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Modafinil does not reduce cocaine use in methadone-maintained individuals

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ABSTRACT

Introduction: There are no approved medications for the treatment of cocaine use disorder (CUD). Modafinil, a cognitive-enhancer with weak stimulant-like effects, has shown promise in initial studies as a treatment for CUD. Its potential efficacy has not been examined in individuals dually dependent on cocaine and opioids.

Methods: This study examined the efficacy of modafinil, in combination with contingency management (CM), for reducing cocaine and opioid use and improving cognitive function in methadone-stabilized individuals with opioid and cocaine dependence. We conducted a 17-week, double-blind, randomized controlled trial in which participants were randomized to one of four conditions: 1) modafinil + CM; 2) modafinil + yoked-control (YC); 3) placebo +CM; or 4) placebo + YC. Additionally, all subjects received platform treatments of cognitive behavioral therapy (CBT) and methadone. While the original planned sample size was $N = 160$, a total of 91 participants were randomized. The two primary cocaine use outcomes were percentage of urine specimens positive for cocaine and percent of days of self-reported abstinence from cocaine during treatment. Cognitive function, opioid use, and secondary cocaine use outcomes were also considered.

Results: Modafinil was well-tolerated with minimal reports of adverse effects. Modafinil was no more effective than placebo in reducing cocaine or opioid use or improving cognitive performance.

Conclusions: In the context of a trial with robust control conditions and platform treatments, these findings did not provide support for the efficacy of modafinil treatment for the treatment of CUD in methadone-stabilized individuals with dual opioid and cocaine dependence.

1. Introduction

Cocaine use disorder (CUD) is a significant public health problem, with an estimated 5.5 million individuals who used cocaine within the past year, in the United States (SAMHSA, 2017). An alarming development is the recent increase in overdose deaths related to cocaine, which tripled between 2013 to 2018 (Hedegaard et al., 2022). Over the past 3 decades, many medications with different pharmacological effects have been tested as potential treatments for CUD. Unfortunately, despite some promising findings, including with modafinil, many findings could not be consistently replicated in larger clinical trials and there are no approved medication treatments for CUD (Buchholz and Saxon, 2019 Kampman, 2019;). To overcome this impasse, the prevailing focus has been to identify novel treatment targets for CUD. However, others have emphasized the need to consider existing medications while focusing on the heterogeneity or individual differences among those with CUD and methodological factors in treatment trials (e.g., outcomes, study duration, sample size) as potential sources of inconsistent results across studies (Brandt et al., 2020). Among these potential confounds, co-occurring mental health or substance use disorders (e.g., such as co-occurring opioid use disorder (OUD) and methadone-maintenance) may affect the treatment response among those with CUD.

Modafinil is a medication that yielded mixed results in clinical trials for CUD. It is a cognitive-enhancer with weak stimulant-like effects and is approved for the treatment of narcolepsy, obstructive sleep apnea, and shift work sleep disorder (Murillo-Rodríguez et al., 2018). Its pharmacological mechanisms of action include inhibition of dopamine and norepinephrine transporters as well additional actions on brain γ-Aminobutyric acid (GABA), glutamate, and orexin systems (Mereu et al., 2013 Minzenberg and Carter, 2008;). Modafinil was suggested to be a candidate for agonist or replacement pharmacotherapy for CUD since it blocks the dopamine transporter, resulting in in-

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creased synaptic dopamine levels, as does cocaine (Grabowski et al., 2004). In some randomized clinical trials, modafinil was found to be more effective than placebo in reducing cocaine use (Dackis et al., 2005 Kampman et al., 2015; Morgan et al., 2016;), or other outcomes (e.g., craving for cocaine (Anderson et al., 2009 Kampman et al., 2015;); indicators of sleep quality (Morgan et al., 2016, 2010)). However, other RCTs did not support these promising findings, in terms of primary cocaine use outcomes (Anderson et al., 2009 Dackis et al., 2012; Karila et al., 2016; Nuijten et al., 2016;, 2015 Schmitz et al., 2014;, 2012), or other outcomes (e.g., craving and withdrawal (Dackis et al., 2005, 2012), cognitive function (Nuijten et al., 2016)). Importantly, a recent meta-analysis of 11 double-blind randomized clinical trials did not find modafinil to be superior to placebo in improving abstinence from cocaine (Sangroula et al., 2017). The meta-analysis also noted the findings supported a good safety profile of modafinil and that some secondary post-hoc analyses provided preliminary indications that modafinil may be effective in some subgroups of CUD (Sangroula et al., 2017); such as within cocaine users without a history of alcohol use disorder (Anderson et al., 2009 Kampman et al., 2015;)(Anderson et al., 2009 Kampman et al., 2015;), or males (not females) in analyses split by gender (Dackis et al., 2012). One CUD subgroup of interest is individuals who use cocaine and are on opioid agonist treatment (e.g., methadone) for opioid use disorder (OUD). Cocaine use continues to be an intractable problem among those who are on opioid agonist treatment (Roux et al., 2016). In a systematic review, co-occurring cocaine use was associated with lower retention in opioid substitution treatment (e.g., with methadone or buprenorphine) (O'Connor et al., 2020). To our knowledge, modafinil has not been evaluated in individuals with CUD who are maintained on methadone.

The goal of this study was to test the efficacy of modafinil plus contingency management (CM), compared to modafinil plus yoked control (YC), placebo plus CM or neither treatment (placebo plus YC), in a sample of individuals with co-occurring CUD and OUD who are all also receiving platform treatments of cognitive behavioral therapy (CBT) and methadone. CM provided reinforcers (payment) contingent upon participant's own cocaine-negative urine specimens; YC served as a control for the CM condition wherein participants received payments which were not contingent upon their own cocaine-negative urine specimens but were instead matched to a CM participant's urinalysis results. In previous clinical trials, CM was found to be effective in reducing cocaine use and improving treatment retention beyond what is achieved by counseling alone (Petry, 2000). In a previous study with opioid and cocaine dependent participants (Poling et al., 2006), a combination of bupropion and CM was more effective than either treatment alone, or placebo, in reducing cocaine, but not opioid, use. Based on these results, we hypothesized that the combination of modafinil plus CM would have greater efficacy in reducing cocaine use than either treatment alone or neither treatment (placebo plus YC). In addition, we hypothesized that cognitive function would be improved in response to modafinil treatment, and that improvements in the cognitive domains would contribute to improved treatment outcomes for CUD.

