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Provigil (Modafinil) Plus Cognitive Behavioral Therapy for Methamphetamine Use in HIV+ Gay Men: A Pilot Study

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Abstract

Objectives—To evaluate the efficacy of modafinil combined with cognitive behavioral therapy (CBT) for treatment of methamphetamine (MA) dependence among HIV+ gay men.

Methods—In a single blind trial, modafinil was administered for 12 weeks, followed by a 4-week placebo phase. CBT was conducted for 18 sessions over the 16-week study. Primary outcome measures were self-reported use of days per week plus urine toxicology assays. Additional measures included the Beck Depression Inventory, Cravings Scale, and O/C Crystal Use Scale. Response was defined as > 50% decline in days used per week. Thirteen patients were enrolled over an 18-month period.

Results—Ten patients (77%) completed the trial, although two discontinued modafinil due to side effects. Six of the ten study completers reduced their MA use by > 50%.

Conclusions—These preliminary results suggest good retention using combined medication and psychotherapy, and support further examination of modafinil and CBT in double-blind placebo controlled trials.

Keywords

Cognitive behavioral therapy; drug dependence; HIV/AIDS; methamphetamine abuse; modafinil

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

INTRODUCTION

Methamphetamine (MA) use in the gay community in New York City has escalated since the late 1990s. Its use is associated with rising rates of new HIV infection in men under 30 (1) as well as striking negative personal consequences including neuropsychiatric sequelae, occupational impairment, and financial losses. Since 2004, leaders in the New York City gay community have led efforts to address the problem through advertising programs and community meetings (2, 3). Among HIV+ MA users, adherence to antiretroviral medications is often reduced (4), which can lead to medication resistance and escalation of viral levels. Since unsafe sex is widespread during MA use, transmission of medication-resistant HIV to either infected or uninfected partners is a particularly unfortunate consequence.

Current NIDA guidelines for treatment include a course of structured time-limited psychotherapies and 12-step programs which are of limited effectiveness, with substantial attrition and relapse rates (5). This has led to explorations of combined treatment, adding a pharmacologic agent to time limited psychotherapy programs. Pharmacologic trials conducted with MA users have included selegeline, ondansetron, paroxetine (6), bupropion (7), and sertraline (8), usually accompanied by a structured therapy. None has shown clear-cut efficacy and attrition rates were as high as 85% (6).

Following Dackis' (9) encouraging preliminary results using modafinil for cocaine abuse, we chose this medication to accompany time limited structured psychotherapy in a pilot treatment study. Modafinil is a wakefulness-promoting agent approved to treat narcolepsy, sleep apnea, and shift-related sleep disorders. Modafinil seems particularly promising for MA abuse/dependence because it counteracts fatigue and concentration difficulties common after cessation of MA use; it may help correct maladaptive sleep patterns; and its onset of action is rapid, unlike that of antidepressants. Also, it does not cause euphoria (10) or tolerance (11) and has little abuse potential.

In this 16-week pilot study combining modafinil and psychotherapy, specific aims were: 1) to assess feasibility of recruitment, retention, and relapse rates; and 2) to determine whether the combined treatment curtails or ends MA use, as measured by urine toxicology screens, MA craving, and self-report.

METHOD

Study Design

The 16-week pilot study included both modafinil and cognitive behavioral therapy (CBT). The medication trial was single-blind with 12 weeks of modafinil followed by 4 weeks of placebo. The 16-week therapy component started with two weeks of twice weekly sessions with a motivational enhancement emphasis followed by weekly CBT sessions for the remaining 14 weeks. The sessions followed the structure and topics outlined in the National Institute on Drug Abuse's *A Cognitive-Behavioral Approach: Treating Cocaine Addiction* (12).

Procedure

Recruitment included letters to physicians in private practice and at HIV clinics in New York City, and flyers at community based organizations serving an HIV+, gay clientele.

