cocaine-induced effects: A randomized, double blind, placebo-controlled human laboratory study

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ABSTRACT

Background: Concurrent administration of dopamine and serotonin reuptake inhibitors reduces cocaine self-administration in monkeys. Consonant with this, clinical trials assessing modafinil and selective serotonin reuptake inhibitors alone show some efficacy as potential pharmacotherapies for cocaine dependence. We hypothesized that combining modafinil with escitalopram would attenuate the euphoric effects of cocaine to a greater degree than modafinil alone.

Methods: In a randomized, double blind, parallel groups design participants received either placebo (0 mg/day; $n = 16$), modafinil (200 mg/day; $n = 16$), escitalopram (20 mg/day; $n = 17$), or modafinil + escitalopram (200 + 20 mg/day; $n = 15$) for 5 days. On day 5, during separate sessions participants received an intravenous sample of cocaine (0 or 20 mg; randomized) and five $1 bills. Participants rated the subjective effects of the infusions and subsequently made choices to either return $1 and receive another infusion or keep $1 and receive no infusion.

Results: Compared to saline, cocaine (20 mg) significantly ($p \leq 0.008$) increased most ratings, including "good effects", "stimulated", and "high". Relative to placebo, modafinil significantly ($p \leq 0.007$) attenuated subject-rated increases of "any drug effect", "high", "good effects", and "stimulated" produced by cocaine. Compared to saline, participants chose cocaine infusions significantly more; however, no treatment significantly reduced choices for cocaine infusions. Escitalopram did not enhance the efficacy of modafinil to reduce any measure.

Conclusions: Modafinil attenuated many positive subjective effects produced by cocaine; however, escitalopram combined with modafinil did not enhance the efficacy of modafinil to reduce cocaine effects.

1. Introduction

According to the World Health Organization report, an estimated 17 million people worldwide had used cocaine at least once in 2008 (UNODC, 2010). This is consistent with the 2012 National Survey on Drug Use and Health (NSDUH) report, which estimated that 9.2% of Americans aged 12 or older (23.9 million) were current (past month) illicit drug users and 8.5% met criteria (Substance Abuse and Mental Health Services Administration, 2013a). Cocaine users accounted for 1.1 million of all those in 2012, an increase of nearly 34% since 2011 (Substance Abuse and Mental Health Services Administration, 2013a). Estimates from the Treatment Episode Data Set and NSDUH indicate that 13.1–15.6% of all Americans who reported receiving treatment for illicit substance use received treatment for their cocaine use (Substance Abuse and Mental Health Services Administration, 2013a,c) and

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70.5% of cocaine user admissions reported having at least one prior treatment episode (Substance Abuse and Mental Health Services Administration, 2013c). Further, out of the 1.25 million emergency department visits made by patients in 2011 that involved illicit, cocaine was the most, accounting for over 40% of all illicit drug use visits (Substance Abuse and Mental Health Services Administration, 2013b). Unfortunately, despite extensive efforts to identify potential pharmacotherapies for cocaine dependence, none exists.

Efforts to identify pharmacotherapies have concentrated heavily on medications that influence dopamine (DA; Verrico et al., 2013). This approach was based logically on the ability of cocaine to acutely increase intrasynaptic DA to supraphysiological levels, viablockade of the DA transporter (DAT; Volkow et al., 2002), which correlates with both the positive subjective effects (Volkow et al., 1997) as well as the reinforcing effects (Hart et al., 2008) produced by cocaine. Further, long-term cocaine use appears to cause neuroadaptations within the mesocorticolimbic system (Verrico et al., 2013), including cortical hypofrontality and reduced dopaminergic neurotransmission, which have been associated with deficits in executive functioning (Groman and Jentsch, 2012; Kalechstein et al., 2013), poor treatment response (Martinez et al., 2011), and an increased vulnerability to relapse (Sofuoglu, 2010).

The wake-promoting medication modafinil targets the DAT, although it also produces appreciable effects on noradrenergic, GABAergic, and glutamatergic neurotransmission (Ferraro et al., 1998; Madras et al., 2006; Volkow et al., 2009). In preclinical models, modafinil attenuated reinstatement of cocaine self-administration (Mahler et al., 2012), as well as methamphetamine self-administration (Reichel and See, 2010). In human laboratory studies, modafinil attenuated the positive subjective effects of intravenous (IV) cocaine (Dackis et al., 2003; Malcolm et al., 2006) and decreased choices to smoke cocaine (Hart et al., 2008). Further, modafinil significantly reduced cocaine-positive urines in an outpatient clinical trial (Dackis et al., 2005), and while two larger subsequent clinical trials of modafinil were negative (considering group means), modafinil reduced cocaine-positive urines in subsets of participants—specifically in males, but not females (Dackis et al., 2012), and in those without a history of alcohol dependence (Anderson et al., 2009).