2. Methods

2.1. Participants

A total of 91 individuals (33 female), aged 18 to 65, who were seeking treatment for both cocaine and opioid dependence were recruited between 1/29/2008 and 10/1/2013 from the greater New Haven area for this study (See Consort Diagram (Fig. 1)). It should be noted that the original planned sample size of $N = 160$ was not reached. Eligible participants met the criteria for current opioid and cocaine dependence, as determined by the study physician and confirmed by the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1996). Participants were required to have previous treatment for opioid dependence or signs of withdrawal, history of using a minimum of 0.5-gram cocaine during the preceding 30 days and have a urine screen confirmation of cocaine use within 2 weeks prior to admission. Women of child-bearing age were required to provide a negative urine pregnancy test, agree to use adequate birth control and to have monthly urine pregnancy tests during study participation. Potential participants were excluded if they met criteria for current criteria for abuse or dependence for drugs other than cocaine, opioids, or tobacco; had current serious medical problems (e.g., major cardiovascular, renal, endocrine, hepatic or neurological illnesses) or current suicidality or major psychiatric disorders (e.g., schizophrenia, major depression or bipolar disorder); current use of over-the-counter or prescription psychoactive drugs (e.g., antipsychotics, mood stabilizers, antidepressants, anxiolytics, psychostimulants); known allergy to modafinil or methadone; or were unable to read and understand the consent form. Eligibility was determined at screening through physical and psychiatric examination, blood work, electrocardiogram (ECG), urine analysis, and urine toxicology screening.

This study was registered at clinicaltrials.gov (NCT00838981) and approved by the VA Connecticut Human Studies Subcommittee and the Yale University Human Investigations Committee. Participants received weekly compensation to mitigate transportation costs for study attendance, plus additional payments as part of treatment, as described below.

2.2. Procedure/Interventions

This study was a randomized, double-blind, placebo-controlled, outpatient clinical trial in which subjects were randomized to one of four treatment groups: 1) modafinil + Contingency Management (CM); 2) modafinil + yoked-control (YC); 3) placebo + CM; or 4) placebo + YC. A computerized urn randomization program to balanced groups on gender, age, and self-reported days of cocaine use within the month prior to the study.

Participants attended clinic 6 days/week (Monday - Saturday) to receive methadone and the assigned study medication under direct supervision. On Saturdays, participants received take-home bottles of methadone and the study medication to be taken on Sundays. In addition to receiving methadone and the study medication, all participants were offered weekly individual sessions of manual-guided Cognitive Behavior Therapy (CBT) (Carroll, 1998) as the 'behavioral platform' (Carroll, 1997). CBT was provided weekly throughout study participation, in individual (one-on-one) sessions. CBT was delivered by counselors with Masters-level training (or above) and who were supervised in their delivery of this treatment by a licensed psychologist. Participants were asked to complete weekly assessments and submit urine samples 3 times/week.

The study had 3 phases: methadone induction (1–2 weeks), treatment (11 weeks) and detoxification/transfer (4 weeks) phases. For the methadone induction, participants who were not on methadone were started on 30 mg of methadone during the first week and the dose was increased to reach a stable dose over a 2-week period with an approximate target dose of 60 mg/day and a maximum dose of 120 mg/day methadone. Those who were already on methadone were kept on their stable dose.

In the treatment phase, the randomized treatments (modafinil or placebo, and CM or YC) were initiated and continued throughout the treatment phase. Modafinil treatment was initiated at 200 mg/day dose and titrated up to 400 mg/day after 3 days, given as a two 200 mg tablets in the morning. The 400 mg dosage is within the recommended dosage range for modafinil for its clinical use (Murillo-Rodríguez et al., 2018). Participants randomized to placebo were administered two placebo pills in the morning. Treatment groups remained on their full dosage for 11 weeks.

During the treatment phase, the participants earned CM vouchers (with monetary value) based on cocaine-free urine specimens. Urine specimens were collected thrice weekly. Participants were administered vouchers up to thrice weekly; all vouchers could be traded in for their

