Buprenorphine/Naloxone Maintenance Therapy: an Observational Retrospective Report on the Effect of Dose on 18 months Retention in an Office-Based Treatment Program

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ABSTRACT

CONTEXT AND OBJECTIVE: Buprenorphine has been available with few reports of the dose range necessary to adequately maintain patients. We report on the effect of 8 mg/d versus 16 mg/d of buprenorphine on long-term patient retention in office-based opioid maintenance (OBOMT).

DESIGN, SETTING, AND PARTICIPANTS: Case series, at an urban hospital-based primary care clinic providing OBOMT to 157 opiate-dependent, low socioeconomic status, uninsured, nonhomeless patients.

INTERVENTION: The OBOMT program operated by a comprehensive sobriety treatment program experienced State funding cuts. Thus, after 2 years, the program was required by the State funder to decrease the buprenorphine maintenance dose from 16 to 8 mg/d for all new admissions. We report on patient retention before and after dose reduction.

MAIN OUTCOME MEASURES: The primary outcomes of this study were to measure and compare patient retention in the 2 cohorts at each point of treatment transition over the 18 months following OBOMT initiation.

RESULTS: No significant differences in patient retention were observed between the 16 and 8 mg/d patient cohorts. Lower dose buprenorphine maintenance (8 mg/d) in uninsured patients enrolled in publicly funded long-term OBOMT combined with comprehensive sobriety counseling was as effective as higher dose therapy (16 mg/d) in promoting patient retention throughout the study period. This lower dose resulted in a substantial saving to the public funding agency.

CONCLUSIONS: In an observational retrospective report, retention in treatment of opiate-addicted patients was the same at 8 and 16 mg/d buprenorphine doses after 18 months. These data have implications for public and managed care funding of OBOMT, for the general prescribing of buprenorphine in outpatient care, and may be instructive in the ongoing debate about the relationship between buprenorphine dose.

KEYWORDS: Buprenorphine, office based, dose, retention, treatment cost

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Introduction

Approved by the Food and Drug Administration (FDA) in October of 2002, the buprenorphine/naloxone sublingual combination tablet (Suboxone) (hereafter referred to as bup/nx) became the first opioid agonist approved for use in this office-based opioid maintenance (OBOMT) setting.[1] This paved the way for major changes in the way opioid addiction is treated in the United States, potentially making opioid maintenance therapy available to a much larger population of patients.[1–4] Despite significant patient care experience with buprenorphine maintenance in the United States, the 13 years since FDA approval have left many clinical issues unresolved. This report addresses questions surrounding the effect of buprenorphine/naloxone (bup/nx) dose on treatment retention. It also provides some insight regarding dosing practices and growing concern about bup/nx diversion in the State of Ohio.

Much is known about office-based buprenorphine maintenance, including data about the pharmacology of buprenorphine,[5–7] the effect of different dosing intervals on patient retention,[8–10] and comparisons of efficacy versus methadone in opioid maintenance treatment.[11–25] Understanding has evolved regarding the recommended maximum dose range for buprenorphine including a therapeutic effect in the 8 to 16 mg range, a ceiling effect in the 24 to 32 mg range,[6] and efficacy in improving treatment retention and increasing abstinence over a range of dosing intervals including daily and thrice weekly schedules.[9,22]

Some of the questions that remain regarding buprenorphine include further defining its utility in chronic pain and addiction populations, intermediate and short-term use for stabilization and medical withdrawal, and a comparison of the effect of dose on retention when used in OBOMT. This study reports on the effect of using a decreased dose of 8 mg/d versus 16 mg/d of buprenorphine on 18-month retention in a sobriety-oriented comprehensive residential and outpatient addiction treatment program.

