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Modafinil is a novel wake-promoting drug with FDA approval for the treatment of narcolepsy, shift work sleep disorder, and sleep apnea. It is also prescribed for many off-label uses such as ADHD and it is currently being assessed as a treatment for psychostimulant dependence. Previous research assessing the abuse liability of modafinil in animals and humans suggests it is less potent and has a low abuse potential compared to traditional psychomotor stimulants. However, modafinil has not been carefully assessed in combination with other psychostimulant drugs. The current study used an unbiased place conditioning procedure simultaneously with locomotor screening procedures to assess the combined behavioral effects of modafinil and d-amphetamine in adult male Sprague-Dawley rats. Eight 30-min conditioning trials were conducted in a 2 compartment apparatus with distinct visual and tactile cues. Drug and vehicle conditioning trials were alternated with 1 trial per day separated by 24 hr. On drug conditioning trials, rats were administered either modafinil (64 mg/kg, i.g.), d-amphetamine (0.3 or 2.0 mg/kg, s.c.), a combination of modafinil (64 mg/kg) and d-amphetamine (0.3 mg/kg), or vehicle injections. On vehicle conditioning trials, all groups received vehicle injections. Preference for either compartment was assessed by recording time spent in each compartment during a 15-min test conducted 24 hr after the last conditioning trial. Results indicated that this low oral dose of modafinil did not significantly increase locomotor activity or establish conditioned place preference (CPP). Moreover, modafinil did not significantly alter the hyperlocomotor or CPP effects of d-amphetamine. To confirm that modafinil is behaviorally active at this low oral dose, a separate assessment of horizontal and vertical activity was conducted with male Sprague-Dawley rats in an open field apparatus. Results confirmed that modafinil increased locomotor activity relative to vehicle, with increases in vertical activity especially prominent, a measure that was not assessed in place conditioning trials. Although the current results predict a low abuse liability with concurrent use of modafinil and d-amphetamine, additional research with higher dose combinations may be warranted before ruling out the possibility that these drugs could have additive or synergistic effects.

Keywords: amphetamine, conditioned place preference, modafinil, drug combinations, abuse liability

Modafinil is a wake-promoting drug with FDA approval for the treatment of narcolepsy and reportedly effective in the treatment of chronic fatigue syndrome (Turkington, Hedwat, Rider, & Young, 2004), obstructive sleep apnea/hypopnea syndrome, and shift work sleep disorder (Keating & Raffin, 2005). It has also been investigated to treat fatigue in patients with Parkinson's disease (Högl et al., 2002), amyotrophic lateral sclerosis (Carter et al., 2005), and dementia (Howcroft & Jones, 2005). Modafinil's wake-promoting (Hermant, Rambert, & Duteil, 1991; Silvestri, Sanford, Ross, Mann, Pavlock, & Morrison, 2002; Webb, Pollock, & Mistlberger, 2006) and cognitive enhancing effects (Turner, Robbins, Clark, Aron, Dowson, & Sahakian, 2003) are similar to those of traditional psychostimulants, apparently without the side effects (e.g., tolerance, abuse potential, sleep rebound, and increased locomotor activity or hyperactivity) typically associated with these substances (Deroche-Gamonet, Darnaudery, Bruins-Slot, Piat, & Piazza, 2002; Hermant, Rambert, & Duteil, 1991; Lin, Roussel, Akaoka, Fort, Debilly, & Jouvet, 1992).

Research exploring modafinil's neuropharmacological actions has implicated several neurotransmitter systems, including orexin, serotonin, GABA, and dopamine (Dopheide, Morgan, Rodvelt, Schachtman, & Miller, 2007; Minzenberg & Carter, 2008; Wisor

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et al., 2001; Zolkowska et al., 2009). Zolkowska et al. reported that pretreatment with modafinil decreased methamphetamine-induced dopamine release in male Sprague-Dawley rats, consistent with a previous report (Wisor et al., 2001) that the dopamine transporter is involved in its primary mechanism of action. Given the similar receptor mechanisms underlying the central nervous system actions of modafinil and psychomotor stimulants, a thorough evaluation of modafinil's abuse liability is warranted.

