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Reducing hospital presentations for opioid overdose in patients treated with sustained release naltrexone implants

Gary K. Hulse [a], Robert J. Tait [a,*], Sandra D. Comer [a,b], Maria A. Sullivan [a,b], Ian G. Jacobs [c], Diane Arnold-Reed [a]

[a] *School of Psychiatry & Clinical Neurosciences, University of Western Australia, QE II Medical Centre, Nedlands, WA 6009, Australia*
[b] *Division on Substance Abuse, Department of Psychiatry, Columbia University, New York, NY, 10032, USA*
[c] *Emergency Care Hospitalisation & Outcome Study, Emergency Medicine, University of Western Australia, QE II Medical Centre, Nedlands, WA 6009, Australia*

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Abstract

Background: Non-fatal overdoses represent a significant morbidity for regular heroin users. Naltrexone is an opioid antagonist capable of blocking the effects of heroin, thereby preventing accidental overdose. However, treatment with oral naltrexone is often associated with non-compliance. An alternative is the use of a sustained release preparation of naltrexone. The aim of this study was to assess the change in number of opioid and other drug overdoses in a large cohort of heroin dependent persons ($n = 361$; 218 males) before and after treatment with a sustained release naltrexone implant. A sub-group of this cohort ($n = 146$; 83 males) had previously received treatment with oral naltrexone, which also allowed a comparison of overdoses pre- and post-oral and also post-implant treatments.
Method: We used a pre–post design, with data prospectively collected via the West Australian Health Services Research Linked Database, and the Emergency Department Information System. Participants were treated under the Australian Therapeutic Goods Administration's special access guidelines.
Results: Most (336, 93%) of the cohort was in one or both databases. We identified 21 opioid overdoses involving 20 persons in the 6 months pre-treatment that required emergency department presentation or hospital admission: none were observed in the 6 months post-treatment. This is consistent with the existing pharmacokinetic data on this implant, which indicates maintenance of blood naltrexone levels at or above 2 ng/ml for approximately 6 months. A reduced number of opioid overdoses were also observed 7–12 months post-implant. The study found a significant increase in sedative "overdoses", some of which occurred in the 10 days following implant treatment and were likely associated with opioid withdrawal and/or implant treatment. For those previously treated with oral naltrexone, more opioid overdoses occurred in both the 6-months prior to and after oral compared to the 6-months post-implant treatment.
Conclusions: The findings support the clinical efficacy of this sustained release naltrexone implant in preventing opioid overdose. However, given the high prevalence of poly-substance use among dependent heroin users, programs offering this type of treatment should also focus on preventing, detecting and managing poly-substance use.

Keywords: Opioid dependence; Naltrexone; Sustained release; Record linkage; Overdose; Heroin

1. Introduction

Morbidity and mortality rates for regular intravenous heroin users are approximately 13 times greater than that for the general population, with accidental overdose accounting for between 30 and 45% of all-cause mortality (Hulse et al., 1999). Non-fatal overdoses also result in significant morbidity (Warner-Smith et al., 2002) and cognitive decline (Darke et al., 2000). In a survey of 218 heroin users, 48% had experienced at least one non-fatal overdose in their lifetime (median, two overdoses) and 11% reported having overdosed in the last 6 months (McGregor et al., 1998).

A number of pharmacotherapies are available either as accepted treatments or are currently being tested as long-term therapies for heroin addiction. These include methadone,

* Corresponding author. Tel.: +61 8 9346 2281; fax: +61 8 9346 3828.
E-mail address: rjtait@cyllene.uwa.edu.au (R.J. Tait).

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LAAM (levo-alpha-acetylmethadol), buprenorphine and naltrexone. Debate on the efficacy of heroin (diacetylmorphine) maintenance as a treatment is continuing (Hando et al., 1998). The most widely used form of pharmacotherapy is methadone maintenance treatment (MMT), with buprenorphine becoming an important alternative agonist treatment.