Methods

Patient population

The patient population consisted of urban, low socioeconomic status (SES),[26] uninsured patients with opiate dependence who met the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) criteria for opiate dependence and admission into the Rosary Hall—Alcohol and Drug Abuse Services Board of Cuyahoga County (ADASB)-funded bup/nx treatment program.[22] All treatment services including pharmacotherapy were funded by a grant from the Ohio Department of Addiction Services through the ADASB.[22]

Eligible patients received preadmission demographic and clinical assessment of their substance use disorder and were admitted for 24 to 48 hours to the detoxification unit for buprenorphine induction to a dosage of 16 mg daily in the first treatment group and a dose of 8 mg daily in the second group.[3,21,22] Patients were discharged to residential treatment in a Halfway House for 4 and 8 weeks and then transitioned to an intensive outpatient treatment (IOP) level of care (3 h/d, 4 d/wk for 5 weeks [20 sessions]). After IOP, patients entered weekly aftercare monitoring for an additional 12 weeks. Following aftercare, there was monthly follow-up in OBOMT clinic, with requirements of 3 Alcoholic Anonymous (AA) meetings a week (including a "home group" and sponsor), and ongoing random urine toxicology screening.[21,27,28] The ADASB grant covered a total of 2 years of participation per patient in this program.

All publicly funded patients begun on buprenorphine during fiscal years 2005 and 2006 were started on 16 mg/d. All publicly funded patients begun on buprenorphine on fiscal year 2007 and 2008 received 8 mg/d. There was no individualization of dose, and there was no option for patients in the 8 mg group to receive a higher dose. For each person enrolled in treatment, after 18 months, the maintenance dose of 16 or 8 mg, respectively, was gradually tapered, based on requirements of the State Funding Agency. To be admitted into this publicly funded OBOMT program, patients agreed to full adherence to the treatment plan at the time of intake. Therefore, all aspects of the treatment program were considered mandatory, and nonadherence or positive urine toxicology screening lead to continuation of buprenorphine and patient referral to a prior higher level of care. If patients were unwilling to participate in the next higher level of care or urine toxicology screens continued to be positive for any substance use, they were discontinued from the buprenorphine treatment grant as stipulated by the State Funding Agency.

After 28 months of enrolling patients, there were substantial State budget cuts for mental health and addiction treatment resulting in less funding for bup/nx treatment and a State Agency mandatory dose decrease for all newly enrolled patients. Therefore, due to governmental budget cuts outside the control of the treatment provider, beginning in 2007, all newly admitted grant-funded patients were treated with 8 mg/d bup/nx rather than 16 mg/d. This resulted in 2 cohorts of patients, treated in the same program, but differing on bup/nx dose.

Data collection/study design

After receiving Human Subjects Committee Review from the Medical Center's Institutional Review Board, retrospective chart reviews of inpatient and outpatient records were conducted by a single reviewer. The charts were audited for demographic information including age, sex, and ethnicity, drug of choice, ancillary drug use history, induction dosage of buprenorphine, and hospital discharge diagnosis. Data were obtained regarding a patient's completion of or discharge prior to each of the following program milestones: induction, residential treatment, IOP, aftercare, and the following 1 year of monthly OBOMT clinic follow-up. Chart audit information regarding completion of different levels of care was cross-checked against ADASB billing records to assure accuracy. All information was entered electronically, databased, and numerically coded for export to a statistical analysis program.

Data analysis. Demographic data and drug use history were analyzed using the Student *t* test for continuous measures and the χ^2 test for categorical variables. Treatment outcome results were compared using the χ^2 test for retention at each change in treatment level of care.

Results

Demographic, drug use, and treatment characteristics

Our study population consisted of 157 uninsured low SES patients. Demographics, drug use, and selected treatment characteristics are displayed in Table 1. The study group largely composed of middle-aged, male (73%), white (78%), heroin users (85%). The large majority had a history of polysubstance abuse (78%) meaning a combination of primary opioid use along with the use of at least one of the following on a regular basis: cocaine, amphetamine, and marijuana. In addition to all currently having opioids as their drug of choice, most also at least intermittently used another nonopioid drug (66%). Table 1 also indicates that the 2 cohorts of patients in this study were not different from each other in pretreatment characteristics including demographics, drug use, and prior treatment. The average length of residential treatment for our patients was

Table 1. Demographic and drug use data.

