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HIV Risk Reduction With Buprenorphine-Naloxone or Methadone: Findings From A Randomized Trial

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Abstract

Objectives—Compare HIV injecting and sex risk in patients being treated with methadone (MET) or buprenorphine-naloxone (BUP).

Methods—Secondary analysis from a study of liver enzyme changes in patients randomized to MET or BUP who completed 24-weeks of treatment and had 4 or more blood draws. The initial 1:1 randomization was changed to 2:1 (BUP: MET) after 18 months due to higher dropout in BUP. The Risk Behavior Survey (RBS) measured past 30-day HIV risk at baseline and weeks 12 and 24.

Results—Among 529 patients randomized to MET, 391 (74%) were completers; among 740 randomized to BUP, 340 (46%) were completers; 700 completed the RBS. There were significant reductions in injecting risk ($p < 0.0008$) with no differences between groups in mean number of times reported injecting heroin, speedball, other opiates, and number of injections; or percent who shared needles, did not clean shared needles with bleach, shared cookers, or engaged in front/back loading of syringes. The percent having multiple sex partners decreased equally in both groups ($p < 0.03$). For males on BUP the sex risk composite increased; for males on MET, the sex risk

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decreased resulting in significant group differences over time ($p < 0.03$). For females, there was a significant reduction in sex risk ($p < 0.02$) with no group differences.

Conclusions—Among MET and BUP patients that remained in treatment, HIV injecting risk was equally and markedly reduced, however MET retained more patients. Sex risk was equally and significantly reduced among females in both treatment conditions, but increased for males on BUP, and decreased for males on MET.

INTRODUCTION

Research over the past 20 years has shown that methadone maintenance reduces opioid use and is an effective HIV risk reduction intervention^{1,2,3,4,5,6,7,8}. This finding has been observed when methadone patients are compared to their community counterparts who are not in treatment^{9, 10, 11} and when opioid use during treatment is compared to pre- and post-treatment use³. Further, significantly lower rates of opioid use have been observed when patients with regular methadone program attendance are compared to those with poor attendance¹², and when patients receiving minimal ancillary services are compared to those receiving more intensive services^{13, 14}.

Consistent with these reductions in opioid use, methadone maintenance markedly reduces opioid injection and needle sharing. This finding has been reported in cross-sectional, prospective, and retrospective designs comparing methadone patients to heroin users who are not in treatment^{5, 9, 15, 16, 11}, and in studies measuring changes among methadone patients during treatment^{14, 17}. Findings have also been reported showing significantly lower rates of injection among patients who remain in treatment when compared to patients who left treatment^{10, 18}.

Importantly, prior research demonstrates strong associations between participation in methadone maintenance and lower rates of HIV prevalence and incidence. For example, heroin users who remained in methadone treatment during periods of rapid HIV transmission in their local communities had a dramatically lower prevalence of infection^{19, 20, 21}. In both prospective and retrospective studies, the incidence of HIV infections has been associated with participation^{10, 7, 12} and time receiving methadone treatment^{22, 23, 7}. Although none of these studies were randomized trials, the strength and consistency of the findings indicate that participation in methadone maintenance is strongly associated with protection from HIV infection and that methadone treatment reduces the risk behaviors that can spread HIV^{10, 24, 25, 26}. This risk reduction occurs both directly via reduction of injecting behaviors, but also by facilitating adherence to antiretroviral medication and reducing the viral load among persons who are infected²⁷.

Buprenorphine is a Schedule III, mu-opioid partial agonist with a greater margin of safety and a less intensive withdrawal^{28, 29}. It is available in the U.S. as a tablet or film with 4 parts buprenorphine to one part naloxone in an attempt to reduce abuse if crushed and injected and is approved for treatment of opioid addicted individuals aged 16 and above^{30, 31, 32}. Like methadone, treatment with buprenorphine-naloxone appears to reduce HIV risk^{33, 34} and we know of only one study that directly compared HIV risk in patients treated with buprenorphine vs. methadone. It was conducted in Baltimore and randomized

47 patients to buprenorphine and 51 to methadone. Methadone doses ranged from 60-100 mg/day; buprenorphine doses were 16-32 mg on Mondays and Wednesdays with a 50% higher dose on Fridays. HIV risk was assessed at baseline and at weeks 1, 2, 3 and 18 using the Risk Behavior Interview³⁵. Patients in both groups had marked and equal reduction in injecting risk but only the methadone group had consistent declines in sexual risk³⁶. Here, we present the results of a similar comparison of a much larger sample in a secondary analysis of data from a study conducted by the National Institute on Drug Abuse in the Clinical Trials Network³⁷.

