Serious adverse events in the Australian National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD)

E. Digiusto\(^1,3\), A. Shakeshaft\(^1\), A. Ritter\(^2\), S. O’Brien\(^1\), R. P. Mattick\(^1\) and the NEPOD Research Group*

National Drug and Alcohol Research Centre, University of New South Wales, Sydney; \(^1\) Turning Point Alcohol and Drug Centre Inc., Fitzroy, Melbourne, Australia; \(^2\) National Centre in HIV Social Research, UNSW, Sydney, Australia

ABSTRACT

Aims The study estimated serious adverse event (SAE) rates among entrants to pharmacotherapies for opioid dependence, during treatment and after leaving treatment.

Design A longitudinal study based on data from 12 trials included in the Australian National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD).

Participants and settings A total of 1244 heroin users and methadone patients treated in hospital, community and GP settings.

Intervention Six trials included detoxification: all included treatment with methadone, buprenorphine, levo-alpha-acetyl-methadol (LAAM) or naltrexone.

Findings During 394 person-years of observation, 79 SAEs of 28 types were recorded. Naltrexone participants experienced 39 overdoses per 100 person-years after leaving treatment (44% occurred within 2 weeks after stopping naltrexone). This was eight times the rate recorded among participants who left agonist treatment. Rates of all other SAEs were similar during treatment versus out of treatment, for both naltrexone-treated and agonist-treated participants. Five deaths occurred, all among participants who had left treatment, at a rate of six per 100 person-years. Total SAE rates during naltrexone and agonist treatments were similar (20, 14 per 100 person-years, respectively). Total SAE and death rates observed among participants who had left treatment were three and 19 times the corresponding rates during treatment.

Conclusions Individuals who leave pharmacotherapies for opioid dependence experience higher overdose and death rates compared with those in treatment. This may be due partly to a participant self-selection effect rather than entirely to pharmacotherapy being protective. Clinicians should alert naltrexone treatment patients in particular about heroin overdose risks. Duty of care may extend beyond cessation of dosing.

KEYWORDS Adverse events, buprenorphine, heroin overdose, methadone, LAAM, naltrexone, NEPOD, opioid dependence.

*Please see Acknowledgements for the list of names for the NEPOD Research Group.
INTRODUCTION

A clinician’s decision to administer a medication is usually based on weighing up its expected benefits against its associated risks. However, reports of pharmacotherapy trials include typically little information regarding adverse events or about the methods used to gather such information (Hayashi & Walker 1996; Ioannidis & Lau 2001). In particular, data regarding the nature and incidence of adverse events that occur among participants in pharmacotherapies for opioid dependence are limited.

The most commonly used pharmacotherapies involve the two full opioid agonists methadone and levo-alpha-acetyl-methadol (LAAM), the partial agonist buprenorphine and the opioid antagonist naltrexone. Foy, Sadler & Taylor (1998) reported that three of 44 participants ceased naltrexone treatment within 2 weeks because of adverse events (seizure, severe headache and depression, depersonalization and depression). Miotto et al. (1997) reported that 13 of 81 participants in naltrexone treatment experienced overdose (four fatal), involving heroin in 11 cases. These events occurred after participants had stopped taking naltrexone, and represented heroin overdose and death rates of 14 and 5, respectively, per 100 person-years of observation.

Reported death rates among participants in opioid agonist and partial agonist maintenance have been lower. Caplehorn et al. (1996) reported that entrants to methadone treatment experienced a death rate of 0.5 per 100 person-years during treatment, compared with 1.6 while out of treatment. This difference was due mainly to a lower incidence of death by overdose or suicide during treatment. Caplehorn et al.’s (1996) meta-analysis found a reduction in death risk to one-quarter while participants were in methadone treatment. Zanis & Woody (1998) reported four deaths among 397 people who remained in methadone treatment for one year (i.e. one death per 100 person-years). In comparison, 8.2% of 110 participants who were discharged from treatment during the year died; six of those nine deaths were from heroin overdose. Ling et al.’s (1996) study involved 225 participants allocated to 8 mg of buprenorphine or 30 mg or 80 mg of methadone daily. Adverse events included 14 hospitalizations and two deaths, with no difference in incidence between treatments. The overall death rate was 0.9 per 100 person-years, with about 50% of the observation time having been during treatment (estimated from retention data). Pani et al. (2000) also found no significant difference in adverse event rates between methadone and buprenorphine treatment; there were no hospitalizations or deaths during 6 months of observation. Ling et al. (1998) reported a study of 736 participants that compared four buprenorphine dosage levels. There were 51 serious medical events, but no deaths, and no evidence that incidence was dose-related. This represented an event rate of about 23 per 100 person-years of observation, with about 75% of observation time having been during treatment (estimated from retention data).

