Published in final edited form as:

J Subst Abuse Treat. 2015 January ; 48(1): 70–76. doi:10.1016/j.jsat.2014.06.006.

Buprenorphine Pharmacotherapy and Behavioral Treatment: Comparison of Outcomes among Prescription Opioid Users, Heroin Users and Combination users

Suzanne Nielsen, PhD¹, Maureen Hillhouse, PhD², Larissa Mooney, MD², Alfonso Ang, PhD², and Walter Ling, MD²

¹University of New South Wales, National Drug and Alcohol Research Centre, Randwick, NSW, 2031 Australia

²UCLA Integrated Substance Abuse Programs, Los Angeles, CA 90025, USA

Abstract

Most research examining buprenorphine has been conducted with heroin users. Few studies have examined buprenorphine pharmacotherapy for prescription opioid users. Data were from a randomized controlled trial of behavioral treatment provided for 16 weeks on a platform of buprenorphine pharmacotherapy and medication management. We compared heroin (H, n=54), prescription opioid (PO, n=54) and combination heroin+prescription opioid (POH, n=71) users to test the hypothesis that PO users will have better treatment outcomes compared with heroin users. The PO group provided more opioid-negative urine drug screens over the combined treatment period (PO:70%, POH:40%, H:38%, $p<0.001$) and at the end of the combined treatment period (PO:65%, POH:31%, H:33%, $p<0.001$). Retention was lowest in the H group (PO:80%, POH:65%, H:57%, $p=0.039$). There was no significant difference in buprenorphine dose between the groups. PO users appear to have better outcomes in buprenorphine pharmacotherapy compared to those reporting any heroin use, confirming that buprenorphine pharmacotherapy is effective in PO users.

Introduction

An increasing population of prescription opioid (PO) users in the United States is well documented (Compton & Volkow, 2006; Maxwell, 2011). With the increased use of prescription opioids, there has been a growing demand for treatment for PO dependence (Fischer, Nakamura, Rush, Rehm, & Urbanoski, 2010), and the high mortality associated

© 2014 Elsevier Inc. All rights reserved.

Corresponding Author: Suzanne Nielsen, National Drug and Alcohol Research Centre, University of New South Wales, 22-32 King St, Randwick, 2031, Australia, + 61 2 8936 1017, + 61 2 9385 0222, suzanne.nielsen@unsw.edu.au.

The contents of the published material are solely the responsibility of the authors and do not reflect the views of the NHMRC.

Portions of this paper were presented at the NIDA International Forum, Palm Springs 2012.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

with PO dependence (Paulozzi, 2012; Warner, Chen, & Makuc, 2009) suggests an urgent need for empirical research to identify effective treatments.

Buprenorphine pharmacotherapy is well-established for the treatment of illicit opioid dependence (Amass, Kamien, & Mikulich, 2000; Ling & Wesson, 2003; Ling, Wesson, Charuvastra, & Klett, 1996; Mattick, Kimber, Breen, & Davoli, 2004). Buprenorphine has an advantageous safety profile including a low risk of respiratory depression (Walsh, Preston, Stitzer, Cone, & Bigelow, 1994), and its availability in primary care or other office based settings makes it an ideal candidate for treating PO dependence. Depending on the treatment setting, buprenorphine also allows medication by prescription to be taken at home, thereby avoiding daily attendance at opioid treatment programs, which may be a potential barrier for treatment.

Several studies have assessed the use of buprenorphine for PO dependence and found that PO users have similar induction experiences compared to heroin users, and require similar doses of buprenorphine (Nielsen, Hillhouse, Mooney, Fahey, & Ling, 2012). More PO users were able to successfully complete a buprenorphine taper compared to heroin users (Nielsen, Hillhouse, Thomas, Hasson, & Ling, 2013), although a large study examining short and intermediate buprenorphine pharmacotherapy for PO users found that 93% of participants relapsed to opioid use after a 2-week stabilization period and 2-week taper, and after receiving a 12-week stabilization and 4-week taper, 91% had relapsed when followed up 8 weeks post taper (Weiss et al., 2011). There is a lack of research to inform longer-term outcomes in buprenorphine pharmacotherapy for PO users.

One retrospective case series compared treatment outcomes for heroin users and PO users in office-based buprenorphine pharmacotherapy (Moore et al., 2007), and found that PO users had better treatment outcomes with regard to opioid-negative urine tests and retention. Heroin use in a sample of PO users was found to be a negative predictor of outcomes (Weiss, et al., 2011). To the authors' knowledge, however, no study has compared outcomes for PO and heroin users using clinical outcome data from a clinical treatment study.

