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A two-phased screening paradigm for evaluating candidate medications for cocaine cessation or relapse prevention: Modafinil, levodopa–carbidopa, naltrexone

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ABSTRACT

Background: Cocaine pharmacotherapy trials are often confounded by considerable variability in baseline cocaine-use levels, obscuring possible medication efficacy. Testing the feasibility of using a prerandomization, abstinence-induction protocol, we screened three candidate medications to explore treatment response in patients who did, or did not, achieve abstinence during an extended baseline phase.
Method: Eligible treatment-seeking, cocaine-dependent subjects entered a 4-week baseline period (Phase I) with high-value abstinence contingent vouchers and two motivational interviewing sessions, followed by a 12-week medication trial (Phase II) with random assignment stratified on Phase I abstinence status to (1) modafinil (400 mg/d), (2) levodopa/carbidopa (800/200 mg/d), (3) naltrexone (50 mg/d), or (4) placebo. Treatment consisted of thrice-weekly clinic visits for urine benzoylecgonine testing and weekly cognitive behavioral therapy with contingency management targeting medication compliance.
Results: Of the 118 subjects enrolled, 81 (80%) completed Phase I, with 33 (41%) achieving abstinence, defined a priori as 6 consecutive cocaine-negative urines. Tests of the interaction of each medication (active versus placebo) by baseline status (abstinent versus nonabstinent) permitted moderator effect analysis. Overall, baseline abstinence predicted better outcome. Cocaine-use outcomes for levodopa and naltrexone treatment differed as a function of Phase I abstinence status, with both medications producing benefit in nonabstinent but not baseline-abstinent subjects. There was no evidence of a moderator effect for modafinil.
Conclusions: The two-phase screening trial demonstrated that subgrouping of patients with respect to baseline abstinence status is feasible and clinically useful for exploring cocaine cessation and relapse-prevention effects of candidate medications.

1. Introduction

Numerous candidate medications have been evaluated for treating cocaine dependence, but none have shown sufficient evidence of efficacy to receive US Food and Drug Administration approval. This has prompted a shift in medication development, away from the goal of finding a single "magic bullet" medication toward phased medication treatment sequences. Broadly, two phases of cocaine cessation and relapse prevention can be identified. For patients actively using cocaine, an effective pharmacotherapy for inducing abstinence might do so by reducing the severity of cocaine withdrawal symptoms or providing partial replacement. Alternatively, for the patient who has achieved initial abstinence, pharmacotherapy for preventing relapse might work by mediating conditioned effects of stimuli previously associated with cocaine. An experimental design and paradigm for evaluating medication efficacy in cocaine cessation versus relapse prevention entails using a prerandomization lead-in period with high-value voucher contingency management (CM).

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The utility of a lead-in period to establish level of cocaine use prior to randomization in a cocaine pharmacotherapy trial has been demonstrated in a series of studies by Bisaga et al. (2010, 2006, 2005). These reports indicate that approximately 44% of the participants achieve initial abstinence, defined as four or more cocaine-negative urine specimens during two weeks of lead-in with an intensive contingency reinforcement intervention. This methodology has permitted evaluation of differential medication effects of gabapentin (Bisaga et al., 2006) and memantine (Bisaga et al., 2010) in subgroups of early responders and nonresponders. Moreover, this subgrouping method responds to the FDA call for "enrichment" strategies to decrease heterogeneity in clinical-trial samples and increases the likelihood that a drug effect can be detected if one exists (FDA, 2013).

Each of the three medications selected for this study, modafinil, levodopa–carbidopa, and naltrexone, was previously evaluated for treating cocaine dependence and showed some evidence of benefit, although mixed. Determination of whether stronger treatment effects might emerge within homogeneous cocaine-dependent patient subgroups that achieved or did not achieve initial abstinence was critical. In addition to favorable safety profiles, the three medications have distinct mechanisms of action that might modulate cocaine use.

Modafinil, along with other effects, increases extracellular dopamine via transporter inhibition and has modest stimulant-like and cognitive-enhancing properties that might ameliorate cocaine-withdrawal symptoms. Initial positive clinical-trial findings (Dackis et al., 2005, 2003), while not fully confirmed in later trials (Anderson et al., 2009; Dackis et al., 2012), along with recent human laboratory research (Sofuoglu et al., 2013), suggest that modafinil may promote abstinence in chronic cocaine users by improving cognitive functions (Mereu et al., 2013) or by blunting cocaine euphoria (Dackis et al., 2003; Hart et al., 2008; Malcolm et al., 2006). Therefore, we hypothesized a stronger treatment effect of modafinil among the non-abstinent subgroup of patients.