Several double-blind, placebo-controlled studies have evaluated the subject rated effects of modafinil in healthy adults with or without substance abuse histories. For example, in a sample of 16 healthy adults without a substance abuse history, subject-rated effects of a single oral dose of 300 mg modafinil were reported to differ from those of 15 mg amphetamine (Warot, Corruble, Payan, Weil, & Puech, 1993). In a more recent study evaluating a wider range of doses in 12 healthy adults without a substance abuse history, modafinil and amphetamine were reported to produce qualitatively and quantitatively similar effects (Makris, Rush, Frederich, Taylor, & Kelly, 2007). However, findings are generally consistent that participants with a history of psychostimulant abuse can readily distinguish the effects of modafinil from either cocaine or amphetamine (Malcolm et al., 2006; Rush, Kelly, Hays, Baker, & Wooten, 2002). Furthermore, cocaine users do not reliably self-administer modafinil over placebo, at least in a controlled laboratory setting (Vosburg, Hart, Haney, Rubin, & Foltin, 2010).

Although clinical observations seem to indicate modafinil has a relatively low abuse liability even in people with a history of psychostimulant dependence, an extensive evaluation of its reinforcing effects using standard preclinical drug screening procedures may be warranted before promoting its use in a population with a substance abuse history. To date, only a few preclinical studies have evaluated modafinil in abuse liability screening procedures, such as drug self-administration and conditioned place preference (CPP). The first of these studies by Gold and Balster (1996) demonstrated that modafinil substituted for cocaine in four of six rhesus monkeys that had been previously trained to self-administer cocaine. The number of modafinil infusions was comparable to or greater than the number of cocaine infusions by the same animals, although a larger dose of modafinil was required to produce effects similar to that of cocaine (Gold & Balster, 1996). In contrast, Deroche-Gamonet et al. (2002) reported that modafinil did not substitute for cocaine self-administration in rats, nor did it induce reinstatement after cocaine self-administration was extinguished. Evaluation of modafinil in place conditioning procedures has yielded somewhat inconsistent findings. For example, Deroche-Gamonet et al. (2002) assessed a range of modafinil doses (32–256 mg/kg), none of which reliably established CPP in rats. In contrast, Wuo-Silva et al. (2011) reported that 64 mg/kg modafinil established CPP in mice. Besides species differences, a number of methodological differences between these studies could account for the discrepant findings.

Modafinil's effects in the place conditioning reinstatement paradigm appear to depend on the particular drug used to establish CPP. Tahsili-Fahadan, Carr, Harris, and Aston-Jones (2010) reported that 300 mg/kg modafinil completely blocked a morphine-primed reinstatement of morphine place preference. In contrast, following extinction of cocaine-induced place preference, 128 mg/kg modafinil has been reported to reinstate a place preference (Bernardi, Lewis, Lattal, & Berger, 2009). Based on these findings, Bernardi et al. (2009) suggested modafinil may increase responsivity to stimulant cues and this could precipitate relapse in humans with a cocaine abuse history. Such a possibility might preclude its use as a treatment for cocaine dependence.

Despite some promising preliminary findings regarding modafinil as a potential treatment for psychostimulant dependence (Dackis, Kampman, Lynch, Pettinati, & O'Brien, 2005; Hart, Haney, Vosburg, Rubin, & Foltin, 2008), clinicians may want to proceed with caution until further research determines whether modafinil could pose a risk for precipitating relapse to stimulant use. Of particular concern is the risk of additive or synergistic effects if modafinil were to be administered in combination with other psychostimulants. Preclinical abuse liability screening with drug combinations may provide valuable information in this regard. Toward that aim, the current study examined a low dose combination of modafinil (64 mg/kg) and d-amphetamine (0.3 mg/kg) in comparison to each drug alone and to a higher dose of d-amphetamine (2.0 mg/kg) using place conditioning procedures in rats.

Methods

Subjects

Forty male Sprague-Dawley rats (Charles River Laboratories, Portage, MI) 50–60 days old at the start of the experiment were acclimated to the animal facilities for at least 1 week prior to initiation of place conditioning experiments. A separate group of 15 adult male Sprague-Dawley rats were assessed in a supplemental experiment to determine the effects of 64 mg/kg modafinil on locomotor activity. Animals were individually housed in polycarbonate cages with corncob bedding where ad libitum access to food and water was available. All animals were housed in Western Michigan University's animal facilities in a humidity and temperature-controlled room with a 12:12 hr light/dark cycle with lights on at 7:00 a.m. All procedures were conducted in accordance with the *Guide for the Care and Use of Laboratory Animals* (National Research Council of the National Academies, 2011) and were approved by the Institutional Animal Care and Use Committee at Western Michigan University.

