The relative risk of fatal poisoning with methadone or buprenorphine

A UK retrospective study found that methadone is associated with a significantly increased risk of fatal overdose compared with buprenorphine. This study looked at the number of deaths caused by methadone or buprenorphine poisoning among people who were prescribed these medicines and also in people who were not prescribed them and had consumed them illegally. However, a number of important limitations to the study prevent firm conclusions being made. Prescribers should continue to follow NICE guidance on the management of opioid dependence and make decisions on a case by case basis when considering whether to use methadone or buprenorphine for opioid substitution treatment. The summary of product characteristics for methadone includes information about the risks of overdose, accumulation and death.

Overview and current advice

Methadone (oral solution and parenteral) and buprenorphine (certain strengths of the sublingual tablet) are licensed for use as opioid substitution therapy in people who are opioid-dependent. Buprenorphine is available as either a single-ingredient tablet or in a combined formulation with naloxone. Compared with buprenorphine (half-life of 2 to 5 hours\(^1\)), methadone has a longer half-life (12 to 18 hours\(^2\)) and so repeated doses of methadone on a daily basis can lead to accumulation and possibly death\(^2\). Both methadone and buprenorphine are controlled drugs. The Misuse of Drugs Act 1971 classifies controlled drugs into 3 classes, A, B, and C. Methadone is listed as a Class A drug and buprenorphine is listed as a Class C drug. Legislation and regulation govern the use of controlled drugs and ensure risk minimisation measures are in place to prevent them being removed for unauthorised use (diversion). Supervised treatment with methadone and buprenorphine reduces the risk associated with adverse effects and prevents diversion of prescribed treatment.

In the UK, the NHS provides a range of treatment services for opioid dependency, including medical, social and psychological. With regard to medical interventions, NICE guidance on the management of opioid dependence recommends methadone and buprenorphine (oral formulations) as options for maintenance therapy for the management of opioid dependence. The decision about which medicine to use should be made on a case by case basis taking into account a number of factors including an estimate of risks and benefits of each treatment. The guidance recommends methadone to be prescribed as first choice if both medicines are equally suitable to prescribe, and for at least the first 3 months, methadone and buprenorphine should be administered under supervision. The NICE guidance on opioid detoxification in over 16s, also recommends methadone or buprenorphine as first-line treatment in opioid detoxification and the factors to take into account when deciding between
these medicines includes the preference of the service user. Further information is provided in the guidance on the use of other medicines for managing detoxification and the dosage and duration of detoxification. See also NICE guidance on drug misuse in over 16s: psychosocial interventions and naltrexone for the management of opioid dependence.

The NICE guidance on the safe use and management of controlled drugs provides recommendations for systems and processes involving controlled drugs, including prescribing, supplying and administering. The guidance recommends prescribers to: take into account risks of prescribing, including dependency, overdose and diversion when making decisions about prescribing controlled drugs; provide advice on safe disposal of unwanted controlled drugs at a community pharmacy; and provide advice and information to people who are prescribed controlled drugs about how to store controlled drugs safely. The NICE pathway on drug misuse brings together all related NICE guidelines and associated products on managing opioid dependence in a set of interactive topic based diagrams.

New evidence

A retrospective study examined the population-wide overdose risk emerging from the prescription of methadone and buprenorphine for opioid substitution treatment in England and Wales. This study looked at the number of deaths caused by methadone or buprenorphine poisoning among people who were prescribed these medicines and also in people who were not prescribed them and had consumed them illegally. Drug-related mortality information was obtained from the Office for National Statistics (ONS) ‘Deaths related to drug poisoning in England and Wales 2012’ data set. Deaths were included when the underlying cause was drug poisoning, and buprenorphine or methadone were mentioned on the death certificate. When both drugs were referenced on a death certificate, the authors recorded the death under each medicine. Prescription data for buprenorphine-naloxone, buprenorphine and methadone were obtained from prescription cost analysis data reports for England and Wales from 2007 to 2012. The number of prescription items for each drug was estimated by dividing the total yearly prescribed quantity of each drug by an average dose, assuming a prescription duration of 14 days. The study excluded prescriptions based on methadone or buprenorphine preparations used to manage licensed indications other than opioid substitution, such as methadone tablets and buprenorphine patches (both licensed for pain only). The authors also included the UK Borders Agency data of Class A and Class C drugs seized while entering the UK between 2006 and 2012 to control for potential confounding influence of illegally imported quantities of methadone and buprenorphine.