METHODS

The main study (“START”) was a randomized trial that evaluated transaminase changes in patients randomized to treatment with MET or BUP. Participants were consenting individuals who were applying for treatment at 1 of 8 methadone programs located across the United States. Eligibility criteria included being age 18 or older; meeting DSM-IV-TR criteria for opioid dependence; and not having an alanine amino transferase (ALT) or aspartate amino transferase (AST) value > 5 times or alkaline phosphatase (ALP) >3 times above the upper limit of normal. Exclusion criteria included serious medical conditions that could make study participation unsafe or impractical; schizophrenia, Bipolar I disorder, homicidal or suicidal ideation, or cognitive impairment that made informed consent difficult to obtain; and poor venous access such that repeated blood samples to measure liver enzymes would be difficult to obtain. Recruitment occurred between May 2006 and October 2009 with follow-up assessments through August 2010.

The FDA requested this study based on reports of elevated liver enzymes in patients treated with BUP and required a minimum of 300 “evaluable” participants on each medication. The criteria for evaluable were completing 24 weeks on the assigned medication and providing at least half of the eight liver tests that were scheduled at weeks 1, 2, 4, 8, 12, 16, 20, and 24. Test windows included ± 2 days for weeks 1 and 2, and ± 7 days for all other weeks. Due to a higher dropout rate in the BUP condition, the initial 1:1 randomization was changed to 2:1, BUP to MET, in December 2007. The initial BUP dose ranged from 2-8mg with increases for persistent withdrawal to a maximum of 16mg on the first day. Dosing was flexible and based on clinical response with further increases up to a maximum of 32mg; the mean maximum daily dose among study participants was 22.1mg (SD = 8.2; median = 24mg). The maximum initial MET dose was 30mg with an additional 5-10 mg if needed on day 1 after 3 or more hours to suppress withdrawal symptoms. As with BUP, MET dosing was based on clinical response and could be increased in 5-10mg increments with no maximum dose specified; the mean maximum MET dose was 93.2mg (SD = 42.2; median = 90mg).

Observed dosing occurred daily except on Sundays and holidays or when take-homes were permitted by local regulations. BUP participants were titrated to a maintenance dose, typically over the first few days; MET participants over several weeks. Both groups remained on study medication for 24 weeks and then tapered to zero over 8 weeks or were referred for continuing treatment. Assessments were done at pre-specified intervals and included urine drug tests, self-reported drug use, HIV risk, and blood samples for liver tests.

The analyses presented here were obtained from the HIV Risk Behavior Survey (RBS), an interviewer-administered measure of injecting and sexual HIV risk behavior³⁸. It takes 6-10 minutes, was administered at baseline and at weeks 12 and 24, and collects information about drug and sexual behaviors over the past thirty days. Questions include number of times injected; sexual activity; condom use; times exchanged sex for drugs, money or both; and HIV-testing history. For these analyses, individual questions were used to create composite scores of injecting and sex risk. The injecting risk composite was defined as reporting at least one risk behavior (sharing needles, not using bleach to clean needles, sharing cooker, front/back loading of syringes [e.g. pulling out the barrel of one syringe and filling it with another or vice-versa]). The sexual risk composite was defined as reporting more than one sexual partner and/or sex without a condom. Injection risk outcomes were modeled as count data and negative binomial distribution was specified in GENMOD procedure. Needle sharing and sexual behavior outcomes were modeled as Yes/No, and the PROC GENMOD/GEE option was used to compare the data.

RESULTS

There were 731 evaluable participants (BUP=340, MET=391) who completed the baseline RBS and of these, 700 (95.8%) completed the 12-week RBS and 705 (96.4%) completed the 24-week RBS. At baseline, BUP participants reported more past 30-day non-heroin opioid use than MET participants (9.3 vs. 7.3 days; $p=0.043$); but MET participants had a higher percentage of cocaine-positive urine tests (39.0 vs. 29.7; $p=0.006$) and a higher percentage reported injecting drug use in the past 30 days (69.3 vs. 61.8; $p=0.03$). Average age and all other baseline characteristics showed no statistically significant differences between groups.