Recruitment for this study was difficult, which led us to enrol HIV– men who were otherwise eligible. Prospective patients were screened by telephone and then evaluated in person to assess medical and psychiatric history; perform blood work, and collect urine toxicology samples. Exclusion criteria were current psychotic or bipolar disorders, and untreated major depressive disorder. Inclusion required a current diagnosis of stimulant abuse or dependence. A letter was faxed to the patient's care provider requesting signed approval for his participation.

Patients were seen by the study psychiatrist (R.R.) at baseline to confirm eligibility and weeks 1 and 2, and then biweekly throughout the 16-week study for medication management. Starting modafinil dose was 50 mg/day for those taking HIV antiretroviral medications and 100 mg/day for others. The dose was increased up to 200 mg/day in the absence of clinical response and significant side effects.

Measures

The psychotic screen, substance use disorders, and mood episode modules of the Structured Clinical Interview for DSM-IV (SCID) (13) were used to determine study eligibility. The Structured Interview Guide for the 21-item Hamilton Rating Scale for Depression (HAM-D) (14) was administered at baseline to assess symptom severity and was repeated at biweekly visits with the study psychiatrist.

MA use was assessed during the evaluation interview using a two-week follow back method documenting use including the context, duration, and route. MA use was assessed at each therapy visit for the past week to determine days used. The University of Minnesota Cocaine Craving Scale (15) was adapted to assess MA cravings at each therapy visit and has a possible range of 0 (none/weak) to 10 (very strong). Similarly, the Obsessive Compulsive Drinking Scale (16) was adapted for MA use (using the term "crystal" instead of alcohol). This "O/C Crystal Use Scale" was also completed at therapy visits and has possible scores of 0 to 40. The Beck Depression Inventory II (BDI) (17) was administered at baseline and biweekly intervals throughout the trial.

Urine samples were collected at every visit, using a dipstick and also sent to the laboratory for confirmatory analysis. Blood pressure and pulse were assessed at each medication visit.

Data Analysis

Given the small sample and exploratory nature of the trial, results are for study completers only and are primarily descriptive.

RESULTS

Sample Characteristics

Sixteen patients seeking to reduce or stop MA use were evaluated and found eligible; 13 agreed to enter the study. Average age was 38 years ($SD = 6$); 9 (69%) were white, 3 (23%) Hispanic, and 1 (8%) black; average education was 16 years ($SD = 2.5$); 5 (38%) worked full-time, 3 (23%) worked part time, and 5 (38%) were unemployed. Eleven of the 13 men were HIV+ and had tested positive an average of 82 months ($SD = 67$) earlier. Mean CD4 cell count was 432 ($SD = 121$), and 6 (55%) were on antiretroviral therapy.

Seven of 13 participants (54%) met DSM-IV criteria for stimulant abuse, and 6 (46%) met criteria for dependence. Those diagnosed with abuse tended to binge on weekends, using on average 2.2 days per week ($SD = .8$); those diagnosed as dependent used an average of 6 days per week ($SD = .9$); $t = -8.280$, $p < .001$.

Mean estimated duration of abuse or dependence was 43 months ($SD = 20$, range 12–72). For 9 participants (69%), smoking was the primary route of use; 4 (31%) used intravenously. At study entry, mean reported days used per week was 4 ($SD = 2.1$, range 1–7).

Study Attrition

Ten patients (77%) completed the 16-week trial. Dropouts completed an average of 5 weeks (range 4–8). The 3 patients who dropped out did not differ from the 10 completers on sociodemographic variables. Two left treatment because they were not ready to reduce use, and the third obtained a full-time job that made study participation unfeasible.

Medication Response and Side Effects

Seven (54%) of the 13 patients experienced medication side effects including headaches, nausea, tachycardia, and irritability, which tended to appear early in the trial and were mild and transient. Two patients discontinued modafinil due to side effects, while continuing in psychotherapy. One was eventually classified as a responder and the second as a nonresponder.

