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A randomized investigation of methadone doses at or over 100 mg/day, combined with contingency management☆

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ABSTRACT

Background: Methadone maintenance for heroin dependence reduces illicit drug use, crime, HIV risk, and death. Typical dosages have increased over the past few years, based on strong experimental and clinical evidence that dosages under 60 mg/day are inadequate and that dosages closer to 100 mg/day produce better outcomes. However, there is little experimental evidence for the benefits of exceeding 100 mg/day, or for individualizing methadone dosages. We sought to provide such evidence.
Methods: We combined individualized methadone dosages over 100 mg/day with voucher-based cocaine-targeted contingency management (CM) in 58 heroin- and cocaine-dependent outpatients. Participants were randomly assigned to receive a fixed dose increase from 70 mg/day to 100 mg/day, or to be eligible for further dose increases (up to 190 mg/day, based on withdrawal symptoms, craving, and continued heroin use). All dosing was double-blind. The main outcome measure was simultaneous abstinence from heroin and cocaine.
Results: We stopped the study early due to slow accrual. Cocaine-targeted CM worked as expected to reduce cocaine use. Polydrug use (effect-size $h = .30$) and heroin craving (effect-size $d = .87$) were significantly greater in the flexible/high-dose condition than in the fixed-dose condition, with no trend toward lower heroin use in the flexible/high-dose participants.
Conclusions: Under double-blind conditions, dosages of methadone over 100 mg/day, even when prescribed based on specific signs and symptoms, were not better than 100 mg/day. This counterintuitive finding requires replication, but supports the need for additional controlled studies of high-dose methadone.

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1. Introduction

Methadone maintenance is an effective treatment for opioid dependence, particularly when given with other psychosocial services (Ball et al., 1988; Barthwell et al., 1989; Gerstein and Lewin, 1990; McLellan et al., 1993; Caplehorn et al., 1994; Goldstein and Herrera, 1995; Bell et al., 1997). Nevertheless, some methadone patients continue to abuse heroin during treatment, even with extensive psychosocial services (McLellan et al., 1993).

One longstanding issue in methadone maintenance is appropriate dosing. Historically, methadone dosage practices have sometimes been ideologically driven (Williams, 1970; Maddux et al., 1991). The average methadone dose in community clinics has increased over the past few decades, with the proportion of patients receiving doses <80 mg decreasing from 94% in 1988 to 56% in 2005 (Maddux et al., 1991; D'Aunno and Vaughn, 1992; D'Aunno et al., 1999; D'Aunno and Pollack, 2002; Pollack and D'Aunno, 2008), and prior outside approval of doses over 100 mg/day is no longer required (Rettig and Yarmolinsky, 1995). The trend toward higher doses has been supported by clinical trials and by retrospective analyses of outcome in clinical populations (Caplehorn and Bell, 1991; Strain et al., 1993; Maremmani et al., 1994; Hartel et al., 1995; Ling et al., 1996; Schottenfeld et al., 1997; Strain et al., 1999; Farré et al., 2002). A Cochrane review of randomized trials found that higher doses of methadone (60–100 mg/day) were more effective than lower doses (1–39 mg/day) in reducing heroin use (Faggiano et al., 2003). Some addictions specialists have advocated for doses above 100 mg (Maremmani et al., 2003; Fareed et al., 2009), particularly in special populations (McCarthy et al., 2005). One criticism of nearly all recent major trials, including our previous studies, is that they used fixed doses (Strain et al., 1993; Ling et al., 1996; Schottenfeld et al., 1997; Preston et al., 2000) rather than the more

☆ Supplementary material can be found by accessing the online version of this paper. Please see Appendix A for more information.

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flexible, individualized approach to dosing now endorsed by Center for Substance Abuse Treatment (CSAT, 2005) and currently used in most community clinics.

A complication in clinical practice is that many methadone patients abuse nonopiate drugs such as cocaine. Cocaine abuse during methadone maintenance indicates poor prognosis, both in terms of treatment dropout (Greenfield et al., 1996; Simpson et al., 1997; Kidorf et al., 1998) and heavy concurrent use of heroin (Hartel et al., 1995). In many cases, the relationship between cocaine abuse and heroin abuse appears causal: 36% of cocaine-abusing methadone patients report using heroin to modify the effects of cocaine, either by co-injection or to lessen dysphoria as cocaine effects dissipate (Kidorf and Stitzer, 1993). All these data suggest that methadone programs seeking to reduce treatment dropout and heroin abuse should put a high priority on reducing cocaine abuse.

One of the most effective treatments for cocaine abuse is contingency management (CM), in which desired behaviors are externally reinforced (Prendergast et al., 2006; Dutra et al., 2008). We previously showed that CM targeted at opiate abstinence, along with a fixed increase in daily methadone dose from 50 mg to 70 mg, each significantly increased opiate abstinence (Preston et al., 2000).

