DRUG & ALCOHOL FINDINGS *Review analysis*

This entry is our analysis of a review or synthesis of research findings considered particularly relevant to improving outcomes from drug or alcohol interventions in the UK. The original review was not published by Findings; click Title to order a copy. Free reprints may be available from the authors – click prepared e-mail. Links to other documents. Hover over for notes. Click to highlight passage referred to. Unfold extra text The Summary conveys the findings and views expressed in the review. Below is a commentary from Drug and Alcohol Findings.

Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies.

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BMJ: 2017, 357(j1550).

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Opioid substitution therapy is a safe and effective approach for suppressing illicit opioid use. Helping to guide optimal provision, this review investigates the relative effects of methadone and buprenorphine on the rate of mortality over time.

SUMMARY Methadone and buprenorphine maintenance are safe and effective opioid substitution therapies – suppressing illicit opioid use and reducing the rate of all-cause and overdose-related deaths. However, there is growing evidence to suggest that mortality risk varies over time and by type of drug. For example, methadone might pose a particular risk of death from overdose during the 'induction phase' (typically the first four weeks) if initial doses are too high or if the patient continues to use illicit opioids. Buprenorphine, on the other hand, is less effective in retaining patients in treatment, a major weakness because mortality increases significantly in the period immediately after treatment stops.

This review sought to provide evidence on the mortality risk of people dependent on opioids at different periods of methadone and buprenorphine treatment, which could guide clinicians and policymakers in the optimal provision of opioid substitution therapies.

In total 19 studies were identified between 1965 and 2010. These followed 18 cohorts (122,885 patients) prescribed methadone and three cohorts (15,831 people) prescribed buprenorphine. Each of the studies were set in high-income countries: 11 in Europe/Israel; four in North America; and four in Australia. More than 70% of subjects were men, and the average age at baseline ranged from 23 to 40.

The average daily dose ranged from 47–116 mg of methadone and 10–12 mg of buprenorphine. Treatment was initiated by addiction medicine specialists in 11 cohorts and general practitioners or mixed staff in eight cohorts on an outpatient (as opposed to inpatient) basis. Patients were followed-up for between 1.3 and 13.9 years for methadone and 1.1 and 4.5 years for buprenorphine, with patients unable to be followed up exceeding 10% in only four cohorts.

Key points
From summary and commentary

Opioid substitution treatment is an effective way of suppressing illicit opioid use and reducing mortality rates. However, there is growing evidence to suggest that the risk of death may vary according to whether methadone or buprenorphine is used, and depending on the point of time in or out of treatment.

Examining reported deaths from patients prescribed opioid substitutes, this study found that mortality risk during the first four weeks of methadone treatment was high, as it was during the four weeks immediately after cessation of both methadone and buprenorphine treatment.

Overall, methadone maintenance was more strongly associated than buprenorphine with risk reduction.

The studies included in the review had reported patient mortality in two ways:
• all-cause mortality (total number of deaths) during follow-up periods in and out of treatment was reported for all but two methadone cohorts;
• overdose mortality (total number of deaths related to drug poisoning) was reported for 11 methadone cohorts and one buprenorphine cohort.

Main findings

The headline finding was the fluctuating level of risk associated with methadone and buprenorphine over time. The first four weeks of treatment and the first four weeks after treatment ended were the highest risk periods within methadone treatment. The pattern this followed was of a swift decline in risk from the first to the fourth week, followed by a stable level of risk, whereas after cessation there was a high but quite stable risk during the first four weeks and then a progressive decline. During the first four weeks after cessation of buprenorphine treatment there was significantly increased mortality compared with the remaining time out of treatment, while during treatment there was no difference between the first four weeks and the

remaining time in treatment.

For methadone, while all-cause mortality rates varied significantly across the 16 cohorts, rates were consistently higher out of treatment than in treatment. The mortality rate in treatment was less than a third of the rate out of treatment, with the greatest difference in deaths from overdose. The mortality rate was higher during the first four weeks of treatment, the equivalent of 11 deaths among 1000 people over a year ('11 deaths per 1000 person-years'), than the remainder of time in treatment, and during the first four weeks after cessation of treatment (32 deaths per 1000 person-years) than in the remainder of time out of treatment (14 deaths per 1000 person-years). After excluding a high-risk cohort of injectors who were receiving antiretroviral medication for HIV, the all-cause mortality rates were 11 deaths per 1000 person-years in the first four weeks and six deaths per 1000 person-years over the remaining time on methadone treatment.

Opioid substitution treatment with buprenorphine was also associated with a reduction in mortality relative to not being in treatment. However, unlike methadone, buprenorphine induction and the rest of treatment had a similar level of risk (four deaths per 1000 person-years), consistent with its safety profile. The risk after cessation was higher during the first four weeks out of treatment (32 deaths per 1000 person-years) than the remainder of time out of treatment (11 deaths per 1000 person-years). While the absolute difference in death rate out versus in treatment was not statistically significant, the ratio of deaths out versus in treatment was statistically significant.

At four and 10 deaths per 1000 person-years in versus out of treatment, the overall rate of mortality for buprenorphine patients was much lower than the equivalent figures of 11 and 36 for methadone patients. However, the *reduction* in deaths associated with being in treatment was greater for methadone, in respect of which there were over three times (3.2) more deaths out versus in treatment, while for buprenorphine the ratio was just over two (2.2).

For overdose deaths in particular, among methadone patients the three and 13 deaths per 1000 person-years in versus out of treatment equated to nearly five times (4.8) more deaths when out of treatment – a greater reduction in deaths associated with being in treatment than for overall deaths. Similar figures were available for just one buprenorphine cohort, among whom there were one and five fatal overdoses per 1000 person-years in versus out of treatment.

