Interactions on Mixing Diazepam With Methadone or Buprenorphine in Maintenance Patients

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Abstract: Benzodiazepine use by patients in methadone and buprenorphine substitution treatment is common, despite safety concerns regarding these drug interactions. The relative safety of diazepam use by methadone- or buprenorphine-treated patients has not been systematically examined. This study aimed to examine the effect of single diazepam doses, within normal therapeutic range (doses: 0, 10, and 20 mg), upon physiological, subjective, and performance measures in stable methadone and buprenorphine-treated patients. In a double-blind, randomized within-subjects design, methadone- or buprenorphine-treated patients were administered their normal opioid dose and either placebo, 10-, or 20-mg diazepam, in balanced order over 3 sessions. Eight methadone- and 8 buprenorphine-prescribed patients with no concurrent benzodiazepine dependence or significant comorbidity were recruited from an outpatient addiction clinic in London. Measures were taken at baseline and for 6 hours after dosing, and included physiological responses (pulse rate, blood pressure, pupil size, respiratory rate, and peripheral pO_2), subjective drug effects (Addiction Research Center Inventory subscales, visual analog scales of *strength of drug effect*, *drug-liking*, and *sedation*), and performance measures (simple reaction time, cancellation task, digit symbol substitution task, and balance). The 10- and 20-mg diazepam doses resulted in comparable subjective experiences of greater sedation and strength of drug effects in both patient groups, and had minimal impact on physiological parameters. However, diazepam had greater peak effects on performance measures (simple reaction time, digit symbol substitution task, and cancellation time) in methadone-treated than in buprenorphine-treated patients. Diazepam may significantly alter the response to opioid substitution treatment with methadone or buprenorphine.

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Opioid substitution treatment is a major treatment response to heroin dependence worldwide, with more than 600,000 patients in methadone or buprenorphine treatment in Europe and the United States. Benzodiazepines (BZDs) are commonly used among opioid-dependent populations, with approximately a third of opioid maintenance patients reporting recent BZD use.[1–3] The high prevalence of BZD use may be in response to the high incidence of psychiatric comorbidity in this population[4–6] and/or for abuse (intoxication) purposes.[1]

Concerns regarding interactions between opioids and BZDs include sedation, impaired motor and cognitive performance, respiratory depression, and death. BZDs are frequently identified at autopsy in methadone-related deaths.[7–11] However, despite these concerns, few studies have examined the interaction between methadone and BZDs in humans. Preston and associates[12] examined the effects of placebo, 20-, or 40-mg diazepam with 100%, 150%, or 200% of normal daily methadone doses (range, 50–60 mg) in 5 patients. High-dose (40 mg) diazepam and high-dose methadone led to greater subjective and physiological effects than either drug alone did. Farre and associates[13] compared the effects of placebo, 1-, 2-, and 4-mg flunitrazepam or 0.5- or 0.75-mg triazolam in 10 methadone maintenance patients (daily dose, 40–50 mg), demonstrating that both BZDs produced dose-related subjective changes and impairment of psychomotor tasks.

As a partial opioid agonist, high-dose buprenorphine (even up to 32 mg) is well tolerated in individuals with previous opiate exposure,[14] suggesting that it may be safer in overdose than methadone. However, it is unclear if this safety profile is maintained in the context of BZD use. Sedation and severe respiratory depression have been reported in opiate-naive individuals administered low-dose buprenorphine and BZDs perioperatively,[15–18] and BZDs are commonly identified at postmortem in buprenorphine-related deaths. For example, BZDs were detected in 91% of a series of 34 buprenorphine-associated deaths (and in 100% of 35 methadone-related deaths in the same article) and in 78% of a series of 117 buprenorphine-associated deaths.[10,19] Although there is a small literature examining BZD-methadone interactions in humans,[12,13] no published account of the effects of BZDs in opioid-dependent patients taking buprenorphine was identified by Medline or EMBASE.searches.

Animal research[20] has shown that high-dose buprenorphine (dose, 30 mg/kg) and high-dose midazolam (dose, 160 mg/kg) each produced a mild and transient increase in $Paco_2$ in rats, whereas the combination of these doses of buprenorphine and midazolam resulted in rapid, profound, and prolonged respiratory depression.

Only 1 published animal study has examined the lethality of BZDs in combination with different opioids. Borron and associates[21] examined the median lethal doses of morphine, buprenorphine, and methadone in rats, with and without pretreatment with flunitrazepam (dose, 40 mg/kg). Flunitrazepam loading caused the median lethal doses to drop significantly for methadone (from 23 to 13 mg/kg) and buprenorphine (from 235 to 24 mg/kg), but not for morphine (from 64 to 60 mg/kg). This study suggests the increased potential for overdose when combining BZDs with methadone or buprenorphine.