Favorable treatment outcomes for PO users may be related to differences observed between PO users and heroin users. A retrospective review of PO users entering methadone treatment found that PO users were more likely to have ongoing pain and mental health problems compared to heroin users, although no differences were detected on measures of social stability (Brands, Blake, Sproule, Gourlay, & Busto, 2004). Moore et al. (2007) found that PO users had shorter opioid use and treatment histories, with heroin users having used opioids for around 5 years longer, and most (59%) reporting more than one previous treatment attempt, compared to 29% of PO users. PO users were more likely to be white, have higher income, and be Hepatitis C antibody negative. Fisher et al. (Fischer, Patra, Cruz, Gittins, & Rehm, 2008) also found that opioid-dependent patients using only PO were more likely to be white and have legal income, although some patterns of polysubstance use were identified in the PO use groups. These studies demonstrate important differences in opioid use history and resources (social and financial) that exist between PO and heroin users. These studies find that PO users appear to do well in treatment with characteristics such as

employment that bode well for successful treatment outcomes (Brewer, Catalano, Haggerty, Gainey, & Fleming, 1998; Heinrich & Fournier, 2005).

The current secondary analysis addresses treatment outcomes compared across three opioid use groups using data from a recently completed clinical trial. We hypothesize that PO users who do not use heroin will have better treatment outcomes compared with those who use a combination of PO and heroin, or who use heroin alone.

Methods

Design

This secondary analysis forms part of a planned series of analysis to examine buprenorphine pharmacotherapy outcomes in previously conducted clinical trials that included heroin and PO users. The parent study was a randomized controlled trial to test the comparative efficacy of four behavioral treatment conditions provided for 16 weeks on a platform of pharmacotherapy and medication management for the treatment of opioid dependence (Ling, Hillhouse, Ang, Jenkins, & Fahey, 2013) (Clinical Trials Registration: NCT00591617). Study participants received buprenorphine (as Suboxone®) and medication management (MM), an approximation of the care provided by physicians when prescribing buprenorphine in private practice, and were randomized to one of four behavioral conditions: Cognitive Behavioral Therapy (CBT), Contingency Management (CM), Both CBT+CM, and MM alone. Descriptions of the main study and study findings are published elsewhere (Ling, et al., 2013).

Potential participants were consented and screened for eligibility, inducted and stabilized on buprenorphine for two weeks, and were then assigned to a behavioral condition for a 16-week combined treatment phase of pharmacotherapy and behavioral treatment. A subsequent second 16-week medication-only phase followed. Follow-up assessments were administered at weeks 40 and 52.

Participants

Recruitment methods included advertising, word-of-mouth, study announcement flyers posted in treatment programs and community locations, and referrals such as from local narcotic treatment and outreach programs, alcohol and drug abuse clinics, primary care providers, and mental health centers.

Eligibility criteria included being at least 15 years of age, meeting the Diagnostic and Statistical Manual of Mental Disorders, Fourth edition – Text Revision (DSM-IV-TR) criteria for opioid dependence (American Psychiatric Association, 2000), of general good medical and psychiatric health, with no sensitivity to buprenorphine or naloxone, and no pattern of alcohol, benzodiazepine or other drug use that would require immediate medical attention or be unsafe in the context of the study. Female participants could not be pregnant or nursing, and must have agreed to use an acceptable method of birth control. A total of \$410 compensation was provided for completing all assessments (see Ling et al 2013 for further details).

For this analysis, participants were classified as Prescription Opioid only (PO), Prescription Opioid and Heroin (POH) and Heroin only (H) based on self-reported opioid use in the 30 days prior to screening.

Procedures

Screening—Appointments were made with interested individuals who met preliminary screening criteria. After voluntarily signing informed consent, participants were assessed to determine eligibility and to provide baseline information. All procedures followed were in accord with the Helsinki Declaration of 1975.

Eligible participants met with a study physician to review a Suboxone Treatment Information sheet outlining proper use of medication for take-home dosing; a Handbook for Recovery from Opiate Dependence, developed by the PI; a Suboxone Treatment Information booklet provided by the manufacturer of the study medication; and a wallet card that identified the participant as being in a clinical research study.

Medication Induction and Randomization—Suboxone, a combination of buprenorphine and naloxone in a 4:1 ratio taken sublingually, was used in this trial. Participants were inducted onto buprenorphine starting at 4 mg (expressed as amount of buprenorphine), and stabilized over two weeks. On Day 1 a 4mg dose was dispensed in the clinic and monitored by medical personnel to assess any adverse effects. An additional 2–4mg dose could be provided at the study physician’s discretion. The total dose for Day 1 was 8–16mg. Day 2 induction doses ranged between 8–16mg, and Day 3 doses ranged between 12–24mg. Induction procedures are described in detail elsewhere (Nielsen, et al., 2012).

After induction, the daily dosage could be adjusted to range from 2–24mg for the balance of the 2-week induction/stabilization phase. At the end of this phase, participants were randomized to behavioral condition. Participants were not stratified by opioid category (PO; POH; H), however there was no significant difference in the percentages of the three opioid group types randomized to each condition.