VARIABLE	TOTAL (N = 157)	INDUCED ON 8 MG/D (N = 70)	INDUCED ON 16 MG/D (N = 87)	*P*
	NO. (%) (SD)	NO. (%) (SD)	NO. (%) (SD)	
Age	38 (11)	38 (12)	38 (11)	.916
Sex				
Male	72.9% (113)	72.3% (47)	73.3% (66)	1.000
Ethnicity				
Asian	0.7% (1)	0.0% (0)	1.1% (1)	.803
Black	15.5% (24)	13.9% (9)	16.7% (15)	.803
White	78.0% (121)	80.0% (52)	76.7% (69)	.803
Hispanic	5.8% (9)	6.1% (4)	5.5% (5)	.803
Drug of choice				
Heroin	84.5% (131)	84.6% (55)	84.5% (76)	.644
Rx	1.9% (3)	3.1% (2)	1.1% (1)	.644
Both	13.6% (21)	12.3% (8)	14.4% (13)	.644
Polysubstance abuse	78.1% (121)	81.5% (53)	75.6% (68)	.434
Secondary drug/s				
Any	65.8% (102)	64.6% (42)	66.7% (60)	.864
Alcohol	31.6% (49)	30.8% (20)	32.2% (29)	.863
Cannabis	20.0% (31)	27.7% (18)	14.4% (13)	.066
Cocaine	36.8% (57)	33.9% (22)	38.9% (35)	.613
Other	12.9% (20)	9.2% (6)	15.6% (14)	.333

Table 2. Overall retention in treatment.

	TOTAL	8 MG/D	16 MG/D
	STARTING THIS LOC	FINISH LOC	FINISH LOC
		START LOC	START LOC
Residential TX	157	62/70 (89%)	77/87 (89%)
IOP TX	139	48/70 (67%)	60/87 (69%)
Aftercare TX	108	37/70 (53%)	47/87 (54%)
End of 1 y of bup/nx clinic TX	84	35/70 (50%)	43/87 (49%)

Abbreviations: IOP, intensive outpatient treatment; LOC, level of care.

57 days with a standard deviation of 11 days and was similar for both cohorts (56 days SD = 12 versus 59 days SD = 9).

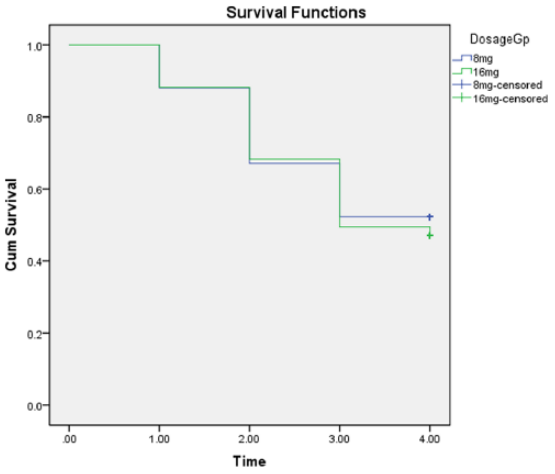
Retention in treatment by induction dose

Approximately 50% of the patients left the bup/nx treatment program at some point, either by dropping out or by being discharged for nonadherence, as shown in Table 2. Table 3 demonstrates the patient retention rate per treatment program milestone, comparing 16 mg/d dose patients with 8 mg/d dose patients. The retention rates at each level of care were very similar regardless of bup/nx dose. Of 157 patients starting residential treatment, 89% in both groups completed this level of care. Of the 139 patients beginning the IOP counseling program, 77% and 78% in the 8 and 16 mg groups completed this level of care. Of the 108 patients beginning 3 months of weekly aftercare sessions, 77% and 78% of the 8 and 16 mg cohorts, respectively, completed this level of care. About 84 patients began monthly OBOMT clinic monitoring after successfully completing each prior level of care, and 95% and 91% of the 8 and 16 mg groups, respectively, completed at least

Table 3. Retention in treatment during each level of care.

