

A randomized, double-blind, placebo-controlled safety study of high-dose dextromethorphan in methadone-maintained male inpatients

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Abstract

The NMDA antagonist dextromethorphan hydrobromide (DM) may be useful in the treatment of opioid dependence, particularly as a means of reducing tolerance to methadone during replacement therapy. As a prelude to clinical efficacy studies, a randomized, double-blind, placebo-controlled study examined the safety of DM in combination with methadone in inpatient, opiate-dependent volunteers. Male participants received daily methadone (50–70 mg/day) and either DM ($n = 10$) or placebo ($n = 5$) during the 12-day active medication phase of the study. DM participants received doses of 120, 240, and 480 mg/day in increasing order (4 days each). DM at high doses caused mild elevations of heart rate, blood pressure, temperature, and plasma bromide. However, none of these effects was clinically significant. DM caused no significant changes in respiration, pupil diameter, or subjective drug effects measured by standard scales. Participants in the DM group reported many more adverse events than did subjects on placebo (173 vs. 21), but these effects were not clinically serious. The most commonly reported side effects were sleepiness and drowsiness. Several participants reported intoxicating effects at the highest dose. Overall, DM was well-tolerated by the methadone-maintained opiate-dependent subjects studied here. These results support the further exploration of DM as an adjunct medication during methadone replacement therapy. © 2002 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

Recent research findings indicate that glutamatergic systems may play an important role in the development of opioid dependence by contributing to the development of tolerance (see Herman et al., 1995; Bisaga and Popik, 2000). Dextromethorphan (DM) is a noncompetitive NMDA antagonist that has produced few side effects during its decades of use in the treatment of cough (see Bem and Peck, 1992). A number of studies suggest that DM may be useful in the treatment of

opioid dependence in at least three ways (see Bisaga and Popik, 2000 for a review).

First, DM may serve to reduce the development of opiate tolerance. Elliott et al. (1994, 1995) showed that DM both prevents and reverses the development of tolerance in mice to the analgesic effects of morphine. To date, no study has investigated the effect of DM on opioid tolerance in humans. A medication that reduces the development of opioid tolerance could be particularly useful in methadone maintenance therapy. Reduced tolerance development to methadone would mean that patients could be maintained at lower doses and might experience fewer withdrawal symptoms when terminating therapy.

Second, DM may reduce withdrawal symptoms experienced during acute detoxification from opioids. DM has been shown to reduce naloxone-precipitated

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opiate withdrawal in rats (Koyuncuoglu et al., 1990). Both Koyuncuoglu and Saydam (1990) and Bisaga et al. (1997) reported that DM appeared to decrease opiate withdrawal symptoms in heroin users undergoing detoxification. However, Isbel and Fraser (1953), Rosen et al. (1996) and Jaskinski (2000) failed to observe such effects. Clearly, a medication that reduces withdrawal would be useful during the acute detoxification phase of treatment for opioid dependence.

Third, DM may serve to inhibit conditioned reactions to drug-related cues that play a role in drug seeking and relapse following treatment (see Childress et al., 1986; O'Brien et al., 1998). NMDA antagonists have been shown in mice to inhibit morphine self-administration (Semenova et al., 1999) and to inhibit both the development and expression of morphine conditioned place preference (Del Pozo et al., 1996; Kim et al., 1996; Tzschentke and Schmidt, 1997; Popik et al., 1998). Although these studies employed other NMDA antagonists, results suggest that DM could have clinical utility as a means of preventing the development and expression of conditioned drug effects in humans.

The study results reviewed above suggest that DM may serve a useful role in treatment for opioid dependence, particularly as an adjunctive therapy during methadone maintenance. Although DM has a well-established safety record at low doses in the treatment of cough (Bem and Peck, 1992), much higher doses may be necessary to affect opioid dependence. For example, Bisaga et al. (1997) used 375 mg/day in their study of heroin addicts undergoing withdrawal. No randomized trials have yet examined the safety of DM, either when taken in such high doses or when used in conjunction with methadone. The present safety study was intended to set the stage for efficacy studies of DM plus methadone by exploring adverse effects resulting from the addition of DM to a stable dose of methadone in opiate-dependent inpatient participants.

