Opioid use, especially injecting heroin use, makes a substantial contribution to premature mortality [1]. In North America, western Europe and Australia, untreated opioid users’ mortality risk can be 1–2% annually, generally more than 10 times higher than the general population [1]. Overdose is a major cause of death prior to long-term cessation of injection/opioid use (contributing to 50–80% of deaths) [2–4]. The risk of overdose is influenced by multiple factors such as polydrug use, but especially by a reduction in ‘tolerance’, occurring typically after a period of voluntary or enforced abstinence [3,5,6].

During specialist drug treatment, including opioid substitution therapy (OST) but also psychosocial interventions and therapeutic communities, mortality rates are generally halved compared to the risk of dying out of treatment [1,7]. Several large-scale cohorts have observed increases in mortality risk in the month immediately following treatment cessation or dropout [7–9]. Elevated risks of death also are seen in the period immediately following prison release [10]. The most likely explanation for the excess mortality risk is the combination of high rates of relapse and lowered opioid tolerance so that, compared to other time-periods, proportionally more opioid users have resumed heroin use but without having maintained or re-established tolerance to the effects of opioids on respiratory depression [3]. Survival generally improves with prolonged exposure to treatment [2,11].

One may expect that mortality in naltrexone treatment—either oral or implant—should resemble that in other drug therapies, i.e. mortality should be reduced while patients remain in treatment (i.e. while sufficient levels of naltrexone are present), as the antagonist blocks the Mu opioid receptors. Randomized controlled trials suggest that, compared to placebo, implants prevent relapse to opioid dependence during the effective life of the implant [12]. There is, however, poor adherence with oral naltrexone, even when it is combined with contingency management [13,14], making relapse to opioid use highly likely and, therefore, presumably increasing risk of mortality.

These expectations are borne out in the study: the crude mortality rates (CMRs) in the first 4 months after oral naltrexone treatment enrolment were higher than those for people who received a naltrexone implant [15]. We (and the authors) do not know when people ceased their naltrexone treatment, although it is likely that many of those who initially began oral naltrexone discontinued its use [14,16], whereas those on implants were still exposed to naltrexone in the first 4 months of follow-up. Thus, the elevated mortality among those entering oral naltrexone (26.3 deaths per 1000 person-years at the first 4 months) reflects the same mortality risks experienced by opioid users who cease treatment and return to opioid use [7–9], an important reminder of the increased mortality following treatments that are followed by high rates of relapse [17].

It would be more appropriate to compare mortality in implantable naltrexone treatment with that in another form of treatment for dependent opioid users, namely OST. In Australia, the crude mortality rates in OST are very similar and perhaps slightly lower (CMR 0.6 deaths per 100 person-years) [8] than those in the naltrexone implant group (0.74 per 100 person-years), and clearly substantially lower than the oral naltrexone mortality rates (26 per 100 person-years), indicating that the mortality risk in oral naltrexone is unacceptably high.

Mortality differences between treatments may also reflect other factors that are not controlled in observational studies of treatment outcome, such as confounding and selection bias. It is unlikely that the characteristics of patients (such as age, gender, drug use patterns) selected into the two treatments were identical, so some of the differences in mortality risk following treatment may be confounded due to differences in patient characteristics exposed either to oral or implant naltrexone. Other studies have shown that it is important to adjust for possible confounders when investigating treatment effects in observational studies, which was not conducted in this study [18]. The balance of the oral/implant entrants to the study also varied by calendar year (with proportionally greater implants in more recent years), and as we know that Australia experienced major changes in overdose mortality risk because of changes in heroin availability [8,19], calendar differences may have had a bearing on the mortality risk after treatment, but were not accounted for in the analyses presented in the paper. Intriguingly, Kelty & Hulse’s Table 1 suggests that women have a proportionally smaller mortality risk following implant than men compared to the mortality risk after oral naltrexone. Unfortunately, we do not know how many women are in the sample, nor what influence these differences by gender may have on the risk of mortality in the first 4 months after treatment.

These potential confounders and selection biases, however, are secondary to the main issue: the treatment
exposures in this study are not comparable. It may not be feasible or practicable to conduct an adequately powered randomized controlled trial of the effect of OST plus/minus implantable naltrexone on mortality risk. Therefore, it is very important that observational studies, such as this one, measure the intervention appropriately (onset, duration and cessation), and measure and take account of patient characteristics and confounders, to enable other meta-analyses that could address the role that naltrexone treatment may play in reducing opioid-related overdose deaths.

Declarations of interest

None.

Keywords Drug treatment, mortality, naltrexone, naltrexone implants, opiates, oral.

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