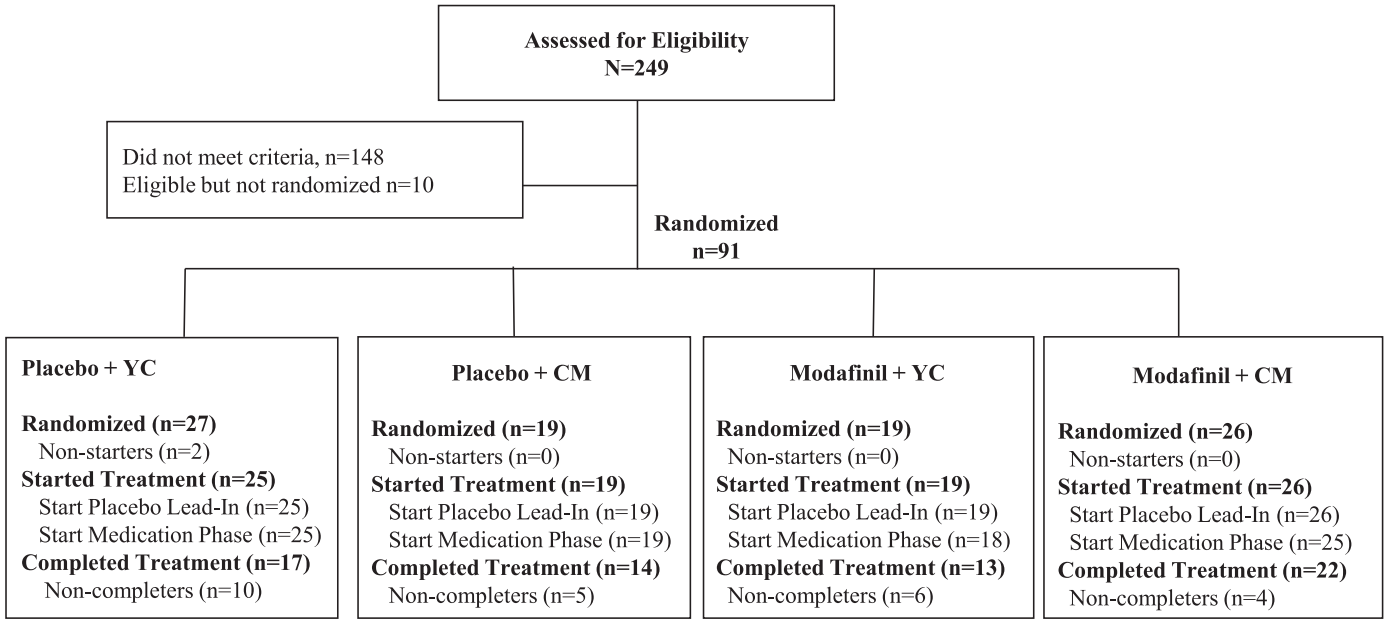

Fig. 1. CONSORT Diagram: Flow of Participants through the Protocol.
Treatment consisted of 12 weeks of randomization to a medication condition (Modafinil or Placebo), plus a behavioral treatment condition (Contingency Management (CM) or Yoked Control (YC)). In addition, all treatment conditions were methadone-maintained and offered Cognitive Behavioral Therapy (CBT) as a platform treatment. Regardless of treatment condition, treatment began with a Placebo Lead-In period. The Medication Phase consisted of titration period, followed by the medication maintenance period. All participants who started the titration period also started the medication maintenance period. After completion of the 12-week treatment, there was medication taper period. "Completed Treatment" refers to completing the titration period and the medication maintenance period. All participants who completed treatment also completed the taper.

monetary value at the end of each week. Participants randomized to the CM condition received a voucher if their urine specimen was negative for cocaine, starting at $3 for each negative urine specimen and escalating by $1 per consecutive cocaine-free urine specimen submitted up to a maximum of $15 per cocaine-free specimen. If participants failed to provide a scheduled specimen or provided a specimen that was positive for cocaine, the voucher reset back to $3 for the next cocaine-free specimen they provided. The purpose of the YC condition was to provide a control for CM wherein participants received a similar amount and schedule of reinforcers, but the crucial difference was that the reinforcers were not contingent upon the participant's own substance use behavior. Participants in the YC condition were yoked with (i.e., paired with) a CM participant and the participant in the YC condition received the schedule of payments of the CM participant to whom they were yoked. If their paired CM participant terminated early, the YC participant continued to receive vouchers in an amount equal to the average voucher value for the last two weeks of the paired CM participant's study participation. Participants in the CM condition were informed that the vouchers were contingent on the cocaine-free urine specimens they provided, as described above; participants in the YC condition were informed that they would receive vouchers according to an unpredictable schedule, and that they could not control when they would receive these vouchers or how much they would be worth. In total, CM and YC participants could earn up to $462 in vouchers.

During the detoxification/transfer phase in the last four weeks of the study, the dose of the study medication was reduced by half (to 200 mg/day modafinil) for one week and discontinued the following week with no modafinil given in the final weeks. Participants underwent detoxification from methadone, if needed. Those who wished to continue with methadone treatment, were referred to a methadone program.

Throughout the study, participants could have their medication withheld or be discharged from the study for several reasons, including excessive use of alcohol or other substances, repeatedly missing doses, or treatment sessions, or due to adverse reactions to any of the treatments. Detailed protocols for medication withholding or study discharge are included in the Supplemental Materials.

2.3. Outcomes

Cocaine use was determined by thrice weekly urine toxicology results and self-reports of drug use. Urine specimens were analyzed to detect opioid, cocaine metabolite (benzoylecgonine), and other drugs of abuse (e.g., benzodiazepines, marijuana, amphetamines). The cutoff range for positive urine was >300 ng/ml for cocaine and >200 ng/ml for opioids. These analyses were performed at the clinical laboratory of the VA CT Healthcare System. Self-reported drug use (cocaine, any opioids (heroin, other opioids), alcohol) was obtained through the Timeline Follow Back (TLFB) method. The primary cocaine use outcomes were 1) percentage of urine specimens positive for cocaine (out of all urine specimens submitted during the treatment trial) and 2) percent of days of self-reported abstinence during treatment (out of all days in the treatment protocol). Secondary cocaine use outcomes were longest duration of self-reported abstinence during treatment, and percent reduction in self-reported days of use from baseline to end of treatment; the same outcomes were calculated where possible for any opioids (heroin, other opioids), and alcohol use.

The cognitive domains assessed included impulsivity (Sustained Attention to Response Test (SART)(Robertson et al., 1997)), memory (Hopkins Verbal Learning Test-Revised (HVLT-R) (Brandt, 1991), and tasks from Cambridge Neuropsychological Test Automated Battery (CANTAB) (www.cambridgecognition.com) assessed memory (Pattern Recognition Memory (PRM) and Delayed Matching to Sample (DMTS)) sustained attention (Rapid Visual Information Processing (RVP)) and spatial planning (Stockings of Cambridge (SOC)). The full cognitive assessment was completed at baseline and approximately mid-way through the treatment phase (Week 6).

Adverse effects were assessed weekly with an in-house Brief Symptom Checklist (BSC), which was used in prior trials (e.g., (Sofuoglu et al.,

Table 1
Demographics and baseline measures.