Pharmacotherapy and Behavioral Therapy Phase—During the 16-week combined-treatment phase, participants were scheduled to attend clinic twice weekly for collection of data and urine specimens and to receive study medication. Participants also met weekly with the study physician for medication management, and attended their assigned behavioral therapy (CBT, CM). All participants received weekly medication management and, during these sessions, dose adjustments and limited discussion of progress, symptoms, and medication issues as normally provided to patients in private office-based practice settings were provided by study physicians. Weekly CBT sessions focused on relapse prevention skills, and CM was administered twice weekly to provide incentives for opioid-negative Urine Drug Screens (UDS).

Medication only phase, taper and follow up—Participants attended clinic weekly after the combined treatment phase through week 40 for data collection, medication management visits, and UDS. Between weeks 34 and 40 participants were tapered off

buprenorphine. Study physicians were encouraged to reduce the buprenorphine dose over one week per previous research showing no advantage in prolonging taper (Ling et al., 2009). However, participants could request up to six weeks to finish their taper. Participants could have been referred to pharmacotherapy at the study physician's discretion, rather than entering the taper phase. All participants continued to receive standard medical management during the taper phase. A final assessment visit occurred at week 52.

Assessments

Assessments used in this analysis include UDS, the Addiction Severity Index (McLellan et al., 1992), the SF-36 (Ware & Sherbourne, 1992), withdrawal and craving scales (Childress, McLellan, & O'Brien, 1986; Wesson & Ling, 2003), an opioid use questionnaire, and a Substance Use Report (SUR). The SUR was completed to capture the prior week's self-reported use of alcohol, meth/amphetamine, barbiturates, benzodiazepines, cannabis, cocaine, opiates and other substances. Participation in ancillary psychosocial treatment was also recorded.

Urine drug screens (UDS) tested for opiates, oxycodone, propoxyphene, phencyclidine, barbiturates, benzodiazepines, cocaine, amphetamines, methamphetamine, marijuana, methadone, and Ecstasy at each visit. A urine dip test was used to confirm the presence of buprenorphine once weekly, and a medication dose log was maintained.

Analyses

The decision was made to collapse the behavioral treatment arms for the primary analysis, based on the finding of no differences between the behavioral groups in the main trial outcome (Ling, et al., 2013). The primary outcome measures were unsanctioned opioid use (both over the combined treatment phase and at the end of the medication-only phase), and retention at the end of the combined treatment phase. Opioid use during the combined treatment phase was computed with the Treatment Effectiveness Score (TES; (Ling et al., 1997), a percentage based on the number of opioid-negative UDS over the number of UDS possible. Opioid use at the end of the combined treatment phase was defined as the number of opioid-negative UDS, out of the two collected during the final week of this phase. As the TES reports the number of opioid-negative UDS over the total number of UDS; missing UDS and opioid-positive UDS are treated the same way in the analyses. Retention was defined as being on medication at the end of the combined treatment phase. Secondary outcomes include buprenorphine dose, non-opioid substance use, mental and physical health, retention at the end of the medication-only phase prior to the commencement of taper (Week 34), and opioid use in the week prior to taper, and at the two follow-up time-points (Week 40 and Week 52). Missing data for non-opioid substance use were not assumed to be positive, and for this reason only available data were analysed for non-opioid substance use.

As differences in baseline characteristics have been reported with PO and heroin users, and these differences may influence treatment outcomes (Fischer, et al., 2008; Moore, et al., 2007), regression analyses were conducted to control for differences in baseline demographic characteristics among the three opioid -use groups in the primary outcomes.

Sensitivity analyses were also conducted to determine if reduced sensitivity for hydrocodone in urine assays affected the results. Sensitivity analysis confirmed that the inclusion of participants using hydrocodone as their only PO did not change the results, and therefore these participants were included in the analyses.

We performed multiple imputations with five datasets created using the Markov Chain Monte Carlo Approach (Little & Ruben, 2002) primarily due to missing data for change in Physical and Mental Health Component Scores over the combined treatment phase (60 of the 179 cases from baseline to week 18). Sensitivity analyses using complete-case analysis led to similar conclusions.

One-way ANOVA was used to examine whether the behavioral condition was associated with a change in TES scores. Chi-square tests were used to examine the dichotomous outcome of providing two opioid-negative UDS in the final week of the combined treatment phase. Due to small cell numbers across the three opioid use groups, we combined all behavioral intervention conditions (CBT, CM, CBT+CM) and compared results to the medication management (MM) group. Where the expected number in one or more cells is less than five, we report the results of the 2-sided Fisher's Exact test.

To control for the multiple analysis conducted, a significance level of $p < .016$ was used for the primary outcome measures examined. All statistical analyses were performed using SPSS V.22.

Results

Participants

A total of 366 individuals completed the consent process, 241 were inducted onto buprenorphine-naloxone and stabilized for two weeks, and 202 individuals were randomized to behavioral condition.