The main mechanisms for the interaction between opioids and BZDs are most likely pharmacodynamic. Pharmacokinetic interactions are possible, particularly as methadone, buprenorphine and many BZDs share common hepatic (CYP450) metabolic pathways; however, several studies have excluded any significant pharmacokinetic interaction between BZDs and buprenorphine in animals[22] and humans,[23] or between BZDs and methadone in humans.[24,25]

Given the widespread use of BZD among patients in methadone and buprenorphine treatment, a better understanding of these interactions should better guide decisions regarding the safer use of these medications. In particular, as methadone and buprenorphine are broadly comparable regarding their effectiveness in reducing heroin use and treatment retention,[26] such information may be important in selecting between methadone and buprenorphine for heroin users with a history of BZD use who present for treatment.

The clinical context in which BZD-opioid interactions occur are important. Specifically, there are 3 scenarios that warrant further examination: (a) the therapeutic use of BZDs in methadone or buprenorphine-treated patients (eg, short-term use at therapeutic doses for the management of temporary anxiety or sleep disorders); (b) chronic administration of BZDs in methadone and buprenorphine-treated patients (usually at therapeutic doses in stabilization or gradual reduction programs for the management of BZD dependence); and (c) misuse or abuse of BZDs (often at supratherapeutic doses) by methadone- or buprenorphine-treated patients. Although much of the drug-related harm arising from BZD-opioid interactions seem to occur in this latter group,[9,10,19] it is nevertheless important to establish the comparative safety of BZDs at therapeutic doses in methadone and buprenorphine-prescribed patients. Furthermore, it is not ethically acceptable to examine high-dose BZD effects until the effects of therapeutic doses have been better characterized in this patient population. Hence, the objectives of this research were to examine the effect of single doses of diazepam, within the usual therapeutic range of up to 20 mg, in stable methadone- and buprenorphine-maintained patients, upon physiological, subjective, and cognitive-performance measures.

METHODS

A double-blind, randomized, within-subjects design was used to examine the impact of single doses of placebo, 10-, and 20-mg diazepam administered orally to patients in buprenorphine or methadone maintenance treatment. The study was conducted under conditions of voluntary informed consent and approved by the Institute of Psychiatry Human Research Ethics Committee.

Subjects

Selection criteria were as follows: (a) aged 18 years or older, (b) in methadone or buprenorphine treatment for at least 4 weeks, and on stable doses for at least 2 weeks within the range of 30 and 100 mg for methadone-treated patients, or between 4 and 16 mg for buprenorphine-treated patients; (c) having a history of BZD use, but no recent use within the past 2 weeks (confirmed by urine drug screen [UDS]); (d) not currently dependent on heroin, cocaine, or alcohol, and able to abstain from these substances for at least 2 days before each session; (e) having no significant medical or psychiatric condition, including severe hepatic disease (liver function tests more than 3 times greater than normal range); (f) not pregnant (confirmed by urinary β−human chorionic gonadotropin test); (g) not using psychotropic medications or other medications known to have significant interaction with either methadone, buprenorphine, or diazepam. The study aimed to recruit 9 subjects in methadone and 9 subjects in buprenorphine treatment, with each subject acting as his or her own control.

Procedures

Each subject attended 3 test sessions, each approximately 1 week apart. The subjects were screened with a UDS and breath alcohol reading before commencing each session. Each session involved a series of measures (as described in the succeeding sections) at baseline and at regular intervals for 6 hours after study medication. After baseline measures, the subjects were administered their normal methadone (10-mg/mL oral solution) or buprenorphine (sublingual 2- or 8-mg Subutex tablets) dose and simultaneously administered either 0- (placebo), 10-, or 20-mg diazepam (in random order). Diazepam oral solution (dose, 2 mg/mL) and placebo diazepam solution were dispensed by a study pharmacist (a total of 15-mL solution dispensed at each session). A block randomized-dosing schedule was used, with sequential allocation by the study pharmacist. The subjects were reimbursed the equivalent of £30 in supermarket vouchers for each test session completed, and an additional £30 for completing all 3 tests sessions.

Outcome Measures and Data Collection

All tests sessions were conducted in the same research laboratory room under consistent lighting and temperature conditions. Physiological measures were conducted at baseline (0), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, and 6 hours after dosing. Pulse rate, blood pressure (taken while in a sitting position), and peripheral pO_2 were measured using a pulse oximeter (KTMED Model KTPS-01). Pupil size and respiratory rate (over 1 minute) were measured manually.

Subjective measures of drug effects included the Addiction Research Center Inventory (ARCI) morphine-benzedrine group (MBG) subscale (measuring euphoria) and pentobarbital-chlorpromazine-alcohol (PCAG) subscale (measuring sedation),[27] completed at 0, 1, 2, 3, and 5 hours after dosing. The subjects also completed visual analog scales (VASs; range, 0–100 mm) of *strength of drug effect*, *drug liking*, and *sedation* at 0, 0.5, 1, 1.5, 2, 3, 4, 5, and 6 hours after dosing.

Performance measures were conducted at 0, 1, 3, and 5 hours after dosing. These included simple visual reaction time, a measure of sensory-motor performance; cancellation of *4*s task, a measure of focussed attention[28]; Digit Symbol Substitution Test (DSST), a subtest of the Wechsler Adult Intelligence Scale designed to measure coding skills[29]; and a balance task, a measure of the ability to maintain whole body equilibrium.[30] Prose recall, a measure of immediate and delayed episodic memory,[31] was measured at 0 and 3 hours after dosing.

