Optimising the benefits of unobserved dose administration for stable opioid maintenance patients: Follow-up of a randomised trial

James R. Bell a,c,* , Anni Ryan a , Carolyn Mutch a , Robert Batey b , Felicity Rea a

a The Langton Centre, 591 South Dowling Street, Surry Hills, NSW 2010, Australia
b Royal Newcastle Hospital, King Street, Newcastle, NSW 2300 Australia
c National Drug and Alcohol Research Centre, University of New South Wales, Sydney, NSW 2031 Australia

Received 22 September 2007; received in revised form 26 February 2008; accepted 26 February 2008
Available online 18 April 2008

Abstract

Background: The registration of combination buprenorphine/naloxone, a formulation designed to reduce risk of diversion, has led some Australian jurisdictional authorities to allow treatment without direct observation of dosing for stable, opioid-dependent patients.

Aim: To compare two approaches (1) initiating treatment with observed dosing, then allowing patients who demonstrate stability to change to unobserved dosing; or (2) initiating patients with unobserved dosing, subsequently requiring those who fail to stabilize to change to observed treatment.

Methods: This study builds on an RCT comparing efficacy of observed and unobserved treatment at 3 months. At the conclusion of the RCT, clinically “stable” subjects were allocated to continue without observed dosing, while those who did not demonstrate stability were allocated to observed dosing. Subjects were followed for a further 3 months. Primary end-point was retention in treatment.

Results: Of 119 subjects randomised, 70 were retained in treatment to 3 months. Forty-five stable subjects were allocated to unobserved dosing, 25 to observation. Unstable subjects allocated to observed treatment were more likely to drop out thereafter (OR 2.14, 95% CI 1.09–4.19). There was a non-significant trend for people initiated with observed dosing to be better retained during the allocation phase; at 6 months, 13 subjects (22%) from the original unobserved group, and 22 (34%) from the observed group, were retained in treatment (χ² = 2.10, 1 df, p = 0.15).

Conclusions: Withdrawal of unobserved doses led to marked attrition from treatment. If access to unobserved dosing is to be restricted to stable patients, it appears preferable to initiate dosing with observation and allow unobserved doses for people who successfully stabilize, than to initiate with unobserved doses and transfer unstable patients to observation.

Crown Copyright © 2008 Published by Elsevier Ireland Ltd. All rights reserved.

Keywords: Buprenorphine; Naloxone; Heroin; Maintenance treatment

1. Introduction

We recently reported that dispensing buprenorphine–naloxone to take without observation is as effective in managing opioid dependence, and cheaper to deliver, than treatment involving direct observation of dosing (Bell et al., 2007). The availability of opioid maintenance without direct observation of dosing offers reduced costs of delivering treatment, both for the health care system and for consumers. It has the potential to make treatment more accessible.

However, there remain concerns about misuse, particularly injection of medication prescribed for oral or parenteral use, and diversion to the black market. While combining naloxone with buprenorphine reduces the risk of intravenous misuse, there is still potential for diversion. In Australia, as in many jurisdictions, current guidelines (Henry-Edwards et al., 2003) recommend restricting unobserved dosing to “stable” patients—those who are not regularly abusing drugs and alcohol, have stable housing and social functioning. There is some observational evidence supporting such guidelines. People continuing to inject drugs frequently, and those without stable housing or employment, are more likely to inject prescribed medications (Guichard et al., 2003; Vidal-Trecan et al., 2003).

If unobserved dosing is restricted to stable patients, it is unclear whether it is preferable to start dosing under observation,
and provide unobserved doses to those who achieve stability, or to start dosing unobserved, and require those who fail to stabilize to attend for observed administration. To investigate this question, we have studied retention of subjects who had participated in a randomised trial comparing the effectiveness of observed and unobserved dosing. On completion of this efficacy study, patients were allocated, in accordance with existing guidelines, to either observed or unobserved administration. We proposed to compare retention over the next 3 months, to determine whether there were any differences in retention between the randomised groups.

2. Methods

Details of the efficacy study have been reported elsewhere (Bell et al., 2007). Both studies were approved by the ethics committee, South Eastern Sydney Area Health Service, and subsequently by ethics committees of other participating centres.

2.1. Clinical procedures

At the completion of the three-month efficacy trial, subjects remaining in treatment underwent a clinical assessment by the prescribing doctor and case manager to assess stability. “Unstable” drug use was defined as use of heroin, amphetamines and or cocaine on >4 occasions per month; a daily average alcohol intake >60 g, or episodic intoxication with benzodiazepines. Unstable accommodation and living arrangements included unsatisfactory storage facilities, or the presence in the home of children < 4 years of age, when child protection concerns suggested high levels of supervision and monitoring were in the child’s interest. Medical or psychiatric instability included any condition (such as depression with suicidal ideation, psychosis, decompensated liver disease) which might make unsupervised medication unsafe. Diversion of medication was taken as indicating instability.

