Available online at www.sciencedirect.com
SCIENCE DIRECT®
Drug and Alcohol Dependence 74 (2004) 205–209
DRUG and ALCOHOL DEPENDENCE
www.elsevier.com/locate/drugalcdep

Short communication

A dose–effect study of repeated administration of buprenorphine/naloxone on performance in opioid-dependent volunteers

Miriam Z. Mintzer[b,*], Christopher J. Correia[a,b], Eric C. Strain[b]

[a] *Department of Psychology, Auburn University, Auburn, AL 36849, USA*
[b] *Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD 21224, USA*

Received 27 August 2003; received in revised form 2 December 2003; accepted 4 December 2003

Abstract

Based on its unique pharmacological profile, buprenorphine may produce less impairment in psychomotor and cognitive performance than methadone. However, the few studies that have investigated the performance effects of buprenorphine in opioid-abusing volunteers examined effects of single acute doses rather than effects of repeated dosing and included a very limited range of measures. The present inpatient study evaluated dose-related effects of repeated administration of the buprenorphine/naloxone combination product (8/2, 16/4, 32/8 mg, sublingual tablets) in eight opioid-dependent volunteers on performance of a broad range of tasks, following a period of 7–10 days of dosing at each level, in a double-blind, within-subject, crossover design. The testing battery included measures of psychomotor speed, time perception, conceptual flexibility, focused attention, working memory, long-term/episodic memory, and metamemory. Supporting the hypothesis of limited impairment with buprenorphine, results revealed minimal impairment in performance as buprenorphine/naloxone dose was increased four-fold. The only significant effect of dose was an impairment in episodic/long-term memory (recognition memory) performance at the highest dose (32/8 mg) relative to the two lower doses. Future studies incorporating larger sample sizes and non-drug controls, as well as directly comparing buprenorphine to methadone and LAAM are needed to further test the hypothesis of limited impairment with buprenorphine.

Keywords: Buprenorphine; Opioid-dependence; Cognitive performance; Pharmacotherapy; Neuropsychology

1. Introduction

Buprenorphine, a mu opioid partial agonist and kappa antagonist, is currently used as an analgesic and as a treatment for opioid-dependence (cf. Fudala and Bridge, 2003). For the latter indication, buprenorphine was first approved in France in 1995 and is currently approved in 34 countries worldwide, including the United States (Dr. Rolley E. Johnson, Reckitt Benckiser, personal communication, November 2003). Buprenorphine is approved for sublingual administration alone (Subutex) and in combination with the opioid antagonist naloxone (Suboxone; as a treatment for opioid-dependence, United States only). The buprenorphine/naloxone sublingual combination product was designed to minimize intravenous abuse of buprenorphine by dependent opioid abusers. Because naloxone has poor sublingual bioavailability (Preston et al., 1990), use of buprenorphine/naloxone tablets by the therapeutic sublingual route produces a predominantly buprenorphine effect; however, when the tablets are dissolved and injected by a dependent opioid abuser, naloxone precipitates a withdrawal syndrome (Fudala et al., 1998; Mendelson et al., 1997; Preston et al., 1988; Stoller et al., 2001). Due to its unique pharmacological profile, buprenorphine is thought to have several advantages for treating opioid-dependence relative to pure mu agonists such as methadone and levomethadyl acetate (LAAM), including a better safety profile (e.g., less respiratory depression), less physical dependence, and the ability to dose less-than-daily (a property shared with LAAM).

As a partial agonist, buprenorphine may also produce less impairment in psychomotor and cognitive performance

* Corresponding author. Tel.: +1-410-550-0529; fax: +1-410-550-0030.
E-mail address: mmintzer@jhmi.edu (M.Z. Mintzer).