The Subjective and Objective Opiate Withdrawal Scales[32] were conducted at baseline and at 6 hours to ensure that the subjects were not in significant opioid withdrawal, a potential confounder of other measures.

Data Analysis

Data were inputted and analyzed using SPSS 11.0 for Windows. Two-way repeated-measures analysis of variance (ANOVA) was used to examine the effects of diazepam condition (diazepam doses: 0 [placebo], 10, and 20 mg) and time since dosing on all pharmacodynamic measures. Peak effects (maximal effect compared with baseline) were analyzed using paired *t* tests to examine the effect of diazepam administration relative to placebo, and independent *t* tests to compare the peak effects for methadone and buprenorphine within each diazepam condition. Comparisons between demographics, significant ages, and recent substance use between the methadone- and buprenorphine-treated subjects were made using Fisher exact test (categorical) and Mann-Whitney test (continuous) measures, given the small population in each group. All tests of statistical significance were 2-tailed and used 0.05 α level.

RESULTS

Subject Characteristics

Sixteen subjects maintained on either methadone (n = 8) or buprenorphine (n = 8) completed the study; demographics and treatment details are summarized for each group in Table 1. One subject reported BZD (temazepam) use within the past 4 weeks (14 days earlier on self-report) but provided a BZD-negative UDS before recruitment. Six subjects reported a lifetime history of daily BZD use for at least 1 month (5 buprenorphine- and 1 methadone-treated subjects); however, all subjects reported that their last regular use of BZDs was at least 2 years earlier. There were no statistically significant differences between the methadone-treated and buprenorphine-treated groups on any demographic or treatment-related parameters.

TABLE 1. Subject Characteristics at Baseline by Prescribed Opioid Medication

	Methadone (N = 8)	Buprenorphine (N = 8)
Age, mean ± SD (yrs)	38.5 ± 11.2	36.6 ± 10.0
First heroin use	22.4 ± 3.8	25.5 ± 12.0
First regular heroin use	24.5 ± 4.4	27.0 ± 12.7
First BZD use	20.9 ± 3.1	21.8 ± 6.9
Current treatment duration, mean ± SD (yrs)	3.8 ± 5.4	1.5 ± 0.9
Current dose, mean ± SD		
Range (mg)	55.0 ± 21.4 [35–100]	10.5 ± 3.2 [6–16]
Duration (mos)	27 ± 40	4.5 ± 3.5
Self-report substance use in past 4 weeks, n (%)		
Heroin	5 (63%)	2 (25%)
Alcohol	3 (38%)	4 (50%)
Cannabis	5 (63%)	7 (88%)
Cocaine	3 (38%)	5 (63%)
BZD	1 (13%)	0
Tobacco	8 (100%)	7 (88%)
Ethnicity		
White British	6 (75%)	5 (63%)
Asian British	1 (13%)	0
Black British	1 (13%)	3 (38%)
Sex		
Men	6 (75%)	6 (75%)