Tennant et al. (1986) followed 959 LAAM patients for up to 3 years and reported three deaths, one permanent coma and one case of neuropathy. Two randomized studies of LAAM versus methadone, with a total of 829 participants, each reported two deaths in the LAAM group (Senay, Dorus & Renault 1977; Ling, Klett & Gillis 1978). Another comparison between LAAM and methadone involving 99 participants reported no drug-related deaths or serious illnesses (Savage et al. 1976).

Clark et al.’s (2003) Cochrane review of 10 comparative studies of LAAM versus methadone with a total of 1441 participants found five deaths reported among patients randomized to LAAM: two through violence, one from heroin overdose during LAAM induction, one through liver failure and one by motor vehicle accident. One death (from brain tumour) occurred in the methadone group, and the difference in mortality rates between LAAM and methadone was non-significant. LAAM has been under increased scrutiny recently following reporting of cases life-threatening cardiac rhythm disorders (Deamer et al. 2001), and the European Medicines Evaluation Agency suspended marketing of LAAM in 2001. These disorders are a serious problem, but occur rarely: no such events were reported among the 1071 LAAM patients included in Clark et al.’s (2003) Cochrane review.

In summary, the above data suggest that:
• participants who enter naltrexone treatment are more likely to experience a heroin overdose or die than those who enter methadone or buprenorphine treatment;
• there is no evidence of significant differences in serious adverse event rates between methadone, LAAM and buprenorphine, or between different doses of buprenorphine; and
• most of the overdoses and deaths associated with pharmacotherapies for opioid dependence actually occur after participants have left treatment.

However, our knowledge about these issues is limited by the absence or brevity of serious adverse event data in most published reports, particularly relating to naltrexone. The present study used a large pooled data set to (a) describe and quantify the serious adverse events (SAEs) that occurred among entrants to a range of pharmacotherapies for opioid dependence; (b) compare SAE rates among entrants to opioid agonist/partial-agonist versus antagonist (naltrexone) pharmacotherapies; and (c) compare SAE rates during treatment with rates observed after participants had exited from treatment.
METHOD

Participants and treatments

The Australian National Evaluation of Pharmacotherapies for Opioid Dependence (NEPOD) project included 13 trials of pharmacotherapies for opioid dependence (DiGuisto et al. 2001). The individual trials are being reported separately (e.g. Bell et al. 1999; Glasgow et al. 2001; lintzeris et al. 2002; McGregor et al. 2002; Ritter 2002; Mattick et al. 2003). The present study included 1244 participants who began some type of pharmacotherapy maintenance treatment in 12 of those trials (the 13th trial was limited to detoxification of methadone patients). Six trials began with a detoxification phase that involved use of either symptomatic medications, buprenorphine or naltrexone/naloxone under anaesthesia or sedation. Two hundred and eighty participants (23%) were already stable in methadone treatment when they entered the trials, whereas the other 964 participants (78%) were regular heroin users assessed as opioid dependent by Diagnostic and Statistical Manual (DSM-IV) criteria. All participants entered a maintenance treatment involving either methadone (n = 403), buprenorphine (n = 402), LAAM (n = 115) or naltrexone (n = 324). The study data set did not include data from any untreated control groups; between one and three active treatments were compared in each trial, and the follow-up and SAE reporting procedures utilized were the same for all groups within each trial.

