Chronic pain: unintentional overdose in people receiving opioid analgesics for non-cancer pain

A US observational study found that when used for chronic non-cancer pain, the use of long-acting preparations of opioids was associated with an increased risk of unintentional overdose compared with using short-acting preparations of opioids. The study found the risk of unintentional overdose was greatest during the first 2 weeks of treatment and when higher daily doses of opioids were used. A number of important limitations to the study prevent firm conclusions being made. Prescribers should continue to follow guidance in the Rapid Response Report on Reducing dosing errors with opioid medicines.

Overview and current advice

Opioid medicines are invaluable for the treatment of acute and chronic pain, including cancer and non-cancer pain. However, there are risks if opioids are not prescribed, dispensed or administered appropriately.

With regard to chronic, non-cancer pain, NICE guidance on low back pain (currently being updated, anticipated publication date November 2016) recommends regular paracetamol as the first-line medication option, with non-steroidal anti-inflammatory drugs (NSAIDs) and/or weak opioids (for example codeine or dihydrocodeine) recommended for when paracetamol alone provides insufficient pain relief. Strong opioids (for example buprenorphine, diamorphine, fentanyl and oxycodone) can be considered for short-term use for people in severe pain. The guidance recommends considering referral for specialist assessment for people who may require prolonged use of strong opioids. The risk of opioid dependence and side effects should be considered for both strong and weak opioids. The NICE guidance on osteoarthritis recommends if paracetamol or topical NSAIDs are insufficient for pain relief for people with osteoarthritis, then the addition of opioid analgesics should be considered, but that the risks and benefits of this should be considered, particularly in older people.

New evidence

A US cohort study examined the relationship between the use of prescribed opioids and unintentional overdose among military veterans receiving care within the US Department of Veterans Affairs health care system. Clinical and pharmacy data were extracted from the health care systems database.
The study involved 840,606 veterans (median age 60 years, 94% men) who received a prescription opioid for chronic non-cancer pain between January 2000 and December 2009. Most participants had back or neck pain, osteoarthritis or other arthropathies. Participants were opioid naïve, having not had an opioid prescription in the past 6 months. The study included 801,729 participants who initiated treatment with short-acting opioid analgesics and 18,887 who initiated treatment with long-acting opioid analgesics commonly prescribed in the USA. The included short-acting opioids were codeine, immediate release oxycodone and hydrocodone (not licensed in the UK), all given orally either as single agents or combination products with paracetamol or aspirin. The included long-acting opioids were oral sustained-release morphine, controlled-release oxycodone, methadone hydrochloride, levorphanol tartrate (not licensed in the UK) and fentanyl transdermal patches. Liquid methadone was excluded from the study because it is used to treat opioid addiction, as were opioids combined with other agents in elixirs and opioid injections.

A total of 319 unintentional overdoses were observed, of which 282 occurred in people initiated on short-acting opioids (0.035% of group), and 37 in people started on long-acting opioids (0.196% of group). After adjustment for age, sex opioid dose and all available covariates, the study found the risk of unintentional overdose during the study period was approximately 2-fold higher for people initiated on long-acting opioids compared with short-acting opioids (adjusted hazard ratio [HR] 2.33, 95% confidence interval [CI] 1.26 to 4.32). During the first 2 weeks of treatment, this risk was approximately 5-fold higher (HR 5.25, [95% CI 1.88 to 14.72). There was no statistically significant difference in overdose risk after the first 2 weeks (for days 15 to 60 HR 2.30, 95% CI 0.67 to 7.90, for after 60 days HR 1.50, 95%CI 0.68 to 3.33). People receiving higher opioid doses (more than 50 mg morphine equivalent a day) were at more than twice the risk of overdose compared with those receiving lower doses (1 mg to 20 mg morphine equivalent a day).

There are a number of important limitations with this study. People receiving long-acting opioids received a higher initial mean daily dose compared with the short-acting opioid group (45 mg morphine-equivalent compared with 15 mg), were more likely to have depression (31.5% compared with 21.0%) and were more likely to have drug-related disorders (9.1% compared with 5.0%). The actual number of people prescribed long-acting opioids was relatively low, being approximately 2.3% of the total cohort. Some adjustment for confounding factors was made but because information was extracted from a claims database, the authors had limited ability to adjust for severity of substance use disorder, physical illness and psychiatric illness, all of which may increase risk of overdose. Also, the database only contains information on when a prescription was dispensed meaning it is not known if the person took the medication. It is not known if participants were taking non-prescription medications or illegal drugs.

**Commentary**

*Commentary provided by David Gerrett, Senior Pharmacist Patient Safety, NHS England*

There are many issues with the data from this study and how it relates to UK practice. These data still do not help us accurately predict who is most likely to unintentionally overdose with opioids.

The NPSA analysis of patient safety incidents reported to the National Reporting and Learning System identified the issue of overdose from opioids and issued a Rapid Response Report on Reducing dosing errors with opioid medicines in 2008. This applies to all organisations providing NHS-funded care in England and is still in force at this time.

This report states that, when prescribing, dispensing or administering opioids the healthcare practitioner or their clinical supervisor should:

- Confirm any recent opioid dose, formulation, frequency of administration and any other analgesic medicines prescribed for the patient.
- Ensure where a dose increase is intended, that the calculated dose is safe for the patient.
- Check the usual starting dose, frequency of administration, standard dosing increments, symptoms of overdose, and common side effects of that medicine and formulation.

In essence, there is a requirement on healthcare professionals prescribing, dispensing or administering opioids to be reassured that it is safe to do so. Previous doses of any opioids taken must be taken into account, as well as being aware of potential safety issues in opioid naïve patients.

The previous pattern of administration must be confirmed, including any over-the-counter use of opioids.

Provided these patient safety directives on NHS practice are implemented, the risks of overdose described in this paper in relation to observations from the USA should be minimised.

**Study sponsorship**

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**References**


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