Abstract

This pilot randomized clinical trial evaluated whether the efficacy of office-based buprenorphine maintenance treatment (BMT), provided with limited counseling or oversight of medication adherence is improved by the addition of individual drug counseling and abstinence-contingent take-home doses of buprenorphine. After a 2-week buprenorphine and stabilization period, heroin dependent individuals (n = 24) in Muar, Malaysia were randomly assigned to Standard Services BMT (physician administered advice and support, and weekly, non-contingent medication pick-up) or Enhanced Services (nurse-delivered manual-guided behavioral drug and HIV risk reduction counseling (BDRC) and abstinence-contingent take-home buprenorphine (ACB), 7 day supply maximum). Outcomes included retention, proportion of opioid-negative urine tests, self-reported drug use, and self-reported HIV risk behaviors. 12/12 (100%) of Enhanced Services and 11/12 (92%) of Standard Services participants completed the entire protocol. The proportion of opioid-negative urine tests increased significantly over time for both groups (p < 0.001), and the reductions were significantly greater in the Enhanced Services group (p < 0.05); Enhanced Services group achieved higher overall proportions of opiate negative urine toxicology tests (87% vs. 69%, p = 0.04) and longer periods of consecutive abstinence from opiates (10.3 weeks vs. 7.8 weeks, p = 0.154). Both groups significantly reduced HIV risk behaviors during treatment (p < 0.05), but the difference between Enhanced and Standard Services (26% vs. 17% reductions from the baseline levels, respectively) was not statistically significant (p = 0.9). Manual-guided behavioral drug and HIV risk reduction counseling and abstinence-contingent take-home buprenorphine appear promising for adding to the efficacy of office-based BMT provided with limited drug counseling and medication oversight.

Keywords: Buprenorphine treatment; Drug counseling; HIV risk reduction counseling

1. Introduction

Buprenorphine maintenance treatment (BMT) is expanding the availability of opioid maintenance treatment (OMT) in the United States (Fiellin et al., 2006) and internationally, including in Malaysia (Chawarski et al., 2006; Mazlan et al., 2006). Although the efficacy of BMT was established mainly in clinical trials that provided drug counseling and direct observation of buprenorphine ingestion (Johnson et al., 1995; Kosten et al., 1993; Ling et al., 1996), drug counseling is often not provided with office-based BMT, and patients often receive buprenorphine for unobserved, self-administration on a weekly or even less frequent basis (Fiellin, 2007). This approach is consistent with the general medical approach to treating other chronic diseases, such as diabetes or hypertension, and may be particularly advantageous in developing countries with few specialists in addictions or psychotherapy. The improved efficacy of office-based BMT including drug counseling has been evaluated in few studies (Fiellin et al., 2006; Montoya et al., 2005) and the impact of medication take-home doses as incentives for abstinence in BMT has not been studied. Several considerations suggest that treatment response may be enhanced by these services.

At least one randomized clinical trial (McLellan et al., 1993) and several meta-analyses (Amato et al., 2004; Prendergast et al., 2001) support the efficacy of drug counseling and other psy-
chosocial interventions for reducing illicit drug use and HIV risks during methadone maintenance treatment (MMT). However, interim MMT with minimal or no counseling has also been shown to be effective for many patients (Schwartz et al., 2006, 2007).

Providing take-home doses of methadone contingent on abstinence as an incentive to refrain from illicit drug use reduces illicit drug use during methadone maintenance treatment (Chutuape et al., 2001; Iguchi et al., 1996; Stitzer et al., 1992). Using this approach in BMT might also lead to greater reductions in illicit drug use and greater medication adherence, since patients who are not abstinent would receive directly observed medications on a three times per week dosing schedule (Schottenfeld et al., 2000).

Malaysia has significant problems with heroin abuse and the associated spread of HIV, but until recently drug treatments were not widely available (Chawarski et al., 2006; Mazlan et al., 2006). Following its introduction in Malaysia in 2002, BMT was widely disseminated through private general practitioners. However, problems with non-prescribed and injection use of buprenorphine led to increased government restrictions on BMT. Improving the overall efficacy of BMT is an urgent priority of the country’s treatment providers and health care policy makers.

Consequently, we conducted a pilot randomized clinical trial in Malaysia to compare the efficacy for reducing illicit drug use and HIV risk behaviors of a largely medical Standard Services approach (physician management (PM) and weekly, non-contingent dispensing of take-home buprenorphine) with Enhanced Services (behavioral drug and risk reduction counseling (BDRC) with abstinent contingent buprenorphine take-home doses (ACB) in addition to PM). We hypothesized that Enhanced Services would be associated with greater reductions of illicit drug use and HIV risk behaviors, compared to Standard Services.

