HIV risk behaviors during pharmacologic treatment for opioid dependence: A comparison of levomethadyl acetate, buprenorphine, and methadone

David C. Lott, (M.D.)a,b,*, Eric C. Strain, (M.D.)c, Robert K. Brooner, (Ph.D.)c, George E. Bigelow, (Ph.D.)c, Rolley E. Johnson, (Pharm.D.)c,d

aChemical Dependency Program, Linden Oaks Hospital at Edward, 825 S. West St., Naperville, IL 60540, USA
bDepartment of Psychiatry, The University of Chicago, Chicago, IL 60637, USA
cDepartment of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, Baltimore, MD 21224, USA
dReckitt Benckiser Pharmaceuticals, Richmond, VA 23235, USA

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Abstract

The efficacies of three opioid substitution medications for reducing HIV risk behaviors in opioid-dependent patients were assessed in a randomized double-blind clinical trial comparing levomethadyl acetate (LAAM), buprenorphine (BUP), and methadone (METH). Individually optimized flexible dosing was used for each group, with weekly possible doses of 255–391 mg of LAAM, 56–112 mg of BUP, and 420–700 mg of METH. An interview regarding specific HIV risk behaviors, including injecting, equipment sharing, and sexual activity, yielded data for pretreatment and four in-study time points for 137 subjects. Declines in risk behaviors during treatment were evident in all groups for most measures of injecting and equipment sharing. Only the METH group showed consistent declines in measures of sexual behaviors. These results demonstrate that all three medications can be highly effective in decreasing HIV risk behaviors when the dose is optimized. Reductions in sexual behaviors for the METH group are consistent with known METH side effects. © 2006 Elsevier Inc. All rights reserved.

Keywords: Methadone; LAAM; HIV; Buprenorphine; Opioid agonist

1. Introduction

Methadone hydrochloride (METH) has been clearly demonstrated to be efficacious in reducing illicit opioid use in numerous trials (Marsch, 1998; Mattick, Breen, Kimber, & Davoli, 2003). Two other opioid agonist medications have also been studied and approved by the Food and Drug Administration (FDA) for the treatment of opioid dependence. Levomethadyl acetate (LAAM) was approved for use in the United States by the FDA in 1993 for treatment of opioid dependence (Fudala, Voci, Montgomery, & Trachtenberg, 1998). Unfortunately, LAAM was removed from the European market in 2001 owing to concerns of QTc prolongation and was withdrawn from the U.S. market by its manufacturer in 2004 (Newcombe, Bochner, White, & Somogyi, 2004). The third opioid agonist medication, buprenorphine (BUP), produces limited physical dependence and opioid agonist effects as compared with full opioid agonists such as METH and LAAM. Several clinical trials have shown that BUP can produce efficacy similar to that seen with METH (Johnson, Jaffe, & Fudala, 1992; Kosten, Schottenfeld, Ziedonis, & Falcioni, 1993; Ling, Wesson, Charuvastra, & Klett, 1996; Strain, Stitzer, Liebson, & Bigelow, 1994).

Opioid treatment is an important setting and mechanism for addressing HIV risk behaviors. Rates of HIV infection...
are high among substance abusers, and METH treatment has been shown to reduce many behaviors that increase risk of acquiring HIV, including needle injection, sharing of injection equipment, number of sexual partners, condom use, and prostitution (i.e., sex in exchange for drugs or money; Abdul-Quader et al., 1987; Ball, Corty, Bond, Myers, & Tommasello, 1988; Ball, Lange, Myers, & Friedman, 1988; Bellis, 1993; Carballo-Diéguez et al., 1994; Longshore, Hsieh, Danila, & Anglin, 1993; Longshore, Hsieh, & Anglin, 1994; Meandzija, O’Connor, Fitzgerald, Rounsaville, & Kosten, 1994; Metzger et al., 1993). Of these, the most commonly examined risk behavior is drug injection, the frequency of which is consistently lower during METH maintenance treatment (MMT; Ball, Corty, et al., 1988; Ball, Lange, et al., 1988; Carballo-Diéguez et al., 1994; Meandzija et al., 1994; Metzger et al., 1993). Many other studies have also documented the efficacy of MMT in reducing illicit opioid use, which provides further evidence that it is associated with declines in injection frequency (Hargreaves, 1983).