Baseline and Demographics	Placebo + YC (*N* = 27)		Placebo + CM (*N* = 19)		Modafinil + YC (*N* = 19)		Modafinil + CM (*N* = 26)		Total Sample (*N* = 91)		Treatment Group (4 groups) Statistics		
Categorical Variables	n	%	n	%	n	%	n	%	n	%	X^2	df	p
Sex/Gender: N Female,% Female	11	40.7	6	31.6	9	47.4	7	26.9	33	36.3	2.41	3	0.49
Race/Ethnicity[a]											8.31	6	0.22
White	15	55.6	14	73.7	10	52.6	20	76.9	59	64.8			
Black	4	14.8	3	15.8	4	21.1	5	19.2	16	17.6			
Latine/Hispanic	8	29.6	2	10.5	5	26.3	1	3.8	16	17.6			
Education Level[a]											6.28	6	0.39
At least some College	7	25.9	7	36.8	7	41.2	6	23.1	27	30.3			
High School	19	70.4	11	57.9	7	41.2	16	61.5	53	59.6			
Less than High School	1	3.7	1	5.3	3	17.6	4	15.4	9	10.1			
Continuous Variables	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	df	p
Age	38.20	11.40	34.50	10.20	41.47	10.23	38.90	10.80	38.24	10.80	1.43	3,87	0.24
Years of cocaine use	20.04	14.61	17.78	12.45	21.41	12.11	21.16	16.58	20.13	14.17	0.25	3, 82	0.86
Years of heroin use	14.88	17.06	9.22	10.07	14.00	12.25	16.28	15.27	13.93	14.37	0.90	3, 82	0.44
Years of other opioid use	11.12	12.29	4.33	8.78	9.94	13.63	4.76	7.47	7.62	10.96	2.35	3, 82	0.08
Years of alcohol use	19.19	14.32	17.33	11.09	23.88	12.05	18.44	14.15	19.51	13.19	0.84	3, 82	0.48
Days cocaine use in 28 days prior to baseline	10.42	8.15	12.39	8.18	10.24	7.91	10.96	7.41	10.95	7.80	0.28	3, 82	0.84
Days of heroin use in 28 days prior to baseline	7.42	9.91	13.72	10.44	7.24	10.49	13.40	11.61	10.44	10.92	2.42	3, 82	0.07
Days of other opioid use in 28 days prior to baseline	4.85	8.48	2.94	6.59	2.59	7.03	1.80	5.03	3.12	6.91	0.88	3, 82	0.46
Days of alcohol use in 28 days prior to baseline	1.15	3.36	0.00	0.00	1.06	2.56	0.76	2.09	0.78	2.44	0.89	3, 82	0.45
HAM-D: Depressive symptoms at baseline	6.08	5.81	5.95	7.65	2.94	3.61	4.84	5.53	5.07	5.86	1.16	3, 82	0.33
ESS: Sleepiness at baseline	7.69	3.98	6.37	3.52	7.44	4.30	8.92	6.05	7.72	4.68	1.12	3, 83	0.34

Abbreviations: YC=Yoked Control; CM= Contingency Management; HAM-*D*= Hamilton Depression Scale; ESS=Epworth Sleepiness Scale.

[a] Statistics for Race/Ethnicity and Education Level are shown for descriptive purposes only as some cell sample sizes for these variables preclude inferential interpretation.

2017)). The BSC includes 67 items grouped into 8 categories: psychiatric, allergic, neurological, endocrine, autonomic, cardiovascular, gastrointestinal, or other

Secondary domains assessed included withdrawal symptoms (Cocaine Withdrawal Symptoms (CWS), Opiate Withdrawal Scale (OWSC), sleepiness/wakefulness (Epworth Sleepiness Scale (ESS) (Johns, 1991)), and depressive symptoms (Hamilton Depression Scale (HAM-D) (Hamilton, 1960)) and impulsivity (Barratt Impulsiveness Scale, version 11 (BIS-11; (Patton et al., 1995)). CWS, OWSC, ESS and BIS-11 were administered weekly; HAM-D was administered monthly.

Structured Clinical Interview for DSM–IV (First et al., 1996) was administered at intake to determine any DSM–IV Axis I psychiatric diagnoses to determine eligibility. The Addiction Severity Index (ASI) was also administered at baseline.

More details on the assessments and outcome measures are presented in the Supplemental Materials.

2.4. Statistical analyses

The full randomized (intent-to-treat) sample was used for data analyses (for the CONSORT Diagram, see Fig. 1). Treatment group (4 groups) comparisons for baseline measures were conducted using chi-square tests for categorical measures and ANOVA for continuous measures. Two sets of chi-square tests assessed whether the frequency of within-treatment adverse events differed across all four treatment groups, or between the medication conditions (modafinil, placebo). Treatment group comparisons for substance use outcomes and secondary domain outcomes (e.g., withdrawal, sleepiness) were conducted using ANOVA for continuous measures, with two treatment group factors: medication group (modafinil, placebo), CM group (CM, YC); and included the interaction between these conditions (medication*CM interactions). For cognitive outcomes, which were collected at two timepoints, repeated measures ANOVAs included time (baseline (week 0), mid-treatment (approximately week 6)) as a within-subject factor, two treatment group factors as between-subject factors: medication group (modafinil, placebo), CM group (CM, YC), and all interactions. Since the key comparisons for cognitive outcomes were the change in cognitive performance from baseline to within-treatment the modafinil versus placebo groups, the time*medication group interaction was the main outcome of interest.

Treatment group comparisons on baseline measures are presented in Table 1. Treatment group comparisons on adverse effects, treatment engagement and retention, primary substance use outcomes, and primary cognitive measures are presented in Table 2. Uncorrected p-values are reported in the tables, and table legends report the Bonferroni-corrected p-value threshold for each outcome domain. For visualization purposes, cocaine or opioid use per week (self-report) and overall (urine specimens) are presented in Fig. 2.