2. Methods

2.1. Subjects

Treatment seeking volunteers were enrolled after providing informed, voluntary consent, if they met DSM-IV criteria for opioid dependence, had an opioid positive urine toxicology test, and were age 18–65. Alcohol or benzodiazepines dependence, greater than three times normal liver enzymes, current suicide or homicide risk, current psychotic disorder or major depression, life-threatening or unstable medical problems were exclusion criteria. Fifty-four individuals expressed interest in study participation; 46 completed the screening process; 17 were excluded because of current dependence on benzodiazepines (n = 5), 3 x or greater elevations of liver enzymes (n = 6), not meeting criteria for opioid dependence (n = 5), or current participation in substance abuse treatment (n = 1). Twenty-nine individuals were enrolled into the protocol. Three patients did not complete induction and were not randomized. Two female patients were offered compassionate treatment in the Enhanced Services arm of the study and were not randomly assigned to treatment. Twenty-four patients were randomized.

The study protocol was approved by the Human Investigation Committee (HIC) for the Yale University School of Medicine and the Malaysian Ministry of Health’s HIC. The study was conducted in a community-based outpatient center in Muar, Malaysia.

2.2. Treatment conditions

After completion of a 2-week buprenorphine induction protocol, study participants were randomly assigned, using a computer-generated simple randomization procedure, to either Standard Services (n = 12) or Enhanced Services (n = 12).

2.3. Medications

Buprenorphine mono tablets (Subutex) were the only formulation available during the study period and used for all participants. Buprenorphine dosages, starting at 8 mg per day on the first day of induction, could be increased to 12–16 mg per day depending on the patient’s symptoms, reports of craving, or evidence of continued heroin or other illicit opioid use. Buprenorphine doses were administered daily under direct observation during induction. Subsequently, participants assigned to Standard Services received weekly take-home doses of buprenorphine.

Participants assigned to Enhanced Services were administered directly observed buprenorphine on a three times per week schedule, with double the daily dose administered on Mondays and Wednesdays and triple the daily dose administered on Fridays. Urine toxicology testing was performed prior to medication dispensing. Immediately following the first negative test, participants received a 1- or 2-day supply (sufficient to last until the following scheduled three times weekly dosing day). Participants with two successive opioid-negative tests (and no missed appointments between visits) received a 1-day dose at the clinic and were provided three or four daily take-home doses (sufficient to last, for example, from Monday to Friday, Wednesday to Monday or Friday to Wednesday). Participants with three successive opioid-negative tests (and no missed appointments) received a 1-day dose at the clinic and were provided six take-home doses. A positive test or failure to submit a scheduled urine sample resulted in immediate suspension of take-home medications and return to three times per week dosing under direct observation. Subsequently, participants could regain take-home privileges following the same protocol as initially used.

All study participants received PM, consisting of brief weekly visits with a physician. The first PM visit lasted approximately 45 min, followed by 10–12 min visits once per week throughout the entire study period. In PM, the physician evaluated medication adherence, medication efficacy, and potential medication adverse effects; reviewed urine toxicology results; and provided brief advice on how to become or remain abstinent. PM was provided by a single general practitioner with 3 years of experience in treating patients with substance use disorders.

Participants assigned to Enhanced Services also received weekly, manual-guided BDRC in individual sessions lasting 45–60 min. Designed to be delivered by available nursing personnel in medical offices, BDRC is educational, directive, and prescriptive and uses short-term behavioral contracts aimed at improving treatment adherence and getting patients to make initial lifestyle changes, including cessation/reduction of drug use and cessation/reduction of drug- and sex-related risk behaviors. BDRC counselors provide immediate feedback and positive reinforcement of patient progress and utilize exclusively positively or gain-framed communication style, which may increase the likelihood of patient adherence to treatment recommendations and engagement in behavioral change (Rothman et al., 1993; Rothman and Salovey, 1997). Initial stages of BDRC focus on behavioral changes necessary to achieve and maintain drug abstinence, while later treatment stages help link the patient’s progress made in treatment with longer term recovery goals.

BDRC was provided by three nurse counselors, all with several years of drug counseling experience in an earlier clinical trial and all of whom completed additional training in BDRC consisting of several didactic workshops, case conferences, and three or more closely supervised BDRC practice cases. The fidelity of counseling and counselors’ adherence to the manual was monitored via biweekly supervision sessions with the author of the BDRC manual (MCC).

