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Journal of Substance Abuse Treatment 23 (2002) 409–413

Journal of Substance Abuse Treatment

Brief article

Sensitivity to acute methadone dose changes in maintenance patients

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Received 29 November 2001; received in revised form 17 May 2002; accepted 22 May 2002

Abstract

This study assessed whether methadone patients can identify acute dose changes in their maintenance dose, and explored the relationships between self-reported drug effects and real or perceived dose changes. Four times each week patients (N = 10) unpredictably received either 80%, 90%, 100%, 110% or 120% of their usual daily dose (50–100 mg). Approximately 24 hr later they indicated which dose they had received on the previous day, and rated the previous day's dose in terms of good effects, bad effects, and change in medication taste. Correct estimation of the doses received was always at the levels expected by chance alone. Furthermore, this sample of patients could not detect dose-related changes in medication taste. However, self-reports of good effects were significantly higher when patients believed that they had received a dose increment, and ratings of bad effects were higher when patients believed that they had received a dose decrement.

Keywords: Methadone maintenance; Dosing; Drug discrimination; Opiates; Withdrawal

1. Introduction

Dose adjustments are regularly made in Methadone Maintenance Treatment (MMT) during induction, maintenance and medical withdrawal. As in the case of all opioids, drastic reduction or suspension of methadone is followed by the onset of withdrawal symptoms. Dose increments on the other hand, can produce acute undesirable side-effects such as increased sedation, constipation, decreased pain sensitivity, nausea, respiratory depression, cough suppression, itching, urinary retention, drowsiness, and slowed reaction time. Patients, therefore, are quite watchful of their methadone dose, and emotional reactions to the prospect of withdrawal from opiates have been well documented (Gentile & Milby, 1992; Raczynski, Wiebe, Milby, & Gurwitch, 1988; Schumacher, Milby, Fishman, & Huggins, 1992). Indeed, it is not uncommon in clinical practice to hear patients complain that their methadone dose is being maliciously altered by clinic staff, especially in treatment programs that follow a ''blind dose'' policy. But while unplanned dose changes are possible in any treatment clinic, it is also possible that MMT patients might interpret unrelated environmental events, mood changes, or short term adjustments in metabolic rate, as due to changes in their methadone dose (Eap et al., 2000; Kreek, 1986; Robles, Miller, Gilmore-Thomas, & McMillan, 2001; Wolff et al., 1997). Strictly assessing subjective events as potential causes for the patient's complaints may be methodologically challenging. In contrast, it is possible to study under what conditions MMT patients can detect real changes in their stable methadone dose. The resulting information will help us better understand patients' responses and expectations regarding real and perceived methadone dose changes, and may be useful in designing clinically appropriate dosing procedures.

In a study by Stitzer, Bigelow, and Liebson (1984), patients assigned to one of two groups received either small (±30–40%) or large (±80%) single-day blind alternate doses, or their regular dose. During the 6-week study, each patient was exposed five times to the same set of 3 test doses (one increased dose, one dose decreased by an equal magnitude, and their regular dose). Immediately after dosing, patients were asked to estimate on the basis of taste which dose they had received and to rate on a visual analog scale the magnitude (in milligrams) of the

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0740-5472/02/$ – see front matter
PII: S0740-5472(02)00274-X

dose received. The following day, patients were asked to complete a 59-item symptom checklist and again to estimate whether or not they had received their regular dose the previous day, and to rate on a visual analog scale the magnitude of the dose received. Stitzer and colleagues found that regardless of the dose tested, patients were able to estimate on the basis of taste the direction of the dose change (higher, lower or no change). Reports collected on the following day were consistent with those based on taste alone. In addition, the relative estimated magnitude of the dose received corresponded with the dose change received (small vs. large), although patients in that study were not able determine the magnitude of the doses received. The authors concluded that detectability is an orderly function of the size of the dose change, with dose changes of 50% above or below their normal maintenance dose representing the limit of detectability.

The purpose of this study was to further assess whether methadone patients can identify acute dose changes in their maintenance dose when five alternate doses are tested, and to explore the relationships between self-reported drug effects and real or perceived dose changes.

2. Method

2.1. Study sample

Ten methadone maintenance patients at the University of Arkansas for Medical Sciences Substance Abuse Treatment Clinic participated in the study. To participate, patients must have received a steady daily dose of methadone in the 50–100 mg range for at least 4 weeks prior to the beginning of the study. Pregnant women were excluded from participation. The study sample was composed of 3 females and 7 males who had been enrolled in methadone maintenance for a period of 2 to 66 months (mean = 17 months) at the beginning of the study. Mean age for the sample was 39 years (SE = 2.9), and average daily methadone dose was 81 mg (55, 65, 75, 75, 80, 85, 85, 95, 95, 99). The study protocol was explained in detail, and all participants signed the consent form approved by the institution's Human Research Advisory Committee.