Followup assessments showed significant reductions from baseline ($p<0.0008$ or more) in the mean number of times heroin, speedball, or other opioids were injected in the last 30 days, as well as the overall number of injection events. Significant reductions ($p<0.0001$) were also noted in the percentage who shared needles, did not clean shared needles with bleach, shared cookers, engaged in front/back loading, and the needle risk composite score. There were no significant differences between groups on any of these outcomes. The only significant group difference on injecting risk was for amphetamines in which the mean number of times injected rose from 0.05 at baseline to 1.9 at 24 weeks in BUP participants vs. a decrease from 0.29 to 0.22 in MET participants ($p<0.05$). The mean number of times cocaine was injected dropped approximately equally in both groups but did not meet the threshold for statistical significance.

Sexual risk behaviors in the last 30 days (> one partner, sex without a condom), and sex risk composite were compared across time (baseline, 12- and 24 weeks) and between treatment groups. There was a significant reduction in sex with more than one partner over time and no group differences. Percent having multiple sex partners decreased equally in both groups ($p<0.03$), however MET participants reported greater reduction in the sex risk composite score than BUP participants ($p<0.05$).

Sexual risk behavior was analyzed separately for males and females (Tables 4a and 4b, respectively), and time effect and interactions were found. For males on BUP, the sex risk

composite increased over time whereas for males on MET there was a reduction in sex risk over time, and a significant difference between groups with more overall sex risk reduction on MET. For females, there was a significant reduction in the sex risk composite over time with no differences between groups.

DISCUSSION

These findings show marked and approximately equal reductions in injection and injection related risk among participants who remained in their assigned treatment condition and completed 4 or more blood draws over 24-weeks. Reasons for the small but significant increase in amphetamine use in BUP participants are unclear and may be an incidental finding as it has not been previously reported.

The much smaller but significant decrease in the sexual risk composite among MET as compared to BUP participants could be the result of a greater impact on sexual hormone production among patients taking methadone, particularly males. This would be consistent with reports from the 1970's that methadone decreases gonadal hormone secretion during the first months of treatment with accompanying reductions in sexual activity^{39, 40} and with a more recent study that found much lower total testosterone levels in 83 men on methadone maintenance as compared to 19 on buprenorphine⁴¹. The decrease in sex risk composite among males on MET, and the absence of a decrease in males on BUP (Table 4a), is consistent with these data, and with another study that also found lower testosterone levels in patients on MET as compared to BUP⁴². These differences in sexual effects could be a reflection of the full opioid agonist effects of MET vs. the partial agonist effects of BUP.

The higher dropout rate among participants assigned to BUP³⁷ suggests that methadone may be more generally effective than buprenorphine-naloxone at reducing HIV risk over time, at least among individuals who enroll in treatment at methadone clinic sites. Despite these differences in dropout rates, the data clearly show that injecting risk was markedly and equally reduced regardless of medication assignment among those who remained in treatment. This finding indicates that buprenorphine-naloxone, like methadone, is a successful HIV risk reduction intervention for patients who remain in treatment, but with the added advantage of being accessible in settings other than methadone programs in the U.S. For individuals who drop out of buprenorphine-naloxone, methadone, naltrexone, residential treatment, or intensive self-help group participation could be helpful, depending on patient choice and available resources. In addition to the differential dropout rate, a study limitation was that approximately 75% of the participants were Caucasian, thus these findings may not apply to populations with higher representations of minorities. Findings may also differ in populations with higher rates of amphetamine, cocaine or benzodiazepine use.