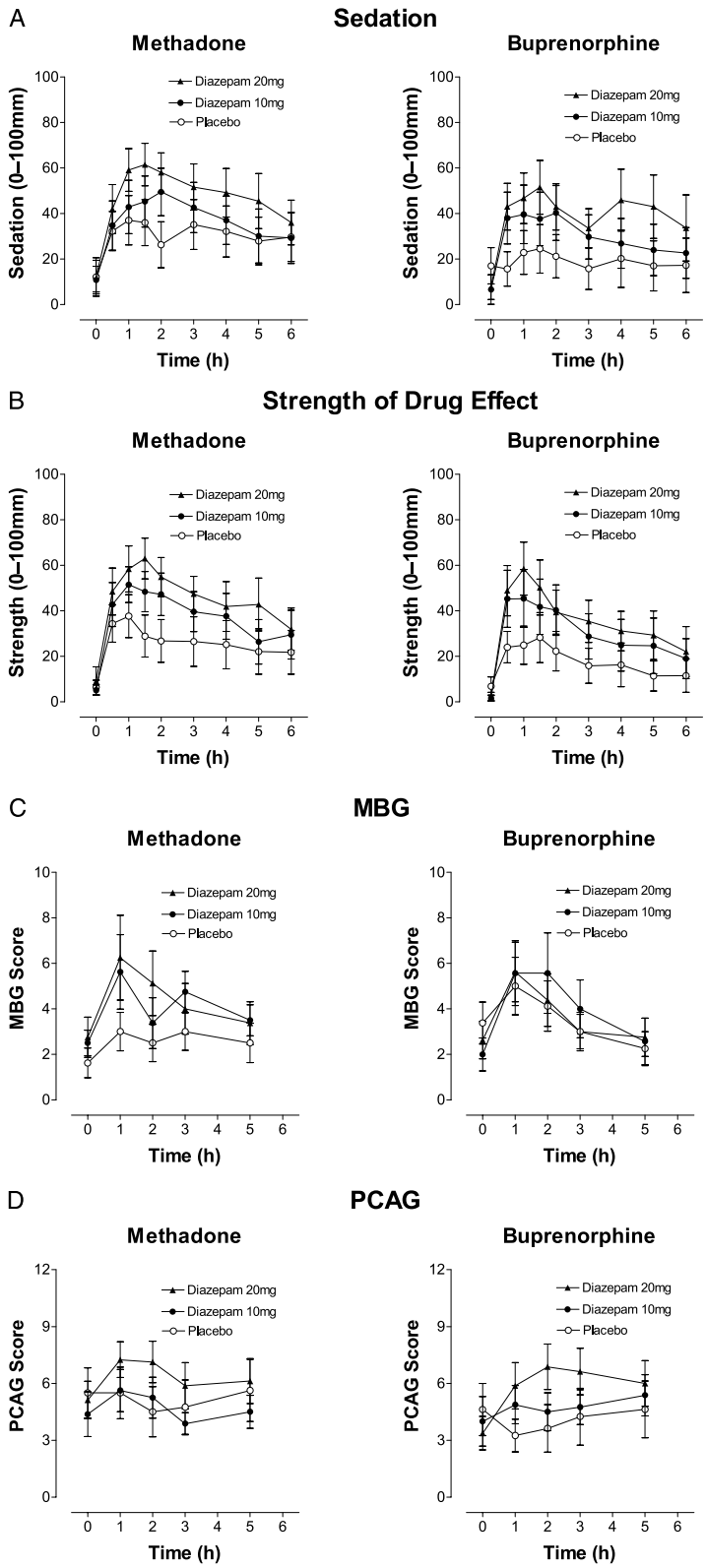

FIGURE 1. Visual analog scale ratings (range, 0–100 mm) of sedation (range, from *not sedated* to *very sedated*) and strength of drug effect (range, from *no effect* to *very strong*) and the morphine benzedrine group (MBG) and pentobarbital-chlorpromazine-alcohol group (PCAG) subscales of the Addiction Research Center Inventory after double-blind coadministration of either placebo, 10-mg diazepam, or 20-mg diazepam, with open-label methadone (n = 8) or buprenorphine (n = 8) in maintenance patients. Data are expressed as mean ± SEM.

Pharmacodynamic Responses

Temporal changes in subjective drug effects after drug administration for VAS ratings of *sedation* and *strength of drug effect* and for the MBG and PCAG ARCI subscales are shown in Figure 1. For each of these measures, the mean responses tended to show a dose-dependent increase in response to coadministration of diazepam with both methadone and buprenorphine. Response patterns were similar for methadone and buprenorphine across each diazepam condition, with peak responses being observed 1 to 2 hours after drug administration, before gradually declining toward baseline values.

ANOVA (Table 2) indicated a significant main effect for diazepam condition on VAS ratings of *sedation* and *strength of drug effect* for both methadone and buprenorphine groups. Analyses of ARCI subscales indicated a main effect for diazepam condition on the MBG scale for methadone, but not for buprenorphine; conversely, the PCAG scale showed a marginally nonsignificant main effect for diazepam condition and a significant diazepam condition × time interaction for buprenorphine, but not for methadone.

Temporal changes in psychomotor performance and physiological response measures for reaction time, cancellation time, the DSST, and oxygen saturation are shown in Figure 2. For each performance task, diazepam administration was generally associated with a dose-related performance deficit relative to placebo that was maximal in the 20-mg diazepam condition, 1 hour after dose; these effects were minimal at 5 hours after dose. Whereas diazepam produced performance deficits on these tasks, the mean profiles for the placebo session suggested that neither methadone nor buprenorphine administered alone was associated with decreased performance relative to baseline.

ANOVA (Table 2) indicated significant main effects for diazepam condition and the diazepam condition × time interaction for reaction time and cancellation time in the methadone group; for buprenorphine, there was a significant main effect for diazepam condition on reaction time and a diazepam condition × time interaction for cancellation time. Balance test scores were highly variable between individuals and were not associated with any statistically significant diazepam-mediated effects.

There were also no statistically significant diazepam-mediated ANOVA effects for the key physiological safety parameter, oxygen saturation, which remained stable over the observation period (Fig. 2), or any other physiological parameter. Pupil diameter, heart rate, and respiratory rate decreased after dosing in a manner consistent with opioid administration; however, these response patterns were not significantly affected by diazepam administration (data not shown).

Measurement of peak effects relative to baseline were used to further characterize the effect of diazepam on subjective drug responses (absolute change relative to baseline) and performance measures (percentage change relative to baseline Table 3). Peak subjective drug responses (VAS, ARCI) in both methadone and buprenorphine groups tended to increase in a dose-related manner in the 10- and 20-mg diazepam conditions relative to baseline (Fig. 3). Peak performance deficits also tended to increase in a dose-related manner in the 10- and 20-mg diazepam conditions relative to baseline; however, this pattern of diazepam-mediated performance deficits was more pronounced in the methadone group than in the buprenorphine group (Fig. 3). For simple reaction time, the percentage changes (Table 3) corresponded to peak absolute reaction times in the placebo, 10-mg diazepam, and 20-mg diazepam conditions of 274 ± 29, 297 ± 35, and 324 ± 60 milliseconds for methadone, and 258 ± 37, 272 ± 48, and 281 ± 62 milliseconds for buprenorphine, respectively.