Definition of a serious adverse event

The study used the Australian Therapeutic Goods Administration’s (TGA) definition of an SAE: any untoward medical occurrence that results in death or persistent or significant disability/incapacity; is life-threatening; requires in-patient hospitalization or prolongation of existing hospitalization; or is a congenital anomaly/birth defect. Consistent with TGA guidelines, we included events which may have required intervention to prevent one of these outcomes (Therapeutic Goods Administration 2000). In some instances where it was difficult to determine whether an event was ‘serious enough’, we chose to be over-inclusive. Most of the in-patient detoxification procedures in the trials did not have a defined standard length of in-patient stay. Consequently, no instances of relatively long initial in-patient stays per se were counted as SAEs, unless a specific SAE was reported during the stay. We also collected data regarding elective admissions for in-patient detoxification (excluding the initial admissions in in-patient detoxification trials). However, as such admissions are not ‘untoward’ events in themselves, they were not counted as SAEs.

Data collection

NEPOD encouraged and supported standardization of data collection methods; however, the trials were managed independently, and their investigators employed a range of specific local methods to collect SAE-related data. In all trials, relevant information was collected during routine contact with treating clinicians and recorded in case-notes. In most trials, participants were also regularly questioned about occurrence of events by trial research staff. NEPOD monitoring staff contacted and visited each trial site on several occasions to encourage trial staff to be proactive in asking participants about SAEs, and to collect data. Finally, trial staff were asked to conduct a systematic review of all records towards the end of the project to ensure that all relevant information had been reported to NEPOD.

Data coding and analysis

To calculate the total observation period for each participant, the last of three possible end-dates was used, with a maximum of 183 days (6 months): the date of treatment termination; the actual last follow-up date (corresponding to nominal 1-, 3- or 6-month follow-up); or the actual date of the last recorded SAE. To enable comparison of event rates during treatment versus while out of treatment, the end of the treatment period for methadone, buprenorphine and LAAM was taken to be the last date on which the medication was administered, including one takeaway dose where applicable. Most naltrexone trials provided naltrexone on a takeaway basis, 7–14 tablets (i.e. 1–2 weeks’ supply) at a time. If the date on which the last naltrexone tablet taken was not known precisely, the midpoint of the takeaway period was used. Some participants may have participated in other treatments after leaving their trial treatments without this being communicated to trial staff or to NEPOD. Thus, nominal out of treatment data may not represent purely participants who were not in treatment at all. As the treatments differed in terms of retention, and the trial designs differed in terms of their follow-up periods, incidence data were standardized in the form of rates per 100 person-years of observation.

Events were grouped into seven mutually exclusive categories for descriptive purposes: heroin overdose (including all those in which heroin was recorded as being involved); general illnesses; accidents/injuries; other drug reactions; events of a psychiatric nature; pregnancy-related events; and admissions for in-patient detoxification (excluding initial admissions in detoxification trials). Our review of the literature provided no reason to expect significant SAE rate differences between methadone, buprenorphine and LAAM. In most
analyses, these three treatments were therefore pooled and labelled as ‘agonist treatments’ and were compared with naltrexone treatment, on the basis of considerations regarding statistical power and Type 1 error control.

The statistical unit of analysis was an event rather than a participant, meaning that more than one event per participant could be counted. Each event incidence rate was calculated by dividing the number of events recorded in a given participant group by the relevant number of person-years of observation, and then standardizing to a rate per 100 person-years. Confidence intervals (95%) were calculated by exact methods, based on the Poisson distribution for incidence rates and on the binomial distribution for incidence density ratios (IDRs) between pairs of rates (Daly & Bourke 2000). This analytical approach allowed for multiple events for any given participant and different follow-up periods for different participants. The IDR analyses focused on two types of ratio: (a) a rate observed among a group of participants after they had exited from treatment (‘out of treatment’) divided by the corresponding rate during treatment; and (b) a rate observed among participants in naltrexone treatment divided by the corresponding rate among participants in agonist treatment. Fisher’s exact two-tailed $P$-values were calculated to test null hypotheses of no difference between each given pair of rates (i.e. IDR = 1). In any instance where an IDR involved an incidence of zero in the denominator, this was replaced with one (according to convention) to avoid infinite IDRs.