Overall, these findings further support the importance of expanding availability of evidence-based medical treatments for opioid addiction⁴³. At the same time it is often difficult to balance expanded access with diversion control. In the case of methadone, one approach that current U.S. law permits but is rarely used, is to involve local pharmacies as medication dispensing stations. Another is to involve primary care providers in methadone treatment as was done in one RCT where stable methadone patients were transferred to primary care for

ongoing treatment, however current US law does not allow primary care providers to prescribe methadone for opioid dependence⁴⁴. In contrast, such a development has occurred in the U.K. over the past ten years with apparent success in reducing overdose deaths^{45, 46}

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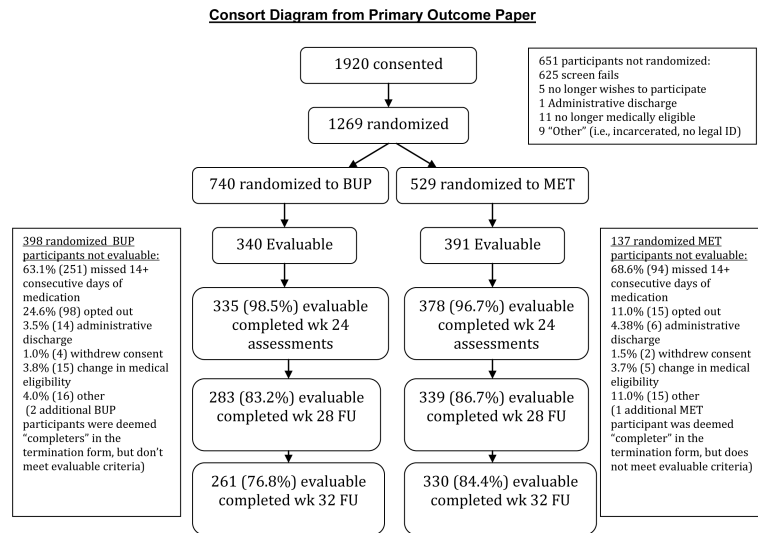


Figure 1.
 Consort Diagram from Primary Outcome Paper

Table 1

Baseline Characteristics of Evaluable Participants

Demographic Characteristics %, n, except as noted	BUP (n=340)	MET (n=391)
Mean Age (sd)	39.3 (11.3)	38.4 (11.3)
Gender		
Male	71.2 (242)	64.7 (253)
Female	28.8 (98)	35.3 (138)
Ethnicity/Race		
Hispanic	15.6 (53)	14.3 (56)
White	72.9 (248)	79.3 (310)
Black or African American	12.1 (41)	10.7 (42)
American Indian/Alaskan Native	0.9 (3)	0.5 (2)
Asian	0.9 (3)	0.3 (1)
Native Hawaiian/Pacific Islander	0.3 (1)	0.0 (0)
Other	12.7 (43)	8.7 (34)
Unknown	0.3 (1)	0.5 (2)
Self-Reported Mean Days of Drug Use in the Past 30 Days (sd)		
Cocaine	3.0 (6.3)	2.9 (5.9)
Heroin	24.3 (9.9)	24.2 (9.8)
Non-heroin opioids*	9.3 (12.0)	7.3 (11.0)
Amphetamines	0.8 (2.5)	1.0 (3.2)
Self-Reported Mean Days of Injection Drug Use (sd)		
Heroin by injection	20.0 (12.9)	20.6 (12.3)
Non-heroin opioids by injection	0.8 (4.0)	0.9 (3.9)
Percent Positive Urine Drug Test (n)		
Opiates (morphine)	85.3 (290)	86.7 (339)
Oxycodone	14.7 (50)	15.1 (59)
Cocaine**	29.7 (101)	39.4 (154)
Benzodiazepines	19.7 (67)	18.7 (73)

Demographic Characteristics %, n, except as noted	BUP (n=340)	MET (n=391)
Cannabis	25.3 (86)	20.5 (80)
HIV Risk Behaviors Reported for Last 30 Days		
Mean times injected w/shared needles	2.1 (6.1)	4.8 (25.7)
% Reporting multiple sex partners (n)	6.8 (23)	8.2 (32)
% Reporting injection drug use past 30 days *** (n)	61.8 (210)	69.3 (271)
Laboratory Results		
Hepatitis B Surface Antibody	32.6 (97)	35.3 (138)
Hepatitis C Core Antibody	1.5 (5)	1.5 (6)
Hepatitis B Surface Antigen	0.3 (1)	0.5 (2)
Hepatitis C Antibody	43.5 (148)	43.5 (170)
HCV RNA	32.9 (112)	28.4 (111)
HIV positive	1.2 (4)	0.5 (2)