During a 6 year period (2007 to 2012), the authors identified a total of 2,366 methadone-related deaths from 17,333,163 prescriptions issued and 57 buprenorphine-related deaths from 2,602,374 prescriptions (including buprenorphine-naloxone). The study found that during 2007 to 2012, the pooled overdose death rate was 13.7 per 100,000 prescriptions of methadone and 2.2 per 100,000 prescriptions of buprenorphine (including buprenorphine-naloxone). The relative risk (RR) of fatal poisoning with methadone was reported to be around six times that of buprenorphine for the whole population of England and Wales (RR, 6.23; 95% confidence interval [CI] 4.79 to 8.10). The authors reported that data from the UK Borders Agency indicated a very low quantity of methadone entering the UK and no buprenorphine was reported to be seized and that this may suggest domestic diversion.

The study summarised in this commentary is retrospective with no patient level data as the data were obtained from prescription analysis reports and a database of registered deaths. Given the type of data used for analysis in the study, it would not be possible to find out if the patient groups prescribed methadone or buprenorphine were comparable as confounding factors such as demographics, history of addiction, comorbidities, or other risk factors have not been considered. The authors acknowledge that the study was limited in that they could not establish if there were differences in severity of dependence between the 2 patient groups. The authors estimated the number of people taking
methadone or buprenorphine for the analysis using mean or average daily dose. The mean dose of buprenorphine was obtained from a survey completed by NHS treatment centres. This approach may over- or underestimate the number of people calculated as doses of methadone or buprenorphine taken in practice vary between people. Although the authors report a very low amount of seized methadone from the data collected from the UK Border Agency and that this may suggest domestic diversion, data for methadone were unavailable for 2010 to 2012 and data for buprenorphine were unavailable for 2008 to 2012. In addition, this attempt to control for potential confounding influence of illegally imported quantities does not account for methadone or buprenorphine sold illegally over the internet or by other undetected means.

There are several limitations with using mortality data from the ONS. Fatal overdose could have been caused by the preparations that were excluded from the prescription selection criteria (such as methadone tablets or buprenorphine patches) as the ONS bulletin does not specify the preparation of the medicine. No data on other drugs mentioned on the death certificate were reported, therefore, the included deaths caused by drug poisoning in the study may not have been caused primarily by methadone or buprenorphine and may have been caused by other substances. This makes it difficult to guarantee that methadone or buprenorphine were responsible for these deaths. Methadone has a longer half-life than buprenorphine and so it is more likely to be detected on post-mortem toxicology, even if it is not the primary cause of death.

**Commentary**

**Commentary provided by Nat Wright, Clinical Research Director Transform Research Alliance, visiting Associate Professor Leeds University Spectrum Community Health CIC**

The key finding of this study was that, compared with methadone substitution for opiate dependence, there was a statistically significant reduced risk of fatal overdose with buprenorphine substitution treatment. The results of this study should be interpreted with caution, since this relationship observed for a group may not necessarily be the same as for individuals.

In the reported study, there is uncertainty around whether or not the treatment services were more likely to allow unsupervised administration (take home) of methadone, which may have increased the likelihood of diversion and subsequent drug related death amongst an opiate naïve population. Alternatively, it is possible that as a partial (rather than full) opiate agonist, buprenorphine does indeed have a better safety profile than the full agonist, methadone. However, the risk of diversion of buprenorphine may be greater than with methadone as sublingual buprenorphine takes longer to dissolve and be absorbed than liquid methadone. NICE guidance on the [management of opioid dependence](https://www.nice.org.uk/guidance/CG107) emphasises the importance of both methadone and buprenorphine treatments for the management of opioid dependence and the need for individualised care plans taking into account risks and benefits of each treatment. Due to the competing risks of increased likelihood of diversion versus possible benefit of reduced fatal overdose, immediate changes in UK clinical practice are unlikely.

This study highlights the need for further research into the relative safety of using methadone and buprenorphine in the wider community for example with individuals who are taking diverted medicines. The study adds to the information on the risks of methadone overdose. Prescribers should continue to follow guidance from the summary of product characteristics, the MHRA and NICE ensuring that the decision to prescribe should be made on a case by case basis taking into account a number of factors including the person's history of opioid dependence, their commitment to a particular long-term management strategy, and an estimate of the risks and benefits of each treatment.
Declaration of interests:
Dr Nat Wright has received honoraria for the Spectrum research team budget for training and medical advice provided to Camarus and Indivior pharmaceutical companies. Dr Nat Wright also receives payment for his role to the Royal College of General Practitioners as lead for the substance misuse course.

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References
1. Ranbaxy (UK) Limited (2016) Buprenorphine 2 mg sublingual tablets summary of product characteristics
2. Auden Mckenzie Ltd (2015) Methadone 1 mg/ml oral solution sugar free summary of product characteristics

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