In a more recent CM study (Epstein et al., 2009), we administered higher doses of methadone (70 or 100 mg/day) combined with CM to promote abstinence from both heroin and cocaine. We used a novel contingency that reinforced abstinence from either drug while doubly reinforcing simultaneous abstinence from both. Each intervention was effective in specific ways: cocaine-targeted CM reduced cocaine use, and the methadone dose increase reduced heroin use. However, achievement of polydrug abstinence was difficult for most patients. This finding suggested that for CM to promote simultaneous abstinence from cocaine and heroin, a relatively high dose of methadone is necessary. Therefore, we decided to investigate an approach in which CM was targeted exclusively toward cocaine use, while methadone was deployed against heroin use more effectively.

The aim of this study was to evaluate the efficacy and safety of individualized methadone doses over 100 mg/day (based on each patient's opioid use, craving, and withdrawal symptoms and on avoidance of side effects such as constipation and sedation) combined with voucher-based cocaine-targeted CM to reduce opioid and cocaine use. We hypothesized that the individualized dose increases would increase abstinence from heroin and that the addition of CM would result in greater simultaneous opioid and cocaine abstinence, and higher treatment retention, when compared to methadone doses fixed at 100 mg and a control condition for CM. As described below, surprisingly, these hypotheses were not supported. One limitation of the study is a partial failure of randomization (discussed below), but that limitation does not seem to account for the unexpected results.

2. Methods

2.1. Participants

Participants were selected from 140 outpatients admitted for methadone maintenance at a research clinic in Baltimore, MD. Screening included medical, psychiatric, and drug-use histories, physical examination, standard laboratory tests, and a battery of assessment instruments, including the Addiction Severity Index (ASI) (McLellan et al., 1985) and the Diagnostic Interview Schedule (DIS-IV; Robins et al., 1995). Eligibility criteria for initial enrollment were: age 18–65, cocaine and opiate use (by self-report and urine screen), and physical dependence on opiates. Exclusion criteria were: current psychotic, bipolar, or major depressive disorders; current physical dependence on alcohol or sedatives (because our outpatient clinic did not have the resources to meet the medical needs that would arise during detoxification); unstable serious medical illness; estimated IQ below 80, per the Shipley Institute of Living Scale (Zachary, 1986); and conditions precluding urine collection. Eligibility for randomization to a group was based on subsequent heroin and cocaine use during a six-week baseline (see below). DSM-IV diagnoses of heroin or cocaine dependence were not required. Of 140 patients enrolled, 38 failed to meet continued-drug-use criteria for randomization, and 38 dropped out before being randomized. Six were assigned to a group whose only purpose was to maintain the blind (details below); the remaining 58 were randomized to one of the three experimental groups (Fig. 1).

This study was approved by the Institutional Review Board of the NIDA Intramural Research Program; each participant gave written informed consent.

2.2. Standard treatment

All participants received daily methadone and weekly individual counseling for up to 40 weeks, of which the last 10 weeks were a scheduled dose taper (before and during which, our clinic staff helped participants transfer to community methadone clinics). In weekly individual-counseling sessions, counselors completed a semistructured psychosocial assessment and treatment plan for each participant. Reduction of substance use was the primary goal. Methadone HCl (Mallinckrodt, Inc., St. Louis, MO) was administered orally in a fixed volume of 95 ml of cherry-flavored solution throughout the study. Dose was stabilized at 70 mg/day within seven days.

2.3. Urine and breath toxicology

Mondays, Wednesdays, and Fridays, urine specimens were collected under observation. Testing was conducted with an Enzyme Multiplied Immunoassay Technique (EMIT; Syva Corp., Palo Alto, CA) system that provided qualitative results for cocaine (benzoylecgonine equivalents; BZE), opiates (morphine), marijuana, and benzodiazepines (oxazepam). Cutoffs were 300 ng/ml for cocaine, opiates, and benzodiazepines, and 50 ng/ml for marijuana. Breath alcohol was determined with an Alco-Sensor III (Intoximeters, Inc., St. Louis, MO). Use of alcohol, benzodiazepines, and nonheroin opiates was rarely detected or reported; use of cannabis was detected in approximately 19% of urine screens.

2.4. Other measures of treatment response

Once a week, in clinic, participants completed questionnaires in which they rated on a scale of 0–4 how much they had "wanted" heroin or cocaine in the past week, with the response anchors "not at all," "a little," "moderately," "quite a bit," and "extremely." On the same occasions, with the same 0–4 response anchors, participants rated 24 symptoms of opiate withdrawal (nausea, runny nose, etc.) in the last two days. The 24 opiate-withdrawal items were summed to generate a score between 0 and 96. Cronbach alphas, computed separately for each week, ranged from .93 to .95.

Every two weeks, during the experimental phase of the study, participants completed questionnaires on which they rated their degree of constipation and sedation, the two main side effects expected from high doses of methadone. In addition, every two weeks, a staff member rated the participants' objective signs of opiate withdrawal, using the Clinical Opiate Withdrawal Scale (COWS; Wesson and Ling, 2003). A study physician (JPS or KAP) reviewed participants' progress at least every two weeks to determine whether dose adjustments were appropriate. Actual dose increases were based on randomization group assignment and were