2.4. Outcome measures

The primary outcome measures, specified in advance, were proportions of opiate-negative urine tests aggregated over 2-week periods, self-reported days of drug use per week, and the maximum consecutive weeks abstinent from opiates (the longest consecutive period of opioid-negative urine tests), reductions in self-reported HIV risk behaviors, and treatment retention. Illicit drug use during treatment was measured by weekly urine testing using rapid/instant urine
tests for opiates, benzodiazepines, amphetamine, methamphetamine, and THC (Redwood Biotech, Panel/Dip instant test). The AIDS risk inventory (ARI), assessing drug-related and sexual risk behaviors associated with HIV transmission (Chawarski et al., 1998), was administered at baseline and at treatment completion.

2.5. Statistical analyses

Baseline characteristics of the two treatment groups were compared using the Chi-square and t-test as appropriate. Between group differences in changes in illicit opiate use during treatment, as well as changes in self-reported HIV risks from pre-treatment baseline were analyzed using a repeated measures analysis of variance procedure (ANOVA). The completion rate of scheduled assessments was high: 96% (346/360) of scheduled urine tests and 96% (46/48) of scheduled ARI assessments were obtained. Statistical analyses were planned in advance, and all randomized patients were included in the analyses of baseline differences. One study participant did not complete the entire study protocol, and his end of treatment HIV risks and urine toxicology screens were not available. Due to the small sample size, these missing data points were not replaced or estimated.

3. Results

There were no significant baseline differences between the two treatment groups on demographic or drug use characteristics. 12/12 (100%) of participants in the Enhanced Services and 11/12 (92%) of participants in the Standard Services groups completed the entire study protocol. One participant in the Standard Services group was protectively transferred to outpatient psychiatric treatment in the 7th week of the study due to developing psychotic symptoms.

The proportion of opiate-negative urine tests increased significantly over time during treatment for both treatment groups ($F(7,147)=36.3, p<0.001$); these increases were significantly greater in the Enhanced Services than in the Standard Services group ($F(1,21)=4.8, p<0.05$) (Fig. 1). Self-reported days per week of opiate use followed a similar pattern of results. Participants assigned to Enhanced Services also achieved a higher overall proportion of opiate negative urine toxicology tests during treatment (87% vs. 69%, $p=0.04$) and longer periods of consecutive abstinence from opiates (10.3 vs. 7.8 weeks, $p=0.154$). Both groups significantly reduced HIV risk behaviors from baseline during treatment ($F(1,21)=10.2, p<0.05$); the reductions were larger but not statistically different between the Enhanced Services and the Standard Services group (26% vs. 17% reductions from baseline, respectively; $p=0.9$) (Fig. 2).

4. Discussion

The results of this pilot randomized clinical trial support the feasibility and potential efficacy of providing Enhanced Services with buprenorphine maintenance treatment in Malaysia. Both treatment groups significantly reduced illicit opiate use over time during treatment, but these reductions were significantly greater for patients who were provided BDRC and ACB. Both groups also significantly reduced HIV risk behaviors from baseline during treatment, but between group differences were not significant. Notably, retention in both treatment groups was excellent, suggesting that the added potential burdens to patients assigned to BDRC and ACB did not lead patients to discontinue treatment prematurely.

With its focus on a limited number of problem areas and prescriptive approach for addressing specific problems with short-term goal-setting and behavioral contracts, and its efficacy when provided by nursing or other medical personnel who do not have advanced training in psychology or social work, BDRC seems particularly suitable for Malaysia and other developing countries where masters or doctoral level therapists are not available.

Some limitations of this pilot study include the small sample size and a study design that combined in one study group both BDRC and ACB and thus does not allow determination of the separate contributions of counseling, contingency management or dosing schedule to the observed increased treatment efficacy. The use of the rapid urine toxicology screens in the study did not allow objective monitoring of prescription/synthetic opiate use (only self-report data on use of prescription opiates and illicit use of buprenorphine was collected). Although counselors in this study had previous experience in treating opiate dependent individuals, they also represent a group of medical professionals (i.e., nurses) that are available in Malaysia as well as in other resource poor countries. The close supervision provided to all patients during the 2-week induction period may have contributed to the overall good results for patients in both treatment groups.
BMT reduces illicit opioid use and HIV risk behaviors, but providing specialized counseling (BDRC) and ACB instead of weekly (or less frequent) dispensing of buprenorphine to all patients, regardless of current drug use, may improve its effectiveness. Replication of these results in a larger study enrolling a more diverse sample of patients, including women; evaluation of the separate contributions of BDRC and ACB (or the combination of the two); identification of specific patient subgroups that do or do not need (or respond to) enhanced services; and evaluation of the cost-effectiveness of the components of enhanced or standard services are all needed to develop evidence-based guidelines for office-based BMT.

References


Chawarski, M.C., Mazlan, M., Schottenfeld, R.S., 2006. Heroin dependence and HIV infection in Malaysia. Drug Alcohol Depend. 82, 39–42.