Another risk behavior related to injecting drugs is sharing injection equipment, including needles, syringes, and cleaning equipment. MMT is associated with decreased sharing of equipment, in terms of frequency of sharing (Abdul-Quader et al., 1987; Ball et al., 1988), proportion of patients engaged in sharing (Metzger et al., 1993), and number of sharing partners (Longshore et al., 1994). Furthermore, after controlling for reductions in injection frequency, MMT is still significantly associated with a reduction in the number of sharing partners (Longshore et al., 1993).

MMT has been postulated to have a positive effect on treatment of sexual risk behaviors for HIV transmission, including number of sexual partners, rate of condom use, and frequency of prostitution (Abdul-Quader et al., 1987; Longshore et al., 1994). However, although MMT clearly reduces injection rates and equipment sharing, studies have reported conflicting results about the effect of MMT on sexual risk behaviors. Several studies have found positive effects (Bellis, 1993; Longshore et al., 1994; Meandzija et al., 1994; Metzger et al., 1993), whereas others have not (Abdul-Quader et al., 1987; Longshore et al., 1994). Three studies showed decreasing frequencies of prostitution (Bellis, 1993; Meandzija et al., 1994; Metzger et al., 1993), and two showed lower numbers of sex partners (Longshore et al., 1994; Metzger et al., 1993). In contrast, it appears that MMT has little effect on condom use rates, as two studies have shown similarly low rates of condom use for injection drug users in treatment and those out of treatment (King et al., 1994; Metzger et al., 1993). Despite the disagreement of some studies, the preponderance of evidence supports the view that MMT can reduce HIV exposure by decreasing some sexual risk behaviors. In a meta-analysis of eight studies, it was concluded that MMT significantly reduces HIV risk behaviors, including sexual behaviors (Marsch, 1998).

Most previous studies on HIV risk behaviors during MMT took one of four forms: they cross-sectionally compared self-reported behaviors of patients in treatment with those of patients not in treatment (Carballo-Diéguez et al., 1994; Longshore et al., 1993, 1994; Meandzija et al., 1994); they prospectively compared self-reported behaviors of patients in treatment with those of patients not in treatment (Metzger et al., 1993); they compared behaviors of the same patients before and during treatment (Ball et al., 1988; Bellis, 1993); or they compared behaviors of patients who had been in treatment for different lengths of time (Abdul-Quader et al., 1987). None of these studies was randomized or patient blinded. Furthermore, none reported blinding of clinic or research staff to patient treatment and none compared different opioid agonist medications.

There is a need for more thorough assessment of the effects of treatment for opioid dependence on HIV risk behaviors, especially because there is no study comparing the efficacies of different opioid agonist medications in reducing these behaviors. As study on these treatments progresses, it is important to evaluate their effects on HIV risk behaviors because of the significant health risks that HIV poses, particularly in opioid-dependent populations (Sullivan et al., 2005). The present study addresses this need (1) by assessing the effects of treatment with METH, LAAM, and BUP on HIV risk behaviors and (2) by comparing the relative efficacies of the three medications in reducing HIV risk behaviors.

2. Materials and methods

2.1. Subjects

Subjects were enrolled in a randomized controlled clinical trial comparing LAAM, BUP, and METH in the treatment of opioid dependence. Participants were eligible for the clinical trial if they (1) were aged between 21 and 55 years, (2) were opioid dependent based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria (APA, 1994), (3) had evidence of recent opiate use (positive urine specimen at intake), (4) had no serious medical or psychiatric illness, and (5) had negative serum pregnancy test results (for women). This study was approved by the local institutional review board, and all subjects provided written informed consent. Two hundred twenty subjects (of 322 screened) were enrolled at an outpatient substance abuse research/treatment clinic between January 1996 and November 1997. Participants were stratified by age, race, sex, cocaine use, marital status, and DSM-IV antisocial personality disorder diagnosis (APA, 1994) and were randomized to receive LAAM, BUP, high-dose METH, or low-dose METH. This last group received a fixed daily dose of 20 mg of METH and served as a control group. However, there were insufficient numbers to include this group in the present report because of the high rate of therapeutic rescue to higher doses of METH. There was no
significant difference among the four groups' subjects with regard to age, race, marital status, and other demographic features. The primary outcomes from the clinical trial are reported elsewhere (Johnson et al., 2000).