Naltrexone is a long acting opioid antagonist that has been used as a maintenance pharmacotherapy with a recommended daily oral dose of 50 mg in persons who have detoxified completely from heroin (Callaghan et al., 1980; Anton et al., 1981; Chan, 1996; Julius, 1976). Notwithstanding the unequivocal pharmacological efficacy of naltrexone to block the actions of heroin (Tennant et al., 1984; Hamilton et al., 2002; Olmedo et al., 2000; Verebey et al., 1976; Brewer, 2002) clinical trials have shown that, while having some clinical value, oral naltrexone is often associated with non-compliance resulting in many patients withdrawing from treatment (Anton et al., 1981; Bell et al., 1999; Hulse and Basso, 2000).

One alternative to an oral naltrexone formula is the injection or surgical insertion of a sustained release preparation of naltrexone, which removes the onus on patients to use daily medication (Willette, 1982). The concept of a sustained-release preparation of naltrexone is not new. In the USA in the late 1970s–1980s a device suitable for subcutaneous implantation was developed through the National Institute on Drug Abuse (Willette, 1982), but this does not appear to have been deployed widely. More recently, pharmaceutical companies in the USA (e.g. Biotek Incorporated, Woburn, MA and Wedgewood Pharmacy, Sewell, NJ) have developed a number of naltrexone implants. These have been used in America and Europe since 1997, though limited to a small number of clinics. These implants maintain blood levels of naltrexone at therapeutic levels ($\geq$2 ng/ml) for between 3 and 6 weeks (Brewer, 2001; Brewer, 2002; Comer et al., 2002). In Australia, a formulation of sustained release naltrexone, suitable for subcutaneous depot administration has also recently been developed. Data indicates that this implant can maintain blood naltrexone levels above 2 ng/ml for 188 days (Hulse et al., 2004).

Between January 2001 and December 2002, approximately 437 heroin dependent persons received naltrexone implant treatment for heroin dependence in Western Australia. The aim of this study was to assess the change in the type and number of opioid and other drug overdoses before and after treatment in all heroin dependent persons treated with naltrexone implant over this period. In addition, a sub-group had previously received treatment with oral naltrexone, which also allowed a comparison of overdoses pre- and post-oral treatment and also post-implant treatments.

2. Method

2.1. Study procedure

The study used a pre–post design, which looked at hospital admission and emergency department events prior to, and following implant treatment. This was done by utilised the prospectively collected data of the West Australian Health Services Research Linked Database (WA Linked Database) and the Emergency Department Information System (EDIS). The WA Linked Database systematically and prospectively assembles data, including hospital morbidity, mental health and mortality data at the time of the event and covers the entire population of Western Australia from 1980 onwards. The WA Linked Database is a well-established and validated system for linking administrative health information about an individual across time and location in Western Australia (Holman et al., 1999). Of relevance to this study were the hospital admission and mortality data sets. The EDIS system under the auspices of the Emergency Care Hospitalisation and Outcome Study (ECHO) prospectively records at the time of treatment, information on emergency department (ED) presentations. ED events do not qualify as bona fide hospital admissions and are thus not recorded in the WA Linked Database. Although the four teaching hospitals in Perth were using the EDIS system by August 1999, the last of the public outer metropolitan hospitals did not install the system until February 2002. At the current time, records have been linked from the 1st July 2000 onwards which covers the period 6 months prior to and 6 months following treatment for the cohort under investigation. The most recent date in the file was 30th June 2003. The most recent date in the WA Linked Database was 19th August 2003. For the sub-group previously treated with oral naltrexone more than 6 months prior to implant ($n = 146$, 40%), the 6-months before to and after their first oral treatment were examined and compared to the 6-months period after implant.

The study received University human research ethics committee approval plus appropriate institutional approval to access linked data.

2.2. Treatment

For the current cohort, naltrexone implant treatment was performed on a day outpatient basis simultaneously with rapid opioid detoxification (ROD). Implants are inserted subcutaneously in the lower abdomen through a small incision under local anaesthetic and patients monitored for 4–6 h before discharge. This combined opioid withdrawal and implant procedure involved the discharge of patients following heavy sedation including benzodiazepines, and with benzodiazepine scripts to use as necessary to help mitigate subsequent anticipated withdrawal sequelae. Patients were also instructed to attend the local hospital ED if they felt distressed or unwell after rapid opioid detoxification and implant treatment (O'Neil et al., 2002).