	TOTAL STARTING THIS LOC	8 MG/D FINISH LOC START LOC	16 MG/D FINISH LOC START LOC	*P*
Residential TX	157	62/70 (89%)	77/87 (89%)	.990
IOP TX	139	48/62 (77%)	60/77 (78%)	.944
Aftercare TX	108	37/48 (77%)	47/60 (78%)	.481
End of 1 y of bup/nx clinic TX	84	35/37 (95%)	43/47 (91%)	.667

Abbreviations: IOP, intensive outpatient treatment; LOC, level of care.



Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	.226	1	.634

Test of equality of survival distributions for the different levels of Dosage Group.

Figure 1. Survival curve for retention in treatment.

1 year of OBOMT clinic following aftercare. About 18 months following induction, 50% (35/70) of the 8 mg cohort and 49.4% (43/87) of the 16 mg cohort were retained in OBOMT. Survival curve for retention in treatment is outlined in Figure 1.

Discussion

This report takes advantage of a "natural experiment" due to changes in State funding where the public funding stream for a bup/nx OBOMT program used by uninsured patients was abruptly and arbitrarily changed. This resulted in 2 cohorts of patients on bup/nx maintenance differing only on bup/nx dose: 1 group on 16 mg/d and 1 on 8 mg/d. Treatment retention and opiate abstinence in each dose group were the same at each level of care, with the lower dose bup/nx proving to be just as effective for treatment retention as the higher dose. Demographic and pretreatment drug use data indicate no differences between the 2 cohorts, and the treatment program was not altered in any way other than decreasing the bup/nx daily dose.

The treatment program directors and the funding agency were quite concerned that this 50% decrease in daily buprenorphine dose would result in fewer patients applying for OBOMT, fewer patients stabilizing on bup/nx, and more patients dropping out of treatment at each level of care. Anecdotally there were more subjective complaints from patients on the 8 mg dose, but these patient reports were not systematically gathered for analysis. Regardless, higher patient symptom reports did not translate into lower retention or a higher relapse rates in the 8 mg treatment group. Our hypothesis is that the increased subjective symptoms reported by patients on lower dose were not severe enough to translate into behavioral actions to relapse. Finally, despite the decrease in available dose, the program continued to be overwhelmed with applicants.

Buprenorphine/naloxone in OBOMT has been available since 2003, and much experience has been gained on practical issues related to the upper therapeutic range of prescribing including new recommendations from the manufacturer and oversight agencies that support limiting typical dosing to 16 mg/d or less. This is the first report to favorably compare the use of a lower dose of bup/nx with a 16 mg/d dose. These results have implications for addiction treatment providers and for insurers with limited budgets. After the induction and residential treatment phase, the largest cost of this bup/nx-assisted addiction treatment was the bup/nx medication pharmacy cost (due to the fact that these patients were all treated prior to generic form of Sublingual (SL)-bup/nx being available). In this study, the medication cost was able to be halved in the lower dose cohort without an increase in relapse rate.

This report provides data that when combined with an extensive sobriety-oriented treatment program, 8 mg/d of bup/nx produced clinically identical opioid addiction remission rates to those seen with 16 mg/d of bup/nx. In addition, in recent years, both the manufacturer and Center for Substance Abuse Treatment (CSAT) have recommended efforts to keep doses at 16 mg/d or lower. This report can be reassuring to clinicians attempting to prescribe buprenorphine at doses lower than the 24 or 32 mg/d initially recommended in the early years of buprenorphine's clinical release and doses lower than the currently recognized 16 mg/d dose range.