0376-8716/$ – see front matter © 2004 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.drugalcdep.2003.12.008

than full agonists such as methadone. A recently reported comparison of opioid-dependent patients being maintained on methadone versus buprenorphine in a German clinic suggests less impairment in the buprenorphine patients on several psychomotor performance measures relevant to driving skills (Soyka et al., 2001). However, it is important to note that conclusions from that report are limited due to the absence of controlled procedures and of matching of patients in the two groups. To our knowledge, no controlled study has directly compared the performance effects of buprenorphine and methadone although there have been separate studies of both methadone and buprenorphine. The literature on methadone's effects on performance is mixed. Results of several early studies in methadone maintenance patients suggest only minimal performance impairment (Appel, 1982; Appel and Gordon, 1976; Gordon, 1970; Lombardo et al., 1976; Moskowitz and Robinson, 1985; Robinson and Moskowitz, 1985; Rothenberg et al., 1977). However, as Zacny (1995) commented in a review of effects of opioids on psychomotor and cognitive functioning, most early studies of methadone have methodological problems such as use of a small sample size, absence of appropriate controls, failure to control for concurrent use of other drugs, and use of a very limited range of measures. A few recent studies which addressed some of these methodological problems provide evidence for impairment in methadone maintenance patients in a wide range of psychomotor and cognitive functions (Darke et al., 2000; Mintzer and Stitzer, 2002; Specka et al., 2000; cf. also Gritz et al., 1975).

Given buprenorphine's relatively recent introduction as a treatment for opioid-dependence, to our knowledge there have been no controlled studies of performance in buprenorphine-maintained patients. However, a few studies have examined the performance effects of acute experimental dosing of buprenorphine (or buprenorphine/naloxone) in opioid-abusing volunteers. Results of these studies suggest that buprenorphine produces mild impairment in gross psychomotor performance, but does not impair more complex cognitive functions (Pickworth et al., 1993; Preston et al., 1988, 1989, 1992; Stoller et al., 2001; Strain et al., 1992, 2000; Walsh et al., 1994, 1995). However, it is important to note that conclusions are limited because all these studies examined the effects of single acute doses of buprenorphine rather than repeated dosing (the pattern in which buprenorphine is administered clinically) and included a very limited range of measures. To address these issues, the present inpatient study evaluated the dose–effects of buprenorphine/naloxone (8/2, 16/4, and 32/8 mg, sublingual tablets) in opioid-dependent volunteers on performance of a broad range of tasks, following a period of 7–10 days of administration at each dose level, in a double-blind, within-subject, crossover design. The testing battery included measures of psychomotor speed, time perception, conceptual flexibility, focused attention, working memory, long-term/episodic memory, and metamemory.

2. Methods

2.1. Participants

Participants were eight healthy adult community volunteers (five males, six African Americans/two Caucasians), with a diagnosis of current opioid-dependence and eligibility for (but not enrollment in) opioid agonist treatment. Participant recruiting and screening procedures were similar to those described in detail previously (Strain et al., 2000). Participants ranged in age from 26 to 41 years (mean = 36) and in years of education from 10 to 14 (mean = 12). Reported duration of lifetime illicit opioid use ranged from 4 to 12 years (mean = 8). The study was approved by the Institutional Review Board of the Johns Hopkins Bayview Medical Center. Participants gave their written informed consent before beginning the study and were paid for their participation.

2.2. Procedures

This study was conducted as part of a larger study of buprenorphine/naloxone which will be reported elsewhere. For the duration of the study, participants resided on a closed 14-bed residential unit. The order of buprenorphine/naloxone dose conditions (8/2, 16/4, and 32/8 mg) was derived from a Latin Square for six subjects. Participants were assigned one of the schedules using a random number table. Participants received sublingual tablets, under nursing supervision, daily at 8:00 am under double-blind conditions; each morning, participants received four tablets, combining active tablets with placebo tablets to maintain blinding. At each dose condition, performance testing was initiated after the participant had received 7–10 days of buprenorphine/naloxone administration at that dose, and was conducted at three separate timepoints: 12 h before the daily dose (i.e., 12 h after the previous daily dose), and 1 and 6 h after the daily dose. Thus, participants completed a total of nine performance testing sessions (three at each dose condition) during the study.