2.2. Dosing

Participating MMT patients were required to attend the clinic Monday through Saturday for the 5-week duration of the study. All patients received their daily methadone during regular dosing hours in the morning. On Saturdays participants also received a take-home dose to be consumed on Sunday. The methadone solution used in the study was made from a stock solution of 10 mg/ml (Roxane, Columbus, OH) dispensed into a plastic cup by a computer-controlled precision pump, to which $\sim$50 ml of commercial fruit punch was added.

2.3. Experimental procedures

At the beginning of the study patients were informed that on 8 unpredictable test days they would receive alternate doses of either 80%, 90%, 110% or 120% of their usual daily dose, and that on the remaining days they would receive their usual dose. The experimenter also pointed out that by the end of the study they would have received, on the average, the full amount of their usual methadone dose for the 5-week period, no more and no less. Furthermore, they were informed that dose increases or decreases would occur no more often than twice each week.

Tests doses were dispensed 4 times per week, for a total of 20 tests per participant. Of the 20 test doses, 8 were alternate doses (2 times each) and 12 were regular doses. On Fridays and Saturdays all participants received their regular dose. On Monday through Thursday participants received a test dose of either 80%, 90%, 100%, 110%, or 120% of their regular dose. And on the following day (Tue–Fri), approximately 24 hr later, each participant filled out a questionnaire indicating which of the 5 possible doses they had received on the previous day. In addition they were asked to rate, using 3 visual analog scales (VAS), the previous day's dose in terms of *good effects*, *bad effects*, and *change in taste* of the medication. After completing the questionnaire, patients were dosed for the day.

Out of all possible permutations, five counterbalanced schedules of dose presentations were prepared in advance such that no more than 2 alternate doses (80%, 90%, 110%, and 120%) were planned for any given week, and that no two 80% or 120% doses occurred in the same week. At intake, one of the five possible schedules was randomly assigned, by having each participant draw a sealed envelope from a box. The code of the selected schedule was recorded by the experimenter, and the participant signed and dated the sealed envelope, which was then stored in a safe box until the end of the subject's participation in the study.

Participants received a $2.00 credit toward their clinic fee for each test completed (dose ingestion plus completion of the questionnaire). In addition, each time they correctly identified the dose received, $3.00 more were credited toward their clinic bill, for a possible total of $5 per test. Thus, participants earned a minimum of $40 in credits during the 5-week study if they completed all tests but never identified the dose correctly, and a maximum of $100 if all of their estimates were correct. Participants were not given feedback as to whether or not their individual dose estimates were correct, since that information could be used to estimate the likelihood of receiving alternative doses later in the week. Instead, on Saturdays the total number of correct estimates for the week was revealed, and the amount earned was credited to their accounts. Participants were not told which estimates had been correct during the previous week, but only the number of estimates that were correct. Magnitude of the specific doses received was disclosed only at the end of the subject's participation in the study, when

they were given the envelope containing the actual dose schedule used. Study participants could use this information to verify their earnings.

2.4. Visual analog scales

The following directions were printed on all forms: "Mark the point along each line below that indicates how you feel about the dose you received yesterday." The VAS used consisted of 4-inch (100 mm) horizontal lines delimited by 0.25 inch (~6 mm) vertical lines. The following 3 scales were used:

- The flavor of your dose yesterday was (same as the regular dose.....very different from the regular dose)
- How much of a *good* drug effect did you feel? (none.....a lot)
- How much of a *bad* drug effect did you feel? (none....a lot)

The location of the mark along each line was measured three times, and the average distance from the origin transformed to a percentage of the 4-inch line.

2.5. Data analysis

Two subjects dropped out before completing all of the observations. One observation from one subject was discarded because a 30% rather than 20% dose reduction was accidentally made. Overall, a total of 178 tests were completed. Table 1 shows the percentage of tests performed with each dose, and the percentage of correct estimates of each dose. The results of these tests were analyzed as independent observations to assess the possibility that the obtained proportion of correct and incorrect estimates could have occurred by chance alone. In addition, estimates of alternate doses were compared within subjects using a *t*-test for paired data to explore possible sequential effects between the two dose administrations. Pearson product-moment correlation coefficients were computed between actual and estimated doses, and between actual doses dispensed and the corresponding VAS ratings of taste change.