**RESULTS**

Participants had a mean age of 30.4 (SD = 7.7) years, they had started using heroin at a mean of 20.4 (SD = 4.9) years of age and 65% were male. Table 1 shows the numbers of participants who entered each treatment, and the number and nature of the SAEs that were recorded among participants during treatment and while out of treatment.

Naltrexone treatment participants were observed for a total of 44.4 person-years during treatment and 62.2 person-years while out of treatment. Participants who entered agonist treatments were observed for a total of 267.6 person-years during treatment (135.6, 87.9, 44.0 person-years for methadone, buprenorphine and LAAM, respectively) and 19.7 person-years while out of treatment (5.7, 12.5, 1.5 person-years, respectively). Thirty-three per cent of naltrexone-treated participants and 88% of agonist-treated participants had no out of treatment observation time, either because they did not leave treatment within the study’s timeframes, or because they could not be followed-up after leaving.

A total of 96 events were recorded, including 32 heroin overdoses (27 naltrexone, five agonist—all buprenorphine), 17 admissions for in-patient detoxification (16 naltrexone, one agonist), 15 general illnesses (four naltrexone, 11 agonist), 12 accident/injuries (three naltrexone, nine agonist), eight adverse drug reactions (four naltrexone, four agonist), eight psychiatric events (one naltrexone, seven agonist), and four pregnancy-related events (one naltrexone, three agonist).

Inferential analyses were restricted to four categories of events: heroin overdose; all other SAEs; deaths; and admissions for in-patient detoxification. Table 2 shows event rates during treatment and during out of treatment observation time for participants who exited treatment within the study’s timeframes. When examining Table 2, it should be noted that a pair of rates may be significantly different even if their confidence intervals overlap (Daly & Bourke 2000).

Five heroin overdoses occurred during buprenorphine treatment (5.7 per 100 person-years), three occurred during naltrexone treatment (6.8 per 100 person-years) and none occurred during either methadone or LAAM treatment. The three that occurred during naltrexone treatment occurred after 31, 33 and 56 days of treatment. The five overdoses during buprenorphine treatment occurred after 2, 28, 35, 72, and 76 days of treatment. The IDRs relating to overdose incidence during buprenorphine and naltrexone treatment, with methadone (the most common treatment) used as the comparator, were both non-significant (buprenorphine versus methadone IDR = 7.7 (95% CI = 0.9–365; $P = 0.08$; naltrexone versus methadone IDR = 1.0 (95% CI = 0.1–52; $P = 1.0$).

The overall heroin overdose rates (per 100 person-years) were 1.9 and 6.8 during agonist and naltrexone treatment, respectively, with rates of 0.0 and 38.6, respectively, while out of treatment. Naltrexone participants were about six times more likely to experience a heroin overdose while out of treatment than during treatment (IDR = 5.7; 95% CI = 1.7–29.6; $P = 0.0012$). Overdose rates were similar during versus out of agonist treatment (IDR = 0.0; 95% CI = 0.0–14.8; $P = 1.0$). In order to compare directly the out of treatment overdose rates in the two participant groups, following convention, the observed count of zero overdoses in the agonist group was replaced by one to avoid an infinite ratio in the IDR analysis. Given this adjustment, naltrexone participants were 7.6 times more likely than agonist participants to experience an overdose after exiting treatment (95% CI = 1.2–312.6; $P = 0.018$).

To examine the heroin overdose phenomenon in the naltrexone group more closely, the number of days until the first overdose for the 16 participants who overdosed after stopping naltrexone use was calculated. Four
participants reported more than one overdose, but only the first overdose for each participant was included in this post hoc descriptive analysis. In order to deal with uncertainty regarding when the last naltrexone tablet was taken, time to overdose was categorized into 2-week blocks (Fig. 1). Seven of the 16 overdoses (44%) occurred in the first 2 weeks after participants stopped using naltrexone, with a lower and fairly uniform overdose rate thereafter.