The performance testing battery included a computerized version of the digit symbol substitution test (DSST; McLeod et al., 1982; Wechsler, 1955) (a measure of psychomotor/cognitive speed), two computerized trail-making tests (Mintzer et al., 1997) analogous to Part A and Part B of the paper/pencil Trail-Making Test of the Halstead–Reitan Neuropsychological Test Battery (Halstead, 1947; Reitan, 1955) (measures of psychomotor speed and cognitive flexibility), and a time estimation task which assessed the participant's ability to accurately estimate the duration of 5, 20, and 80 s time intervals (Mintzer et al., 1997) (a measure of time perception). The battery included two measures of short-term/working memory and focused attention: a digit recall task which assessed the participant's ability to recall 8-digit strings following short delays (Mintzer et al., 1997) and the '*n*-back' task which assessed the participant's ability

to recall letters presented *n*-positions back in a continuous string of letters (i.e., one or two positions back; 0-back was a non-memory control condition in which participants were simply required to respond to a specified target letter in the continuous string) (Jonides et al., 1997; Mintzer and Stitzer, 2002). The battery also included a word memory paradigm (Mintzer and Stitzer, 2002) that assessed the participant's ability to recognize (recognition memory) and recall (free recall) a list of words presented in a study list at the beginning of the testing session, following an 80 min delay (measures of long-term/episodic memory). The word memory paradigm also assessed participants' confidence in their recognition memory responses (a measure of metamemory: awareness and knowledge of one's own memory). The word memory paradigm was administered during the 1 h post-dose testing session only. These tasks have all been described in detail previously (see references cited above) and were administered by a staff member on a Macintosh computer in a quiet session room outside the residential unit.

3. Results

Data from the performance testing battery were analyzed by repeated measures analyses of variance (ANOVAs) with dose condition (8/2, 16/4, and 32/8 mg buprenorphine/naloxone), timepoint (12 h pre-dose, and 1 and 6 h post-dose) (except for data from the word memory paradigm, administered at the 1 h post-dose timepoint only), and other task-specific variables as factors. Due to technical difficulties, data were not available for one participant in the recognition memory test, and reaction time data were not available for three participants in the *n*-back task. In addition, gamma correlations (between confidence ratings and recognition memory accuracy in the word memory paradigm; used to measure metamemory; Goodman and Kruskal, 1954) could not be computed for one participant because he used the same confidence rating option for all responses. For all statistical tests, $P \leq 0.05$ was considered significant.

Overall, results revealed little impairment in performance as buprenorphine/naloxone dose was increased four-fold. Data presented in Table 1 are collapsed over timepoint, since there were no significant interactions of time with dose condition. In the recognition memory test, there was a significant effect of dose condition on d', which is the signal detection measure of the participant's sensitivity in discriminating between words presented in the initial study list and words not presented in the study list (measure of long-term/episodic memory), such that d' was significantly lower in the 32/8 mg buprenorphine/naloxone condition, relative to both the 8/2 and 16/4 mg conditions. The mean gamma correlations in the recognition memory test (metamemory) were in the direction of impairment in the 32/8 mg condition, although the effect was not statistically significant (possibly due to small sample size as gamma analyses only included data from six participants). There were no other significant effects of dose condition, nor interactions between dose condition and any other factors. In the *n*-back task, there was a significant main effect of '*n*' on performance, such that performance

Table 1
Mean scores (standard deviation in parentheses) on experimental measures as a function of buprenorphine/naloxone dose