TABLE 2. Repeated-measures ANOVA of Diazepam Effects on Pharmacodynamic Responses and Psychomotor Performance Measures for the Methadone-treated (n = 8) and Buprenorphine-treated (n = 8) Patient Groups*

	Methadone		Buprenorphine	
	Diaz	Diaz × Time	Diaz	Diaz × Time
VAS strength of effect†	14.6 (<0.001)*	1.68 (0.06)	4.45 (0.03)*	1.36 (0.18)
VAS sedation†	4.98 (0.02)*	1.55 (0.10)	4.51 (0.03)*	1.31 (0.20)
MBG‡	4.78 (0.03)*	1.27 (0.28)	0.38 (0.69)	1.56 (0.16)
PCAG‡	1.79 (0.20)	1.00 (0.45)	3.62 (0.054)	4.26 (<0.001)*
Pupil diameter§	2.12 (0.16)	1.63 (0.06)	1.03 (0.38)	1.69 (0.049)*
Reaction time‖	4.18 (0.04)*	4.30 (0.002)*	4.97 (0.02)*	1.55 (0.19)
Cancellation time‖	9.75 (0.002)*	4.19 (0.002)*	0.93 (0.42)	2.89 (0.02)*
DSST‖	0.74 (0.50)	2.05 (0.08)	0.09 (0.92)	2.37 (0.046)*

Data are expressed as F ratio (*P* value). Diaz indicates diazepam main effect; Diaz × Time, diazepam dose × time interaction.

*Only measures for which a significant diazepam main effect or diazepam × time interaction effect were found are shown. Asterisks in figures indicate statistical significance ($P < 0.05$).

†Diaz and Diaz × Time *df* values were 2,14 and 16,112, respectively.

‡Diaz and Diaz × Time *df* values were 2,14 and 8,56, respectively.

§Diaz and Diaz × Time *df* values were 2,14 and 18,126, respectively.

‖Diaz and Diaz × Time *df* values were 2,14 and 6,42, respectively.