The overall rates of all other SAEs were 11.2 and 13.5 during agonist and naltrexone treatment, respectively, and were 20.3 and 11.3, respectively, while out of treatment. These rates were not significantly different during treatment versus out of treatment, either for naltrexone participants (IDR = 0.8; 95% CI = 0.2–3.0, \( P = 0.95 \)) or for agonist participants (IDR = 1.8; 95% CI = 0.5–5.1; \( P = 0.40 \)).

Five SAEs were fatal—three heroin overdoses (naltrexone), a motor vehicle accident and a probable suicide (both agonist). These all occurred after participants had exited from treatment, and represented a death rate of 1.3 per 100 person-years based on total study observation time, or 6.1 per 100 person-years if only the time out of treatment is considered. With the observed count of zero

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**Table 1** Event incidence during treatment (in) and after exiting treatment (out).

<table>
<thead>
<tr>
<th>Type of treatment</th>
<th>Methadone</th>
<th>Buprenorphine</th>
<th>LAAM</th>
<th>Naltrexone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>403</td>
<td>402</td>
<td>115</td>
<td>324</td>
</tr>
<tr>
<td>Treatment status</td>
<td>In (out)</td>
<td>In (out)</td>
<td>In (out)</td>
<td>In (out)</td>
</tr>
<tr>
<td>Person-years of observation</td>
<td>135.6 (5.7)</td>
<td>87.9 (12.5)</td>
<td>44.0 (1.5)</td>
<td>44.4 (62.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Methadone</th>
<th>Buprenorphine</th>
<th>LAAM</th>
<th>Naltrexone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heroin overdose</td>
<td>5</td>
<td>3 (24–3F)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission for in-patient detox</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### General illness

- Appendectomy: 1
- Brain haemorrhage, cog. impairment: 1
- Chest pain: 1
- Dehydration—given iv. fluids: 1
- Epileptic seizure: 2
- Exacerb. peptic ulcer, splenomegaly: 1
- Fainted—fractured nose: 1
- Hypoglycaemic collapse: 1
- Liver infection: 1
- Pneumonia: 1
- Pneumonia, presumed encephalitis: 1
- Vomiting blood: (1)

### Accident/injury

- Assault: 2 (1F)
- Motor vehicle accident: 3
- Other incident requiring surgery: 1

### Other drug reaction

- Benzodiazepine overdose: 1
- Clonidine overdose: (1)
- Acute opioid withdrawal: 1
- Severe allergic reaction: 1
- Seizure (possible benzo abuse): 1

### Psychiatric

- Psych. symptoms; possible overdose: 1
- Suicidality: 2
- Suicide attempt: 2
- Probable suicide: (1F)

### Pregnancy-related

- Ectopic pregnancy: 1
- Miscarriage: 1
- Termination of pregnancy: 2

F = fatal.
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deaths during treatment replaced by one, participants were 19 times more likely to die after they exited treatment than during treatment (95% CI = 2.1–900.6; \( P = 0.0019 \)).

Rates of elective admission for in-patient detoxification (subsequent to initial trial detoxification) were 0.4 and 0.0 per 100 person-years during agonist and naltrexone treatment, respectively, with rates of 0.0 and 25.7, respectively, while out of treatment. With the observed count of zero admissions for detoxification during naltrexone treatment was replaced by one, naltrexone participants were 11 times more likely to be admitted for inpatient detoxification while out of treatment than during treatment (IDR = 11.4; 95% CI = 1.8–479.0; \( P = 0.0028 \)). There was no significant difference between the rates during versus while out of agonist treatment (IDR = 0.0; 95% CI = 0.0–529.8; \( P = 1.0 \)).

Pooling the heroin overdoses plus the other SAEs observed in all treatment groups gave overall rates of 14.4 (95% CI = 10.2–18.6) during treatment, and 42.7 (95% CI = 28.6–56.9) while out of treatment. These rates corresponded to one SAE every 6.9 years during treatment, and one SAE every 2.3 years while out of treatment. The associated IDR of 3.0 (95% CI = 1.8–4.7) was significant (\( P < 0.0001 \)). Finally, the overall rate of 20.3 SAEs during naltrexone treatment was not significantly different from the rate of 13.5 during agonist treatment (IDR = 1.5; 95% CI = 0.6–3.2; \( P = 0.36 \)).