Visual inspection of scatter plots showed no relationship between VAS ratings and individual doses tested. Therefore ratings of *taste change, good,* and *bad* effects of the methadone dose were analyzed by one-way ANOVA (Kruskal-Wallis), using the subjects' estimates of dosage change (increments, decrements, or no change) to form 3 groups. Post hoc determination of significance was made using Dunn's procedure.

Table 1
Distribution of tests (N = 178) performed with each methadone dose, and correct estimations obtained for each dose

	Dose tested				
	80%	90%	100%	110%	120%
Percent of All Tests	10.1%	10.1%	60.1%	9.6%	10.1%
Percent of Correct Estimates	11.0%	33.0%	55.0%	29.0%	11.0%

3. Results

3.1. Dose received

Table 1 shows the proportion of tests conducted with each test dose, and the proportion of test doses correctly estimated. Fig. 1 shows the proportion of doses estimated for each methadone dose received. Bars in each panel show the relative frequency with which patients estimated having received each dose. For both 10% increments and 10% decrements in the dose, the correct estimate was the most frequent estimate; however, in both instances the total number of errors far exceeded the number of correct identifications of the dose. For both the 20% increments and 20% decrements in dose, correct estimates were not the most frequent estimates, accounting for only a small percentage of the total number of estimates (see also Table 1). Patients rarely estimated that they had received a 20% increase in the dose, even when that was the actual dose administered. On the other hand, participants correctly estimated receiving their regular dose 55% of the time, close to what would be expected by chance alone. Overall, the correlation between actual and estimated doses (r = 0.048) was not statistically significant. A pair-wise comparison of the estimates obtained during the first and second administration of each alternate dose showed no significant differences (t = 0.423, df = 32, p = .675).

3.2. Taste change

No significant differences in VAS scores of taste change were observed when participants received decrements, increments or their regular dose (H = 0.145, df = 2, 175, p = .93).

3.3. Drug effects

Subjects' VAS ratings of *good effects* as a function of methadone dose were not statistically different, regardless of the actual doses received (H = 0.343, df = 2, 175, p = .84). However, significantly different ratings of good effects occurred as a function of perceived dose (H = 7.48, df = 2, 175, $p < .05$). Post hoc analysis revealed that ratings of *good* effects were higher when they estimated that they had received dose increases than when they estimated that they had received their regular dose. Similarly, subjects' VAS ratings of *bad* effects as a function of methadone dose were not different, regardless of the actual doses received (H = 0.827, df = 2, 175, p = .96). Although, again, significantly different ratings of *bad* effects occurred as a function of perceived doses (H = 9.84, df = 2, 175, $p < .01$). Post hoc