2.3. Study cohort

Since their introduction in 2000, the size of implants and the expected release rate (ERR) of naltrexone changed as the most effective pharmacokinetic combination was sought.

However, between January 2001 and December 2002, the standard implant had a naltrexone mass of approximately 3.4 g and an ERR of 0.4%/day. The cohort of people treated during this period provides an opportunity of evaluating the morbidity and mortality associated with this type of implant.

During this period, a total of 437 heroin dependent persons received a standard naltrexone implant. These individuals had not previously received any other form of naltrexone implant. Of this cohort, 384 had their usual place of residence in Western Australia, and were thus appropriate to follow-up via the WA Linked Database. However, five people did not consent to their records being accessed and three of the patients had their implants removed in the first week. Two of these were at 1-day post-implant, and one at day 6. These were removed at the patients' request: two were classified by the clinic as removal for psychological reasons and the third for infection at the wound site. Additionally, 15 cases entered implant treatment straight from prison. Although all met DSM-IV dependence criteria (American Psychiatric Association, 1994) for the previous 12-months they were not physically dependent at the time of treatment. Most medical problems would be treated by the prison medical system, which is not included in either of the study databases: these 15 cases were removed before conducting the final analyses. Thus, 361 (94%) of the 384 possible participants were considered eligible for inclusion.

There was one death in the cohort involving a man aged 54 years who died following head trauma that resulted in a subdural haematoma. His first implant was 22 months prior to his death: a second procedure was conducted 5 months prior to his death. At the time of data extraction, the coroner's report was not available. In addition to the early removal of three implants noted above, a fourth person had an implant removed at 169 days post-implant due to an allergic reaction (itching). Data on both the person who died and the forth implant removal are included in the study data.

Of the baseline cohort ($n = 361$) the majority were male (218, 60%). The age of first heroin use (mean, 20.6; S.D., 6.0) and years of regular heroin use (mean, 5.7; S.D., 5.3) were similar for males and females, but the males were significantly older than the females (mean, 28.5; S.D., 7.2 versus mean, 26.6; S.D., 7.9; t, 2.4 (359); $p = .017$). Nearly half (174, 48%) had previously been inducted onto oral naltrexone maintenance, with 17% of these having entered into oral naltrexone maintenance on at least three occasions.

2.4. Definitions and analysis

Substance related "overdoses" were identified and grouped into the following categories using ICD-10 codes (World Health Organization, 1992). Overdoses were categorized as: "Opioid poisoning" (e.g. heroin, morphine, methadone: codes T40.0-40.4 and T40.6); "Sedative poisoning" (e.g. benzodiazepine: codes T42.4, T42.6-T42.7) and "Other substance poisoning" (e.g. cocaine, marijuana, psycho-stimulants, alcohol and inhalants: T40.5, T40.7-9, T42.3, T43.6, T43.9, T51.0-3, T51.8-9, T52.0-4, T52.8-9 and T53.0-9). For the analysis relating to oral naltrexone, ICD-9-CM codes were inspected to identify opioid, sedative and other substance poisoning for admissions prior to July 1999. The WA Linked Database includes up to 20 diagnostic fields plus external cause fields. Therefore, an admission may involve more than one category of substance.

3. Results

3.1. ED database

Of the 361 people in the study cohort, 257 (71%) were identified in the EDIS data with a total of 996 hospital presentations (mean, 3.9; S.D., 3.6). The minimum potential period of pre-treatment data (from 1st July 2000) was 200 days with a mean of 490 days (S.D., 183). Post-treatment, the minimum potential follow-up (to 30th June 2003) was 208 days with a mean of 603 days (S.D., 183). In the 6 months pre-implant there were 180 ED presentations (mean, 0.7; S.D., 1.2) while in the 6-months post-implant there were 198 presentations (mean, 0.8; S.D., 1.3).