2. Methods

2.1. Research participants

Inclusion criteria required that participants be males and females between 21 and 55 years old, in good general health, and with a DSM-IV diagnosis of opiate dependence. Participants had to be enrolled in a methadone program in which they were stabilized on a consistent dose of 50–70 mg of daily methadone for a minimum of 10 consecutive days immediately prior to study admission. Individuals were excluded if they had a known sensitivity to DM, presence of significant medical conditions, current psychiatric diagnosis requiring psychiatric treatment, and/or psychoactive substance use disorders other than opiate dependence. All partici-

pants gave written consent to participate prior to enrollment into the study.

Thirty-eight patients were screened and 17 passed initial screening, gave informed consent, and entered the initial placebo phase. A total of 16 subjects completed the initial placebo phase and were randomized to double-blind study medication. One randomized individual was subsequently withdrawn because he was diagnosed as having hepatic failure (pre-existing). Of the remaining 15 participants, ten received DM and five received placebo (2:1 active medication to placebo ratio).

Demographic data were available for all participants except for one in the DM group. For the DM group, eight of nine individuals were African-American and all were male. For the placebo group (Group P), four of five participants were African-American and all were male. Group DM participants had a mean age of 45.1 (S.D. = 6.1) and a mean of 12.9 years of education (S.D. = 2.1). For Group P, these values were 42.8 (S.D. = 2.7) and 11.8 (S.D. = 1.8), respectively. Participants in the DM group reported heroin use for an average of 23.2 (S.D. = 10.8) out of the 30 days immediately prior to the start of the study, and for an average of 18.6 years (S.D. = 7.8) overall. For the placebo group, these values were 17.0 (S.D. = 12.4) and 18.0 (S.D. = 9). DM participants had spent an average of 6.3 years on methadone (S.D. = 4.9, range = 1–15 years) while placebo patients had been on methadone for an average of 3.8 years (S.D. = 3.2, range = < 1–8 years). Thus, Group DM appeared to have a greater severity of heroin dependence than Group P.

2.2. Procedure

2.2.1. Design

This study employed a double-blind, placebo-controlled design to investigate if the addition of DM to a stable dose of methadone (50–70 mg) in opiate dependent inpatients would cause clinically significant adverse events. Measures included spontaneously reported adverse events, resting physiology, and self-reported drug states.

After satisfying entry requirements, participants were admitted to the inpatient Substance Abuse Treatment and Research Unit of the Department of Veterans Affairs Medical Center at Philadelphia (PVAMC). During all phases of the study, patients continued to receive 50–70 mg of methadone daily. The study was divided into three phases: initial placebo, double-blind drug administration, and final placebo.

During the 2-day initial placebo phase, all screening assessments were done (see Section 2.2.3). On both days, patients received, single-blind, placebo study medication, administered in divided doses every 6 hours. At the completion of the baseline phase, participants were

randomly assigned to receive either active dextromethorphan (Group DM) or matching placebo (Group P) in a double-blind fashion. At this point the groups entered the double-blind drug administration phase that lasted for a total of 12 days. Patients randomized to the active study medication received DM at 120 mg/day on Study Days 3–6, 240 mg/day on Study Days 7–10, and 480 mg/day on Study Days 11–14 (see [Section 2.2.2](#)). At the end of Study Day 14 all double-blind medication was stopped and participants entered the 2-day final placebo phase. During this time, single-blind placebo study medication was administered.

2.2.2. Medications

All participants received a daily methadone dose of 50–70 mg throughout the entire study. Methadone and study medication were maintained and dispensed by the Research Pharmacy of PVAMC. The study medication, dextromethorphan hydrobromide and matching placebo capsules, were supplied by ENDO Pharmaceuticals (Chadds Ford, PA). All study medication, single-blind and double-blind, was administered four times daily: 12:00, 18:00, 24:00 and 06:00 h. A predetermined randomization schedule was prepared for packing study medications for each individual subject.

The three doses of DM studied here (120, 240, and 480 mg/day) were chosen in order to determine the maximum safe dose of DM that could be administered. This range was based on an earlier open-label trial of DM that demonstrated reductions in abstinence-produced opioid withdrawal at a dose of 375 mg/day ([Bisaga et al., 1997](#)).

2.2.3. Measures

This clinical trial was designed to determine whether the addition of DM to a stable dose of methadone produces significant adverse events. Throughout the study, reports of adverse events were collected in two ways. First, patients were queried daily as to whether they had experienced any physical or health problems since the day before. This question was open-ended and did not provide complaint categories from which to choose. Second, medical charts were examined daily for any spontaneously reported adverse events. All reported events were evaluated and recorded on a standardized adverse event record ([Levine and Schooler, 1986](#)). Each event was coded as to type of complaint, relationship to the study drug, severity, action taken, and outcome.