Apparatus

The apparatus used for place conditioning and locomotor activity assessments consisted of eight custom designed open field chambers constructed of acrylic and measuring 40.5 cm × 40.5 cm × 40.5 cm. For place conditioning experiments, the chambers were divided into two compartments with an acrylic wall and removable 12.8 cm × 18 cm door. Each compartment contained distinct visual and tactual cues. One compartment contained walls covered with alternating vertical black and white stripes and a textured plastic floor. The other compartment contained walls covered with alternating horizontal black and white stripes and an aluminum floor with 1.1 cm diameter holes spaced approximately 0.5 cm apart. Each chamber was housed within an Accuscan automated activity monitoring system (Accuscan Instruments, Inc., Columbus, OH) equipped with infrared emitters and detectors connected to a microprocessor. Locomotor activity and time spent

in each side of apparatus were processed using Versamax software (Accuscan Instruments, Inc., Columbus, OH).

Procedures

Place conditioning trials. Thirty-two animals were randomly assigned to one of the following four treatment groups: 5% arabic gum + 0.9% saline (VEH + SAL), 5% arabic gum + 0.3 mg/kg d-amphetamine (VEH + AMPH), 64 mg/kg modafinil + saline (MOD + SAL), 64 mg/kg modafinil + 0.3 mg/kg d-amphetamine (MOD + AMPH). These four groups were assessed during the same consecutive 10-day period. Four squads of eight animals were run simultaneously with two animals from each treatment group in each squad. For comparison, a separate squad of eight animals was assessed for place conditioning with 2.0 mg/kg d-amphetamine approximately 1 month later. Assignments of test chamber and drug-paired compartment were counterbalanced within and between treatment groups.

A single habituation session was conducted 24 hr prior to commencing place conditioning. Animals were habituated to the entire test apparatus with the doors removed for a period of 15 min. On the next day, place conditioning commenced for 8 days with a single 30-min trial per day. During conditioning, the removable doors were attached and rats only had access to one compartment. On Conditioning Days 1, 3, 5, and 7, rats were administered their respective drug treatments (see above) prior to placement into one compartment. On Conditioning Days 2, 4, 6, and 8, all rats were administered both 5% arabic gum and saline before placement into the opposite side of the chamber. Modafinil or 5% arabic gum was administered 30 min before and d-amphetamine or saline was administered 10 min before placement into the chambers. Horizontal activity was recording during all conditioning trials.

CPP Test. The test session was conducted 24 hr after the last conditioning session. Rats were placed in the test apparatus for 15 min with the doors removed to allow access to both compartments. Horizontal activity and time spent in each compartment was electronically recorded. During all phases of the experiment, the floors and walls of the apparatus were wiped down with a 35% isopropyl alcohol solution after each rat was removed.

Acute Assessment of Locomotor Activity. A supplemental experiment was conducted with 15 rats to assess the effects of 64 mg/kg modafinil on locomotor activity. The walls and floors used in the place conditioning experiment were not used for this assessment. Animals were administered 64 mg/kg modafinil by oral gavage immediately before placement in the apparatus for a period of 60 min. Horizontal activity and vertical activity were determined from infrared beam breaks.

Drugs

Modafinil was synthesized in the laboratory of Dr. Thomas Prisinzano using previously described methods (Prisinzano, Podobinski, Tidgewell, Luo, & Swenson, 2004), prepared fresh each day of use by suspension in a 5% arabic gum solution (Sigma Aldrich, St. Louis, MO) and administered by oral gavage (i.g.) in a volume of 10 ml/kg. The d-amphetamine-hemisulfate (Sigma Aldrich, St. Louis, MO) was administered subcutaneously (s.c.) in a volume of 1 ml/kg. Doses were based on the weight of the salts.