There are several limitations regarding the data in this report and its applicability to other settings. First, even though there

are 2 different cohorts of patients in this report, it is at its core a case series of consecutively enrolled patients in an OBOMT program who arbitrarily received different bup/nx doses based on State funding changes. As such, it carries the limitations and selection biases entailed in any case series report. In fact, this case series is taken from a very particular program using bup/nx as an adjunct to full sobriety and attendant stringent requirements for both treatment intensity and for treatment adherence. Thus, the applicability of these data for programs with much lower sobriety requirements is questionable and even less applicable to programs with a more harm-reduction treatment goal.[22,26] The overall retention rate of 50% for the 8 mg group and 49.4% for the 16 mg group at 18 months is lower than the much reported 60% to 80% range in other studies and is likely related to several factors including the patient population's low SES,[26] severity of the pretreatment addictive disease, the stringency of the treatment program requirements to remain on bup/nx, and the program and expectations of full adherence to a 12-step–based sobriety program.[29] In addition, it may be that the unusually high levels of psychosocial support and addiction treatment provided in this treatment program enabled patients to do well on lower doses of bup/nx, and that less structure and support for sobriety would not produce similar results at the lower bup/nx dose ranges. These patients had no ability to pursue clinically available alternative sources for bup/nx as they were all unemployed, uninsured, and from a low enough SES. The specific economic situation of our patient population may have contributed strongly to the similar outcomes between different bup/nx doses. Other communities may have different treatment needs and different populations requiring care, so this treatment model and the outcomes that we achieved may not be applicable across communities.

In summary, information about different aspects of patient treatment with OBOMT continues to emerge from the American bup/nx opioid addiction treatment experience. This report provides important results for publicly funded treatment providers and insurers who provide for low SES opiate-addicted patient populations. These results also can inform the debate about the clinical justification for higher dose (greater than 16 mg/d) bup/nx prescribing, can help address concerns about diversion, and can support providing long-term bup/nx maintenance within a reasonably prudent dose range.[30]

Author Contributions

TVP - study design ,data gathering, writing and editing. AGM - data gathering and writing. YJD - data gathering and writing. CAA - study design and editing. MK- writing and editing.