On study days 1 and 2 (initial placebo), patients had a full medical history, physical examination, psychiatric evaluation, laboratory analyses, electrocardiogram, and urinary drug screen (UDS). The Addiction Severity Index (ASI; [McLellan et al., 1980](#)), a 45–60 min structured interview about drug-related life problems, was also administered.

During all three phases of the study, participants received a variety of daily physiological assessments surrounding the 12:00 h administration of study medication. Five daily measurements of temperature, pulse, respiratory rate, and blood pressure were taken: time 0 (immediately prior to drug administration) and times 0.5, 1, 2, and 4 h following capsule administration. Pupil size was measured daily at 0.5 h post-medication; pupillary constriction is a known effect of opiates and could be enhanced by DM. Urine drug screens occurred every other day from study days 4 to 16. An ECG was taken on days 6, 10, 14, and 16 at 2 h after the noon dosing. The ECG was included as part of the standard package of cardiac function measures (along with pulse and blood pressure). Blood specimens for methadone and DM levels were drawn on study days 2, 6, 10, 14 and 16. Blood specimens for bromide levels were drawn on study days 6, 10, and 14. Since DM is administered as a hydrobromide compound, there is the possibility of bromide intoxication when large doses are consumed. Consequently, the US Food and Drug Administration (FDA) requested that we examine bromide levels associated with the DM doses studied here. The laboratory measurements taken during the initial placebo phase were repeated on day 14.

Plasma concentrations of DM were analyzed by means of high performance liquid chromatography with fluorescence detection by PPD Development (Richmond, VA). Bromide levels were determined by ion chromatography at National Medical Services (Glenside, PA). Plasma methadone concentrations were determined by GC/mass spectrometry at the PVAMC.

Participants were also evaluated through the use of several self-report instruments. Subjects daily completed the Addiction Research Center Inventory (ARCI) comprised of three subscales ([Martin et al. 1971](#)): (1) MBG (induction of euphoria); (2) LSD (induction of dysphoria); and (3) PCAG (induction of apathetic sedation). The ARCI was given at each of the five daily measurement points. Participants also recorded their opiate and nicotine craving on visual analog scales (VAS) at time points 0.5 and 2 h throughout the study. For the VAS measures, patients were asked to record the intensity of their greatest craving during the last 24 h on a 100 mm line with anchors of ‘none’ (0) and ‘more than ever’ (100).

2.3. Data analysis

Physiological measurements (heart rate, blood pressure, temperature, respiration, pupil diameter), self-report measurements (ARCI subscales, opiate craving), and plasma drug levels (methadone, bromide) were all summarized in the same way. For each subject, measurements for a given day were averaged together to give

a daily mean value. For the purposes of analysis, the daily means were further combined into means for treatment periods. Five treatment period means were calculated for each measure: days 1–2 (baseline placebo), days 3–6 (120 mg DM), days 7–10 (240 mg DM), days 11–14 (480 mg DM), and days 15–16 (post-treatment placebo). Mean values were analyzed because we were primarily interested in determining whether DM caused significant overall changes in physiology. However, clinical staff monitored individual changes in order to ensure that no patients had severe reactions to the medication. No participants in the trial required clinical intervention due to abnormal physiological measurements.

For each measure, treatment period means were analyzed through a repeated measures ANCOVA in which baseline served as the covariate, the four remaining periods served as the within-factor, and group (DM vs. placebo) served as the between-factor. In each analysis, a significant effect of DM would be revealed as either a main effect of group or a group \times treatment period interaction. Significant interactions were followed up by independent group *t*-tests for each of the four treatment periods. All analyses employed a significance level of $\alpha = 0.05$. This level was not corrected for the many analyses employed so as to maximize sensitivity to any possible adverse effects of DM. For the same reason, no adjustment was made for multiple pairwise tests (e.g. through post-hoc tests or decreased alpha).

3. Results

3.1. Medication compliance

Measurements of plasma DM levels indicated that all participants received the correct study medications. None of the placebo participants produced measurable concentrations of DM, whereas all ten DM participants were found to have measurable plasma levels. The increases in average DM plasma concentrations were proportional to the 2-fold mean increases in dose: 120 mg/day (52 ng/ml), 240 mg/day (118 ng/ml) and 480 mg/day (193 ng/ml).