Secondary analyses are presented in detail in the Supplemental Materials. Briefly, these include: 1) secondary outcome measures; 2) consideration of primary outcome measures across subgroups: a) treatment starters or treatment completers; use of more stringent timing-of-assessment criteria for inclusion in cognitive analyses; b) sex/gender differences; and 3) covarying for baseline cocaine use severity.

3. Results

3.1. Baseline characteristics, treatment adherence and safety

Treatment groups did not differ on baseline measures (Table 1).

3.2. Treatment retention and adherence

No significant group differences were found for indicators of treatment retention or adherence including days retained in the study, days of missed medication, methadone dose, or payments (for CM or YC) or (Table 2A). Of the 91 participants who were randomized, 88 (96.7%)

Table 2
Adverse Effects and Treatment Outcomes.

Outcomes	Treatment Group (Medication and CM Conditions)								Medication Condition				Overall	Statistics (2 Chi-Square Analyses)[b]					
A) # Participants Reporting Adverse Effects	Placebo + YC (n=25)		Placebo + CM (n=18)		Modafinil + YC (n=17)		Modafinil + CM (n=25)		Placebo (YC or CM) (n=43)		Modafinil (YC or CM) (n=42)		Total Sample (n=85)	Medication Condition (Modafinil v. Placebo)			Treatment Group (4 Groups)		
BSC Symptoms Reported by ≥ 5 Participants[a]	N	%	n	%	n	%	n	%	n	%	n	%	n	%	X^2	df	p	X^2	df	p
Disturbed Concentration	1	4.0	2	11.1	0	0.0	3	12.0	3	7.0	3	7.1	6	7.1	0.001	1	0.976	3.029	3	0.387
Agitation	1	4.0	6	33.3	3	17.6	4	16.0	7	16.3	7	16.7	14	16.5	0.002	1	0.962	6.567	3	0.087
Tiredness	5	20.0	6	33.3	5	29.4	10	40.0	11	25.6	15	35.7	26	30.6	1.027	1	0.311	2.438	3	0.487
Drowsiness	1	4.0	3	16.7	2	11.8	7	28.0	4	9.3	9	21.4	13	15.3	2.412	1	0.120	5.767	3	0.124
Insomnia	5	20.0	2	11.1	4	23.5	9	36.0	7	16.3	13	31.0	20	23.5	2.542	1	0.111	3.877	3	0.275
Nightmares	6	24.0	4	22.2	0	0.0	2	8.0	10	23.3	2	4.8	12	14.1	**5.994**	**1**	**0.014**	6.555	3	0.088
Depression	4	16.0	4	22.2	4	23.5	9	36.0	8	18.6	13	31.0	21	24.7	1.741	1	0.187	2.805	3	0.423
Anxiety	2	8.0	4	22.2	5	29.4	8	32.0	6	14.0	13	31.0	19	22.4	3.537	1	0.060	4.796	3	0.187
Numbness	2	8.0	4	22.2	2	11.8	5	20.0	6	14.0	7	16.7	13	15.3	0.121	1	0.728	2.284	3	0.516
Cramps	1	4.0	5	27.8	4	23.5	4	16.0	6	14.0	8	19.0	14	16.5	0.401	1	0.527	5.118	3	0.163
Headache	6	24.0	3	16.7	4	23.5	6	24.0	9	20.9	10	23.8	19	22.4	0.101	1	0.750	0.427	3	0.935
Constipation	3	12.0	8	44.4	3	17.6	11	44.0	11	25.6	14	33.3	25	29.4	0.615	1	0.433	**9.306**	**3**	**0.025**
Decreased Appetite	0	0.0	3	16.7	1	5.9	4	16.0	3	7.0	5	11.9	8	9.4	0.605	1	0.437	5.230	3	0.156

(*continued on next page*)

Table 2
(*continued*)

B) Treatment Outcomes	Treatment Group (Medication and CM Conditions)												Overall			Statistics (ANOVA)[c]								
	Placebo + YC			Placebo + CM			Modafinil + YC			Modafinil + CM			Total			Medication (Modafinil, Placebo)			Contingency Management (CM, YC)			Medication * CM Interaction		
	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	F	df	p	F	df	p	F	df	p
Treatment Retention and Adherence Measures																								
Days in the study treatment protocol	66.85	26.98	27	72.05	20.51	19	68.16	26.02	19	73.50	23.75	26	70.11	24.39	91	0.07	1, 87	0.79	1.01	1, 87	0.32	0.00	1, 87	0.99
Number of missed medication doses	3.16	4.01	25	4.11	7.02	19	2.44	2.87	18	1.88	3.97	24	2.86	4.65	86	2.11	1, 82	0.15	0.03	1, 82	0.85	0.56	1, 82	0.46
Number of scheduled urine specimens submitted	31.44	7.07	25	30.16	8.62	19	28.11	11.18	19	31.96	8.36	26	30.61	8.74	89	0.17	1, 85	0.69	0.47	1, 85	0.50	1.87	1, 85	0.18
Amount of CM (or YC) Payment Received ($)	162.31	147.20	26	166.84	170.36	19	202.50	175.15	18	148.65	164.28	26	167.42	161.40	89	0.10	1, 85	0.76	0.49	1, 85	0.48	0.69	1, 85	0.41
Methadone dose	72.96	31.84	27	66.84	17.81	19	69.71	30.95	17	70.19	25.20	26	70.22	26.90	89	0.00	1, 85	0.99	0.23	1, 85	0.63	0.31	1, 85	0.58
Within-Treatment: Primary Substance Use Outcomes																								
% urine specimens positive for cocaine	51.69	37.20	25	53.92	34.44	19	63.35	31.63	19	55.09	38.70	26	55.65	35.61	89	0.69	1, 85	0.41	0.15	1, 85	0.70	0.46	1, 85	0.50
% urine specimens positive for any opioids	46.86	41.62	25	46.27	38.04	19	51.04	38.24	19	54.51	38.40	26	49.86	38.71	89	0.55	1, 85	0.46	0.03	1, 85	0.87	0.06	1, 85	0.81
% days self-reported abstinence from cocaine	71.87	25.85	23	78.57	21.38	19	75.93	16.90	17	67.62	34.42	25	72.94	26.30	84	0.347	1, 80	0.56	0.019	1, 80	0.89	1.66	1, 80	0.20
% days self-reported abstinence from any opioids	75.67	31.40	23	79.02	23.49	19	81.79	29.90	17	73.82	29.89	25	77.12	28.65	84	0.01	1, 80	0.94	0.13	1, 80	0.72	0.78	1, 80	0.38