Data Analysis

A repeated-measures two-factor analysis of variance (ANOVA) was conducted on horizontal activity during conditioning sessions with treatment group as a between-subjects factor and conditioning trial as a within-subjects factor. Bonferroni post hoc tests were conducted for significant differences between specific treatment groups. For each treatment group, paired *t* tests were conducted on the time spent in the drug-paired compartment and vehicle-paired compartment during the 15-min test session. In the supplemental experiment to assess horizontal and vertical activity over a 60-min period immediately following 64 mg/kg modafinil, a two-way repeated-measures ANOVA was conducted with time as a within subjects factor and treatment as a between subjects factor.

Results

Locomotor activity did not differ significantly among the treatment groups during the 15-min habituation period prior to the onset of conditioning nor was activity different among these groups during the vehicle conditioning trials (data not shown). Figure 1 displays the mean (± S.E.M.) horizontal activity during 30-min drug conditioning trials for each treatment group. Both 0.3 and 2.0 mg/kg d-amphetamine substantially increased activity relative to vehicle, whereas 64 mg/kg modafinil did not. Although the MOD + 0.3 AMPH combination produced slightly greater activity than either drug alone during the first conditioning trial, this enhancement was not observed on subsequent drug conditioning trials. A two-way repeated-measures ANOVA on horizontal activity during drug conditioning trials revealed a significant main effect of treatment group, $F_{(4,35)} = 33.79$, $p < .001$; conditioning trial, $F_{(3,105)} = 4.69$, $p < .01$; and a significant interaction between treatment group and conditioning trial, $F_{(12,105)} = 2.41$, $p < .01$. Significant Bonferroni posttests comparing treatment groups to vehicle and to modafinil on each of the four drug conditioning trials are shown with symbols in Figure 1.

Prior to conditioning, there was no consistent preference among animals for either compartment. Following conditioning trials, vehicle and modafinil treatment groups did not show preference for either compartment, whereas both d-amphetamine treatment groups and the MOD + AMPH treatment group showed a preference for the drug-paired compartment. Figure 2 displays the mean (± S.E.M.) time spent in each compartment on the test day for each treatment group. Paired *t* tests comparing time spent in the drug-paired compartment with time spent in the vehicle-paired compartment were statistically significant for both the 0.3 mg/kg d-amphetamine group, $t(7) = 3.84$, $p < .01$, and the 2.0 mg/kg d-amphetamine group, $t(7) = 3.12$, $p < .05$. The animals in the MOD + 0.3 AMPH treatment group also spent more time in the drug-paired compartment following conditioning trials, but the difference in time spent between drug and vehicle compartments was not statistically significant in this group.

A supplemental experiment was conducted to address concerns that oral administration of 64 mg/kg modafinil might not be behaviorally active. Results of this experiment, shown in Figure 3, indicate that modafinil-treated animals exhibited increased horizontal and vertical activity at nearly all postinjection time intervals compared to vehicle treated animals. A two-way ANOVA revealed the effect of modafinil on horizontal activity was not quite statistically significant, $F_{(1,13)} = 3.65$, $p = .078$, although the main