3.2. Adverse events

Adverse events were reported daily. There were no serious adverse events in either group. Table 1 depicts the number of subjects in each group reporting each event as well as the overall frequency of event reports. Group DM reported far more adverse events than Group P (174 vs. 21). As Table 2 shows, these symptoms showed a strong dose-response relationship; few effects were reported during either placebo phase and over 40%

Table 1
Adverse events reported by groups receiving dextrometorphan (DM) or placebo (P)

Adverse event	Group DM (<i>n</i> = 10) Group P (<i>n</i> = 5)	
	No. of subjects (total events)	
Constipation	4 (15)	2 (6)
Diarrhea	2 (6)	1 (1)
Gastric upset/nervous stomach	1 (1)	2 (2)
Nausea	1 (1)	1 (2)
Vomiting	2 (3)	1 (1)
Drowsiness	5 (23)	1 (2)
Sleepiness	6 (20)	0
Sluggish	1 (1)	0
Nodding	2 (9)	0
High feeling	4 (11)	0
Weird feeling	1 (3)	0
Euphoria	1 (1)	0
Tremors	1 (1)	0
Anxiety	1 (7)	0
Nervousness	1 (5)	0
Jitters	1 (1)	0
Hyperactive	1 (1)	0
Restless	1 (1)	0
Slurred speech	1 (4)	0
Blurred vision	3 (13)	0
Dizziness	2 (5)	0
Confusion	3 (8)	0
Hard to concentrate	4 (7)	0
Headache	4 (8)	2 (4)
Insomnia	1 (1)	0
Nightmares	1 (5)	0
Weird dreams	0	1 (1)
Rhinorhea	0	0
Stuffy	1 (4)	0
Dry mouth, nose, throat	1 (4)	0
Nose bleeds	1 (1)	0
Burning eyes	0	1 (1)
Difficulty breathing	1 (1)	0
Urinary problem	1 (2)	0
Chest pain	1 (1)	0
Pain, not specified	0	1 (1)
Other, not specified	0	0
Total	61 (174)	13 (21)

of the reported events occurred during the 480 mg dose phase of the study.

3.3. Physiological measures

Table 3 shows the effects of DM on the primary physiological measures collected in this study. The ANCOVA failed to reveal significant group differences in pupil diameter, respiration, or diastolic BP. However, group differences in heart rate, systolic blood pressure and temperature were found.

For heart rate, there was a significant Group \times Treatment Period interaction ($F(1, 163) = 4.29$, $P < 0.01$). This interaction reflects the greater difference between groups during the 480 mg dose days compared

Table 2

Total of all adverse events reported by groups receiving dextrometorphan (DM; $n = 10$) or placebo (P; $n = 5$) during each of the study periods

Group	Placebo Days 1–2	DM 120 mg Days 3–6	DM 240 mg Days 7–10	DM 480 mg Days 11–14	Placebo Days 15–16
DM	12	42	39	71	10
P	1	6	5	8	1

to the 120 and 240 dose days. However, none of the differences between DM and P at any of these dose levels reached significance using *t*-tests.

For systolic BP, the main effect for Group ($F(3, 163) = 3.11$, $P = 0.08$) approached significance, reflecting a slightly higher systolic BP level in the DM group. There was a significant Group \times Treatment Period interaction ($F(3, 163) = 3.82$, [$p < 0.05$]) reflecting an effect similar to that described above for heart rate. Once again, *t*-tests failed to reveal significant differences between Groups P and DM at any of the dosage levels.

Finally, the analysis of skin temperature produced a Group \times Treatment Period interaction that almost reached significance ($F(1, 162) = 2.54$, $P = 0.06$). As with the other measures, there was no significant difference between Groups P and DM for the 120 or 240 mg dose conditions. However, there was a small but significant difference in temperature at the highest dose level of DM ($t(12) = 3.30$, $P < 0.01$). Although statistically significant, this difference between groups was less than 1 degree F and carries no clinical significance.

No individual participant demonstrated physiological changes that required clinical intervention. However, the cardiovascular measures showed some indication of elevation at the highest doses of DM (480 mg/day). Across participants, the maximum physiology scores (individual means for the high-dose treatment period) for systolic BP, diastolic BP and heart rate were 165.2 mmHg, 102.4 mmHg, and 97 bpm, respectively. These

scores indicate that future studies of high-dose DM monitor participants closely for possible cardiovascular changes.