**DISCUSSION**

The present study, involving 1244 participants, provides possibly the most comprehensive analysis to date of serious adverse events (SAEs) associated with pharmacotherapies for opioid dependence. In a total of 394 person-years of observation, 79 SAEs were recorded (excluding elective admissions for detoxification), reflecting the high prevalence of polydrug use, psychiatric and physical comorbidity and relatively high-risk life-style among opioid-dependent people.

SAE analyses sometimes use individuals, rather than events, as the unit of analysis. However, in such studies there is usually only one type of adverse event outcome recorded, of a type which does not occur more than once for each individual (e.g. death), such that these two analysis methods give the same results. We recorded 28 SAE types, and the alternative analysis method would have required that we ignore all events of any type that occurred after the first event for each individual. Significance tests based on individuals would have underestimated the higher riskiness, for example, of naltrexone

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**Table 2** Event rates per 100 person-years.

<table>
<thead>
<tr>
<th>Treatment type</th>
<th>All agonists*</th>
<th>Naltrexone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation period</td>
<td>During treatment (267.6 person-years)</td>
<td>Out of treatment (19.7 person-years) (95% CI)</td>
</tr>
<tr>
<td>Event category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heroin overdose</td>
<td>1.9 (0.6–4.4)</td>
<td>0.0 (0.0–18.7)</td>
</tr>
<tr>
<td>All other SAEs</td>
<td>11.2 (7.6–16.0)</td>
<td>20.3 (5.5–52.0)</td>
</tr>
<tr>
<td>Admissions for in-patient detoxification</td>
<td>0.4 (0.0–2.1)</td>
<td>0.0 (0.0–18.7)</td>
</tr>
</tbody>
</table>

*All agonists = methadone, LAAM, buprenorphine.

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**Figure 1** Time until occurrence of first heroin overdose for participants who ceased naltrexone use

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treatment in which some participants experienced multiple overdoses. For most analyses, the three agonists groups were pooled together rather than analysed separately. The wide scatter of SAE types and lack of obvious differences between agonists shown in Table 1 provides post hoc justification for this decision. However, the raw data in Table 1 enables calculation of other rates and IDR by readers who may be interested in doing so.

Heroin overdose

The most common SAE was heroin overdose. Five overdoses occurred among participants in agonist treatment (all during buprenorphine treatment), with similar overall rates during versus while out of agonist treatment (1.9 and 0.0 per 100 person-years, respectively). The remaining 27 overdoses occurred among naltrexone treatment participants, with rates of seven and 39 per 100 person-years during versus while out of naltrexone treatment, respectively. Many patients continue using heroin during pharmacotherapy (Ling et al. 1998; Pani et al. 2000; Tucker & Ritter 2000; Farre et al. 2002). The consequent risk of overdose would depend on many factors, including the size of the regular dose of therapeutic drug, the elapsed time since it was administered, individual differences in metabolism and the size of the heroin dose. Overdose risk may be increased with therapeutic drugs that do not need be dosed daily. It has been suggested that buprenorphine’s ceiling agonist effects may result in some patients not experiencing enough effect to satisfy them (Chadderton 2000), leading possibly to the use of higher-than-usual heroin doses to overcome the blocking effect. Naltrexone is non-addictive, and is usually prescribed on a takeaway basis for periods of a week or more at a time, enabling patients to easily choose to miss doses. Laboratory studies have shown that both naltrexone and buprenorphine suppress subjective responses to agonists for longer than they suppress physiological responses (Navaratnam et al. 1994; Schuh et al. 1999). This effect profile could potentially lead to overdose by patients who may use an unusually high dose of heroin due to absence of their usually experienced subjective feedback. The main mechanism involved in death from opioid agonist overdose is respiratory depression and the resulting hypoxia (White & Irvine 1999). Buprenorphine is regarded as a relatively safe drug, as it exhibits a ceiling effect in terms of agonist properties, including respiratory depression which levels off with increasing dose. This leads to a reduced risk of overdose with buprenorphine itself in comparison with methadone and LAAM (Ling et al. 1998; Chadderton 2000; Pani et al. 2000; Auria-combe et al. 2001). However, administration of buprenorphine could still lead to fatal respiratory depression, especially if co-administered with other sedative drugs (Reynaud et al. 1998; White & Irvine 1999). A large proportion of overdose deaths involving heroin also involve other drugs such as alcohol, benzodiazepines and methadone (Darke et al. 2000; Zador & Sunjic 2000; Jones et al. 2002).