Twenty-three participants were excluded from this analysis as they were already prescribed buprenorphine or methadone at study entry. These participants were excluded due to inability to conclusively class them as heroin or PO users prior to treatment entry, leaving 179 participants in this analysis (see Figure 1).

Table 1 provides a description of randomized participants at baseline by opioid use group. Differences were found between groups on race, with the highest proportion of white and Hispanic participants in the PO group. The PO group also had the lowest proportion of participants who were never married, although more PO users were married compared with the other two groups. Almost half (48%) of the PO group were regularly employed or students compared to 30% in the POH group and 20% in the H group. Significant differences were found in length of opioid use, with the H group reporting the longest opioid use history, but no significant differences were found in age of first opioid use. Differences among groups were not detected in mean age or sex, or years of education.

Opioid Use

The Treatment Effectiveness Score (TES) was used to calculate the main outcome of opioid use. The TES computes a percentage based on the number of opioid-negative UDS results over the number of tests possible during the 16-week combined treatment period. The PO group had significantly more opioid-negative UDS (70%) across the combined treatment phase compared with the other two groups (40% for POH; 38% for H) (Table 2). After controlling for baseline demographic differences, the difference in the percentages of opioid-negative UDS were still significant across groups ($F = 10.79$, $p < .001$).

Results for the final week of treatment were consistent with results over the combined treatment duration. Approximately two-thirds (65%) of the PO group had opioid-negative UDS results for each of the two UDS collected in the final week of the combined treatment phase, compared with 31% of the POH group and 33% of the H group ($p < .001$) (Table 2). These results were significant after controlling for age, gender and baseline demographic differences with the POH group (OR = .186, 95% CI = .078 – .442) and the H group (OR = .181, 95% CI = .072 – .455) both being less likely to give two opioid negative UDS in the final week of the combined treatment phase as compared to the PO group.

Other Drug Use

Significant differences were found when comparing other drug use via UDS among the groups at baseline and the end of the combined treatment phase in benzodiazepine, cocaine, and marijuana use (Table 3). Significant differences in benzodiazepine-positive UDS was documented at baseline ($p = 0.011$), with 32% of the PO group having a positive UDS. The H group had the highest percentage of cocaine-positive UDS at baseline ($p = 0.008$), and the POH group had the highest percentage of marijuana-positive UDS at baseline ($p = 0.029$). Cocaine was the only substance for which significant differences among the groups were detected in positive UDS at the end of the combined treatment phase ($p = 0.011$), with the highest use among the H group.

We examined changes in self-reported non-opioid drug use (alcohol to intoxication, barbiturates, tranquilizers, cocaine, amphetamines, cannabis and polydrug use) in the past 30 days from baseline to the end of the combined treatment period. Paired t-tests revealed that the PO group did not significantly change their other substance use from baseline compared with the last 30 days of the combined treatment period. A non-significant reduction in polydrug use from 11.4 days (SD 12.0) to 8.1 days (SD 10.0) was observed in the PO group ($t = -1.79$, $p = 0.080$). The POH group reduced their cocaine use at baseline from 1.6 days (SD 2.9) to 0.7 days (SD 1.7) ($t = -2.22$, $p = 0.030$) and polydrug use at baseline from 14.9 days (SD 10.7) to 10.5 days at the end of the combined treatment period (SD 10.7) ($t = -3.30$, $p = 0.002$). The H group increased their cannabis use from 3.8 days (SD 7.7) to 6.8 days (SD 10.5) ($t = 2.36$, $p = 0.024$), and had a non-significant increase in tranquilizer use from 0.3 days (SD 1.2) to 1.8 days (SD 5.0) ($t = 1.70$, $p = 0.097$).

Retention

Treatment retention was measured dichotomously by whether the participant remained in the study and was still receiving medication at the end of the combined treatment phase (Table

2). Retention was significantly different by treatment group ($p=0.039$), and was highest in the PO group (80%). After controlling for age, gender, and baseline demographic differences, compared with the PO group, the H group was less likely to be retained in treatment at the end of the combined treatment phase (OR=0.364, 95% CI=0.145–0.911), however the difference in retention did not reach significance when comparing the PO and POH group (OR=0.496, 95% CI=0.203–1.208).

Efforts to assess all participants at the end of the combined treatment phase included those who had ceased buprenorphine pharmacotherapy. The difference in number of participants who attended and provided a UDS by opioid group did not reach significance ($\chi^2=5.630$, $p=0.06$), with 87% of the PO group and 70% of the POH and H groups completing the final assessment of the combined treatment phase.