(*continued on next page*)

Table 2
(*continued*)

C) Cognitive Task: Primary Cognitive Outcomes	Treatment Group (Medication and CM Conditions)												Overall			Statistics (ANOVA)[d]								
	Placebo + YC			Placebo + CM			Modafinil + YC			Modafinil + CM			Total			Medication (Modafinil, Placebo)			Time Point (Baseline, Mid-Treatment)			Medication * Time Interaction		
	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n	F	df	p	F	df	p	F	df	p
RVP: A'																								
Baseline (Week 0)	0.90	0.047	19	0.90	0.08	14	0.90	0.03	12	0.87	0.06	19	0.89	0.06	64	1.30	1	0.26	0.01	1	0.92	0.17	1	0.68
Mid-Treatment (Week 6)	0.89	0.063	19	0.90	0.05	14	0.90	0.05	12	0.88	0.06	19	0.89	0.06	64									
PRM: Percent Correct - Delayed																								
Baseline (Week 0)	71.67	16.00	15	79.76	17.82	14	78.47	9.03	12	80.30	13.74	22	77.78	14.66	63	0.07	1	0.80	1.13	1	0.29	4.86	1	0.03
Mid-Treatment (Week 6)	78.33	8.80	15	86.31	16.86	14	75.00	14.65	12	79.17	13.55	22	79.76	13.86	63									
DMS: Percent correct (all delays)																								
Baseline (Week 0)	72.22	15.21	18	80.48	12.93	14	80.48	11.83	14	74.67	13.09	20	76.46	13.60	66	1.60	1	0.21	1.49	1	0.23	1.29	1	0.26
Mid-Treatment (Week 6)	74.44	10.54	18	78.57	14.60	14	82.38	10.33	14	81.33	12.35	20	79.09	12.15	66									
SOC: Problems solved in minimum moves																								
Baseline (Week 0)	6.28	2.49	18	7.57	1.91	14	7.14	1.66	14	7.10	2.29	20	6.98	2.16	66	0.12	1	0.733	5.42	1	0.02	0.02	1	0.90
Mid-Treatment (Week 6)	6.89	2.72	18	8.14	2.25	14	7.50	1.65	14	7.80	1.85	20	7.56	2.17	66							0.16	1	0.69
SART: Proportion false alarms during target period																								
Baseline (Week 0)	0.66	0.25	15	0.72	0.25	13	0.62	0.22	13	0.72	0.25	20	0.68	0.24	61	0.04	1	0.85	3.68	1	0.06	0.15	1	0.70
Mid-Treatment (Week 6)	0.74	0.21	15	0.73	0.25	13	0.70	0.19	13	0.77	0.20	20	0.73	0.21	61									
HVLT: Total recall																								
Baseline (Week 0)	19.60	4.60	15	22.09	5.15	11	19.83	4.17	12	20.37	3.39	19	20.39	4.23	57	0.72	1	0.40	7.31	1	0.01	0.03	1	0.86
Mid-Treatment (Week 6)	20.87	3.56	15	23.73	3.66	11	22.33	3.77	12	20.42	4.27	19	21.58	3.98	57									

[a] BSC assesses 67 symptoms, within 8 domains. Only the symptoms reported by at least 5 participants are itemized here. In addition, the mean number of symptoms reported per domain did not differ by medication group (see Supplemental Table 2).

[b] For BSC Adverse Effects, two separate Chi-Square analyses are reported here: one compares based only on medication condition (modafinil, placebo), the other includes all four treatment groups.

[c] Analyses of Section B (Treatment Outcomes) were performed with ANOVAs including two between-subject factors (medication (modafinil, placebo) and CM condition (CM, YC)), and the medication*CM interaction. Secondary treatment outcomes are presented in Supplemental Table 1.

[d] Analyses of Section C (Cognitive Outcomes) were performed with ANOVAs including one within-subject factor (time (week 0, 6)) and two between-subject factors (medication (modafinil, placebo) and all interactions. However, since the medication*time interaction is of interest, it is presented here along with main effects of time and medication. The full results of the ANOVA (main and interactive effects of CM) are presented in Supplemental Table 3, which also contains the secondary cognitive outcomes.

Abbreviations: BSC=Brief Symptom Checklist; CM=Contingency Management; YC= Yoked Control; ANOVA=analysis of variance; RVP= Rapid Visual Information Processing; PRM= Pattern Recognition Memory; DMS=Delayed Matching to Sample; SOC= Stockings of Cambridge; SART= Sustained Attention to Response Test; HVLT= Hopkins Verbal Learning Test.

Uncorrected p-values are reported in the table. The following Bonferroni-corrected thresholds provide a more stringent threshold for each outcome domain: adverse events (13 outcomes; $p_{corrected}<0.004$); treatment retention and adherence (5 outcomes; $p_{corrected}<0.010$); primary substance use outcomes (4 outcomes; $p_{corrected}<0.013$); primary cognitive outcomes (6 outcomes; pcorrected<0.008); all outcomes in Table 2 combined (28 outcomes; $p_{corrected}<0.002$). Limited findings are significant at uncorrected thresholds ($p<0.05$) and no findings are significant at Bonferroni-corrected thresholds.