Sixteen participants experienced overdoses after they stopped naltrexone treatment, 44% of which were within 2 weeks after stopping. In comparison, a recently published study of 5200 methadone treatment clients found no increase in overdose mortality soon after clients left treatment (Buster et al. den Brink 2002). The overdose rate of 37 per 100 person-years after leaving naltrexone treatment was slightly higher than other published data on overdose incidence among heroin users that which were equivalent to rates of 14 (Miotto et al. 1997; Warner-Smith, Darke & Day 2002), 22 (McGregor et al. 1998), and 30 per 100 person-years (Bennett & Higgins 1999).

The overdose incidence pattern in the present study presumably reflected the fact that although naltrexone attenuates or blocks the effects of opioid agonists, it does not produce tolerance to them. There is also some evidence that up-regulation of mu-opioid receptors produced by chronic administration of naltrexone may lead to increased potency of opioid agonists following cessation of naltrexone (White & Irvine 1999; Lee & Yoburn 2000; Golovko et al. 2003), although it is unclear whether this occurs to a significant extent in humans. Whatever the mechanisms involved, these data highlight the need for clinicians to alert naltrexone treatment patients in particular about the risk of heroin overdose.

A parallel could be drawn with heroin users who leave residential drug-free treatment or who are released from prison, as both groups usually cease or markedly reduce their heroin use during their residential periods. This would lead to much reduced opioid tolerance (in the absence of opioid agonist treatment while incarcerated). We were unable to locate studies that reported overdose rates following discharge from residential treatment. However, several studies have demonstrated a markedly elevated risk of drug-related death during the first 2 weeks after release from prison (Seaman et al. 1998; Jones et al. 2002; Bird & Hutchinson 2003).

Other serious adverse events

Many other types of SAE were also recorded, including 15 general illnesses, seven injuries, five motor vehicle accidents, four pregnancy-related events involving loss of the fetus, two adverse reactions to prescribed buprenorphine, three overdoses with drugs other than heroin and three other adverse reactions to misused drugs. Eight psychiatric events were recorded, mainly involving suicidality. Other researchers have also reported a significant
incidence of severe depression and suicidality among heroin users (Caplehorn et al. 1996; Miotto et al. 1997; Foy et al. 1998; Ling et al. 1998), indicating a need for careful monitoring and appropriate adjunctive treatment in this population. The rates of all other SAEs were similar during treatment versus out of treatment, for both naltrexone participants and agonist participants (ranging from 11 to 20 per 100 person-years), indicating that the overall incidence of those other events is not affected by the type of treatment entered, and is not reduced by being in treatment. LAAM has recently attracted attention due to its possible role in causing rare, but potentially serious, cardiac rhythm disorders (Deamer et al. 2001). However, no such events were observed in the LAAM sample in the present study.