Task	Measure	Buprenorphine/naloxone dose		
		8/2 mg	16/4 mg	32/8 mg
DSST	# correct	33.46 (9.64)	34.77 (9.82)	38.08 (11.03)
DSST	# attempted	39.75 (11.60)	37.73 (11.26)	41.04 (9.40)
Trail-making A	Total time (s)	41.80 (16.30)	44.31 (14.95)	49.18 (28.26)
Trail-making B	Total time (s)	55.43 (28.65)	59.97 (15.46)	55.60 (30.34)
Time estimation	Estimate (s)—5 s	5.68 (0.73)	5.49 (0.59)	6.19 (2.30)
Time estimation	Estimate (s)—20 s	18.56 (2.56)	19.12 (2.87)	19.79 (1.21)
Time estimation	Estimate (s)—80 s	69.63 (10.42)	71.84 (19.55)	76.47 (11.02)
Digit recall	Number correct	5.08 (2.91)	4.92 (3.39)	6.34 (2.39)
n-back	d' (sensitivity)—0-back	4.05 (0.24)	3.92 (0.35)	3.93 (0.28)
n-back	d' (sensitivity)—1-back	3.38 (1.22)	3.18 (0.91)	3.68 (0.57)
n-back	d' (sensitivity)—2-back	2.79 (0.99)	2.56 (0.91)	2.99 (0.45)
n-back	RT (ms)—0-back[a]	703 (131)	724 (187)	715 (144)
n-back	RT (ms)—1-back[a]	722 (159)	764 (183)	750 (176)
n-back	RT (ms)—2-back[a]	860 (157)	975 (149)	837 (150)
Recognition memory	d' (sensitivity)[b,c]	1.92 (0.55)	2.25 (0.81)	1.61 (0.44)
Recognition memory	C (response bias)[b]	0.32 (0.38)	0.50 (0.38)	0.46 (0.58)
Recognition memory	Gamma (metamemory)[d]	0.54 (0.53)	0.44 (0.40)	0.13 (0.75)
Free recall	# correct responses	14.25 (8.78)	13.88 (9.06)	12.50 (7.35)

[a] $N = 5$.
[b] $N = 7$.
[c] Significant effect of dose condition.
[d] $N = 6$.

worsened as a function of '*n*' (memory load); this effect was reflected both in a decrease in d' and an increase in reaction time as memory load increased. This pattern replicates the results of previous cognitive studies, providing evidence for the sensitivity of the task as implemented in the present study.

4. Discussion

To our knowledge, this is the first controlled study to examine the effects of repeated buprenorphine/naloxone administration on cognitive performance in opioid-dependent volunteers. It is important to note that given that the study was conducted on a closed residential unit where drug use is prohibited, results are not confounded by concurrent use of other drugs. The absence of effect of buprenorphine/naloxone dose condition on performance on the DSST is consistent with results of acute dosing studies indicating that doses up to 32 mg buprenorphine do not impair DSST performance in opioid-abusing volunteers (Preston et al., 1988, 1989; Stoller et al., 2001; Strain et al., 1992, 2000; Walsh et al., 1994, 1995). Likewise, the absence of effect on the digit recall short-term/working memory task is consistent with results of acute dosing studies indicating that doses up to 8 mg buprenorphine do not significantly impair performance on this task (Preston et al., 1988; Strain et al., 1992; Walsh et al., 1995). Results of the present study extend the absence of effect to higher doses administered repeatedly and to another measure of short-term/working memory (the *n*-back task). While two previous acute dosing studies reported impairment of trail-making performance with buprenorphine/naloxone relative to placebo (Stoller et al., 2001; Strain et al., 2000), results of the present repeated dosing study reveal no differences among the tested doses in trail-making performance. To our knowledge, no previous studies have examined the effects of buprenorphine on time perception, long term/episodic memory, and metamemory. Interestingly, the 32/8 mg buprenorphine/naloxone dose significantly impaired long-term/episodic memory performance, as measured by d' on the recognition memory task, relative to the lower doses.

