Prescribing...

Tramadol for Osteoarthritis May 2019

- A large cohort study in UK primary care has reported higher mortality in people with osteoarthritis (OA) who were prescribed tramadol compared with those prescribed a nonsteroidal anti-inflammatory drug (NSAID), or a cyclo-oxygenase 2 (COX-2) inhibitor.
- Differences between the cohorts may explain the increase in mortality with tramadol.
- But this study highlights the need to consider the risks and benefits of opioids, especially in older people.
- Prescribing of tramadol has fallen significantly in the Bailiwick and in the UK since 2014.

Background

OA is associated with joint pain, functional limitation and reduced quality of life. The most commonly affected areas are the knees, hips and small hand joints. Treating OA, particularly in frail older people, is incredibly complex. For drugs there is a constant need to balance the benefits in terms of pain relief with harms of treatments. NICE guidelines on osteoarthritis recommends that all people with OA should receive advice on 'core' treatments: access to information; activity and exercise; and weight-loss (if the person is overweight or obese). It recommends paracetamol and or topical and/or oral NSAIDs with the core treatments.

Pain from OA is hugely distressing for people and tramadol is used when pain is moderate or severe. It is a centrally-acting analgesic with a dual mechanism of action. Tramadol is both a weak opioid agonist and an inhibitor of monoamine neurotransmitter reuptake. Commonly reported adverse effects are dizziness, nausea, headache, drowsiness, vomiting, constipation, dry mouth, fatigue and sweating. Rare side effects include hallucinations, confusion, sleep disturbance, anxiety and nightmares. In 2014, tramadol was reclassified as a schedule 3 controlled drug due to concerns regarding abuse, dependence and an increase in the number of related deaths. Prescribing of tramadol in the Bailiwick has fallen by 35% : from 6,028 items in 2014 to 3,835 in 2018. It has also fallen in England by 20% : from 7.909 million items in 2014 to 6.349 million items in 2018.

Patients

The latest study looked at data from January 2000 to December 2015, with follow-up ending December 2016. It was a retrospective cohort study, using data from a UK database containing the medical records of over 11 million patients from 580 GP practices. It included 88,902 adults with knee, hip or hand OA aged 50 years or older; mean age 70.1 years, 61.2% women, mean OA duration around 6.7 years. The study looked at data from January 2000 to December 2015, with follow-up ending December 2016.

Intervention and comparison:

People who received an initial prescription for tramadol (n=44,451) were split into five groups and matched to people who received an initial prescription of an alternative analgesic, these were:

- naproxen (n=12,397)
- diclofenac (n=6,512)
- celecoxib (n=5,674)
- etoricoxib (n=2,946)

- codeine (n=16,922)

It was specified that people in the groups could not have received either their treatment drug or the comparator during the 12 months before entering the study. For example, in the tramadol and naproxen comparison, participants were required to have been prescribed neither tramadol nor naproxen in the previous year. Participants were matched based on BMI, lifestyle factors, socioeconomic factors, OA duration, comorbidities and previous drug treatments. Mean treatment duration across the six treatments was between 22 and 27 days. The study did not report on the dose of the prescribed drugs.

Outcomes and results

The primary outcome was all-cause mortality one year after initial prescription of tramadol or its comparator. Compared with the NSAIDs and COX-2 inhibitors, tramadol was associated with higher mortality at one year. There was no difference in mortality between tramadol and codeine.

The differences between tramadol and the comparators are summarised below (all deaths are reported as 'deaths per 1,000 person years'):

- Tramadol (23.5 deaths) vs naproxen (13.8 deaths); HR1.71(95% CI 1.41 to 2.07)
- Tramadol (36.2 deaths) *vs.* diclofenac (19.2 deaths); HR 1.88 (95% CI 1.51 to 2.35)
- Tramadol (31.2 deaths) *vs.* celecoxib (18.4 deaths); HR 1.70 (95% CI 1.33 to 2.17)
- Tramadol (25.7 deaths) *vs.* etoricoxib (12.8 deaths); HR 2.04 (95% CI 1.37 to 3.03)

What does this evidence add ?

This cohort study of more than 88,000 people in the UK with OA (mean age 70.1 years) found that tramadol was associated with a higher risk of death over one year of follow-up than naproxen (rate difference [RD] 9.7/1000 person years), diclofenac (RD 17.0/1000 person years), celecoxib (RD 12.8/1000 person years) and etoricoxib (RD 12.8/1000 person years). The strengths of this study were that it was conducted in "real" patients in a "real" UK Primary Care setting. And unlike company-sponsored trials there were no exclusions, the sample sizes were large and no extra support from investigators was involved.

However it had some important limitations:

- Being an observational study there is always the risk of confounders and bias, despite adjustment for multiple factors. There were several key differences between the patients who were prescribed tramadol and those prescribed NSAIDs. People in the tramadol cohort were older, had a higher BMI, a longer duration of OA, a higher prevalence of co-morbidities, received more prescriptions and had more health-care utilisation compared with the NSAID cohorts. Such differences may be responsible for the difference in mortality observed.
- The study did not compare tramadol to paracetamol, the first-line oral analgesic recommended in the NICE guideline and it did not report what treatments had been tried in the past.
- However it does provide us with a very useful reminder of the importance of using tramadol with caution in older people with OA.

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References : EPACT2, Zeng C et al "Association of tramadol with all-cause mortality" JAMA 321(10) 969-982