Deaths

Several studies have found an elevated incidence of death during the first few weeks of methadone treatment (Caplehorn 1998; Zador & Sunjic 2000; Vormfelde & Poser 2001; Buster et al. 2002). However, there were no deaths during any type of treatment in the present study. The five recorded deaths all occurred after participants exited from their trial treatments: two due to heroin overdose (naltrexone), one recorded as a suicide involving fatal levels of morphine and codeine (naltrexone), one recorded as a probable suicide (buprenorphine) and one due to a motor vehicle accident (LAAM). The death rate among participants who had exited from treatment was 19 times the rate during treatment. The rate based on total observation time (1.3 per 100 person-years) was very similar to findings of two other studies of entrants to opioid maintenance treatment, both of which found rates of 1.1 per 100 person-years (Caplehorn et al. 1996; Risser et al. 2001), and another study of entrants to a broader range of drug treatments, which found a rate of 1.2 per 100 person-years (Gossop et al. 2000). Similarly, the death rate of 6.1 per 100 person-years while out of treatment was within the range found in Caplehorn et al.’s (1996) review of studies of heroin addicts who were not in treatment (1.7–8.4). Finally, 60% of the deaths in the present study involved heroin overdose, consistent with two reports that 65–68% of deaths among samples of drug misusers who entered treatment involved drug overdoses (Risser et al. 2001; Gossop et al. 2000).

Admissions for in-patient detoxification

Elective admission for in-patient opioid detoxification was the second most common type of event; it occurred for one agonist participant during treatment, and for 16 naltrexone participants while out of treatment. It is reasonable to assume that most participants who exited any of the pharmacotherapies subsequently resumed or continued regular heroin use. It therefore appears that this agonist-naltrexone difference would have reflected the likelihood that naltrexone treatment participants were more motivated to abstain from opioid use, and thus more likely to re-present for detoxification after they relapsed, and possibly also the longer total post-treatment observation time for naltrexone participants.

Assessing the effect of pharmacotherapy on SAE incidence

The rates of all other SAEs (64% of all SAEs) did not differ significantly during treatment versus out of treatment. This result was unsurprising, as these events generally involved physical illnesses, accidents and psychiatric conditions which are common in this population, and whose incidence is unlikely to be reduced by opioid dependence treatment per se. However, the situation with the other event types was different. Twenty-seven of the 32 overdoses occurred among naltrexone treatment participants, at an out of treatment rate about six times higher than during treatment. The five deaths all occurred while participants were out of treatment, consistent with previous reports (Caplehorn et al. 1996; Zanis & Woody 1998). Finally, nearly all readmissions for in-patient detoxification involved participants who had exited from naltrexone treatment. Obviously, compliance with either agonist or naltrexone treatment reduces risk of overdose pharmacologically, and eliminates any need for heroin detoxification, meaning that being in treatment should indeed be ‘protective’.

In this context, some methodological issues which would also be relevant to other similar studies should be considered. First, accurate estimation of SAE rates depends on the SAEs being notified to researchers, a process that can break down at many points. Consequently, published SAE rates often underestimate ‘true’ rates. Under-recording of SAEs is more likely after patients cease a trialled pharmacotherapy and typically reduce their contact with the treatment research agency. This would mean that out of treatment data probably underestimate true rates more than do during treatment data. In other words, the true differences between the event rates during treatment versus out of treatment were probably larger than are reported herein.

Secondly, the reported higher event rate among naltrexone participants may have been due partly to a greater desire to reduce or abstain from opioid (heroin) use in comparison with agonist participants. Supportive evidence for this idea is the fact that most of the former group had undergone detoxification prior to starting naltrexone treatment. More specifically, abstinence or
CONCLUSIONS

The overall incidence of serious adverse events was similar during naltrexone versus agonist treatments. All deaths and admissions for in-patient detoxification and most overdoses occurred after leaving treatment. Most of these events occurred among naltrexone treatment participants, possibly partly because of differences between the types of patients who chose to enter the two treatment types. Rates of other SAE types were similar during versus after leaving treatment, and were similar for naltrexone versus agonist treatments. Heroin users who enter pharmacotherapy (or drug-free residential treatment or jail) should be educated about the nature of, and ways to minimize, their risk of overdose and death. Furthermore, it is becoming increasingly clear that clinicians’ duty of care may extend beyond cessation of dosing and cessation of drug-free residential supervision.

Finally, the present study represents an attempt to promote more standardized and more detailed reporting of SAEs related to pharmacotherapies and other treatments for illicit drug dependence. Without carefully defined and applied methods for detecting and reporting SAEs, relative risks are difficult to estimate. We recommend that those who design and manage clinical trials give more attention to this topic, and to the issues highlighted in this report.

REFERENCES


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