The absence of impairment on most measures in the present study as buprenorphine/naloxone dose was increased four-fold and the finding of impairment in recognition memory only at the highest dose (32/8 mg) support the hypothesis that buprenorphine is associated with limited impairment of performance. Given that doses of 4–24 mg buprenorphine are generally recommended for treatment of opioid-dependence, an effect at the 32/8 mg dose is unlikely to have clinical implications for most patients. However, these null effects should be interpreted cautiously due to the small sample size as well as due to the absence of a placebo condition or control group. The absence of a non-drug control condition leaves open the possibility that although there were no significant differences among the tested doses, buprenorphine/naloxone administration was associated with overall impairment relative to normative, control conditions. We explored this possibility by comparing results of the present study to those of a previous study in our laboratory (Mintzer and Stitzer, 2002) which examined performance of methadone maintenance patients relative to matched control participants using some of the same tasks as the present study (DSST, trail-making, word memory paradigm). Although the control participants in that study did not have histories of drug abuse, their demographics are similar to those of the participants in the present study (e.g., mean years of education: 12 in both groups; mean age: 36 years in the present study, 35 years in the Mintzer and Stitzer control group). This between-study comparison revealed comparable or higher levels of performance in the 8/2 mg condition in the present study relative to the Mintzer and Stitzer controls across all tasks used in both studies. Although between-study comparisons are inherently limited, results of this analysis suggest it is unlikely that buprenorphine/naloxone administration in the present study was associated with significant impairment relative to normative performance. Future studies incorporating larger sample sizes and non-drug controls, as well as directly comparing buprenorphine to methadone and LAAM are needed to further test the hypothesis of limited impairment with buprenorphine.

Acknowledgements

This project was supported by National Institute on Drug Abuse Research Grants DA08045 and DA00332. The authors thank Heather Cronin and Abigail Yuscavage for technical assistance, John Yingling for computer programming assistance and technical support, and Tim Mudric and Paul Nuzzo for assistance with data analysis.

References

Appel, P.W., 1982. Sustained attention in methadone patients. Int. J. Addict. 17, 1313–1327.

Appel, P.W., Gordon, N.B., 1976. Digit-symbol performance in methadone-treated ex-heroin addicts. Am. J. Psychiatry 133, 1337–1340.

Darke, S., Sims, J., McDonald, S., Wickes, W., 2000. Cognitive impairment among methadone maintenance patients. Addiction 95, 687–695.

Fudala, P.J., Bridge, T.P., 2003. Guest Editors, Supplement: Buprenorphine and buprenorphine/naloxone: A guide for clinicians. Drug Alcohol Depend. 70, S1–S104.

Fudala, P.J., Yu, E., Macfadden, W., Boardman, C., Chiang, C.N., 1998. Effects of buprenorphine and naloxone in morphine-stabilized opioid addicts. Drug Alcohol Depend. 50, 1–8.

Goodman, L.A., Kruskal, W.H., 1954. Measures of association for cross-classifications. J. Am. Stat. Assoc. 49, 732–764.

Gordon, N.B., 1970. Reaction-times of methadone treated ex-heroin addicts. Psychopharmacologia 16, 337–344.

Gritz, E.R., Shiffman, S.M., Jarvik, M.E., Haber, J., Dymond, A.M., Coger, R., Charuvastra, V., Schlesinger, J., 1975. Physiological and