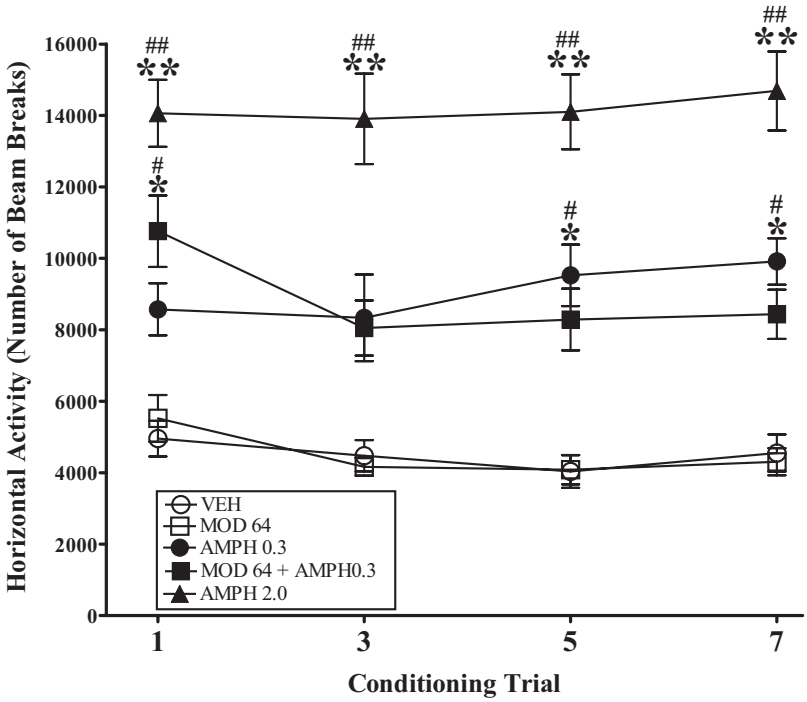

Figure 1. Horizontal activity during 30 min drug conditioning trials. Each data point represents the group mean (±S.E.M.) activity. $^{*}p < 0.05$ or $^{**}p < 0.001$ indicates statistically significant compared to the vehicle control group; $^{\#}p < 0.05$ or $^{\#\#}p < 0.001$ indicates significantly different compared to the modafinil treatment group ($n = 8$ per group).

effect of time was statistically significant, $F_{(11,143)} = 18.99$, $p < .0001$. The main effects of modafinil treatment, $F_{(1,13)} = 9.28$, $p = .01$, and time, $F_{(11,143)} = 6.57$, $p < .0001$, on vertical activity were both statistically significant. There was no significant interaction between treatment and time for either horizontal or vertical activity.

Discussion

Results of the current study indicate that a moderately low oral dose of modafinil (64 mg/kg) does not establish conditioned place preference in adult male Sprague-Dawley rats. These results are consistent with a previous report that modafinil (32–256 mg/kg, i.p.) fails to establish CPP in rats (Deroche-Gamonet et al., 2002), although others have reported 64 mg/kg modafinil to establish CPP in mice (Wuo-Silva et al., 2011). Besides the species difference, several other methodological differences could account for discrepant findings. For example, Wuo-Silva et al. conducted 10-min conditioning trials 30 min after i.p. modafinil injection and both drug and vehicle trials were conducted on the same day with a six hour intertrial interval. Deroche-Gamonet et al. (2002) conducted 30-min conditioning trials immediately following i.p. modafinil injection and drug and vehicle trials were separated by 24 hr. The methods of the current study were modeled after those used by Deroche-Gamonet et al. (2002) with the exception that animals were administered i.g. modafinil 30 min prior to 30-min conditioning trials. Nevertheless, the present findings confirm previous suggestions that modafinil has a low abuse liability in drug naïve individuals, in contrast to most psychomotor stimulants (Bardo, Rowlett, & Harris, 1995). Amphetamine-induced place preference in rodents is a well-established phenomenon at doses ranging from 0.3 mg/kg to 3 mg/kg (Bardo et al., 1995; Deroche-Gamonet et al., 2002) and the current results with d-amphetamine are consistent with these findings. It is somewhat surprising that there was no evidence for the development of sensitization with repeated d-amphetamine exposure in the current study. However, two important measures of activity that typically display sensitization, vertical activity and stereotypy, were not assessed due to constraints of the place conditioning apparatus in which locomotor activity was assessed.

To our knowledge, this is the first assessment of place conditioning following a low oral dose of modafinil. The lack of a significant difference in locomotor activity between modafinil and vehicle treatment groups during drug conditioning trials suggests the possibility that this low oral dose of modafinil was not behaviorally active. Therefore, a supplemental experiment was conducted with a separate group of rats to determine that intragastric administration of 64 mg/kg modafinil does increase locomotor activity (see Figure 3). Results showed a visually evident increase in horizontal activity and a statistically significant increase in vertical activity in modafinil-treated rats compared to vehicle-treated rats. As noted above, vertical activity was not assessed during place conditioning trials. It is possible that confinement to one compartment during place conditioning trials limited horizontal movement and masked any differences between modafinil and vehicle treatment groups. Additional investigations on the im-