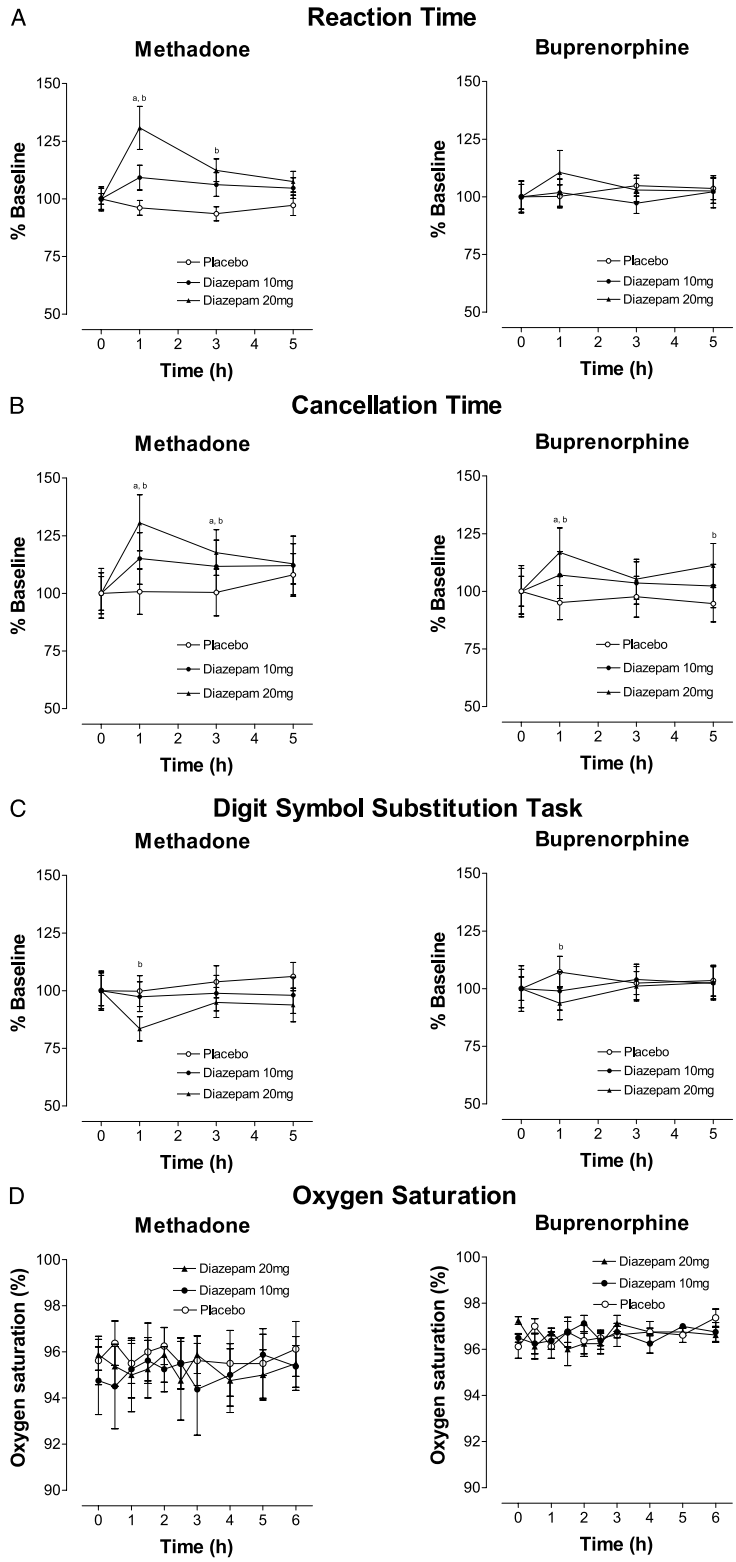

FIGURE 2. Psychomotor performance measures and oxygen saturation (pO_2) after double-blind coadministration of either placebo, 10-mg diazepam, or 20-mg diazepam, with open-label methadone (n = 8) or buprenorphine (n = 8) in maintenance patients. Data for panels A–C have been normalized to represent percentage change from baseline and are expressed as mean ± SEM. Changes relative to baseline that were significant at $P = 0.05$ level are denoted by the letters *a* (placebo vs 10-mg diazepam) and *b* (placebo vs 20-mg diazepam). For the reaction time and cancellation time tasks, higher scores indicate worse performance; for the digit symbol substitution task, lower scores indicate worse performance.

TABLE 3. Peak Effects Relative to Baseline on Subjective and Psychomotor Performance Measures After Double-blind Coadministration of Either Placebo, 10-mg Diazepam, or 20-mg Diazepam, With Open-label Methadone (n = 8) or Buprenorphine (n = 8) in Maintenance Patients

	Methadone Group			Buprenorphine Group		
Diazepam Condition	**Placebo**	**10-mg Diazepam,**	**20-mg Diazepam**	**Placebo**	**10-mg Diazepam,**	**20-mg Diazepam**
Subjective responses						
VAS strength of effect	38 ± 23	54 ± 18*	58 ± 28	30 ± 28	54 ± 31	58 ± 30
VAS sedation	34 ± 28	46 ± 30	56 ± 30	20 ± 27	44 ± 29	56 ± 32†
VAS liking	25 ± 19	29 ± 28	51 ± 37†	29 ± 21	32 ± 25	42 ± 35
MBG	1.9 ± 1.2	4.4 ± 2.8†	4.6 ± 4.4†	1.8 ± 1.7	4.6 ± 3.2†	3.1 ± 2.2
PCAG	1.5 ± 2.0	3.5 ± 3.7	3.3 ± 3.1	1.3 ± 1.0	2.0 ± 1.2	4.1 ± 2.0*
LSD	−1.5 ± 1.5	−2.8 ± 1.8†	−2.0 ± 1.5	−0.9 ± 1.1	−0.9 ± 1.1	−1.0 ± 0.8
Performance measures						
Reaction time	4.6 ± 6.5	14 ± 13.6	34 ± 22†	9.2 ± 6.6	7.9 ± 8.1	15 ± 12
DSST	−4.1 ± 4.7	−8.9 ± 7.6	−17 ± 12†	−3.2 ± 3.6	−4.5 ± 5.4	−8.0 ± 9.0
Cancellation time	−13 ± 12	−23 ± 16†	−37 ± 34	−4.4 ± 5.8	−12 ± 8.7	−22 ± 15†
Balance test	−29 ± 22	−39 ± 27	−52 ± 25	−16 ± 20	−28 ± 32	−52 ± 21*

Data are mean ± SD and represent absolute change relative to baseline for subjective measures and percentage change relative to baseline for performance measures. Only measures that showed a significant effect for diazepam at the 10- or 20-mg dose level for either methadone or buprenorphine are shown.

*With statistical difference at $P < 0.01$ from placebo.

†With statistical difference at $P < 0.05$ from placebo.

Prose recall was only measured at 3 hours; thus, performance was compared with baseline. Immediate recall of prose showed no significant effects at 3 hours, but delayed recall showed impairment after both combinations (Fig. 4). However, as delayed recall was impaired after methadone administration alone, only buprenorphine administration showed a significant difference between the administration of placebo and both doses of diazepam.

Blinding

The proportions of subjects correctly rating the absence or presence of diazepam (1 in 2 chances) for the placebo, 10-mg diazepam, and 20-mg diazepam conditions were 2, 3, and 4 of 8 subjects, respectively (38% correct overall), in the methadone group, and 4, 5, and 6 of 8 subjects, respectively (50% correct overall), in the buprenorphine group ($\chi^2_1 = 3$, $P = 0.08$). The proportions of subjects correctly rating their dose of diazepam for the placebo, 10-mg diazepam, and 20-mg diazepam conditions (1 in 3 chances) were 2, 1, and 2 of 8 subjects, respectively (21% correct overall), in the methadone group, and 4, 2, and 4 of 8 subjects, respectively (40% correct overall), in the buprenorphine group ($\chi^2_1 = 2.42$, $P = 0.12$).