psychological effects of methadone in man. Arch. Gen. Psychiatry 32, 237–242.
Halstead, W.C., 1947. Brain and Intelligence. University of Chicago Press, Chicago.
Jonides, J., Schumacher, E.H., Smith, E.E., Lauber, E.J., Awh, E., Minoshima, S., Koeppe, R.A., 1997. Verbal working memory load affects regional brain activation as measured by PET. J. Cogn. Neurosci. 9, 462–475.
Lombardo, W.K., Lombardo, B., Goldstein, A., 1976. Cognitive functioning under moderate and low dosage methadone maintenance. Int. J. Addict. 11, 389–401.
McLeod, D.R., Griffiths, R.R., Bigelow, G.E., Yingling, J., 1982. An automated version of the digit symbol substitution test (DSST). Behav. Res. Methods Instrum. 14, 463–466.
Mendelson, J., Jones, R.T., Brown, W.S., Batki, S.L., 1997. Buprenorphine and naloxone interactions in methadone maintenance patients. Biol. Psychiatr. 41, 1095–1101.
Mintzer, M.Z., Frey, J.M., Yingling, J.E., Griffiths, R.R., 1997. Triazolam and zolpidem: A comparison of their psychomotor, cognitive, and subjective effects in healthy volunteers. Behav. Pharmacol. 8, 561–574.
Mintzer, M.Z., Stitzer, M.L., 2002. Cognitive impairment in methadone maintenance patients. Drug Alcohol Depend. 67, 41–51.
Moskowitz, H., Robinson, C.D., 1985. Methadone maintenance treatment and tracking performance. In: Kaye, S., Meier, G.W. (Eds.), Alcohol, Drugs and Traffic Safety, U.S. Department of Transportation, pp. 995–1004.
Pickworth, W.B., Johnson, R.E., Holicky, B.A., Cone, E.J., 1993. Subjective and physiologic effects of intravenous buprenorphine in humans. Clin. Pharmacol. Ther. 53, 570–576.
Preston, K.L., Bigelow, G.E., Liebson, I.A., 1988. Buprenorphine and naloxone alone and in combination in opioid-dependent humans. Psychopharmacology 94, 484–490.
Preston, K.L., Bigelow, G.E., Liebson, I.A., 1989. Antagonist effects of nalbuphine in opioid-dependent human volunteers. J. Pharmacol. Exp. Ther. 248, 929–937.
Preston, K.L., Bigelow, G.E., Liebson, I.A., 1990. Effects of sublingually given naloxone in opioid-dependent human volunteers. Drug Alcohol Depend. 25, 27–34.
Preston, K.L., Liebson, I.A., Bigelow, G.E., 1992. Discrimination of agonist-antagonist opioids in humans trained on a two-choice saline-hydromorphone discrimination. J. Pharmacol. Exp. Ther. 261, 62–71.
Reitan, R.M., 1955. Investigation of the validity of Halstead's measure of biological intelligence. Arch. Neurol. Psychiatry 73, 28–35.
Robinson, C.D., Moskowitz, H., 1985. Methadone maintenance treatment and aspects of skilled performance. In: Kaye, S., Meier, G.W. (Eds.), Alcohol, Drugs and Traffic Safety, U.S. Department of Transportation, pp. 1145–1157.
Rothenberg, S., Schottenfeld, S., Meyer, R.E., Krauss, B., Gross, K., 1977. Performance differences between addicts and non-addicts. Psychopharmacology 52, 299–306.
Soyka, M., Horak, M., Dittert, S., Kagerer, S., 2001. Less driving impairment on buprenorphine than methadone in drug-dependent patients? J. Neuropsychiatry Clin. Neurosci. 13, 527–528.
Specka, M., Finkbeiner, T., Lodemann, E., Leifert, K., Kluwig, J., Gastpar, M., 2000. Cognitive-motor performance of methadone-maintained patients. Eur. Addict. Res. 6, 8–19.
Stoller, K.B., Bigelow, G.E., Walsh, S.L., Strain, E.C., 2001. Effects of buprenorphine/naloxone in opioid-dependent humans. Psychopharmacology 154, 230–242.
Strain, E.C., Preston, K.L., Liebson, I.A., Bigelow, G.E., 1992. Acute effects of buprenorphine, hydromorphone and naloxone in methadone-maintained volunteers. J. Pharmacol. Exp. Ther. 261, 985–993.
Strain, E.C., Stoller, K., Walsh, S.L., Bigelow, G.E., 2000. Effects of buprenorphine versus buprenorphine/naloxone tablets in non-dependent opioid abusers. Psychopharmacology 148, 374–383.
Walsh, S.L., Preston, K.L., Stitzer, M.L., Cone, E.J., Bigelow, G.E., 1994. Clinical pharmacology of buprenorphine: Ceiling effects at high doses. Clin. Pharmacol. Ther. 55, 569–580.
Walsh, S.L., Preston, K.L., Bigelow, G.E., Stitzer, M.L., 1995. Acute administration of buprenorphine in humans: Partial agonist and blockade effects. J. Pharmacol. Exp. Ther. 274, 361–372.
Wechsler, D., 1955. A Manual for the Wechsler Adult Intelligence Scale. Psychological Corporation, New York.
Zacny, J.P., 1995. A review of the effects of opioids on psychomotor and cognitive functioning in humans. Exp. Clin. Psychopharmacol. 3, 432–466.