* t = 2.03; p = 0.043;

** Chi-square = 7.5, p = 0.0062;

*** Chi-square =4.60, p=0.0320

Table 2

Injection drug use and needle risk behavior

Variable	BUP				MET				P values <i>a, b</i>		
	Baseline (n=340)	12 week FU (n=326)	24 week FU (n=330)	Baseline (n=391)	12 week FU (n=374)	24 week FU (n=375)	Tx	Time (visit)	Tx*time		
Mean number of times injected cocaine	1.8	1.1	0.77	2.2	1.5	1.2	0.8813	0.1861	0.7585		
Mean number of times injected heroin	64.6	1.9	2.7	65.3	3.9	4.4	0.6695	<.0001	0.4797		
Mean number of times injected speedball	2.3	0.69	0.22	4.1	0.74	0.42	0.5375	<.0001	0.9633		
Mean number of times injected other opiates	1.0	0.02	0.01	1.7	0.01	0.02	0.9919	0.0008	0.7064		
Mean number of times injected Amphetamines	0.05	0.07	1.9	0.29	0.02	0.22	0.0497	0.6135	0.0363		
Mean number of times injected Total	69.7	3.83	5.6	73.5	6.2	6.2	0.8756	<.0001	0.9407		
% Shared needles	14.4	2.5	2.4	14.1	2.9	4.8	0.2008	<.0001	0.1029		
% Didn't clean shared needles w/ bleach	10.3	1.8	1.8	9.9	1.6	3.2	0.3692	<.0001	0.3009		
% Shared cooker	17.1	2.5	3.0	18.9	4.8	4.5	0.7262	<.0001	0.2959		
% Front/back load (any)	21.2	3.1	4.6	20.5	5.9	4.5	0.7049	<.0001	0.5311		
% Needle risk composite	25.0	4.2	5.2	24.8	7.2	6.9	0.4022	<.0001	<.1923		

a PROC GENMOD (Negative binomial distribution);

b PROC GENMOD (GEE) for binary variables

Table 3

Sexual risk behavior

Variable	BUP				MET				P values ^c		
	Baseline (n=340)	12 week FU (n=326)	24 week FU (n=330)		Baseline (n=391)	12 week FU (n=374)	24 week FU (n=375)	Tx	Time (visit)	Tx*tim e	
% Multiple (>1) partners	6.8	7.9	5.2	8.2	4.3	5.1	0.6750	0.0329	0.3539		
% Unsafe sex (without condom)	40.9	40.2	43.0	44.5	40.9	41.3	0.1602	0.2063	0.0914		
% Sex risk composite	44.4	45.7	46.7	49.6	43.6	44.5	0.0894	0.0490	0.0272		

^c PROC GENMOD (GEE) for binary variables

Table 4a

Sexual risk behavior for male

Variable	Male									
	BUP				MET				P values	
	Baseline (n=242)	12 week FU (n=234)	24 week FU (n=234)	Baseline (n=253)	12 week FU (n=243)	24 week FU (n=245)	Tx	Time (visit)	Tx*time	
% Multiple (>1) partners	5.79	8.12	5.13	5.53	3.29	3.27	0.9728	0.1370	0.2931	
% Unsafe sex (without condom)	39.26	39.32	44.02	42.29	40.74	41.22	0.2472	0.8370	0.1279	
% Sex risk composite	41.32	45.30	47.44	46.25	42.39	44.08	0.1575	0.5554	0.0318	

Table 4b

Sexual risk behavior for female

Variable	Female											
	BUP					MET					P values	
	Baseline (n=98)	12 week FU (n=92)	24 week FU (n=96)	Baseline (n=138)	12 week FU (n=131)	24 week FU (n=130)	Tx	Time (visit)	Tx* time			
% Multiple (>1) partners	9.18	7.61	5.21	13.04	6.11	8.46	0.6989	0.1292	0.9470			
% Unsafe sex (without condom)	44.90	42.39	40.63	48.55	41.22	41.54	0.5750	0.1055	0.5598			
% Sex risk composite	52.04	46.74	44.79	55.80	45.80	45.38	0.5489	0.0245	0.5433			