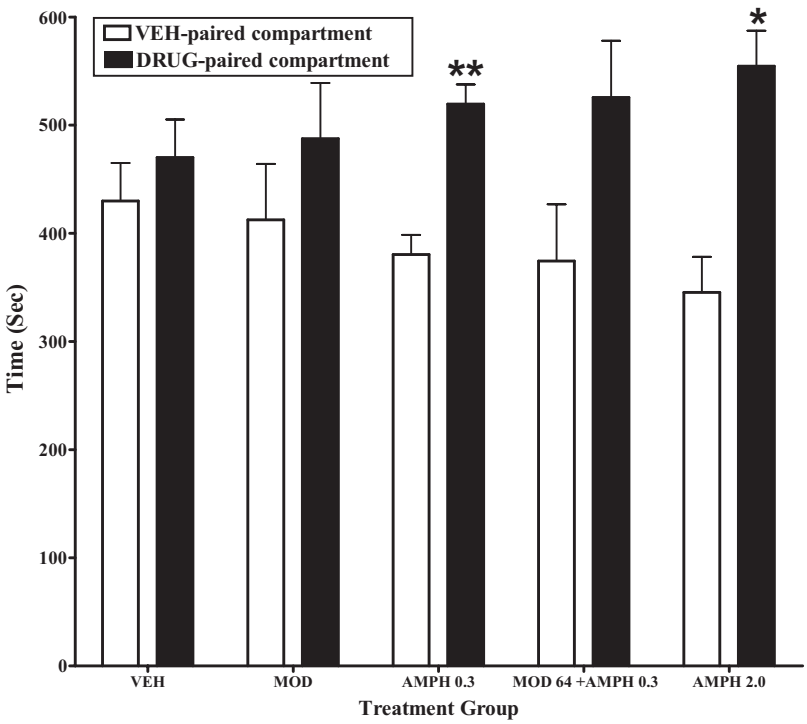

Figure 2. Mean (±S.E.M.) time spent in drug-paired (dark bars) and vehicle-paired (light bars) compartments during the test phase. $n = 8$ per group. $^{*}p < 0.05$ or $^{**}p < 0.01$ indicates time in drug-paired compartment significantly different from time in vehicle-paired compartment. VEH = vehicle; MOD = modafinil; AMPH = d-amphetamine.

pact of environmental context on modafinil's behavioral effects may be of interest. Nevertheless, the results of the supplemental experiment confirm that 64 mg/kg modafinil is behaviorally active following oral administration.

The current findings also established that concurrent administration of a low oral dose of modafinil dose does not enhance the hyperlocomotor effects or CPP established by a low dose of d-amphetamine. There was a visually evident trend toward addi-

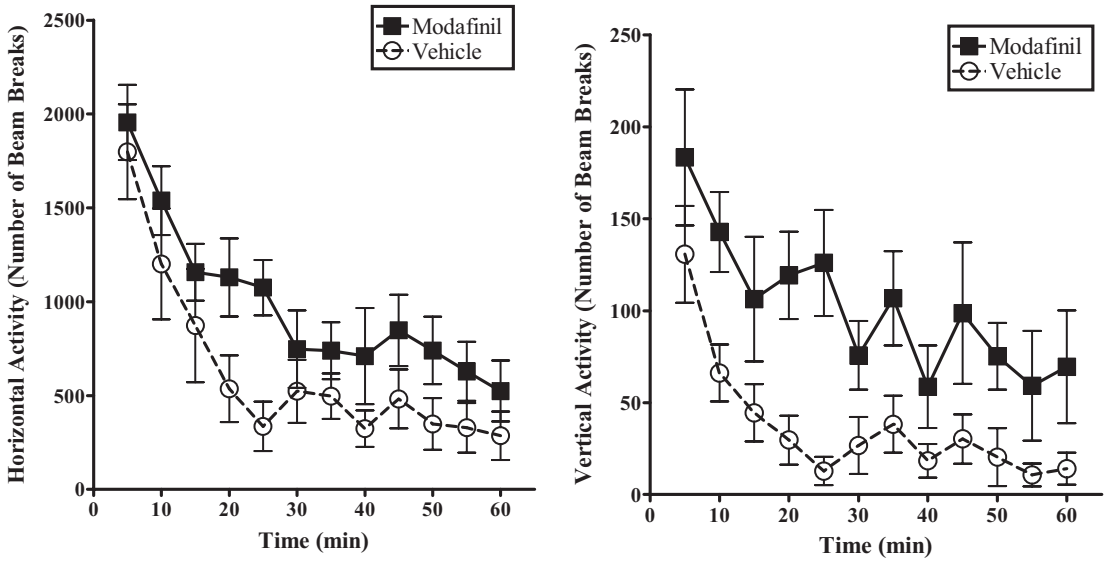

Figure 3. Horizontal (left) and vertical (right) activity during a 60-min period immediately following administration of 64 mg/kg modafinil ($n = 8$) or vehicle ($n = 7$). Each data point represents group means (±S.E.M.) during 5-min intervals.