Changes in physical and mental health

Mean SF-36 physical health component scores increased in all groups from baseline to the end of the combined- treatment phase, although the difference in change between the groups was not significant; PO: mean increase =2.81 (SE=1.33), POH: mean increase =3.32 (SE=1.17), H: mean increase =0.12 (SE=1.09) $F(2)=2.429$, $p=0.119$). Similarly, SF-36 mental health component scores increased over the combined treatment phase, although the difference between the groups was not significant; PO: mean increase=3.61 (SE=2.25), POH: mean increase =3.33 (SE=1.82) and H: mean increase =4.14 (SE=2.11), $F(2)=0.190$, $p=0.831$.

Buprenorphine Dose

Buprenorphine dose during the final week of the combined treatment phase did not differ significantly between the three groups. Doses were 16.8mg (SD 5.4) for the PO group, 16.4mg (SD 4.9) for the POH group, and 16.8mg (SD 4.8) for the H group.

Intervention Effect

Similar to the parent study (Ling, et al., 2013), no difference was found among the four behavioral conditions on percentage of opioid-negative UDS over the combined treatment period for the opioid use groups (PO: $p=0.257$; POH: $p=0.997$; H: $p=0.366$). Due to the small cell numbers, the behavioral treatment groups were combined (CBT, CM, CBT+CM) and compared to the group that received no additional behavioral treatment (MM). The results for the PO group approached significance, in that 71% of those randomized to a behavioral intervention had two opioid-free UDS in the final week of the combined treatment phase compared with 42% in the MM group, $p=0.087$. No effect was seen in the other two opioid groups (POH: 32% behavioral group and 29% MM, $p=1.000$; H: 36% behavioral intervention and 27% MM, $p=0.748$).

Results during the medication-only and follow up phases

At week 34 (prior to commencing buprenorphine taper), retention remained higher in the PO group (61%), compared with the POH (39%) and H groups (37%) ($\chi^2=7.922$, $p=0.019$). More participants in the PO group (56%) were able to provide an opioid-negative UDS at the end of the medication-only phase in week 34 (prior to taper) compared with the POH

(23%), and H (20%) groups ($p<0.001$). A similar result was seen at week 40 (post-taper completion) in the provision of opioid-negative UDS PO: 52%, POH: 18%, H: 17% ($p<0.001$). Differences were not significant at week 52 (PO: 32%, POH: 18%, H: 17%, $p=0.116$).

During the follow up phase, a significant difference was not found in use of self-help groups at week 40 (PO: 43%, POH: 30%, H: 26%, $p=0.146$), or week 52 (PO: 30%, POH: 23%, H: 15%, $p=0.181$). A difference in attendance at any form of non-study counselling was detected between the groups at Week 40 (PO: 30%, POH: 11%, H: 11%, $p=0.010$), with the difference being marginally significant at week 52 (PO: 35%, POH: 27%, H: 15%, $p=0.051$). The differences in opioid use outcomes at week 40 were still significant after controlling for participation in counseling, age, gender and demographic differences at baseline with the POH group (OR=0.23, 95% CI=0.083–0.643) and the H group (OR=0.145, 95% CI=0.044–0.473) both being less likely to give an opioid negative UDS in week 40 as compared to the PO group.

Discussion

This study confirmed our hypothesis that PO users have favorable treatment outcomes with buprenorphine compared with those who report heroin use, either alone or in combination with prescription opioids. Some baseline differences exist between heroin users and PO users that may indicate better social support and stability experienced by the PO group. These baseline differences may facilitate success in treatment and partially explain the greater percentages of opioid-negative UDS in the PO group. However, the proportion of participants in the PO group providing opioid-negative UDS was significantly greater than the other opioid use groups even after controlling for differences in baseline characteristics, suggesting other factors are also at play. Those reporting any heroin use at baseline (H, POH), also reported more ongoing opioid use. It is important to better understand the reasons for ongoing opioid use among these opioid use groups to be able to develop appropriate interventions to improve treatment outcomes.

Differences in other substance use between the POH and the H group were also interesting to note, with reductions in cocaine use in the POH group, and increases in other cannabis use in the H group from baseline to treatment end. These changes in substance use by opioid group may inform treatment planning. Finally, the effect of the psychosocial interventions was examined, although the power for these analyses was limited due to sample size across the three groups. There was a non-significant difference in the effect of the behavioral interventions in the PO group, which was not observed in the other two groups. This finding may warrant further investigation to determine if behavioral interventions may be more effective in some sub-populations of opioid users.

Despite results showing positive treatment responses with regard to opioid use, there are still important issues to address for PO users. PO users had higher rates of benzodiazepine use at baseline. Concerns about the safety of combined benzodiazepine and opioid use, such as risk of overdose and poorer treatment outcomes (Caplehorn & Drummer, 2002; Lintzeris & Nielsen, 2010; Nielsen, Dietze, Lee, Dunlop, & Taylor, 2007), require further research to

address reasons for benzodiazepine use, and appropriate interventions for benzodiazepine use amongst PO users.