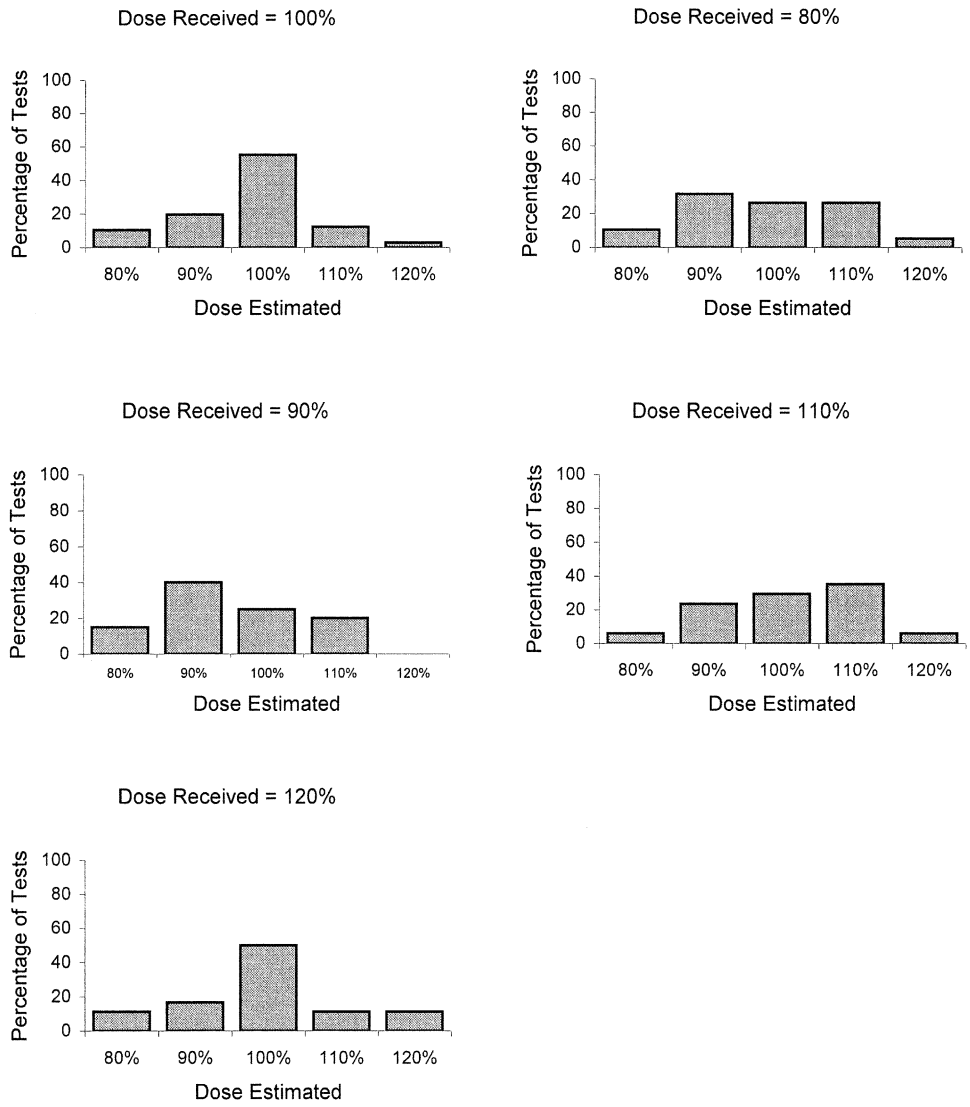

Fig. 1. Panels show the percentage of tests in which patients estimated having received each of the 5 possible doses as a function of methadone dose received. Correct estimates were always at levels expected by chance alone.

analysis showed that ratings of bad effects were higher when these patients estimated that they had received dose decreases than when they estimated that they had received their regular dose.

4. Discussion

In our clinic, some patients have occasionally claimed to have suffered withdrawal symptoms because they had been "shorted" on their daily dose by the clinic staff. Since the methadone solution is automatically dispensed by a computerized system, since methadone is (by law) so precisely accounted for on a daily basis, and since the clinic staff is routinely screened for methadone and other drugs, it is very unlikely that patients in this clinic received doses other than those programmed on the dispensing computer. On the other hand, it is possible for patients to erroneously interpret unrelated events as due to alterations in their methadone dose. This study shows that our sample of MMT patients could not reliably detect acute changes of up to ± 20% of their stable maintenance dose. These results concur with earlier research on the acute effects of methadone maintenance dose changes (Stitzer et al., 1984), where patients could not detect differences smaller than 50% in their dose. Furthermore, patients in this study were not able to detect changes in medication taste associated with actual increases or decreases in the amount of methadone ingested within ± 20% of their regular dose.

Conversely, these results reveal the importance of the patient's subjective experience in judging their methadone dose. In this sample of patients, self-reports of good effects were significantly higher only when they believed they had received a dose increment. In addition, self-reports of bad effects were higher only when they estimated having received a lower dose.

Correct estimation of the doses received was always at or below the levels expected by chance alone. At the beginning of the study patients were informed orally and in writing that they would receive alternative doses on only 8 days out of the 20 test days of the study. Therefore, if they had believed that they could not correctly identify the dose received, it would have been to their advantage to always respond by choosing the no-change option. However, none of the patients in the sample appears to have followed that strategy. In fact, 90%, 100%, and 110% were the most frequent correctly estimated doses (33%, 55%, and 29%, respectively). On the other hand 20% changes in dose were rarely estimated correctly (11%), as if smaller dose changes were easier to identify than larger dose changes. We believe, however, that since patients were not able to detect taste differences, and since their reports of drug effects were not strongly related to actual doses received, these patients guessed on ±10% changes more frequently because they could not detect major changes, but knew that on some occasions they would receive alternative doses. In short, we believe the study shows that MMT patients cannot reliably detect acute changes of up to ±20% of stable methadone doses between 50 and 100 mg. Whether patients could detect dose changes of similar magnitude if they were maintained over several days remains to be seen. The results of this study must be interpreted cautiously, given the relatively small sample of patients.

Nonetheless, these results may have significant practical implications for dosing practices in methadone maintenance clinics. While patients fail to reliably identify dosage changes of up to ±20%, their reports of good and bad drug effects are significantly related to *perceived* dose changes. Therefore, clinics still using blind dosing procedures may benefit from changing a policy that unnecessarily breeds distrust of clinic staff in methadone patients, and may adversely affect patient satisfaction with treatment.

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