Patients meeting any of these criteria of instability were allocated to observed treatment post-day 91. Subjects needed to remain stable to remain eligible to receive unobserved dosing. Thereafter, subjects continued to have weekly reviews with a case manager, weekly urine toxicology and monthly medical reviews until week 26 of treatment. Clinical staff had access to urine test results. All subjects were repeatedly informed of criteria for eligibility for unobserved dosing, and subjects allocated to observation who achieved stability could make unsupervised medication unsafe. Diversion of medication was taken as indicating instability.

Days in treatment were collected from medication charts. Duration of each “treatment episode” was defined as number of days from first dose to the date of dispensing the final dose.

2.2. Analysis

The primary outcome of the study was retention in treatment, comparing the groups originally randomised to observed or unobserved dosing. Hazard ratios were calculated using SAS software, Version 9.1. Retention in treatment (time remaining in treatment at 6 months) was compared using backwards, stepwise Cox regression. Log minus log plots and time dependent co-variates were performed to test assumptions of the model. No breaches of assumptions of proportional hazards were identified.

For this study the experimental (unobserved dosing) and control (observed dosing) variables were time-dependent, since in some cases they changed at day 91. To analyse these data accurately, a time-dependent covariate was included in the model. This is essentially equivalent to dividing single subjects into two observations (before and after 91 days) in those cases where they changed dose administration from observed to unobserved (or vice versa). Variables included in the model were time-dependent treatment, biological sex and age. Backwards stepwise removal was used to identify statistically significant covariates. SPSS software, Version 14.0 was used to calculate 95% confidence intervals for hazard ratios and to produce a survival graph.

All other statistical analyses were performed using SPSS software, Version 14.0. Subsequent allocation of subjects at 3 months was tabulated and the proportion entering unobserved treatment compared using a Chi square test. The proportions remaining in the two allocated treatments at 6 months were compared using a Chi square test. All statistical tests used two-sided p values, with significance set at p < 0.05.

Secondary outcomes were also investigated. Subjects were interviewed by a researcher at 3 months and at 6 months. Heroin use was measured by asking patients at confidential research interviews to self-report the number of days of heroin use over the previous 4 weeks (28 days). Self-report data were backed up by weekly urine testing. Quality of life was assessed using the WHOQoL BREF (WHOQoL Group, 1998), a self-report inventory that contains 26 items. Four domains of quality of life are assessed: physical, psychological, social and environmental. Psychological symptoms were assessed using the depression, anxiety and stress scales-21 items (DASS21) (Lovibond and Lovibond, 1995). This self-report inventory assesses severity of depression, anxiety and stress experienced over the proceeding week.

Repeated measures ANOVAs were performed to compare scores obtained on each of the subscales of the WHOQoL at 6 months follow-up between the two treatment groups. Repeated measures ANOVAs were also used to compare WHOQoL subscale scores for patients retained in treatment and those who had dropped out of treatment at 6 months follow-up. Scores on the subscales of the DASS were not normally distributed and therefore change scores were calculated (scores at baseline were subtracted from scores at 6 months) and change scores for observed and unobserved treatment groups were then compared using Mann–Whitney U tests. Change scores were also compared for those who were retained in treatment and those who had dropped out of treatment at 6 months follow-up.

![Fig. 1. Three months allocation and follow-up recruitment and flow of subjects.](image-url)
3. Results

The recruitment and flow of subjects through the trial is represented in Fig. 1.

At 3 months, 23 (39%) of the subjects originally randomised to unobserved treatment were still in treatment and eligible for allocation to continuing unobserved treatment; 10 subjects were judged not to be stable, and were transferred to observed administration. Among subjects originally randomised to observed administration, 22 (34%) were allocated to unobserved treatment, while 15 subjects continued in observed treatment. The difference in proportions entering unobserved treatment was not significant ($\chi^2 = 0.80$, df = 1, $p = 0.37$).

Retention curves by randomised group are illustrated in Fig. 2. At 6 months, overall retention was 34 subjects (29%); 13 (22%) from the original unobserved group, and 21 (34%) from the observed group. Median survival for the group randomised to observation was 107 days (95% CI 53–161 days), and for the unobserved group was 95 days (95% CI 86–104 days).

Cox regression was performed to identify predictors of retention. Time-dependent treatment, age and biological sex were included in the model. Neither age ($\chi^2 = 1.02$, df = 1, $p = 0.31$) nor sex ($\chi^2 = 0.66$, df = 1, $p = 0.42$) were found to be statistically associated with retention in treatment. The corresponding hazard ratios for age and sex were 0.98 (95% CI = 0.94, 1.02) and 1.37 (95% CI = 0.64, 2.89), respectively. Survival did not differ significantly between observed and unobserved subjects ($\chi^2 = 2.39$, df = 1, $p = 0.12$), and after adjusting for sex and age, the hazard ratio was 1.71 (95% CI = 0.87, 3.38).