REFERENCES

1. Johnson RE, Strain EC, Amass L. Buprenorphine: how to use it right. *Drug Alcohol Depend*. 2003;70:S59–S77.
2. Fiellin DA, Rosenheck RA, Kosten TR. Office-based treatment for opioid dependence: reaching new patient populations. *Am J Psychiatry*. 2001;158: 1200–1204.
3. Fiellin DA, O'Connor PG. Clinical practice. Office-based treatment of opioid-dependent patients. *N Engl J Med*. 2002;347:817–823.
4. Jaffe JH, O'Keeffe C. From morphine clinics to buprenorphine: regulating opioid agonist treatment of addiction in the United States. *Drug Alcohol Depend*. 2003;70:S3–S11.
5. Jasinski DR, Pevnick JS, Griffith JD. Human pharmacology and abuse potential of the analgesic buprenorphine: a potential agent for treating narcotic addiction. *Arch Gen Psychiatry*. 1978;35:501–516.
6. Walsh SL, Eissenberg T. The clinical pharmacology of buprenorphine: extrapolating from the laboratory to the clinic. *Drug Alcohol Depend*. 2003; 70:S13–S27.
7. Wesson DR. Buprenorphine in the treatment of opiate dependence: its pharmacology and social context of use in the U.S. *J Psychoactive Drugs*. 2004;36:119–128.
8. Johnson RE, Eissenberg T, Stitzer ML, Strain EC, Liebson IA, Bigelow GE. Buprenorphine treatment of opioid dependence: clinical trial of daily versus alternate-day dosing. *Drug Alcohol Depend*. 1995;40:27–35.
9. Petry NM, Bickel WK, Badger GJ. Examining the limits of the buprenorphine interdosing interval: daily, every-third-day and every-fifth-day dosing regimens. *Addiction*. 2001;96:823–834.
10. Marsch LA, Bickel WK, Badger GJ, Jacobs EA. Buprenorphine treatment for opioid dependence: the relative efficacy of daily, twice and thrice weekly dosing. *Drug Alcohol Depend*. 2005;77:195–204.
11. Bickel WK, Stitzer ML, Bigelow GE, Liebson IA, Jasinski DR, Johnson RE. A clinical trial of buprenorphine: comparison with methadone in the detoxification of heroin addicts. *Clin Pharmacol Ther*. 1988;43:72–78.
12. Johnson RE, Jaffe JH, Fudala PJ. A controlled trial of buprenorphine treatment for opioid dependence. *JAMA*. 1992;267:2750–2755.
13. Kosten TR, Schottenfeld R, Ziedonis D, Falcioni J. Buprenorphine versus methadone maintenance for opioid dependence. *J Nerv Ment Dis*. 1993;181:358–364.
14. Strain EC, Stitzer ML, Liebson IA, Bigelow GE. Comparison of buprenorphine and methadone in the treatment of opioid dependence. *Am J Psychiatry*. 1994;151:1025–1030.
15. Walsh SL, Preston KL, Stitzer ML, Cone EJ, Bigelow GE. Clinical pharmacology of buprenorphine: ceiling effects at high doses. *Clin Pharmacol Ther*. 1994;55:569–580.
16. Walsh SL, June HL, Schuh KJ, Preston KL, Bigelow GE, Stitzer ML. Effects of buprenorphine and methadone in methadone-maintained subjects. *Psychopharmacology (Berl)*. 1995;119:268–276.
17. Ling W, Wesson DR, Charuvastra C, Klett CJ. A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence. *Arch Gen Psychiatry*. 1996;53:401–407.
18. Schottenfeld RS, Pakes JR, Oliveto A, Ziedonis D, Kosten TR. Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. *Arch Gen Psychiatry*. 1997;54:713–720.
19. Ling W, Charuvastra C, Collins JF, et al. Buprenorphine maintenance treatment of opiate dependence: a multicenter, randomized clinical trial. *Addiction*. 1998;93:475–486.
20. Mattick RP, Ali R, White JM, O'Brien S, Wolk S, Danz C. Buprenorphine versus methadone maintenance therapy: a randomized double-blind trial with 405 opioid-dependent patients. *Addiction*. 2003;98:441–452.
21. Fiellin DA, Kleber H, Trumble-Hejduk JG, McLellan AT, Kosten TR. Consensus statement on office-based treatment of opioid dependence using buprenorphine. *J Subst Abuse Treat*. 2004;27:153–159.
22. Caldiero RM, Parran TV Jr, Adelman CL, Piche B. Inpatient initiation of buprenorphine maintenance vs. detoxification: can retention of opioid-dependent patients in outpatient counseling be improved? *Am J Addict*. 2006;15:1–7.
23. Connock M, Juarez-Garcia A, Jowett S, et al. Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation. *Health Technol Assess*. 2007;11:1–171, iii-iv.
24. Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev*. 2008;3:CD002207.
25. Soyka M, Zingg C, Koller G, Kuefner H. Retention rate and substance use in methadone and buprenorphine maintenance therapy and predictors of outcome: results from a randomized study. *Int J Neuropsychopharmacol*. 2008;11:641–653.
26. Parran TV, Adelman CA, Merkin B, et al. Office-based buprenorphine/naloxone maintenance therapy: outcomes at 18 month follow-up in insured vs. uninsured patients. *Drug Alcohol Depen*. 2010;106:56–60.
27. Bickel WK, Amass L, Higgins ST, Badger GJ, Esch RA. Effects of adding behavioral treatment to opioid detoxification with buprenorphine. *J Consult Clin Psychol*. 1997;65:803–810.
28. Krook AL, Brors O, Dahlberg J, et al. A placebo-controlled study of high dose buprenorphine in opiate dependents waiting for medication-assisted rehabilitation in Oslo, Norway. *Addiction*. 2002;97:533–542.
29. Alford DP, LaBelle CT, Richardson JM, et al. Treating homeless opioid dependent patients with buprenorphine in an office-based setting. *J Gen Intern Med*. 2007;22:171–176.
30. Mitchell SG, Kelly SM, Brown BS. Uses of diverted methadone and buprenorphine by opioid-addicted individuals in Baltimore, Maryland. *Am J Addict*. 2009;18:346–355.