Important New Evidence Service

In Partnership with The Centre for Medicines Optimisation at Keele University

ScriptSwitch™ Rapid Update 2 – December 2017

Gabapentin and opioids: Observational study finds increased risk of opioid-related death when used in combination

A new case-control study from Canada found that people treated with gabapentin and an opioid in combination had a **50%** increased relative risk of opioid-related death compared with people taking opioids alone. People taking higher gabapentin doses (900mg per day or above) appeared to be at the greatest risk.

Prescribers should be aware of recent advice from the MHRA that gabapentin is associated with severe respiratory depression (even without concomitant opioids), and to consider adjusting the dose in those at increased risk of respiratory depression.

Reference: Gomes T, Juurlink DN, Antoniou T et al. (2017) Gabapentin, opioids, and the risk of opioid-related death: A population-based nested case-control study. PLoS Med 14(10): e1002396.

What do we know already?

- Gabapentin and opioids may be prescribed for people with chronic pain, and are often used in combination. Both these medicines can cause respiratory depression. In addition to this, concurrent use of gabapentin and opioids can increase the risk of central nervous system (CNS) depressant effects, which might affect the ability to perform skilled tasks (BNF).
- The NICE guideline 'Neuropathic pain in adults (2013, updated 2017)' makes recommendations on the pharmacological management of neuropathic pain in non-specialist settings.
- The NICE key therapeutic topic 'Medicines optimisation in long-term pain' notes that the use of gabapentin (and pregabalin) can lead to dependence, and these medicines may be misused or diverted.
- In September 2017 the UK government announced that gabapentin and pregabalin are to be re-classified as class C controlled drugs after safety concerns following an increase in deaths linked to the use of these medicines (see BMJ news article for more information).
- In October 2017, the MHRA issued a warning about the risk of severe respiratory depression with gabapentin even without concomitant opioid medicines. People with compromised respiratory function, respiratory or neurological disease, renal impairment, elderly people and those taking other CNS depressants might be at higher risk and dose adjustment may be necessary. People who require concomitant treatment with gabapentin and opioid medicines should be carefully observed for signs of CNS depression, such as somnolence, sedation, and respiratory depression, and the dose of either gabapentin or the opioid should be reduced appropriately.

What does this evidence add?

- A Canadian case-control study that used information from a health database found that people who received opioids and gabapentin in combination were at an increased risk of opioid-related death – approximately 50% higher in relative terms. This risk seemed to increase with doses of gabapentin of 900mg per day or above, and was highest in those taking 2500mg per day or more. The authors of the review suggested that people treated with this combination should be closely monitored and may require dose adjustment.
- It should be noted that this study was based on a population receiving medicines via a public drug programme and many of the patients were in a lower socioeconomic group. The results may not be generalisable to the wider population of people taking opioids. Information on the indication gabapentin was prescribed for was not available to the investigators. As with all observational studies, confounding due to unknown variables may have introduced bias.

Study details

Participants:

- This case control study included adults (aged >15, mean age 48 years, 94% aged <65 years, 57% male) who received at least one opioid prescription under the Ontario Public Drug Programmes between August 1997 and December 2013. Data were collected from an administrative database.
- The Public Drug programme provides medications for people who are aged 65 years and older, unemployed, receiving disability benefits, have high cost drugs (relative to household income), receive home care services, or reside in a long-term care home.
- Cases were defined as people who died from an opioid-related cause during the study period (excluding opioid overdoses thought to be suicide or homicide). The index date was the date of death. Participants were required to have at least one opioid prescription overlapping with their index date.
- People with a previous diagnosis of cancer or evidence of palliative care in the 6 months preceding the index date were excluded.

Intervention and comparison:

- The study included all oral formulations of morphine, codeine, oxycodone, pethidine and hydromorphone, and transdermal fentanyl. Parenteral and intranasal opioids were excluded, along with methadone and rarely used opioids (e.g. pentazocine).

Outcomes and results:

- Nearly 3 million eligible people received an opioid prescription during the study period, from which 1,256 cases were identified and matched to 4,619 controls.
- Overall, 155 cases (12.3%) were prescribed gabapentin in the 120 days before the index date, compared with 313 controls (6.8%). For their primary analysis the investigators found the odds of an opioid-related death was nearly 50% higher for people exposed to both gabapentin and opioids compared to opioids alone (adjusted odds ratio [OR] 1.49, 95% confidence interval [CI] 1.18 to 1.88, p<0.001).
- The investigators found that the risk increased with higher gabapentin doses. People taking moderate (900 to 1,799 mg daily) and high (≥ 1,800mg daily) daily doses had approximately 60% higher risk of opioid-related death compared with opioids alone (adjusted OR 1.56, 95% CI 1.06 to 2.28, p=0.024 for moderate; adjusted OR 1.58, 95% CI 1.09 to 2.27, p=0.015 for high). Low dose gabapentin (<900 mg daily) was not associated with a statistically significant increase in opioid-related mortality (adjusted OR 1.32, 95% 0.89 to 1.96, p=0.174). Risk of opioid-related death was highest for people taking very high doses of gabapentin (≥2,500 mg daily, adjusted OR 1.83, 95% CI 1.04 to 3.22, p=0.036). A degree of caution should be applied when considering this dose-response analysis as the 95% CIs for the different doses overlap considerably.

Level of evidence:
Level 2 (limited quality patient-oriented evidence) according to the SORT criteria.

Study funding:
Ontario Ministry of Health and Long-Term Care.