Efficacy

For the 10 completers, average MA use at baseline was 4 days/week and decreased to an average of 1 day/week at week 16. An initial mean decline in reported MA use of 2 days/week occurred between the week of evaluation and the second week of the study. Average use then hovered around two days per week until another drop occurred around week 14, when it became once per week.

Self-reported use and positive urines corresponded in all but one instance when a patient reported not using within four days of a positive urine sample. Six of the ten completers had positive urines at the baseline visit. The percentage varied across the study with lows of 30% and highs of 70%, and a final decline to 30% at the end of the 16 weeks.

When response is defined as a greater than 50% reduction in reported days used per week at week 16 vs. baseline, 6 of the 10 completers (60%) were responders. Five of the 6

“responders” (83%) had a diagnosis of abuse vs. dependence. Seven of the 10 completers (70%) achieved a three-week or longer period of abstinence, 6 of whom had a diagnosis of abuse vs. dependence.

Craving Scale ratings declined substantially for responders, who started with a lower average baseline craving score than the nonresponders: 4.1 ($SD = 3.4$) vs. 6.8 ($SD = 3.3$); $t = -1.218$, $p = .25$, but also had a greater average drop in this score -3.2 ($SD = 3.5$) vs. -1.8 ($SD = 2.4$); $t = -.696$, $p = .506$.

A similar pattern was noted for the O/C Crystal Use Scale. Responders started with a lower average baseline O/C score than the nonresponders: 14.7 ($SD = 7.1$) vs. 23.3 (8.6); $t = -1.724$, $p = .123$, but had a greater average drop in this score: -10.3 ($SD = 7.4$) vs. -8.8 ($SD = 6.5$); $t = -.346$, $p = .738$.

At baseline, the mean BDI score was 22 ($SD = 11.2$, range 3–37), with 8 patients having scores greater than 15, which indicates significant symptoms of depression. Responders tended to have higher baseline scores compared to the nonresponders 27 ($SD = 8.2$) vs. 14.5 ($SD = 11.7$); $t = 2.01$, $p = .08$, and their scores declined more than those of nonresponders: -18 ($SD = 8.2$) vs. -6 ($SD = 5.4$); $t = -2.560$, $p = .034$.

DISCUSSION

Despite reports of epidemic MA use in the HIV+ gay community, recruitment for this study was difficult. This may either reflect problems in reaching this population, or the lack of recognition on the part of MA users that their use is harmful. For those we enrolled, the combination of modafinil and CBT appeared to be acceptable as evidenced by the high retention rate of 77%. The less dogmatic, more patient-focused approach of CBT seems to be well suited for this patient population, although reported side effects and medication discontinuation was greater than our experience with a non-MA using HIV+ population taking modafinil (18).

Of the six responders, three reported finding modafinil helpful in reducing their MA use. Two of them guessed when they were switched to placebo at week 12 and requested active modafinil. Modafinil appeared to be more useful to patients with a diagnosis of abuse rather than dependence. They found the medication useful in treating the fatigue and dysphoria associated with acute withdrawal from MA as well as maintaining abstinence. Those patients using MA daily did not report a meaningful effect of modafinil until after they reduced their MA use.

The reduction of reported crystal use observed after the switch to placebo at week 12 is notable suggesting that modafinil may be most effective as a short term abstinence-induction agent, which can then be discontinued. Another explanation for the decline in use was patients' push towards abstinence with the end of treatment drawing near.

Examining BDI scores, an expected pattern emerged where symptoms of depression waxed and waned along patterns of use, with increased symptoms occurring after an episode of MA use. The finding that responders entered the study with higher levels of depression than

nonresponders is also not surprising. Men who experience more depressive symptoms may be more motivated to effect a change in their lives.

Because of the prominence of the topic of MA use in conjunction with sexual activity, it is essential that the therapist was comfortable discussing gay male sexual practices.

In summary, these pilot data suggest that modafinil may be most useful for crystal users at the point when they start to taper or discontinue crystal use, and that the combination therapy conducted by a therapist able to address sexual issues promotes treatment retention.

Acknowledgments

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