Introduction

Illicit opioid use causes substantial personal and public health problems in many countries [1–3]. Opioid dependence increases the risk of premature mortality [4] from accidental drug overdose, suicide, trauma and human immunodeficiency virus [4–9]. In Australia, mortality risk among opioid users out of treatment may be eight times higher than among age peers in the general population [10].

Methadone and buprenorphine are listed on the World Health Organization’s Model List of Essential Medicines [11] as opioid substitution therapy (OST) for heroin dependence. Multiple randomised controlled trials have found that methadone treatment decreases illicit opioid use, improves social functioning, decreases offending behaviours and improves health [12–14]. Mortality rates are halved during methadone treatment [15], survival improves with prolonged treatment [16] and overdose risk increases after treatment cessation or dropout [17,18].

The opioid antagonist naltrexone has also been used to treat opioid dependence [19,20]. The oral form is efficacious in blocking the effects of heroin while taken, but it has been shown to have very low rates of retention and compliance, even when combined with contingency management [20,21]. There is also a high risk of overdose on relapse to heroin use after naltrexone cessation [22–24]. In the Australian National Evaluation of Pharmacotherapies for Opioid Dependence, patients receiving oral naltrexone were 7.6 times more likely than those receiving methadone or buprenorphine to experience an overdose event after leaving treatment [22].

There has been limited research into implantable and sustained-release formulations of naltrexone in Norway, Russia, the USA, Australia and other countries. Systematic reviews of this evidence, however, have concluded that the evidence on safety and efficacy of these formulations is limited in quantity and quality [25,26], making it difficult to draw conclusions as to the efficacy and effectiveness of these interventions.

Methadone and buprenorphine are both registered with the Australian Register of Therapeutic Goods for the treatment of opioid dependence. Oral naltrexone was registered for the treatment of opioid dependence in 2000, and naltrexone implants remain unregistered for the treatment of...
opioid dependence in Australia. Despite being unregistered for this indication, prior to 2000, oral naltrexone, and since 2000, naltrexone implants, have been used in the treatment of opioid dependence in Australia. Treatment was permitted under the provisions of the Special Access Scheme (SAS) of the Therapeutic Goods Act (1989) [10,27].

The SAS allows doctors to prescribe currently unregistered medicines to named patients who are severely ill and in whom existing treatments have failed [28,29]. Medications are available to two categories of patients under the SAS. Under Category A, a named patient is prescribed an unapproved or unregistered drug if death is ‘reasonably likely to occur within a matter of months’ or ‘premature death reasonably likely to occur in the absence of early treatment’. A doctor does not seek prior approval from the Therapeutic Goods Administration, but must notify them by letter and name the patient [29]. For Category B patients, a doctor notifies the Therapeutic Goods Administration of their intention to use the medication (including the nature of the product, dose and duration of treatment), as well as details about the patient’s characteristics, the seriousness of their condition, details of past treatment and justification for not using approved treatments. Both uses of the SAS ‘are intended to be temporary measures pending general marketing approval of the product’ (p. 10) [28].

Mortality in patients treated with naltrexone for opioid use under the SAS

In 2012, a report was published on mortality in entrants to oral (n = 1467) and implant naltrexone (n = 1701) and patients who received both forms of naltrexone (n = 688) [10]. Patients were reportedly treated under the SAS. Mortality, four months after entry to oral naltrexone treatment, was 26.3 per 1000 person-years (PY) compared with 7.34 per 1000 PYs among people who received an implant [confidence intervals (CI) not reported]. Over 10 years, mortality rates in people entering oral and implant naltrexone treatment were 8.8 per 1000 PYs (95% CI 7.4–10.2) and 6.6 per 1000 PYs in those receiving an implant (95% CI 5.1–8.1).

The lack of detail on treatment retention in this study limits our capacity to interpret these findings, for multiple reasons that have been detailed elsewhere [30]. Among the major problems were that the mortality rates were not calculated for periods in or out of treatment, and it was not clear whether the follow-up time for oral naltrexone patients was stopped if they entered implant naltrexone (which would depress reported mortality rates in the oral naltrexone group).

Another report of mortality in a smaller cohort from the same clinic did report mortality in and out of treatment for oral naltrexone [31]. We use these data and mortality rates among methadone patients treated in Australia during the same period (1998–2000) to:

- Compare mortality in and out of treatment for oral naltrexone and methadone;
- Estimate the number of deaths that would have occurred had patients treated with oral naltrexone patients been prescribed methadone; and
- Compare the observed number of deaths with the latter to estimate the net impact of the use of oral naltrexone under the SAS on mortality.
Methods

Data sources

Oral naltrexone cohort. Fellows-Smith reported mortality in a cohort of 1097 opioid users who were treated with oral naltrexone at one clinic in Western Australia (WA) between February 1998 and February 2000 [31]. The cohort was treated for ‘problematic opiate use’ defined elsewhere as ‘self and clinically identified problems controlling the patient’s usage of opiates’ [10].