It is interesting to contrast the outcomes for buprenorphine pharmacotherapy in this study to those in a recent multi-site, controlled trial of PO-dependent patients, who were tapered off buprenorphine-naloxone after 12-weeks of treatment (Weiss, et al., 2011). The high rate of relapse (91%) to opioid use following the taper is notable in light of the characteristics of the study population that suggested a better prognosis (i.e., many employed, well-educated, shorter opioid use histories, and little other current substance use) (Brewer, et al., 1998), and prior research suggesting that patients who are PO-dependent have better outcomes than those who are heroin-dependent (Moore, et al., 2007). Results of this study show that a third of this sample provided an opioid-negative UDS 12 weeks after finishing study medication. These results demonstrate that longer-term treatment for PO users may be especially useful as they are associated with better outcomes.

It is important to consider limitations of this research, as some are inherent with secondary analysis. This study was not primarily designed to compare PO and heroin users, and therefore opioid type was not included in the stratification of the sample. Given the differences found by opioid use type and treatment outcomes, it may be appropriate to stratify opioid users by type of opioid used in future clinical trials. Another potential limitation is that we use biological assays for our primary outcome measure of opioid use at the end of the combined treatment phase. Biological assays that are sensitive to the full range of PO are not widely available. Current assays may not detect less frequently used PO such as fentanyl, and are less sensitive to some pharmaceutical opioids such as hydrocodone. With this knowledge, we have conducted sensitivity analysis in this study and confirmed that the results presented here are significant even when hydrocodone users are removed from the analysis. Additionally, as is common practice, missing UDS samples were counted similar to being opioid positive for the main outcome analyses. Although relapse to opioid use has been demonstrated to be very common when opioid users cease treatment (Magura & Rosenblum, 2001; Weiss, et al., 2011), it is possible that some participants who dropped out of the study had not relapsed to opioid use. As differences in follow-up rates by opioid group did not reach significance, this would not be expected to bias the current findings. Also, this study examined PO users in one geographical location in the US (Los Angeles, California). Given that high rates of PO use are reported in many US locations and in other countries, it may be important to confirm that outcomes seen in this study are similar in other locations. Further, we did not have detailed information on participation in opioid pharmacotherapy during the follow-up period to determine if this would explain group differences seen. This would be an important consideration for future studies. Finally, since multiple analyses were performed, p values close to 0.05 should be viewed cautiously due to the possibility of family-wise error.

The findings of this paper, taken in combination with previous studies examining buprenorphine induction (Nielsen, et al., 2012) and buprenorphine taper (Nielsen, et al., 2013), help to inform the evidence base regarding treatment for PO users with buprenorphine. Consistent with findings from previous research, it appears that PO users who do not also use heroin have favorable treatment outcomes with both buprenorphine and

methadone treatment (Moore, et al., 2007; Nielsen, et al., 2012). These combined findings suggest that treatment protocols that were developed based on evidence from studies with heroin users may also be appropriate for PO users. Further research may be needed to identify if there are groups of PO users who do not do well in treatment. This may be particularly important, as PO users have been found to be a heterogeneous group (Wu, Woody, Yang, & Blazer, 2010). Also, given the promising treatment outcomes, future efforts to make treatment more accessible to all PO users appears to be a critical strategy for reducing the currently high mortality rates in young people from PO overdoses.

Acknowledgments

Funding was provided by the National Institute on Drug Abuse NIDA DA020210. The first author is supported by a NHMRC Research Fellowship #1013803. The National Drug and Alcohol Research Centre at UNSW is supported by funding from the Australian Government under the Substance Misuse Prevention and Service Improvements Grant Fund.