DISCUSSION

This study examined the effects of single doses of diazepam within the normal therapeutic range (10–20 mg) in stable methadone- and buprenorphine-maintained individuals without current BZD tolerance. The findings are consistent with earlier reports examining the effects of diazepam in methadone-dependent individuals,[12,13] although this is the first report examining the effects of diazepam in buprenorphine-maintained patients.

This article has focussed on pharmacodynamic interactions, and we are unable to exclude any significant pharmacokinetic interaction because blood levels were not collected. However, as identified in the introduction, the limited available animal and human research[22–25] suggests that any significant pharmacokinetic interaction is unlikely; indeed, because this study examined the effect of single doses of diazepam, any significant impact on hepatic (or other) metabolic pathways for these drugs is, again, unlikely. Nevertheless, further pharmacokinetic research, particularly in the context of longer-term BZD use in this population, is warranted.

As expected, therapeutic doses of diazepam did not result in clinically (or statistically) significant changes in physiological parameters, such as blood pressure, pulse, respiratory rate, or peripheral pO_2. In contrast, these doses did result in significantly altered subjective responses (eg, sedation and strength of drug effects) in both groups of opioid-treated patients. These effects were dose- and time-dependent, and were maximal in the 20-mg diazepam condition at approximately 1 to 2 hours after dose.

Clinically, the greatest concerns regarding possible drug interactions relate to peak drug effects, which is the time at which many adverse events are most likely to occur. For methadone-treated patients, the peak effects after diazepam dosing were significantly greater than that of placebo on subjective measures, such as *strength of drug effects*, *drug liking*, and *euphoria* (MBG). A similar pattern was seen in buprenorphine-treated patients, with diazepam producing significantly greater effects than did placebo for the subjective measures of *sedation* (VAS rated and PCAG).

The impact of diazepam upon cognitive performance measures differed between the methadone- and buprenorphine-maintained patients. Twenty-milligram diazepam doses in

methadone-treated patients resulted in a significant deterioration in the performance measures of reaction time, DSST, and cancellation time. In contrast, the peak effects of 20-mg diazepam compared with placebo in buprenorphine-treated patients were less marked—with a significant deterioration found on cancellation time only.

The extent of the deterioration in these performance measures is somewhat concerning. For example, in methadone-treated patients, the mean peak reaction time (after administration of 20-mg diazepam) increased from 274 ± 29 milliseconds (after administration of placebo) to 324 ± 60 milliseconds, which could be associated with considerable impairment in function. This raises concerns regarding the safety of using even therapeutic BZD doses in circumstances where patients may be performing tasks, such as manual labor, driving, or operating machinery. Patients should be warned about these risks.

Although the study was not designed to perform direct statistical comparisons between the methadone and the buprenorphine groups, comparison of effects within a group enables us to draw some inferences. There were no major differences on physiological and subjective measures between the methadone and the buprenorphine groups with regards to the magnitude or the temporal response to therapeutic doses of diazepam. However, diazepam had greater peak effects on performance measures in the methadone-treated patients than in the buprenorphine-treated patients—suggesting that there may be some advantage in using buprenorphine over methadone in such patients. The exception was the delayed episodic memory measure, which showed significant effects after the combination of buprenorphine and diazepam. However, it is notable that buprenorphine alone showed a slight improvement with this measure, whereas methadone alone showed a decline, confirming previous findings.[33]

There are a number of implications for clinical practice arising from these findings. Coadministration of diazepam significantly alters the response to methadone and buprenorphine on clinically relevant subjective and performance parameters, even at therapeutic doses, and clinicians and patients should be aware of the potential for interaction. In particular, the peak drug effects generally occur approximately 1 to 2 hours after dosing, and if there are concerns regarding the safety of a patient taking these medications, clinical monitoring should extend for at least this period.

Methadone and buprenorphine are of comparable efficacy in the management of heroin dependence for the outcomes of changes in heroin use, other substance use (eg,