The sharp drop in retention between weeks 13 and week 26 was primarily due to a high rate of dropping out among the subjects allocated to observed treatment—only 7/25 (28%) remained in treatment to 26 weeks, compared to 27/45 (60%) in the unobserved group ($\chi^2 = 6.59$, df = 1, $p = 0.01$). Subjects allocated to observed treatment at 3 months were twice as likely to drop out of treatment by 6 months as those allocated to unobserved treatment (odds ratio 2.14; 95% CI 1.09–4.19).

At 6-month follow-up, reported heroin use did not differ between the randomised groups. However, there were significant differences between subjects retained in treatment and those who had dropped out. Subjects who were in treatment at 6 months were more likely to be abstinent ($\chi^2 = 15.6$, $p < 0.001$) and using heroin on fewer days at 6 months ($Z = 260.0$, $p < 0.001$) as compared to those not in treatment. It was notable that 39% of people who had dropped out of treatment reported abstinence from heroin at 6-month interview.

There were no significant differences between randomised groups in reported symptoms of depression, anxiety and stress. A significant reduction in depression was observed in patients retained in treatment as compared to those who had dropped out by 6-month follow-up ($Z = 507.5$, $p < 0.05$). No significant difference was observed in levels of anxiety or stress for those retained in treatment as compared to those who had left treatment. No significant differences between those in the observed and unobserved treatment groups were observed for scores obtained on the physical, psychological, social and environmental quality of life scales.

4. Discussion

The current study provides an opportunity to assess the impact of allocating people to observed administration based on failure to stabilize. It confirms that consumers preferred unobserved dosing, and there was a high drop-out rate among unstable patients required to attend for observed dosing. What was interesting and unexpected about the results is that there was a greater tendency for people who were initially randomised to unobserved dosing to drop out after allocation based on clinical assessment. The observed difference between the randomised groups – 34% versus 22% retained at 6 months – suggests a clinically important difference in retention, but did not reach statistical significance. There is a possibility of a type 1 error, as the study relied on a sample size calculated to ensure an adequate sample for the efficacy study, and was underpowered to demonstrate a clinically important difference in 6-month retention.

A plausible explanation for the high drop-out rate among unstable patients allocated to observed dosing is that people are more accepting of unobserved dosing as a reward after a period of observation, than of observed dosing as a “punishment” after failing to meet criteria of stability. A similar observation was made many years ago in relation to methadone treatment (Patch et al., 1973). That study took advantage of a policy change in which methadone clinics in Boston were required to stop providing takeaway doses. For 3 months after this policy directive, discharge and readmission rates to methadone clinics increased, consistent with a negative reaction from consumers to withdrawal of takeaways. However, after 3 months, discharge and readmission rates returned to baseline, or slightly less than baseline levels. The authors concluded that while withdrawal of takeaways provoked negative reactions, availability of takeaways did not enhance retention in treatment.

In addition to being underpowered, another limitation of the current study is that it is based on retention in treatment. Currently in Australia, where access to methadone and buprenorphine treatment is quite good, many patients appear to want brief
episodes of treatment as a way of becoming abstinent, rather than maintenance. “Dropping out” of treatment may reflect the subjects’ preference to go drug free, as suggested by the observation that 39% of those who had dropped out reported abstinence at 6-month follow-up.

Treatment efficacy is not the only issue in determining the optimal level of observation of dosing. It remains to be determined to what extent the combination with naloxone will reduce the diversion potential of buprenorphine. While the combination of naloxone with buprenorphine may reduce the diversion potential of the drug, it is plausible that appropriate patient selection, involving restricting access to unobserved dosing to stable patients, will also help reduce diversion. If this policy is to be observed, it appears preferable to initiate treatment with observation and select for unobserved treatment those patients responding well to treatment.

Conflict of interest

Author JB has received funding support from ReckittBenckiser to attend conferences. All other authors declare that they have no conflicts of interest.

Acknowledgements

The study team acknowledges the invaluable contribution of the staff at each site, particularly: Kristy Korompay, Gaye Byron, Tracey Burrell, Tim Hennessy, Kim Lloyd, Maxine Whalen, Maria Walker, Jay Jordens, Paul Harvey Sutton and Robert Conaglen; and Doungkamol Poppy Sindhusake for statistical advice.

Role of funding source: Funding for this study was provided by the Centre for Drugs and Alcohol, NSW Health, and from ReckittBenckiser P/L. Neither funder had any role in study design; in the collection, analysis and interpretation of data; in writing of the report; or in the decision to submit the paper for publication.

Contributors: Author JB designed the study and wrote the protocol. Authors CM, FR and AR undertook the data collection and statistical analysis and author JB wrote the first draft of the manuscript. Author RB supervised local clinical and research staff at one site. All authors have contributed to and have approved the final manuscript.

References