Of the 220 subjects enrolled in the clinical trial, 83 were excluded from the analyses reported here. These included 1 subject who declined to participate in the Risk Behavior Interview (RBI), 15 subjects who were discharged from the study before the first RBI was conducted, and 50 subjects from the low-dose METH group. The remaining 17 subjects were excluded because their first RBI was conducted after a change had been made to a shorter version, which did not collect the baseline (pretreatment) information needed for the present analyses. When compared with the 83 excluded subjects, the included subjects (n = 137) had more lifetime cocaine use (p < .005) but did not differ significantly on other baseline characteristics. For the 137 subjects, the three treatment groups had no significant difference with regard to age, race, marital status, and other characteristics shown in Table 1, except for lifetime months of alcohol use.

Table 1
Demographic characteristics of the 137 study patients assigned to one of three treatment conditions

<table>
<thead>
<tr>
<th>Demographic characteristic</th>
<th>LAAM (n = 39)</th>
<th>BUP (n = 47)</th>
<th>METH (n = 51)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years; M)</td>
<td>37.38</td>
<td>36.06</td>
<td>36.16</td>
<td>.64</td>
</tr>
<tr>
<td>Sex (%)</td>
<td>Male</td>
<td>56.41</td>
<td>63.83</td>
<td>60.78</td>
</tr>
<tr>
<td>Race (%)</td>
<td>Non-White</td>
<td>53.85</td>
<td>61.70</td>
<td>52.94</td>
</tr>
<tr>
<td>Marital status (%)</td>
<td>Married</td>
<td>17.95</td>
<td>19.15</td>
<td>23.53</td>
</tr>
<tr>
<td>With antisocial personality disorder diagnosis (%)</td>
<td>20.51</td>
<td>34.04</td>
<td>31.37</td>
<td>.37</td>
</tr>
<tr>
<td>Employed (%)</td>
<td>15.38</td>
<td>31.91</td>
<td>35.29</td>
<td>.09</td>
</tr>
<tr>
<td>Legal involvement (%)</td>
<td>17.95</td>
<td>34.04</td>
<td>29.41</td>
<td>.23</td>
</tr>
<tr>
<td>Education (years; M)</td>
<td>11.31</td>
<td>11.11</td>
<td>11.31</td>
<td>.81</td>
</tr>
<tr>
<td>No. of times received prior treatment (M)</td>
<td>2.38</td>
<td>1.96</td>
<td>2.47</td>
<td>.23</td>
</tr>
<tr>
<td>No. of days of use in the past 30 days (M)</td>
<td>Alcohol</td>
<td>2.41</td>
<td>3.64</td>
<td>2.86</td>
</tr>
<tr>
<td></td>
<td>Cocaine</td>
<td>11.33</td>
<td>7.09</td>
<td>8.96</td>
</tr>
<tr>
<td></td>
<td>Heroin</td>
<td>29.92</td>
<td>29.64</td>
<td>29.59</td>
</tr>
<tr>
<td>Lifetime use (months; M)</td>
<td>Alcohol</td>
<td>10.92</td>
<td>50.91</td>
<td>25.06</td>
</tr>
<tr>
<td></td>
<td>Cocaine</td>
<td>53.23</td>
<td>42.66</td>
<td>34.98</td>
</tr>
<tr>
<td></td>
<td>Heroin</td>
<td>115.15</td>
<td>116.30</td>
<td>108.59</td>
</tr>
<tr>
<td>No. of times of illicit opioid use in the past 7 days (M)</td>
<td>28.67</td>
<td>21.94</td>
<td>25.34</td>
<td>.24</td>
</tr>
</tbody>
</table>

Bold p value indicates significant differences among treatment groups.
Comparisons among groups were made using one-way analyses of variance and χ² tests for frequency data.

2.2. Study procedures

Subjects and clinic staff were blind to group assignment and medication dose. The three treatment groups received clinically flexible doses in response to continued opiate use. The METH group received 60–100 mg of METH once daily. The LAAM group received 75–115 mg of LAAM on Mondays and Wednesdays as well as a dose that was 40% higher on Fridays. The BUP group was on a similar thrice-weekly regimen with 16–32 mg of BUP on Mondays and Wednesdays as well as a dose that was 50% higher on Fridays. BUP was administered sublingually as a solution; all other medications were oral formulations. All subjects received three dose forms to preserve blinding, but only one was active medication. Pharmacologic treatment consisted of three phases: dose induction in Weeks 1–2, maintenance in Weeks 3–17, and poststudy disposition in Weeks 18–26. During induction, subjects’ doses of assigned medications were gradually increased while subjects attended the clinic daily. During the maintenance phase, subjects attended the clinic three times a week (Monday, Wednesday, and Friday) and received take-home bottles of METH (METH subjects) or placebo (LAAM and BUP subjects) for the remaining days of each week. Absence for 5 consecutive days resulted in discharge from the study.