References

- Amass L, Kamien JB, Mikulich SK. Efficacy of daily and alternate-day dosing regimens with the combination buprenorphine-naloxone tablet. *Drug Alcohol Depend.* 2000; 58(1–2):143–152. [PubMed: 10669065]
- American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4. Washington DC: 2000. text rev
- Brands B, Blake J, Sproule B, Gourlay D, Busto U. Prescription opioid abuse in patients presenting for methadone maintenance treatment. *Drug and Alcohol Dependence.* 2004; 73(2):199–207. [PubMed: 14725960]
- Brewer DD, Catalano RF, Haggerty K, Gainey RR, Fleming CB. A meta-analysis of predictors of continued drug use during and after treatment for opiate addiction. *Addiction.* 1998; 93(1):73–92. [PubMed: 9624713]
- Caplehorn JR, Drummer OH. Fatal methadone toxicity: signs and circumstances, and the role of benzodiazepines. *Australian and New Zealand Journal of Public Health.* 2002; 26(4):358–362. [PubMed: 12233958]
- Childress AR, McLellan AT, O'Brien CP. Abstinent Opiate Abusers Exhibit Conditioned Craving, Conditioned Withdrawal and Reductions in both through Extinction. *British Journal of Addiction.* 1986; 81(5):655–660. [PubMed: 3466632]
- Compton WM, Volkow ND. Major increases in opioid analgesic abuse in the United States: Concerns and strategies. *Drug and Alcohol Dependence.* 2006; 81(2):103–107. [PubMed: 16023304]
- Fischer B, Nakamura N, Rush B, Rehm, Urbanoski K. Changes in and characteristics of admissions to treatment related to problematic prescription opioid use in Ontario, 2004 – 2009. *Drug and Alcohol Dependence.* 2010; 109:257–260. [PubMed: 20197216]
- Fischer B, Patra J, Cruz MF, Gittins J, Rehm J. Comparing heroin users and prescription opioid users in a Canadian multi-site population of illicit opioid users. *Drug and Alcohol Review.* 2008; 27(6): 625–632. [PubMed: 19378446]
- Heinrich CJ, Fournier E. Instruments of Policy and Administration for Improving Substance Abuse Treatment Practice and Program Outcomes. *Journal of Drug Issues.* 2005; 35(3):485–505.
- Ling W, Hillhouse M, Ang A, Jenkins J, Fahey J. Comparison of Behavioral Treatment Conditions in Buprenorphine Maintenance. *Addiction.* 2013; 108:1788–1798. [PubMed: 23734858]
- Ling W, Hillhouse M, Domier C, Doraimani G, Hunter J, Thomas C, Bilangi R. Buprenorphine tapering schedule and illicit opioid use. *Addiction.* 2009; 104(2):256–265. [PubMed: 19149822]
- Ling W, Shoptaw S, Wesson D, Rawson RA, Compton M, Klett CJ. Treatment effectiveness score as an outcome measure in clinical trials. *NIDA Res Monogr.* 1997; 175:208–220. [PubMed: 9467800]

- Ling W, Wesson DR. Clinical efficacy of buprenorphine: comparisons to methadone and placebo. *Drug Alcohol Depend.* 2003; 70(2 Suppl):S49–57. [PubMed: 12738350]
- Ling W, Wesson DR, Charuvastra C, Klett CJ. A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence. *Arch Gen Psychiatry.* 1996; 53(5):401–407. [PubMed: 8624183]
- Lintzeris N, Nielsen S. Benzodiazepines, Methadone and Buprenorphine: Interactions and Clinical Management. *The American Journal on Addictions.* 2010; 19(1):59–72. [PubMed: 20132123]
- Little, RJ.; Ruben, DB. *Statistical Analysis with Missing Data.* 2. New York: 2002.
- Magura S, Rosenblum A. Leaving methadone treatment: lessons learned, lessons forgotten, lessons ignored. *Mt Sinai J Med.* 2001; 68(1):62–74. [PubMed: 11135508]
- Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane database of systematic reviews.* 2004; (3):CD002207. [PubMed: 15266465]
- Maxwell JC. The prescription drug epidemic in the United States: A perfect storm. *Drug and Alcohol Review.* 2011; 30(3):264–270.10.1111/j.1465-3362.2011.00291.x [PubMed: 21545556]
- McLellan AT, Kushner H, Metzger D, Peters R, Smith I, Grissom G, Argeriou M. The Fifth Edition of the Addiction Severity Index. *J Subst Abuse Treat.* 1992; 9(3):199–213. [PubMed: 1334156]
- Moore BA, Fiellin DA, Barry DT, Sullivan LE, Chawarski MC, O'Connor PG, Schottenfeld RS. Primary care office-based buprenorphine treatment: comparison of heroin and prescription opioid dependent patients. *J Gen Intern Med.* 2007; 22(4):527–530. [PubMed: 17372805]
- Nielsen S, Dietze P, Lee N, Dunlop A, Taylor D. Concurrent buprenorphine and benzodiazepines use and self-reported opioid toxicity in opioid substitution treatment. *Addiction.* 2007; 102(4):616–622. [PubMed: 17286641]
- Nielsen S, Hillhouse M, Mooney L, Fahey J, Ling W. Comparing buprenorphine induction experience with heroin and prescription opioid users. *Journal of Substance Abuse Treatment. Journal of Substance Abuse Treatment.* 2012; 43(3):285–290. [PubMed: 22301084]
- Nielsen S, Hillhouse M, Thomas C, Hasson A, Ling W. A comparison of buprenorphine taper outcomes between prescription opioid and heroin users. *Journal of Addiction Medicine.* 2013; 7(1):33–38. [PubMed: 23222095]
- Paulozzi LJ. Prescription drug overdoses: A review. *Journal of Safety Research.* 2012; 43(4):283–289. [PubMed: 23127678]
- Walsh SL, Preston KL, Stitzer ML, Cone EJ, Bigelow GE. Clinical pharmacology of buprenorphine: Ceiling effects at high doses. *Clinical Pharmacology and Therapeutics.* 1994; 55(5):569–580. [PubMed: 8181201]
- Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care.* 1992; 30(6):473–483. [PubMed: 1593914]
- Warner, M.; Chen, LH.; Makuc, DM. O. o. A. a. *Epidemiology.* NCHS Data Brief. Vol. 22. Hyattsville, Maryland: 2009. Increase in fatal poisonings involving opioid analgesics in the United States, 1999–2006; p. 1-8.
- Weiss RD, Potter JS, Fiellin D, Byrne M, Connery HS, Dickinson W, Ling W. A Two-Phase Randomized Controlled Trial of Adjunctive Counseling during Brief and Extended Buprenorphine-Naloxone Treatment for Prescription Opioid Dependence. *Arch Gen Psychiatry.* 2011; 68(12):1238–1246. [PubMed: 22065255]
- Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). *J Psychoactive Drugs.* 2003; 35(2):253–259. [PubMed: 12924748]
- Wu LT, Woody GE, Yang C, Blazer DG. Subtypes of nonmedical opioid users: results from the national epidemiologic survey on alcohol and related conditions. *Drug Alcohol Depend.* 2010; 112(1–2):69–80. [PubMed: 20580168]