Naltrexone was provided ‘unsupervised’ (p. 444) [31]. There were ‘no exclusion criteria for entry into the programme’ and hence presumably no requirement that patients had failed to respond to approved medications for opioid dependence (i.e. OST) (p. 444) [31].

Methadone cohorts. We used data on mortality in two patient cohorts. One was from WA, as reported in the Fellows-Smith paper [31]. This consisted of 2520 opioid-dependent patients treated across WA by 65 physicians, typically with pharmacy dosing, during the same period as the oral naltrexone clients above. The second, larger methadone cohort (n = 11,174) came from New South Wales (NSW). Unit records from the Pharmaceutical Drugs of Addiction System, the administrative database of the NSW OST Program, were used to establish a retrospective cohort of opioid-dependent persons who started a treatment episode between 1998 and 2000 (to match the time period of the Fellows-Smith study). Pharmaceutical Drugs of Addiction System records every approved authority to dispense methadone or buprenorphine to a person for the treatment of opioid dependence in NSW. Consistent with previous research [1,32], we excluded those persons who registered but who did not commence treatment and those in temporary programs, for example, interstate clients [15,33]. We defined a new treatment episode as one starting seven or more days after a previous episode had finished [18,32,33]. Records were linked to the Australian National Death Index [18].

Data analysis

Crude mortality rates (CMR) per 1000 PYs for methadone and naltrexone cohorts in WA were extracted from the Fellows-Smith paper. These included total CMRs for methadone and naltrexone, as well as CMRs for patients classified as ‘retained’ and ‘separated’ from treatment. CMRs for the NSW cohort were estimated for the total time period, time in treatment and time out of treatment, to parallel the Fellows-Smith analyses. We assumed that our in-treatment CMR was analogous to the ‘retention’ CMR in Fellows-Smith and that the out-of-treatment CMR was analogous to the ‘separated’ CMR in Fellows-Smith.

Previous mortality studies using the NSW methadone data have classified deaths occurring in the six days following a treatment program as in-treatment deaths [18]. In keeping with the Fellows-Smith approach, deaths were allocated to in- and out-of treatment periods exactly as they occurred.

Mortality rates were expressed as deaths per 1000 PYs with 95% CI calculated (assuming a Poisson distribution). Crude rate ratios (RR) were calculated by dividing one mortality rate by another.
To estimate the number of deaths in those receiving oral naltrexone rather than methadone, we (i) applied the CMRs observed in methadone to the PYs of observation for oral naltrexone and (ii) calculated the difference between the number of deaths observed in those treated with oral naltrexone and the number of deaths expected over the same period (both in and out of treatment) if these patients had received methadone. The logic and approach mirror that used in previous estimates of the impact of OST on mortality in Scotland and England [34,35] and NSW [18]. We stress that our assumptions are likely to underestimate excess mortality in oral naltrexone because we assumed equal retention in methadone and naltrexone when in fact patients in methadone have better retention ([33] than those in oral naltrexone [36]).

Results

Table 1 compares mortality data extracted from Fellows-Smith with mortality for clients entering methadone in NSW in the same calendar period, for in-and out-of-treatment periods. The in-treatment CMR for oral naltrexone was not significantly different from that of methadone in either WA (RR 0.8; 95% CI 0.2–3.0) or NSW (RR 1.8; 95% CI 0.3–5.7) although the width of confidence intervals indicates considerable uncertainty around these estimates.

The crude mortality rate post-treatment for oral naltrexone, by contrast, was 4.9 times that for methadone in WA (95% CI 2.8–8.7) and 3.5 times that for methadone in NSW (95% CI 2.3–5.1). The total CMR for oral naltrexone (across in-and out-of-treatment periods for the two-year follow up) was significantly greater than the total CMR for methadone in both WA (RR 3.5; 95% CI 2.2–5.8) and NSW (RR 3.5; 95% CI 2.4–5.0).

The estimated number of additional deaths in patients who received oral naltrexone treatment instead of methadone is shown in Table 2. We estimate that in a cohort of 1097 patients, there would have been between 25 and 29 additional deaths post-treatment in the period 1998–2000. That is, we estimate that 25–29 deaths would not have occurred if these patients had received methadone instead of oral naltrexone.