3.2. ED presentations: overdoses

In the 6 months pre- and post-implant there were 40 presentations involving opioids and other substance poisoning ("overdose") involving 39 persons (Table 1). Most notably, there were no opioid "overdoses" in the 6 months post-implant compared with 17 in the same period prior to implant. We noted that beyond 6 months post-implant there were two opioid "overdoses", which occurred at 208 and 253 days post-treatment. In addition, there were seven overdoses involving sedatives (primarily benzodiazepines) prior to treatment compared with five in the first three and five in the second sequential 3 months after treatment. All five sedative overdoses in the first 3 months occurred in the first 10 days, including three on the day of implant treatment.

Table 1
Substance related emergency department "overdose" presentations pre- and post-implant procedure

Type of presentation	6 months pre	0–3 months	4–6 months	7–9 months	10–12 months
Opioid poisoning	17 (17)	0 (0)	0 (0)	2 (2)	0 (0)
Sedative poisoning	7 (7)	5 (5)[a]	5 (5)	2 (2)	2 (2)
Other drug poisoning	3 (3)	2 (2)	1 (1)	0 (0)	0 (0)
Total	27 (26)	7 (7)	5 (5)	6 (6)	2 (2)

Note: Some people had more than one type of event in a given period; thus the persons totals are not necessarily the sum of the respective persons columns. See analysis section for full definitions: in brief, opioid poisoning = e.g. heroin overdose: sedative poisoning = e.g. benzodiazepine overdose: Other drug poisoning = e.g. amphetamine overdose. The table shows the number of events and the number of persons (in parenthesis) involved in those events.

[a] All occurred within the first 10 days of implant treatment.

3.3. Hospital admissions database

Out of the original 361 people in the cohort, 326 (90%) were in the WA Linked Database. Overall, 336 (93%) people were in one or both datasets. Of those in the WA Linked Database, 191 (59%) were men and 135 were women. Most of these people were non-indigenous Australians (316, 97%) and had never been married (239, 73%).

3.4. Hospital admissions: overdose

In the 6 months pre- and 12 months post-implant 29 people had 37 admissions that included a diagnosis of poisoning by opioids, sedatives or other drugs of abuse. Of these, eight admissions included opioid poisoning, with five occurring in the 6-months pre-treatment and with three being more than 6-months post-implant (at 208, 210 and 333 days). Table 2 shows the admissions pre- and post-implant treatment for the three "overdose" categories. In the 6 months pre-implant treatment period there was eight sedative overdoses, compared with eight in the first three and six in the second sequential 3 months after treatment. Six of the eight sedative overdoses in the first 3 months occurred in the first 10 days following implant treatment.

Data from the emergency department and hospital admissions were combined giving a total of 50 persons with 64 "overdoses", with no individual having more than three overdoses. To avoid double counting, where ED presentations resulted in a hospital admission, only the hospital admission was included. The 6-month prevalence of opioid "overdoses" pre-treatment was 5.5% (21 "overdoses" involving 20 people) compared with 0% in the same period post-treatment. Fig. 1 shows the time relative to treatment when the various types of "overdose" occurred. Where more than one category of drug was identified in a single episode, the "overdose" was hierarchically assigned to "opioids", "sedatives," or "other" drug.

In the 6-months pre- to post-implant, the proportion of persons with opioid "overdoses" fell (pre- 20 (5.5%): post- 0 (0%)) whilst sedative "overdoses" increased (pre- 8 (1.9%): post- 16 (4.4%) Fisher's exact $p = .004$ two-tailed). However, nine of these cases had an "overdose" in the first 10 days after treatment. If these cases are excluded then the post-implant trend is neutral or downward. The trend for other "overdoses" showed an increase (pre- 2 (0.6%): post- 5 (1.4%)).