Beginning 3 weeks after admission, subjects were eligible for dose increases if they met predetermined attendance and opiate use criteria. Subjects at maximum doses were eligible for rescue to METH if they met similar attendance and opiate use criteria as well as either requesting dose increases or having self-reported opiate use over 50% of that reported at intake. Double blinding was maintained through both dose increase and rescue procedures.

In addition to pharmacologic treatment, subjects were assigned a counselor who developed a treatment plan. Counselors evaluated and addressed subject needs in six areas: activity/recreation, legal, emotional/behavioral, physical/nutritional, social/family, and educational/vocational. Study orientation included an HIV assessment, education about risk behaviors, and the offer of HIV testing with pretest and posttest counseling. Individual and group therapy sessions were scheduled at least weekly to address drug use and relapse prevention. Counseling sessions included material on HIV risk and risk reduction on an as-needed basis. Counselors recorded the number and duration of their contacts with subjects. There was no significant difference among the treatment groups for average time per day in counseling (p = .085). A full-time internist, blind to group assignment and dose, provided onsite medical services.

2.3. Data collection

Subjects’ HIV risk behaviors were assessed using the RBI (Brooner, Greenfield, Schmidt, & Bigelow, 1993). This structured interview collects detailed self-reported information on drug use and sexual practices in 4-week blocks of time. The RBI was administered once at Week 3 (M = 2.8; SD = 0.6) and again at Week 18 (M = 17.6; SD = 0.5). From these structured interviews, data on drug injecting for...
1-week blocks of time ending at Weeks 0 (i.e., the week before treatment entry [baseline]), 1, 2, 3, and 18, for a total of five time points, were examined.

Rates of sexual behaviors were summarized in 4-week blocks of time preceding each of two time points. The first time point for sexual behaviors used data for the 4 weeks ending 1 month before the intake RBI for a baseline measure, and the second time point used data for the 4 weeks immediately preceding the second RBI administration at Week 18.

Drug use behaviors examined included number of injections (any drug, opiates, cocaine, and speedballs [heroin/cocaine mixture]), number of injection equipment shares, number of needle or syringe shares, number of sharing partners, number of injections in gallery-like settings, and frequency of cleaning injection equipment. Sexual behavior estimates included number of sex acts (total, vaginal, oral, or anal), number of sexual partners, patterns of same-sex behavior, and reports of giving or receiving money or drugs in exchange for sex. A timeline follow-back method was used with the RBI to obtain best estimates of behaviors. Data were collected by day for the preceding week and by week for the preceding month. Research supporting this method of data acquisition showed that recall of past behavior improves when recent reference values are used (Bradburn, Rips, & Shevell, 1987). Although RBI retest reliability has not been systematically evaluated, interviewers achieved 100% reliability with a trainer on the RBI and the interview appears to be a valid measure of HIV risk behaviors (Brooner et al., 1993; King, Kidorf, Stoller, & Brooner, 2000).

2.4. Interviewer training

Interviewers were trained on the risk behavior measure using an intensive three-step procedure to achieve excellent rater reliability. Step 1 involved didactic instruction and practice interviewing for approximately 8 hours, which included use of the timeline follow-back approach employed by the measure. Step 2 involved co-rating of participant interviews until achieving five cases in which co-ratings agreed with the experienced rater (individual item agreement). Finally, trainees conducted consecutive interviews that were co-rated by an experienced rater until achieving five consecutive cases of complete agreement (individual items). This training produced 100% initial rater reliability. Interviewer drift from initial training standards was addressed over the course of the study in a weekly meeting of interviewers to review cases and resolve uncertain ratings.

2.5. Analysis

Of the information gathered in the RBI, 10 variables had an adequately high incidence to warrant analysis. Analysis of variables related to injection behaviors (injection frequencies, injection equipment sharing) was conducted only on data from subjects who reported injection drug use (n = 88). Analysis of all other variables included data from injectors and noninjectors. RBI data were missing for 38 time points of a 352 total (11%), mostly from Week 18.