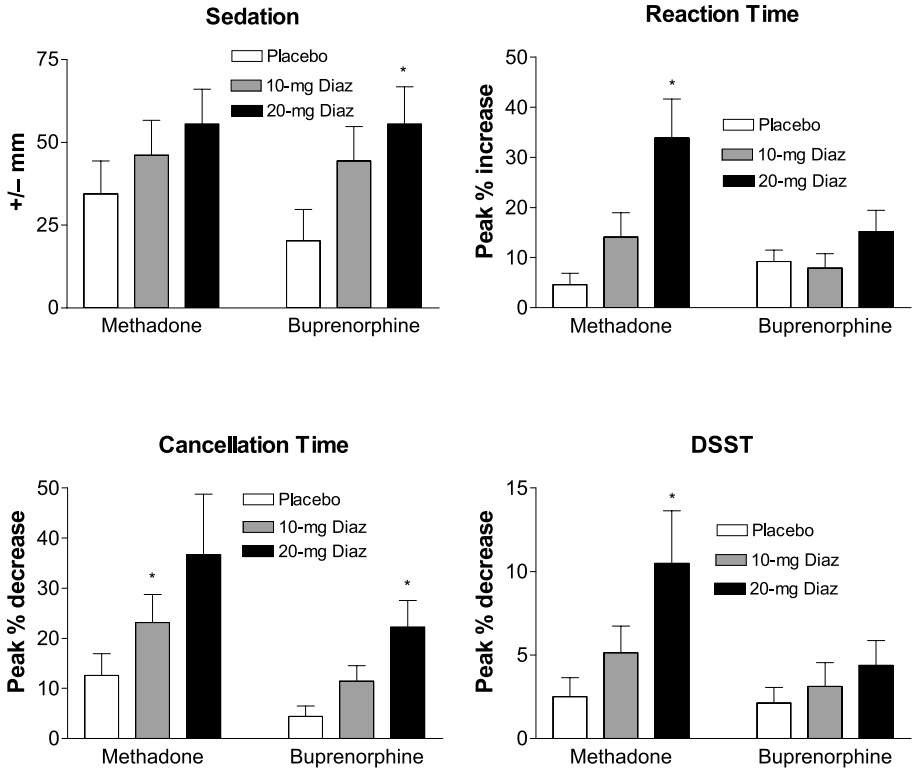

FIGURE 3. Peak effect relative to baseline for visual analog scale ratings (range, from 0 mm, *not sedated*, to 100 mm, *very sedated*) of sedation (absolute change) and for psychomotor performances measures of reaction time, cancellation time, and the digit symbol substitution task (percentage change), after double-blind coadministration of either placebo, 10-mg diazepam, or 20-mg diazepam, with open-label methadone (n = 8) or buprenorphine (n = 8) in maintenance patients. Data are expressed as mean ± SEM. Asterisk (*) indicates changes relative to baseline that were significant at the $P = 0.05$ level within the methadone and buprenorphine groups. There were no significant differences between methadone and buprenorphine for any diazepam condition.

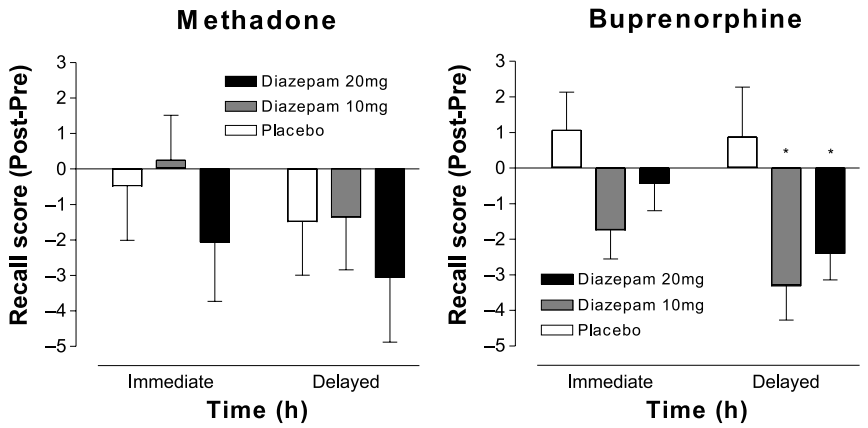

FIGURE 4. Changes in immediate- and delayed-recall scores 3 hours after double-blind coadministration of either placebo, 10-mg diazepam, or 10-mg d diazepam, with open-label methadone (n = 8) or buprenorphine (n = 8) in maintenance patients. Data have been normalized to represent differences from baseline and are expressed as mean ± SEM. Asterisk (*) indicates significant differences relative to the placebo condition for the 10-mg and 20-mg diazepam conditions in methadone and buprenorphine groups.

cocaine, BZD), and treatment retention.[26] Hence, it is of particular interest to establish whether they have different safety profiles about adverse effects. The partial agonist characteristics of buprenorphine are widely believed to make it safer than methadone[14]; however, there have been concerns that this safety margin may diminish in the context of multidrug use involving multiple sedatives. The previously mentioned findings indicate that acute therapeutic doses of diazepam produce minimal impairment in respiratory or other physiological parameters, but significant subjective and performance effects in both methadone- and buprenorphine-treated patients, with psychomotor changes being generally greater in methadone-treated patients. This suggests that although acute BZD use at therapeutic doses seems to be safe in both groups of patients, the patients should be alerted to the likely subjective and psychomotor changes, and be warned against driving or operating machinery under these circumstances. Although these findings suggest that there may be some advantage in using buprenorphine rather than methadone (given that diazepam had greater impact on psychomotor measures in the methadone-treated patients), it is inappropriate to conclude from these findings that either medication should be prioritized in BZD-dependent patients. Any effects seen under short-term BZD use may be attenuated or may disappear with long-term BZD use and the development of tolerance. Similarly, the effects of high-dose BZDs (abuse conditions) have not been examined in this study, and further research is required to establish the comparative safety of BZDs in combination with methadone or buprenorphine under such conditions. Indeed, caution must be exercised before generalizing from the findings of this study to other populations. In particular, the responses may be different in individuals being inducted into substitution treatment (stable maintenance patients were examined in this study), in individuals with concomitant medical conditions, such as severe liver disease, and in patients using methadone or buprenorphine erratically. Similarly, diazepam was examined in this study because it is widely used in this population[10]; however, it is possible that different responses may be seen with other BZDs. Further research in these groups is required.

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