Highlights

- We compared buprenorphine pharmacotherapy outcomes for prescription opioid users, heroin users, and those that use a combination of both.
- PO users have favorable treatment outcomes with buprenorphine compared with those who report heroin any use
- The findings of this paper add to the evidence base demonstrating that buprenorphine pharmacotherapy is an effective treatment for PO users; making this treatment more accessible to all PO users appears to be a critical strategy for reducing mortality rates in from PO.

Figure 1.
Sample selection

Table 1

Demographic Characteristics at Screening/Baseline by Opioid Use Group

<u>Characteristic</u>	<u>Opioid Use Group</u>			<u>F/Chi-sq (P-value)</u>
	<u>PO (N = 54)</u>	<u>POH (N = 71)</u>	<u>H (n=54)</u>	
Mean Age in yrs (sd)	35.6 (11.7)	34.2 (12.2)	39.1 (12.4)	2.477 (0.087)
Sex (% Male)	59	78	65	5.082 (0.079)
Race/Ethnicity				13.140 (0.041)
White	76	70	60	
Hispanic	21	10	17	
Black	4	10	17	
Other	0	10	8	
Mean Yrs. Education (sd)	13.4	13.4	12.8	1.419 (0.245)
Marital Status				26.277 (<0.001)
Married/living with partner	33	25	14	
Never Married	35	67	63	
Widowed/Separated/Divorced	32	8	24	
Regular Employment/Student past 30d	48	30	20	9.940 (0.007)
Age of first opioid use (Mean, SD)	20.1 (7.8)	17.8 (6.1)	17.1 (4.3)	2.526 (0.083)
Years of opioid use (Mean, SD)	15.5 (10.9)	16.4 (11.1)	21.2 (13.1)	3.808 (0.024)
Treatment Assignment (%)				3.106 (0.795)
Cognitive Behavioral Therapy (CBT)	24	32	20	
Contingency Management (CM)	28	24	24	
CBT + CM	26	24	27	
Medication Management	22	20	28	

PO = Prescription Opioid Only, POH = Both Prescription Opioid and Heroin, H = Heroin only

Table 2

Outcomes at the end of the Combined Treatment Phase by Opioid Use Group

Outcome	Opioid Use Group			F/Chi-sq (P-value)
	PO (N = 54)	POH (N = 71)	H (n= 54)	
TES*	70%	40%	38%	13.37 (<0.001)
Opioid-negative UDS at end of Combined Treatment Phase (%)	65	31	33	16.75 (<0.001)
Retained through end of Combined Treatment Phase (%)	80	63	57	6.49 (0.039)
Mean Buprenorphine Dose at end of Combined Treatment Phase (mg)	16.8	16.4	16.8	.085 (0.918)

PO = Prescription Opioid Only, POH = Both Prescription Opioid and Heroin, H = Heroin only

* TES = Treatment Effectiveness Score

Table 3

UDS Results at Baseline and End of Combined Treatment Phase by Opioid Use Group

% Positive UDS (Baseline)	Opioid Use Group			F/Chi-sq (P-value)
	PO (N = 54)	POH (N = 69)	H (n= 51)	
Benzodiazepines	32	25	8	9.11 (0.011)
Cocaine	7	23	31	9.62 (0.008)
Amphetamines	11	4	8	2.02 (0.634)
Methamphetamine	4	9	10	1.66 (0.436)
Marijuana	15	36	28	7.06 (0.029)
% Positive UDS (End of Treatment Phase)	(N = 47)	(N = 50)	(n= 38)	
Benzodiazepines	23	20	13	1.60 (0.449)
Cocaine	6	12	29	8.98 (0.011)
Amphetamines	2	2	8	2.61 (0.272)
Methamphetamine	0	8	8	3.94 (0.139)
Marijuana	15	32	29	4.16(0.125)

PO = Prescription Opioid Only, POH = Both Prescription Opioid and Heroin, H = Heroin only