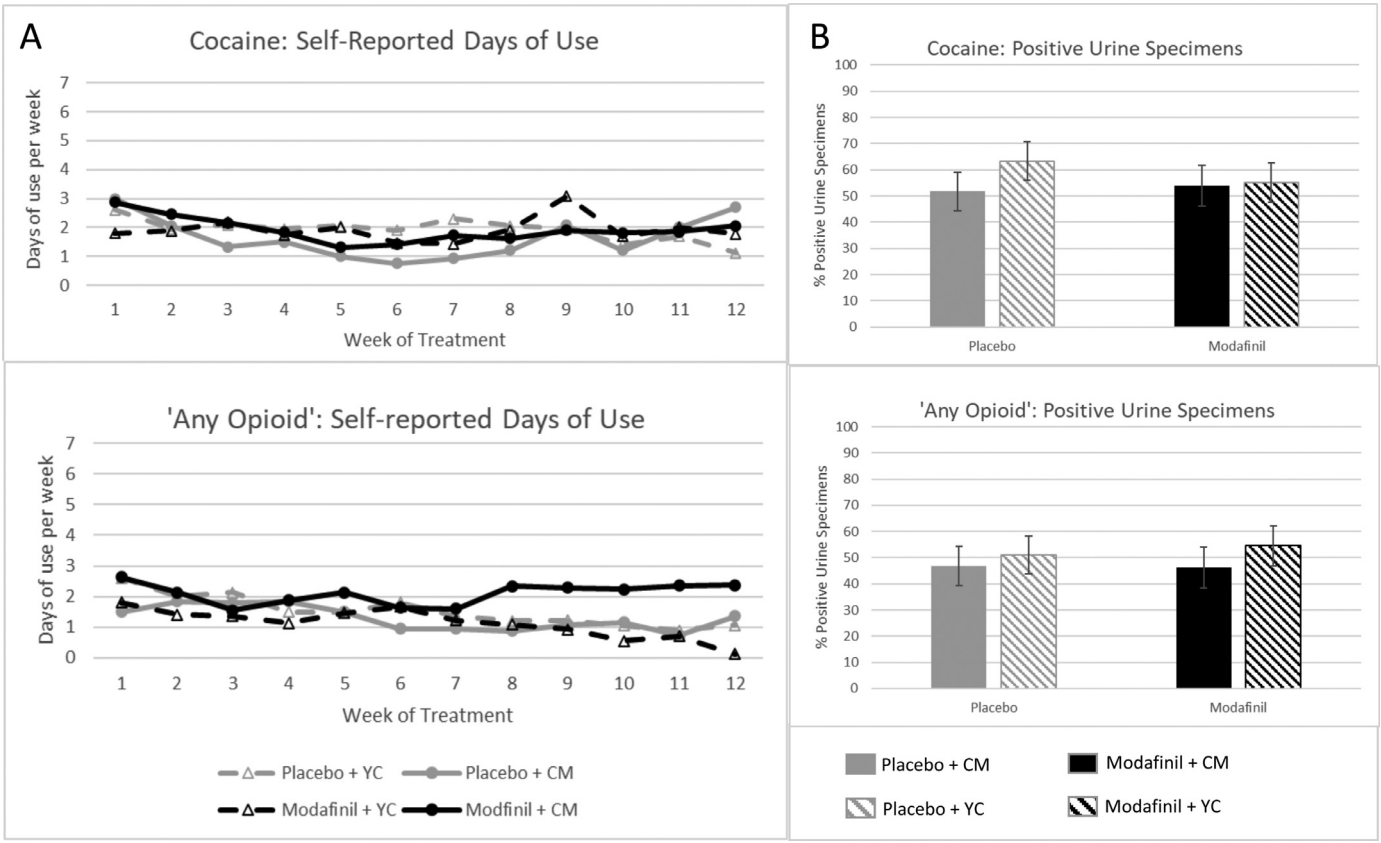

Fig. 2. Substance use during treatment.

started the modafinil (or placebo) titration phase, 87 (95.6%) started the modafinil (or placebo) maintenance phase, and 66 (72.5%) completed the modafinil (or placebo) maintenance phase (i.e., active treatment component) of the study (Fig. 1). Participants did not complete the study for several reasons including non-compliance with the study procedures, withdrawn by the PI due to adverse effects, or participants' request to transfer to another program (Fig. 1).

3.3. Safety and adverse effects

There were no significant differences across treatment groups in terms of adverse effects as measured by BSC, either when considering number of participants reporting individual symptoms (Table 2A), or average weekly symptoms grouped by symptom category (Supplemental Table 2). Two subjects were withdrawn from the study due to adverse effects (1 rash; 1 headache); both were in the modafinil + CM group. Another subject in the modafinil +CM group was withdrawn for assessment of suicidal ideation which was deemed not related to study participation.

3.4. Substance use outcomes

There were no significant effects of modafinil (vs. placebo), CM (vs yoked), or medication*CM on the primary cocaine or opioid use outcomes of percent of positive urines, percent days of abstinence (see Table 2B), or any of the secondary cocaine use or opioid use, other substance use outcomes (Supplemental Table 1).

3.5. Cognitive outcomes

Amongst the primary cognitive outcomes, findings did not support a cognitive enhancing effect of modafinil in this sample (see Table 2C). There were no significant main effects of modafinil.

Although there were two findings that survived a lenient statistical threshold ($p_{uncorrected}<0.05$), these findings did not support cognitive-enhancing effects of the medication, and they did not survive the more stringent Bonferroni-corrected thresholds. Namely, only one measure-delayed pattern recognition memory (percent correct)- showed a significant time*medication group interaction, yet performance slightly worsened in the modafinil group and slightly improved in the placebo group at mid-treatment relative to baseline. The only significant effects of time were improvements on the number of SOC problems solved in minimum moves and total recall on the HVLT, but neither differed by treatment condition.

Findings from the secondary cognitive outcomes and secondary analyses were also largely null (Supplemental Material and Supplemental Table 3).