Discussion

Before being registered for the treatment of opioid dependence, oral naltrexone was prescribed to many patients in WA using the Therapeutic Goods Administration’s SAS. Our estimates, based on recently reported data, indicate that this use of the SAS produced a higher mortality than would have occurred if these patients had been treated with long-registered OST medications. Among a cohort of 1097 people, we estimate that the use of oral naltrexone under the SAS led to an additional 25–29 deaths over a two-year period, that is, these 25–29 deaths would not have occurred if these patients had received methadone.

The excess in deaths was driven by the extremely high overdose mortality after cessation of oral naltrexone: the out-of-treatment mortality rate was almost six times higher than the in-treatment...

mortality rate, in contrast to the less elevated mortality after leaving methadone [15]. It is important to stress that our estimate probably does not represent the total excess number of deaths in patients receiving this treatment overall because it is difficult to ascertain the total number who were treated with oral naltrexone. As of 2009, perhaps as many as 2155 patients had received oral naltrexone in WA [10].

We have focused here upon mortality risk. It is important to acknowledge that other health outcomes could also be considered, including the risk of non-fatal opioid and other drug overdose and the potential health complications arising from such events such as cognitive impairment [37]. There has been limited investigation of those outcomes but one pre-post study of hospital admissions among naltrexone patients in WA found that hospital admissions for opioid overdoses decreased after treatment entry but admissions increased for other drug overdoses, treatment of drug dependence and withdrawal [38].

Our estimates assumed that the baseline mortality risks in patients receiving oral naltrexone and methadone were equivalent. We believe that this underestimated mortality in naltrexone for the following reasons. First, we assumed that retention in oral naltrexone was the same as that in patients in methadone, when there is strong evidence that oral naltrexone has poorer retention than methadone. This means that had patients treated with oral naltrexone entered methadone instead, they would have spent more of the follow-up time in methadone, and hence probably would have had an even lower mortality rate than we estimated.

Second, there is strong evidence that the overdose mortality is higher in patients who are opioid dependent and who have longer histories of dependence [39]. The patients who were given oral naltrexone did not need to meet criteria for opioid dependence [31], unlike patients entering methadone, for whom a history of opioid dependence was required [40]. They were also likely to have shorter histories of opioid dependence than methadone entrants. These differences in patient characteristics mean that the baseline overdose risks in the cohort treated with oral naltrexone was likely to lower than that in the methadone cohort. In order for the estimated number of deaths in the oral naltrexone group to be zero, their baseline mortality rate would need to be three to five times higher than that observed among persons receiving methadone. This is highly implausible given what is known about the increased risk of overdose deaths in older, opioid-dependent persons who predominated in those receiving methadone. These issues could be quickly resolved if the unit record data for those receiving naltrexone were made available for independent evaluation.

Our analyses therefore suggest that use of oral naltrexone under the SAS increased rather than decreased mortality. This undermines the rationale used to treat patients using this unapproved medication. The SAS was intended to provide small numbers of seriously ill patients who had exhausted all treatment options with early access, as a last resort, to unproved but promising new treatments. This rationale was poorly served by the use of oral naltrexone under this scheme. The situation we have described raises concerns about the regular use by medical practitioners of the provisions of the SAS in ways that are arguably contrary to their intended spirit as a method of last resort for small numbers of patients nearing death. Although oral naltrexone is no longer prescribed under the SAS (as it is now registered for such use in Australia), unregistered naltrexone implants are. It is unclear whether the same mortality risks apply, but naltrexone implants have not undergone the rigorous safety and efficacy assessments required of registered therapeutic goods. Previous reviews [41] of the use of the SAS do not appear to have included a significant focus on
naltrexone. The data presented here suggest that there is a need to review the use of the SAS to access unregistered medicines and devices in the treatment of opioid dependence in Australia.

Conclusions

The use of oral naltrexone under the SAS in Australia may have caused 25–29 deaths that would not have occurred if these patients had received approved methadone treatments for opioid dependence. This estimate undermines the justification offered for the use of the SAS in these cases, namely, that oral naltrexone would reduce overdose deaths. It also raises serious doubts about the way in which the SAS has been used, on a large scale and for so long, to provide treatment using unregistered naltrexone implants in the absence of evidence on their superior safety and efficacy.

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Conflict of interest

Louisa Degenhardt has received untied educational grants from Reckitt Benckiser to conduct postmarketing surveillance studies of the introduction of Suboxone tablet and film preparations for the treatment of opioid dependence in Australia. That funder had no knowledge of this paper.

References