3.4. Self-report measures

Mean self-report scores for each of the treatment periods are depicted for the two groups in Table 4. The ANCOVAs did not produce significant effects (main effect of Group or Group \times Treatment Period interaction) for any of the ARCI subscale scores (MBG, LSD, or PCAG) or for opiate craving scores on the VAS. Nicotine craving scores were not analyzed because of the variability in smoking history and patch use across and within subjects during the study.

3.5. Plasma drug levels

Clinical interest in DM stems from the possibility that the medication may inhibit or reverse opiate tolerance in individuals chronically maintained on methadone. If so, then the question would arise as to whether DM increases plasma concentrations of methadone (e.g. by decreasing its metabolism) as opposed to directly affecting the mechanism of drug tolerance. Results of the ANCOVA on plasma methadone concentrations failed to indicate a significant main effect of Group or a Group \times Treatment Period interaction. Mean plasma methadone levels were higher in Group P on each study

Table 3

Physiological responding by groups receiving dextrometorphan (DM; $n = 10$) or placebo (P; $n = 5$) during each of the study periods

Measure	Group	Placebo Days 1–2	DM 120 mg Days 3–6	DM 240 mg Days 7–10	DM 480 mg Days 11–14	Placebo Days 15–16
RESP	DM	15.1 (3.1)	15.6 (2.7)	15.2 (2.3)	15.5 (2.3)	14.7 (1.9)
	P	14.5 (1.6)	16.0 (1.9)	15.3 (1.3)	15.0 (1.9)	15.2 (0.9)
PUPIL	DM	3.4 (0.6)	3.4 (0.6)	3.2 (0.5)	3.0 (0.6)	3.0 (0.5)
	P	3.7 (0.8)	3.4 (0.8)	3.6 (0.6)	3.4 (0.7)	3.4 (0.6)
HR	DM	67.3 (7.4)	68.0 (6.7)	71.7 (7.1)	77.5 (8.8)	75.4 (8.5)
	P	65.4 (6.8)	65.1 (6.7)	66.8 (8.0)	70.0 (8.7)	72.8 (8.9)
SYST	DM	124.7 (8.8)	124.4 (9.4)	126.2 (9.2)	131.1 (13.4)	126.4 (11.0)
	P	117.7 (9.2)	119.3 (8.3)	122.4 (7.0)	122.9 (8.0)	125.0 (7.7)
DIAST	DM	76.9 (9.4)	76.5 (8.6)	76.6 (6.9)	81.0 (10.1)	79.0 (10.7)
	P	70.1 (5.0)	69.6 (4.5)	72.7 (5.1)	75.6 (6.7)	77.2 (4.7)
TEMP	DM	97.8 (0.3)	97.9 (0.4)	98.1 (0.4)	98.4 (0.4)	98.3 (0.4)
	P	97.9 (0.3)	98.0 (0.6)	98.1 (0.4)	98.0 (0.4)	98.3 (0.5)

Note: RESP = respiration in breaths/min. PUPIL = pupil diameter in mm. HR = heart rate in beats/min. SYST = systolic blood pressure in mmHg. DIAST = diastolic blood pressure in mmHg. TEMP = body temperature in degrees F. All values are mean (S.E.M.).

Table 4
Self-report of subjective effects by groups receiving dextrometorphan (DM; $n = 10$) or placebo (P; $n = 5$) during each of the study periods

Measure	Group	Placebo Days 1–2	DM 120 mg Days 3–6	DM 240 mg Days 7–10	DM 480 mg Days 11–14	Placebo Days 15–16
MBG	DM	5.6 (3.4)	5.9 (4.4)	6.5 (4.6)	6.2 (4.1)	7.3 (4.6)
	P	4.2 (3.7)	4.1 (3.8)	4.7 (3.9)	5.4 (3.6)	5.1 (3.8)
PCAG	DM	3.6 (2.2)	3.5 (1.8)	4.0 (2.2)	4.6 (2.6)	4.1 (2.7)
	P	1.2 (1.3)	1.4 (1.4)	2.2 (1.8)	2.5 (1.4)	2.3 (1.5)
LSD	DM	2.8 (1.5)	2.9 (1.4)	3.2 (1.8)	3.7 (2.1)	3.6 (2.2)
	P	1.3 (1.4)	1.6 (1.4)	1.8 (1.6)	1.9 (1.6)	1.9 (1.7)
CRAVE	DM	20.3 (4.4)	22.3 (3.5)	17.4 (3.6)	15.2 (3.6)	9.4 (3.2)
	P	11.4 (4.5)	15.2 (3.4)	9.4 (2.6)	14.7 (5.9)	14.6 (7.6)