3.6. Secondary domains

There were no significant effects of medication, CM, or medication*CM interactions on any of the secondary domains considered, namely cocaine withdrawal symptoms, opioid withdrawal symptoms, sleepiness, depressive symptoms, or self-reported impulsivity (Supplemental Table 1).

4. Discussion

This study showed that in opioid and cocaine dependent participants, treatment with modafinil was not different than placebo in reducing cocaine use over the course of an 11-week treatment. Similar findings were observed for opioid use with no significant difference between modafinil and placebo treatment. These negative findings are consistent with a recent meta-analysis of 11 randomized clinical trials which did not find modafinil superior to placebo in improving abstinence from cocaine

(Sangroula et al., 2017). We were interested to examine the efficacy of modafinil in participants dually dependent on cocaine and opioids. Our findings did not support the potential efficacy of modafinil in reducing cocaine or opioid use.

Modafinil was also not different than placebo in improving cognitive performance during the study participation. In a pilot study, 5 days of modafinil treatment, compared to placebo, improved working memory and sustained attention functions in 60 cocaine dependent participants who were in early abstinence (Kalechstein et al., 2013). Another study showed improvement in risk taking assessed with the Balloon Analogue Risk Task (BART) by modafinil, compared to placebo, in 30 cocaine dependent participants (Canavan et al., 2014). However, meta-analyses did not support the efficacy of modafinil as a cognitive enhancer in individuals with or without psychiatric disorders (Kredlow et al., 2019). Modafinil's actions as a cognitive enhancer may be limited to sleep-deprived individuals. Our results did not support the potential use of modafinil as a cognitive enhancer in opioid and cocaine dependent individuals.

An unexpected finding of our study was that the CM was no more effective than the YC group in reducing cocaine or opioid use. Many previous studies demonstrated the efficacy CM intervention on cocaine use (e.g., (Schmitz et al., 2010)) as well as cocaine use in opioid dependent samples maintained on methadone or buprenorphine (Ainscough et al., 2017), however, other studies reported negative findings (Katz et al., 2002 Schottenfeld et al., 2005; Umbricht et al., 2014;). In the current study, the amount of vouchers earned ($167 out of max $462) were less than those reported in our previous study ((Poling et al., 2006); i.e., $376 out of max $472). In our previous study (Poling et al., 2006), in addition to drug-negative urine specimens, abstinence-related activities were also reinforced. In addition, treatment duration was 25 weeks, compared to 11 weeks in this study. Another possible contributor to the lack of CM effects on cocaine use was the use of vouchers. Although the voucher was awarded on the day of the cocaine-negative urine, it could not be exchanged for money until the end of the week. Therefore, this approach may have reduced the efficacy of CM if the voucher was less reinforcing than direct payment, and the delivery of the primary reinforcer (payment) was delayed. Finally, a robust control condition for CM, namely YC, wherein participants received payments based on a different subject's abstinence (i.e., received equivalent payment but the payment was not *contingent* upon their own behavior), was included in order to isolate the effects of contingent reinforcers. Any generalized effects of the monetary reward (e.g., motivating continued engagement with the study) would be expected to be observed equally in the CM and YC groups. Therefore, inclusion of a YC condition likely reduced the ability to observe the CM effect.

One particular strength of the study was that the study medications were administered under supervision of study staff for 6 days a week. This approach addressed concerns with medication adherence, a common problem in individuals with CUD. The main limitation of this study is the small sample size, with 45 and 46 participants in the modafinil vs. placebo groups. Due to logistical challenges, the study was unable to attain the full target sample size ($N = 160$), so the analyses may not have had sufficient power to detect small effects. In addition, the study participants were both cocaine- and opioid-dependent and were stabilized on methadone. Thus, the study findings may not be generalized to cocaine users who are not maintained on methadone. Another possible limitation is that some study participants did not have high cocaine use at baseline, which may have impacted their motivation to quit cocaine. Baseline cocaine use severity can impact response to treatment (Nunes et al., 2011), for example, lower baseline use could adversely impact the ability capture meaningful reductions in cocaine use within the study period (Trivedi et al., 2021). Baseline cognitive function can also impact the degree to which pharmacotherapies produce cognitive enhancing effects (e.g., (Mehta et al., 2004)). Current CONSORT guidelines advise against covarying for baseline measures which may differ across groups (Moher et al., 2010); so our primary analyses did not include covariates. However, it is important to note that in the current study, the treatment groups did not differ in baseline cocaine use severity (see Table 1) and a secondary analysis which covaried for baseline cocaine use severity (see Supplemental Materials) did not change the pattern of findings (i.e., treatment group effects remained non-significant). Furthermore, the analyses addressing cognitive outcomes did account for baseline cognitive function since they assessed change in cognitive function from beginning of treatment to mid-treatment. So, while baseline function is important, it does not appear to explain the null findings in this case. The robust control conditions for both modafinil (placebo) and CM (yoked-control (YC)) as well as the inclusion of active platform treatments for all participants (CBT, methadone maintenance) are both a strength and a limitation of the study. These aspects of the study design are a strength in that they enable the isolation of specific modafinil and CM effects, above and beyond generalized benefits of other aspects of treatment. However, they are also a limitation in that findings may underestimate the impact that modafinil or CM would have in a clinical setting where such robust controls and platform treatments may be absent.

In conclusion, modafinil treatment neither reduced cocaine use nor improved cognitive function in methadone-maintained cocaine users. These results do not support the potential use of modafinil for the treatment of CUD in this patient population.

Declaration of Competing Interest

No conflicts declared.

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Contributors

JP, KMC, and MS were responsible for the study concept and design. JP and MS contributed to the acquisition of data. EED, TB, CN, KMC and MS assisted with data analysis and interpretation of findings. EED and MS drafted the manuscript. JP, TB, and CN provided critical revision of the manuscript for important intellectual content. All authors, except KMC, critically reviewed content and approved the final version of the manuscript for publication.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dadr.2022.100032.

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