Table 2
Hospital admissions with substance related overdoses pre- and post-implant procedure

Type of presentation	6 months pre	0–3 months	4–6 months	7–9 months	10–12 months
Opioid poisoning	5 (4)	0 (0)	0 (0)	2 (1)	1 (1)
Sedative poisoning	8 (6)	8 (8)[a]	6 (5)	3 (3)	3 (3)
Other drug poisoning	2 (2)	3 (3)	3 (3)	1 (1)	2 (2)
Total	10 (8)	10 (10)	7 (6)	5 (3)	5 (5)

Note: Some people had more than one type of event and an admission may involve more than one substance: thus the total persons and total events are not the sum of their respective columns. See analysis section for full definitions: in brief, opioid poisoning = e.g. heroin overdose: sedative poisoning = e.g. benzodiazepine overdose: Other drug poisoning = e.g. amphetamine overdose. The table shows the number of admissions and the number of persons (in parenthesis) involved in those admissions.

[a] Six occurred within the first 10 days of implant treatment.

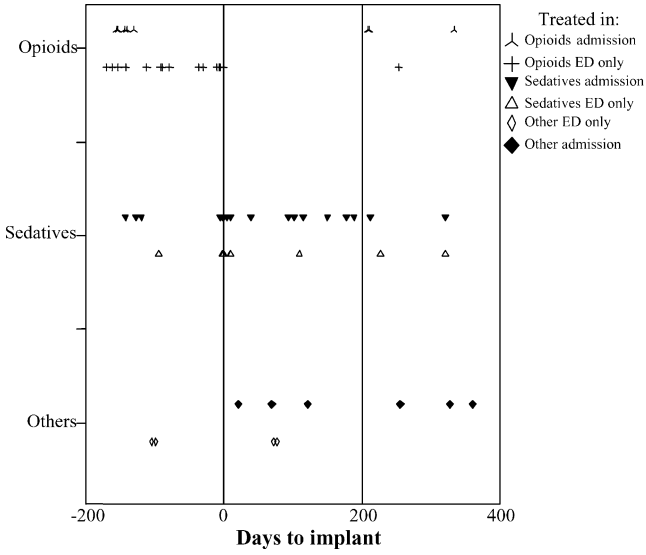

Fig. 1. Combined hospital admission and emergency department presentations involving poisoning ("overdose") in the 6-months pre- to 12-months post-implant treatment.

Fig. 2 shows the temporal relationship between opioid overdoses and naltrexone implants against a chronological reference. The figure also includes the projected 6-months of blockade provided by implants. As can be seen, no

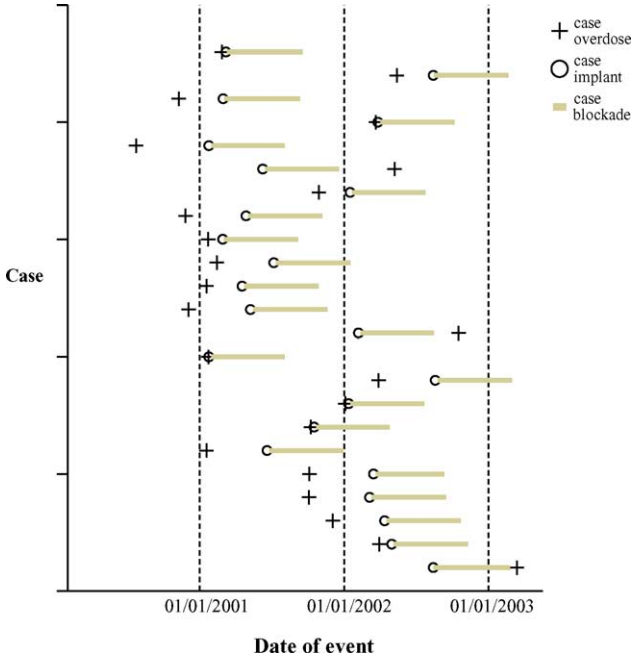

Fig. 2. Opioid overdoses and implants. *Note*: The blockade period shows the 6-months post-implant when naltrexone levels should be above 2 ng/ml.

"overdoses" occurred in the estimated blockade periods: the case at the bottom of the figure had an "overdose" 208 days after receiving an implant. It should also be noted that opioid overdoses occurred across the 2-year period when this cohort entered into treatment and during the subsequent year.