All continuous data were analyzed by time using multilevel analysis with an unstructured covariance (Singer, 1998) using SAS PROC MIXED software (SAS Institute, Cary, NC, USA). The restricted maximum likelihood methods used in multilevel modeling have the flexibility to handle repeated measures data sets with missing observations (Diggle, Liang, & Zeger, 1996). A potential drawback of this technique for clinical trials is that missing data must occur on a random basis and not be related to previous performance for unbiased inference. The potential effect of nonrandom missing data was compensated by using study retention and percentage of missed clinic visits as covariates (Pollan & Wu, 1995). Post hoc analyses were calculated using the Tukey–Kramer method. For all statistical tests, p ≤ .05 (two tailed) was considered significant.

In addition to these primary analyses, a secondary set of analyses was conducted to evaluate changes with the addition of another covariate—the baseline measurement of the dependent variable (pretreatment). Baseline measurements were expected to be correlated with some outcome measures and so were covaried to increase statistical power (Permutt, 1990). These analyses were similar to the primary analyses except for the addition of the third covariate of pretreatment data, such that only four time points were analyzed instead of five in the analysis of covariance (ANCOVA).

3. Results

3.1. Injecting of drugs

Fig. 1 shows the change for several injecting behaviors during the study. There was a significant decrease over time for injecting any drug (p < .0001; Table 2). Examination of specific drugs and drug combinations showed that rates of injecting illicit opioids and cocaine decreased significantly over time (p < .0001; Fig. 1). The frequency of injecting speedballs (the combination of an opioid and cocaine) had a nonsignificant decrease (Fig. 1). There was no significant group effect or Group × Time interaction for rates of opioid, speedball, or cocaine injecting.

The secondary analyses with baseline as a covariate produced similar results with two exceptions. Specifically, there was no significant time main effect for cocaine injections and there was a trend toward a significant time effect for speedball injections (p < .10). However, as in the primary analyses, there was no significant group effect or Group × Time interaction.
3.2. Equipment sharing

The frequency of sharing any equipment declined significantly over time ($p < .005$; Fig. 1). This decline was primarily caused by the METH group, which had a significant decrease in sharing any equipment between baseline and Weeks 2, 3, and 18 ($p < .05$). Although the other two groups also had decreases over time in sharing any equipment, none of these time changes was significant on post hoc testing and there was no significant group effect or Group $\times$ Time interaction. Secondary ANCOVA analyses using the baseline as a covariate yielded similar decreases in sharing (time effect, $p < .05$), indicating that higher sharing in the METH group at baseline did not account for all changes seen. Another measure of equipment sharing (times shared needles or syringes) showed no significant effect in either primary or secondary analysis but trended toward a significant time main effect in both analyses ($p < .10$). Two other sharing variables were not analyzed because of the low frequency of the behavior—number of sharing partners and number of times sharing in a gallery. Only three subjects reported any sharing of injection equipment with more than one person, and only three reported sharing in a gallery setting.

3.3. Sexual activity

Frequency of sexual activity fluctuated over time but with a different pattern among the three groups. This pattern is reflected in the two trend time main effects and two significant Group $\times$ Time interactions found in the ANCOVA (Table 2 and Fig. 2). However, there was no significant effect for the number of different sexual partners. Frequency of any sex act and oral sex act trended toward a significant time effect ($p < .10$), and frequency of any sex act and vaginal sex had significant Group $\times$ Time interactions ($p < .05$). There was no significant difference detected among groups on post hoc testing. However, the METH group did decrease significantly or trend toward significance on all measures of sex act frequency from...
pretreatment to Week 18 (p < .05 for any sex and vaginal sex; p < .10 for oral sex; Fig. 2). There were no reports of anal sex.

4. Discussion

In this randomized controlled trial of three opioid agonist medications, the main finding is the absence of distinguishing differences among the treatment medications for most measures of HIV risk behaviors. Past studies indicated that these three agents have comparable efficacies in reducing illicit drug use, and the present study extends these findings to demonstrate similar efficacies of all three agents in reducing behaviors that increase risk of HIV transmission. One notable exception is the difference among the agents in effects on sexual behaviors.