The dopamine precursor levodopa increases central dopamine availability, which, in turn, is thought to improve brain reward circuits within a normal homeostatic range, as conceptualized by Koob et al. (Koob, 2008; Koob and Le Moal, 2008). Such actions may be particularly relevant during early recovery when a shift in attention toward nondrug rewards predicts success (Martinez et al., 2011). We reported previously that levodopa–carbidopa was associated with higher abstinence rates when administered concomitantly with abstinence-based CM, supporting the notion that this medication may have greater efficacy under conditions of reduced cocaine use or abstinence (Schmitz et al., 2008). Here we hypothesized a stronger treatment effect of levodopa among the subgroup of patients achieving initial abstinence.

Potential efficacy of naltrexone, a nonselective opioid receptor antagonist, for treating cocaine dependence is predicated on central endogenous opioid-system involvement in cocaine's reinforcing effects (Corrigall and Coen, 1991; Ramsey and van Ree, 1991). In a preliminary study ($n = 85$), naltrexone (50 mg/day) combined with relapse-prevention therapy was associated with reduced cocaine use in patients who completed an initial cocaine detoxification program (Schmitz et al., 2001). More recent double-blind, placebo-controlled studies reported no benefit of naltrexone at doses ≥50 mg/day but without regard to baseline abstinence status (Pettinati et al., 2008; Schmitz et al., 2009, 2004). Addressing these equivocal results, we hypothesized that under well-defined conditions of abstinence, stronger treatment effects of naltrexone would emerge.

In summary, the overarching aim of this study was the evaluation of a paradigm for screening multiple medications (compared with placebo) in parallel for ability to reduce cocaine use in active users ("cocaine cessation") and maintain abstinence in recent nonusers ("relapse-prevention"). Here, the two-phase screening trial provided a vehicle to evaluate baseline abstinence status as a general predictor of treatment outcome, and more specifically, as a moderator of medication response.

2. Methods

2.1. Study design

Consenting subjects entered a 4-week non-medicated baseline period (Phase I), during which initiation of abstinence from cocaine was encouraged and supported with brief Motivational Interviewing (MI) sessions and CM. Achievement of abstinence during baseline was operationally defined as six consecutive cocaine-negative urines, i.e., two weeks, consistent with definitions reported in the literature (Bisaga et al., 2010; Crits-Christoph et al., 2013; McCann and Li, 2012). Comparative parallel medication evaluation (Phase II) followed stratification (abstinent/nonabstinent), randomization, and dose titration and lasted 12 weeks (Fig. 1). Subjects who achieved abstinence criteria in less than four weeks entered Phase II immediately to avoid resuming cocaine use prior to starting medication treatment. During Phase II, subjects received weekly individual cognitive-behavioral therapy (CBT) and CM targeting medication compliance. Thrice-weekly clinic visits (MWF)

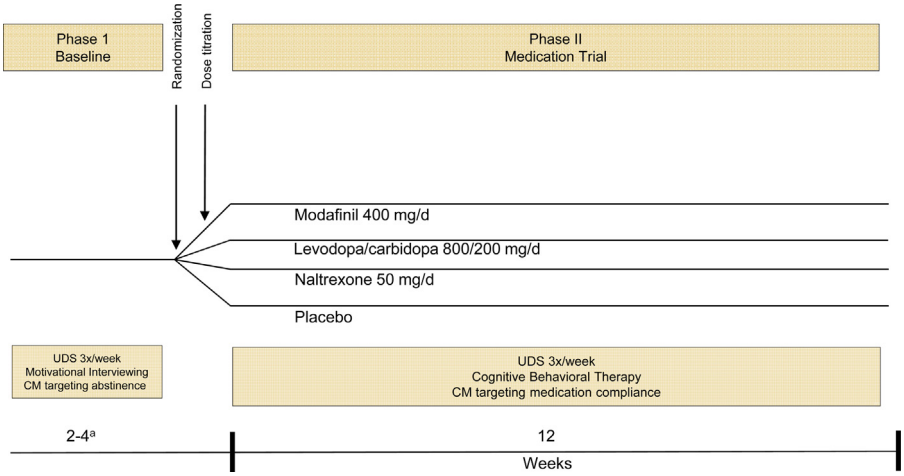

Fig. 1. Diagram of study design. UDS, urine drug screen; CM, contingency management. [a]Phase I baseline period ranged from 2 to 4 weeks to allow subjects who achieved abstinence criteria in less than four weeks to be randomized and begin dose titration on assigned study medication for Phase II that lasted 12 weeks.