Mortality rates across periods in and out of treatment were significantly higher in methadone cohorts that mostly enrolled opioid injectors who were positive for HIV than in studies including both injectors and non-injectors, and marginally higher in studies conducted in Europe and North America than in Australia.

The authors' conclusions

The level of risk associated with methadone and buprenorphine fluctuates over time. For patients receiving methadone, a period of particularly high risk is the induction phase, and for both methadone and buprenorphine patients, there is an elevated risk immediately after leaving treatment – one of the implications of this being that as some patients cycle in and out of opioid substitution treatment they may be exposed to repeated periods of high risk for mortality.

There was greater variability in risk for methadone, consistent with previous findings. The increased risk during the first few weeks of methadone treatment could be explained by an accumulation of methadone that exceeds the opioid tolerance level (the average elimination half-life for methadone is 22 hours), as opioid tolerance does not seem to fully protect against respiratory depression. Psychological factors and co-occurring use of other respiratory-depressant drugs or cocaine could also play a role.

The bulk of evidence in the featured review was drawn from studies in similar settings, somewhat limiting the applicability of the findings outside of these contexts. For example, 96% of deaths and 98% of person-years came from Australian studies. Therefore the conclusions remain tentative until further studies are undertaken to examine this issue in varied treatment settings, ruling out or ruling in differences in mortality reflecting differences in:
• characteristics of patients (eg, age, severity of opioid dependence, injecting drug use, other drug use, and patient preference);
• characteristics of treatment (eg, previous treatment, specialisation of the doctor who controls the treatment, dose, provision characteristics, and retention).

This review aimed to help guide clinicians and policymakers in the optimal provision of opioid substitution therapies. The findings indicated that there are key periods during which efforts should be focused on preventing drug-related deaths, and precautions taken to increase safety, including:
• careful clinical assessment of opioid tolerance before onset of treatment to establish a safe induction dose;
• monitoring during the induction period, especially for methadone, with clinicians mindful that they may need to adjust dosage;
• monitoring mental/physical health problems;
• preventing the use of illicit opioids;
• considering buprenorphine induction followed by transition to methadone;
• educating patients about the risk of overdose risk and the use of take-home naloxone.

FINDINGS **COMMENTARY** Opioid substitution therapies are safe and effective approaches for reducing illicit opioid use and the risk of mortality. However, the protective effect is not consistent.

Among people in methadone treatment, the induction phase is particularly high risk, and among people in both methadone and buprenorphine treatment, the time immediately after leaving treatment carries an elevated risk.

Arguably the key message is: to prevent premature deaths among people who use drugs, the goal should not be to move people through treatment (ie, get them into and then out of opioid substitution treatment); efforts to improve retention are vital as a strategy to reduce mortality.

The review also contributed to the discussion about the relative benefits and drawbacks of methadone and buprenorphine, associated with their different properties:
• Methadone is a 'full opiate agonist', meaning it produces greater opiate-type effects the higher the dose.
• Buprenorphine is only a 'partial opiate agonist', creating a 'ceiling' of opiate-type effects – limiting the respiratory depression typically responsible for overdose deaths and attenuating the effect of 'on top' heroin use.

The findings indicated that the risk associated with methadone was more variable than buprenorphine, but ultimately methadone could be more clearly associated with reduced mortality among people dependent on opioids. The caveat for the latter point was that considerably less data was available on the impact of buprenorphine on overdose-related deaths than for the impact of methadone.

A study of patients in UK primary care found that buprenorphine conferred a lower risk of all-cause and overdose-related mortality than methadone. However, this added protection was undermined by a shorter time in treatment – less than six months versus 12 months, meaning that the lower risk of drug-related deaths in the year after leaving treatment was to a degree counterbalanced by on average six months fewer in treatment. This suggested that across the population buprenorphine was unlikely to give greater overall protection because of the relatively short duration of treatment.

In 2002, giving an overview of clinical trials in the preceding decade that had established buprenorphine's safety and efficacy, Walter Ling wrote for Drug and Alcohol Findings that "once a maintenance dose is reached, buprenorphine and methadone perform comparably. However, with highly dependent patients, getting to this point appears somewhat more difficult with buprenorphine, and more patients drop out during induction." A 2008 analysis of the most clinically relevant studies of buprenorphine versus methadone maintenance treatment of opiate dependence further confirmed that buprenorphine has slightly less 'holding power', but that among patients who are retained, there are equivalent reductions in the illegal use of opiate-type drugs. The findings subsequently informed UK treatment guidelines (published in 2007, and then updated in 2017).

Importantly, and as unpacked in the Effectiveness Bank Drug Treatment Matrix, medications are never all there is to medical care. Even when they *seem* to be all there is, that in itself sends a message to the patient about how they are seen and valued by the service. Founded on a good relationship with the prescriber, effective prescribing requires the collaboration of the patient to stay in or complete treatment and help choose the medication and set an appropriate dose by disclosing their use or non-use of the medication, how they have reacted to it, and their non-prescribed drug use, while appropriate provision of ancillary support depends on a frank admission of needs. In particular, how long patients stay in treatment is related to the quality of their relationship with clinical staff, and retention is the main factor in the effectiveness of 'maintenance' treatments.

There is a wealth of information in the Effectiveness Bank about buprenorphine and methadone, and their relative safety and effectiveness, for which see this tailored search.

Last revised 24 April 2019. First uploaded 12 March 2019

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