Past studies consistently showed an effect of MMT on decreasing injection frequencies. Consistent with these findings, each opioid agent studied produced significant decreases in rates of injection. These were especially notable for rates of opioid injection but also occurred for cocaine injection. For both opioid and cocaine injections, the primary decrease in frequency occurred between baseline and Week 1, with no statistically significant decrease occurring after Week 1. This pattern probably accounts for the absence of a time effect for cocaine in the secondary analysis because that analysis only evaluated the time changes beginning at Week 1. Because of the time delay of full pharmacologic efficacy owing to the long half-life of these agents, as well as the time involved in dose titration, one may have expected to see a larger proportion of the treatment effects occurring beyond the first week. The relatively large changes in the first week may therefore represent an effect from nonpharmacologic interventions occurring at treatment outset. Nevertheless, each treatment group had similar decreases in injecting behaviors, supporting the similar efficacies of all three agents in reducing risk of HIV transmission. Finally, these self-reported findings for drug use are consistent with urine results from this study, which showed no difference in rates of opioid-positive urine screens among the three treatment groups in post hoc pairwise comparisons (Johnson et al., 2000).

Unlike injection behaviors, sexual behaviors have not been widely studied as outcomes of opioid agonist therapy. In our study, sexual behaviors did not appreciably change during treatment, with the notable exception of the METH group. Interestingly, the METH group had higher (although not significant) frequencies of each type of sex act compared with the other groups at baseline (Fig. 2). Despite this higher baseline frequency, this group consistently reported lower rates of sexual behaviors at Week 18. Heroin has also been shown to decrease sexual function (Mirin, Meyer, Mendelson, & Ellingboe, 1980), and previous reports identified the effects of METH in decreasing sexual interest, sex hormone levels, and sex act frequency (Crowley & Simpson, 1978; Strain, 2006). These effects of opioid agonists on sexual behaviors may partially explain the decrease in sexual activity seen in the present study; however, such effects have not been extensively studied for other opioid treatment medications such as BUP and LAAM. Thus, possible reasons for the observed effects on sex associated with METH, but not LAAM or BUP, are not clear and constitute a potentially important focus for future research.

Condor use data during treatment were also collected as part of the RBI. However, the RBI did not provide suitable baseline rates of condom use and formal analysis of condom use rates for this population could not be performed. Consistent with previous findings of low rates of condom

Fig. 2. Sexual behavior variables showing change from pretreatment to Week 18. The METH group had significant decreases in sex act frequency (*p < .05; **p < .10).
use during MMT (King et al., 1994; Metzger et al., 1993), each of the three treatment groups reported low rates of condom use for the preceding month at Week 18. For instance, more than 50% of patients with data available in each group reported never using condoms (16/19 in the LAAM group, 19/29 in the METH group, and 16/21 in the BUP group) during treatment.

There are several important limitations to this study. First, the outcomes are all based on self-report, which is subject to misreporting and recall bias errors. A further limitation is the variability in elapsed time from measured time point to data collection. For instance, the injection data were analyzed across five time points, but these were based on data collected at two time points during the study. Thus, recall for periods more distant from the RBI interview may be less reliable than if there had been five separate interviews. However, despite these drawbacks, the study used generally accepted self-report methods.

The use of opioid agonist medications other than METH has significantly expanded the treatment options for opioid dependence. Although the withdrawal of LAAM as a treatment option is unfortunate, the availability of BUP—especially through office-based treatment—is important progress in expanding treatment capacity and options. The finding in this study that BUP has comparable efficacy with METH in reducing most HIV risk behaviors suggests that wider therapeutic availability of BUP may provide expanded reduction in HIV risk behaviors in the opioid-dependent population. However, it should be noted that the present study evaluated BUP in a research setting that included frequent clinic visits and weekly counseling. It is unclear how the present findings on risk reduction will generalize to office-based practice settings.

In light of the widespread public health problem of HIV and its association with opioid dependence (Ball et al., 1988; Bellis, 1993), continued efforts to reduce HIV transmission remain critically important. The present finding that BUP and LAAM provide efficacy similar to that by METH in reducing HIV risk behaviors is important in efforts to reduce HIV transmission. These findings also suggest that integration of opioid dependence treatment into office-based medical practices provides an additional opportunity to incorporate HIV counseling and risk reduction efforts in primary care settings.

In summary, this study supports previous observations on the efficacy of opioid agonist medication therapy in reducing HIV drug injection risk behaviors. The study also shows that METH, but not BUP or LAAM, is associated with a reduction in self-reported sexual behavior. Finally, the present study also supports previous findings of similar treatment efficacies of the three agonist agents (Johnson et al., 2000), finding no significant difference among the different treatment groups in either primary or secondary analysis, apart from the isolated METH effect on sex frequency.

Acknowledgments

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