tive acute locomotor effects of 64 mg/kg modafinil and 0.3 mg/kg d-amphetamine only on the first drug conditioning day. The lack of a statistically significant increase in activity with repeated exposure and the lack of evidence for CPP with this drug combination indicate these drugs do not have additive effects, at least at low doses. These findings suggest that low oral doses of modafinil will likely not enhance the behavioral effects of psychostimulants. However, in consideration of previous reports that higher modafinil doses significantly increase locomotor activity (Deroche-Gamonet et al., 2002), additional investigations with higher dose combinations of modafinil and d-amphetamine or other stimulants may be required to rule out the possibility that these drugs may have additive psychomotor stimulant effects.

These preliminary findings that a low oral dose of modafinil does not enhance psychomotor stimulant effects of d-amphetamine are somewhat encouraging in consideration of a growing interest in using modafinil as a treatment for psychostimulant dependence. Modafinil has been evaluated as a potential treatment for amphetamine (Mann & Bitsios, 2008), methamphetamine (Shearer et al., 2009), and cocaine (Dackis et al., 2005) dependence and abuse in clinical populations. Modafinil seems promising for this type of pharmacotherapy especially because archival research that examined all known outcomes in cases of reported modafinil ingestion concluded that no major side effects were seen, no deaths occurred, and any effect of modafinil overdose was mild (Carstairs, Urquhart, Hoffman, Clark, & Cantrell, 2010). In a sample of eight participants (one female and seven male African Americans) with a history of cocaine abuse, modafinil attenuated cocaine self-administration as well as subjective measures of craving in controlled laboratory conditions (Hart et al., 2008). In addition, a trend toward attenuation of the subjective effects of methamphetamine was observed after modafinil administration in 13 methamphetamine-dependent individuals not seeking treatment (De La Garza, Zorick, London, & Newton, 2010). However, double-blind placebo controlled studies with larger samples have yielded inconsistent findings. One study evaluating modafinil for the treatment of methamphetamine dependence found no significant differences between modafinil and placebo on subject-rated cravings and methamphetamine use (Heinzerling et al., 2010). Anderson et al. (2009) evaluated modafinil (200 and 400 mg/kg) as a treatment for cocaine dependence and found no statistically significant differences between placebo and modafinil. Although when alcohol dependent subjects were excluded from the analysis, significant differences were reported on the number of cocaine abstinent days.

Results of studies using animal models of drug reinstatement following self-administration also seem to support modafinil as a treatment for psychostimulant dependence. Following extinction of methamphetamine self-administration, modafinil did not reinstate methamphetamine seeking and actually blocked methamphetamine-primed and cue-primed reinstatement (Reichel & See, 2010). In a follow-up investigation, Reichel and See (2012) reported that chronic modafinil treatment attenuated cue-induced and methamphetamine-primed reinstatement, and even reduced methamphetamine-seeking behaviors following discontinuation of treatment. They also reported only a high dose of modafinil (300 mg/kg) reduced methamphetamine intake during maintenance of self-administration.

It is worth noting that it took researchers several years to determine the environmental events necessary to establish nicotine self-administration or CPP in nonhumans (Le Foll & Goldberg, 2006). More recently, results from CPP studies suggest that rats are more likely to express a preference for the nicotine-paired chamber if they are adolescents, food-deprived, or preexposed to nicotine, and it has been established that environmental stimuli paired with nicotine can maintain responding for up to 3 months in a self-administration paradigm (Le Foll & Goldberg, 2006). Further research may be required to determine whether this could also be true with modafinil. The current study is the first to report the combined effects of modafinil and d-amphetamine in the CPP paradigm. It is also worth consideration that some authors have argued that the CPP paradigm is limited to detecting "all-or-none" effects of drugs and may not be amenable to detecting dose-dependent effects (Bevins, 2005). In consideration of this criticism, CPP may not be the best procedure for assessing additive effects of modafinil and other psychostimulants. Therefore, although the results predict a low abuse liability with low doses of these substances in combination, additional research with higher doses and with other procedures may be warranted before ruling out the possibility that this drug combination may have greater addictive potential than modafinil or d-amphetamine alone.

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