3.5. Oral naltrexone versus implant naltrexone

We identified 174 people who received oral naltrexone treatment before their implant. Of this sub-group, 161 (93%) were in the hospital admission database, of whom 146 (83, 57% male) had the required 6-month interval between oral and implant treatment. The mean interval between oral and implant treatment was 842 days (S.D., 398). In the 6 months pre-oral treatment, there were seven opioid overdoses (prevalence $n = 6$ persons, 4.1%) compared with nine overdoses (prevalence $n = 8$ persons, 5.5%) in the 6-months post-oral treatment and zero in the 6-months post-implant. There were 12, nine and five sedative overdoses and one, zero and two other drug overdoses during the respective periods.

4. Discussion

This study investigated drug overdose requiring hospitalization in a large cohort of heroin dependent persons treated with a long acting sustained release naltrexone implant. The key clinical finding was that while opioid overdose (emergency department presentation or hospital admission) were observed in the 6-month period prior to treatment, none were observed in the 6 months post-treatment. A reduced number of opioid overdoses were observed in the 6–12 months post-implant treatment.

This period of prophylaxis against opioid overdose is, therefore, consistent with the reported pharmacokinetic data on this implant, which indicates that blood naltrexone levels are maintained at or above 2 ng/ml for approximately 6 months (Hulse et al., 2004). Blood naltrexone levels of approximately 1–2 ng/ml have been shown to be 87% (Hamilton et al., 2002; Olmedo et al., 2000) and 100% (Olmedo et al., 2000; Verebey et al., 1976) effective in blocking the effects of 25 mg intravenously administered heroin. Further, 2.8 ng/ml was sufficient to block 500 mg of inhaled pure diamorphine (Brewer, 2002).

Current study data showed a prevalence of 5.5% for opioid overdose amongst this cohort of dependent heroin users. This is less than reported in previous Australian data, which found that 11% of current heroin users reported an accidental overdose within the last 6 months (McGregor et al., 1998). Three factors may help explain this apparent discrepancy. First, current data were "overdoses" of sufficient severity to require hospital treatment, rather than self-reported "overdose" events used in this previous work. Second, the use of hospital data means that an exact cut-off at 6 months can be achieved rather than relying on estimation from memory. Third, emergency services are only called to attend approximately 50% of non-fatal heroin overdoses (Darke et al., 1996) and so these cases may not result in hospital presentation.

It is generally acknowledged that the mortality rate for opioid users is considerably greater that that of the general population with an estimated 8.6 deaths per 1000 person-years (Hulse et al., 1999) compared with 1.0 for Australians aged 25–29 years (Australian Bureau of Statistics, 2002). Only one death occurred in the study cohort, and there was no evidence to suggest that opioids were directly involved with it. We estimate that the cohort had a combined total of about 600 person-years of observation post-implant. Whilst this may be confounded by age and sex, the mortality rate would appear to be lower than would be expected for opioid users in general.

Poly-drug use is an increasing part of heroin use. In 1997–1998, 86% of all opioid-related deaths in Victoria involved other drugs, with the major categories being benzodiazepines (45%) and alcohol (36%) (Gerostamoulos et al., 2001). Data from the early 1990s found a similar level of poly-drug use (79%) in opioid deaths in Sydney, New South Wales, with alcohol the most commonly co-used drug (46%) (Darke and Ross, 1999). Indeed co-use of CNS depressants, particularly alcohol, maybe a critical factor in effectively reducing tolerance to opioids (Darke et al., 1997).

Whilst naltrexone may provide protection against opioid overdoses, one concern is that other drug use may replace opioid use, posing a new risk situation for overdose. We found a significant increase in sedative (mainly benzodiazepines) overdoses in the 6 months pre-implant treatment period compared with the 6 months after treatment. At first appraisal current study data are, therefore, not consistent with the early report of a dramatic reduction in opioid overdoses post-implant treatment in "high-risk patients" without a concurrent increase in non-opioid overdoses (Hulse and Tait, 2003). However, interestingly, of the combined ED and hospital admission sedative overdoses, nine of the 16 occurred in the first 10 days following implant treatment: three within hours of discharge from day-treatment.