In addition to DA, studies implicate a role for serotonin in mediating the positive subjective and reinforcing effects produced by cocaine (Filip et al., 2010; Walsh and Cunningham, 1997). Consistent with this interpretation, non-human primate studies have revealed that increasing synaptic serotonin levels reduces the reinforcing effects (Howell, 2008; Rothman et al., 2006) and self-administration (Czoty et al., 2002; Spealman, 1993) of cocaine. In humans, treatment with the selective serotonin reuptake inhibitor (SSRI) fluoxetine significantly reduced the positive subjective effects produced by cocaine (Walsh et al., 1994). In outpatient trials, the SSRI citalopram significantly reduced cocaine-positive urines (Moeller et al., 2007), while the SSRI sertraline delayed relapse in recently abstinent individuals presenting with depressive symptoms (Oliveto et al., 2012). However, a review by Pani et al. (2011) found that SSRIs did not support abstinence from cocaine use over placebo.

Collective evidence to date suggests that as monotherapies neither modafinil (Dackis et al., 2012; Anderson et al., 2009) nor SSRIs (Pani et al., 2011) consistently reduce cocaine use; however, preclinical data suggests that serotonin and DA act together to produce important effects of cocaine in brain. For example, in non-human primates increasing synaptic serotonin levels reduced the reinforcing effects and self-administration of cocaine, as well as cocaine-induced DA release (Czoty et al., 2002; Howell, 2008; Rothman et al., 2006; Spealman, 1993). In fact, administration of an SSRI in combination with the experimental compound RTI-336, which is a highly selective DAT inhibitor (Howell et al., 2007), or administration of a dual DA/serotonin releaser (Rothman et al., 2007, 2008), significantly suppressed cocaine self-administration in monkeys, suggesting this might be a useful therapeutic strategy in humans (Rothman et al., 2008).

We hypothesized that combining a DAT inhibitor (i.e., modafinil; Andersen et al., 2010; Kim et al., 2014; Schmitt and Reith, 2011; Zolkowska et al., 2009) with a SSRI may more robustly reduce the euphoric and reinforcing effects produced by cocaine in humans. To test this hypothesis, we conducted a human laboratory study in non-treatment seeking volunteers who met cocaine dependence criteria to determine whether relative to modafinil alone, escitalopram would enhance the efficacy of modafinil to attenuate the effects produced by cocaine, and choices for IV cocaine over an alternative reinforcer (i.e., money).

2. Methods

The Baylor College of Medicine (BCM) and Michael E. DeBakey Veteran Affairs Medical Center (MEDVAMC) Institutional Review Boards reviewed and approved this study.

2.1. Trial design

This randomized, double blind, placebo-controlled, parallel groups study allocated participants (1:1:1:1) to a treatment group. The MEDVAMC Research Pharmacy used a randomization generated by www.randomization.com to maintain the blind.

2.2. Participants

Potential participants completed an initial telephone screen to assess basic eligibility before completing in-person assessments. Prior to obtaining written informed consent and determining eligibility at the in-person interview, potential risks associated with the study were fully described. Eligibility assessments included medical and drug use histories, urine screens for illicit drugs, electrocardiograms, and vital sign assessments. Exclusion criteria included any psychiatric or medical illnesses, serious neurological or seizure disorders, use of any psychoactive medications, and drug or alcohol dependence, excluding cocaine and nicotine. Women were excluded if they were pregnant, breast-feeding, or not using a reliable form of birth control. To meet inclusion criteria, subjects had to report recent cocaine use, provide a benzoylecgonine-positive urine sample for cocaine during the in-person screening process, meet DSM-IV diagnostic criteria for cocaine dependence, and not be actively seeking substance abuse treatment. All participants received compensation and were in good health with no contraindications to study participation.

2.3. Study procedures

Eligible participants resided at the MEDVAMC Research Commons for nights. Upon arrival, participants were randomly allocated to one of four treatment groups: (1) placebo + placebo, (2) placebo + modafinil (200 mg/day), (3) placebo + escitalopram (20 mg/day), or (4) modafinil (200 mg/day) + escitalopram (20 mg/day). All treatments (Section 2.4) were over-encapsulated in two tablets to maintain the blind, and taken orally at 08:00 on days 1–5. On day 6, participants were discharged once deemed medically stable by a physician. The procedures described below were identical for each group. Sample size was calculated based on a power analysis performed on data obtained by Hart et al. (2008).

2.4. Study medications

The FDA provided an IND for the use of modafinil and escitalopram in this study. Greenpark Compounding Pharmacy (Houston, TX) provided over-encapsulated modafinil, escitalopram, and a matched placebo. A NIDA Drug Supply Program (RTI International, Durham, NC) contractor provided cocaine HCl for human use. The MEDVAMC Research Pharmacy prepared the sterile cocaine and saline solutions.

Treatment with 200 mg of modafinil was equipotent to 400 mg at significantly attenuating the subjective and reinforcing effects produced by smoked cocaine (Hart et al., 2008). In addition, treatment with 200 mg modafinil has been found to attenuate the subjective effects produced by methamphetamine (De La Garza et al., 2010) and to improve cognitive function in both healthy participants (Turner et al., 2003) and in cocaine-dependent individuals (Kalechstein et al., 2013). Absorption of modafinil is rapid, with peak plasma concentrations occurring at ~2–4 h. The effective elimination half-life of modafinil after multiple doses is ~15 h, and steady state plasma concentrations are achieved after 2–4 days of dosing. Treatment with 20 mg of escitalopram is routinely used to treat major depressive disorder and generalized anxiety disorder in humans. Following a single oral dose, peak levels occur in ~5 h. Escitalopram has a mean terminal half-life of ~27–32 h and with once dailydosing,