Note: MGB, PCAG, and LSD = scales from the Addiction Research Center Inventory (ARCI). CRAVE = opiate craving rated on the VAS. All values are mean (S.E.M.).

day including baseline; daily levels in Group DM ranged from 294 to 398 ng/ml, while daily levels in Group P ranged from 371 to 440 ng/ml. High within-group variability prevented the Group main effect from approaching significance ($P = 0.34$).

DM significantly elevated bromide levels; the ANCOVA revealed a main effect of Group ($F(1,11) = 19.5$, $P < 0.005$). However, even at the highest dose of DM (480 mg/day), plasma bromide levels only reached a mean value of 3.2 mg/dl (S.E.M. = 0.4). This value is well below the levels of 50–100 mg/dl that are associated with brominism (Ellenhorn, 1997).

4. Discussion

Taken together, the results of this study indicate that DM was well-tolerated by a group of methadone-maintained, opiate-dependent volunteers. Compared against placebo, DM doses of up to 480 mg/day had only minor impact on cardiovascular function (heart rate and blood pressure), body temperature, and bromide levels and no discernible impact on pupil diameter, self-reported craving, or self-reports of drug-related states collected through the ARCI. The self-report results are similar to those reported by Jasinski (1998) who gave DM in combination with a dose of morphine. These findings did not result from errors in randomization; measurements of plasma DM levels indicated that all 15 individuals were given the correct study medication.

DM produced some statistically significant effects compared to placebo, but these differences are unlikely to indicate potential health risks. Although the analyses of heart rate and systolic blood pressure both produced significant Group by Treatment Period interactions, subsequent t -tests failed to reveal significant differences between groups at any of the dose levels. However, the small sample size employed, the overall 10 bpm increase in HR demonstrated by Group DM, and the levels of BP and HR reached by the peak responders suggest that

future studies continue to monitor the cardiovascular effects of high dose DM. The analysis of temperature produced a near-significant interaction result and the t -tests revealed that DM at the high dose (480 mg/day) produced higher body temperature than placebo. However, the magnitude of this difference was only 0.4 degrees F, a clinically insignificant difference. Finally, DM was associated with increased levels of bromide compared to placebo. However, the highest plasma concentration of bromide produced in this study (3.2 mg/dl) was far below the level associated with brominism.

The results also revealed that patients in the DM group reported far more adverse events overall than did individuals in Group P (174 vs. 21). However, none of the effects reported were severe or serious. Of all the effects documented in Table 1, only sleepiness and drowsiness were reported by half or more of the DM participants. In general, the events reported were similar to those described by Bem and Peck (1992) in their review of DM administration for cough: reductions in overall alertness and wakefulness, gastric upset, and opiate-like high/euphoria. The nature of the events and their strong dose-response relationship indicate that the doses of DM used here were within a clinically active range. Furthermore, increased sedation and euphoria would be expected if DM serves to reduce tolerance to the effects of methadone.

Finally, it should be noted that the statistical tests reported here all used an alpha criterion of 0.05, uncorrected for the many analyses performed. This strategy was employed to maximize sensitivity to any possible adverse effects of DM. Had efforts been made in order to maintain an experiment-wise Type I error rate of 0.05, then even fewer of the analyses would have reached statistical significance. On the other hand, the small sample employed raises the possibility that the study lacked power to statistically detect small differences between groups. In particular, there were indications of elevations in heart rate and blood pressure that might have proved significant with larger groups.

Furthermore, the present results were obtained with inpatient subjects under constant clinical supervision. It remains to be shown that high-dose DM will be similarly tolerated by larger outpatient samples.

In sum, the present study demonstrates that DM is generally well-tolerated by methadone-maintained opiate-dependent individuals. Although not requiring clinical intervention, the levels of BP and HR reached by peak responders suggest that future studies closely monitor cardiovascular changes when high-dose DM is administered. DM did produce far more self-reports of adverse events than did placebo. However, the nature of these events (sedation, euphoria, gastric upset) was consistent with the idea that DM may serve to reduce tolerance development during methadone treatment. Further exploration of this possibility appears warranted.

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