Hospital presentations in a sedated state on day 0 are likely due to the high level of sedative use associated with opioid withdrawal or implant treatment on the same day, rather than abuse of non-opioids. Sedative overdoses in the next 10 days are likely associated with attempts by patients to mitigate continuing withdrawal sequelae. This latter scenario is supported by information that patients were commonly discharge with scripts for sedatives to manage their remaining withdrawal sequelae. That these events were not a movement to non-opioid abuse is supported by findings that patients did not go on to experience additional sedative admissions in the remainder of the first 3 months post-implant treatment after day 10.

It should also be noted that following treatment, sedative overdoses was only experienced by approximately 4% of the 361 patients studied, suggesting that it is not a common feature associated with ROD or implant naltrexone maintenance. This is consistent with findings from other studies reporting on patients entering naltrexone maintenance, either

oral (e.g. Kirchmayer et al., 2002; Hulse and Basso, 2000; San et al., 1991) or implant (Comer, 2004). Notwithstanding these issues, programs offering ROD and/or sustained release antagonist treatment for heroin dependence should have an enhanced emphasis on preventing, detecting and managing poly-substance use. This approach would also help to protect the small percentage of people who either continue with or move to other drug use when implants block opioid use.

About 40% of the cohort had previously received oral naltrexone treatment more than 6-months prior to their implants, which allowed a comparison of the 6 months pre-oral, post-oral and post-implant treatment for this sub-group. The level of opioid overdoses were similar pre- and post-oral treatment in contrast to prior research which has shown a decline with oral treatment (Hulse and Tait, 2003). However, post-implant there were no opioid overdoses. This finding reinforces the interpretation that implants improve treatment efficacy by ensuring naltrexone compliance and provide protection against opioid overdose.

One major difficulty associated with research into problem alcohol and other drug use that involves long-term follow-up is attrition of the study population, which in turn results in potential study bias. Given the transient and marginal lifestyles of many dependent heroin users, follow-up by conventional means would probably result in a significantly biased sample with those incurring the greatest morbidity being the least likely to be traced. In Western Australia, "loss to follow-up" can, however, be largely overcome by use of data from the West Australian Health Services Research Linked Database, which contains comprehensive data (ICD-Codes) covering hospital morbidity and mortality for the entire population of Western Australia. One of the key strengths of this study was the comprehensive and systematic nature of the data on hospital admission. The Emergency Department Information System, covering all major metropolitan public hospitals provided a valuable adjunct to this. Yet, it should be noted that the true level of ED treated "overdoses" may be greater than that reported here, as outer metropolitan hospitals have only recently adopted the EDIS and hospitals outside the metropolitan area are not in the system.

There are a number of other limitations that should be considered in the interpretation of the study data. First, the study design (pre–post without a control group) does not unequivocally allow causality to be imputed. Secondly, fluctuations in the availability or purity of heroin in Australia in and around 2000 to 2002 may have impacted on the incidence of opioid overdose amongst heroin users (Longo et al., 2004). However, within the current study, fluctuations in availability or heroin purity are unlikely to account for the observed absence of opioid overdose in the 6 months post-treatment. Study data were collected across a 3-year period with cases exposed to naltrexone implant treatment at different stages. From Fig. 2 it can be seen that after the first implant in the cohort (January 2001), other cohort members continued to have opioid overdoses. That is, regardless of implant treatment timing, accidental opioid overdose declined following treatment, while others in the cohort who were not treated continued to be hospitalized for opioid overdose.

In conclusion, the findings support the clinical efficacy of this long lasting sustained release form of naltrexone as a prophylaxis against opioid overdose. The authors argue that assuming that hospitalization for accidental overdose is a marker for the relative risk of fatal overdose, implant treatment may provide an important prophylaxis against mortality associated with accidental opiate overdose in dependent heroin users.

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