Medicines Evidence Commentary
commentary on important new evidence from Medicines Awareness Weekly

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Osteoarthritis and low back pain: evidence reviews raise further questions about the efficacy and safety of paracetamol

Two systematic reviews have examined the evidence for the safety and effectiveness of paracetamol. They raise questions about the effectiveness of paracetamol for hip or knee osteoarthritis and in low back pain in the short term. There was some evidence from randomised controlled trials of an increase in abnormal liver function test results with paracetamol and long-term observational studies reported a potential dose-response increase in some adverse events. NICE guidance on osteoarthritis and low back pain recommends non-drug treatments as core treatment for osteoarthritis and NICE plans to review the pharmacological management of osteoarthritis once an MHRA review into the over the counter analgesics is complete.

Overview and current advice

Historically, paracetamol has generally been considered to be safer than other oral analgesics, such as non-steroidal anti-inflammatory drugs (NSAIDs) or opiates. The World Health Organisation (WHO) recommends paracetamol as a first-choice analgesic on its cancer pain ladder for adults. Paracetamol is also recommended as a first-choice analgesic by NICE in several clinical situations, including after hip fracture, for tension-type headache, for low back pain (currently being updated) and for postnatal perineal pain.

The 2014 updated NICE guideline osteoarthritis: care and management in adults recommends non-pharmacological measures for all people with osteoarthritis. These include access to appropriate information; activity and exercise; and interventions to achieve weight loss if the person is overweight or obese. In addition to non-pharmacological measures, the guideline recommends that health professionals should consider offering paracetamol or topical NSAIDs (either singularly or in combination) for pain relief and consider these ahead of oral NSAIDs, cyclo-oxygenase 2 (COX-2) inhibitors or opioids. This update does not make new recommendations on pharmacological management. NICE intends to commission a full review of evidence on the pharmacological management of osteoarthritis to inform a further guideline update. This will start once the MHRA’s review of the safety of over-the-counter analgesics is completed. Until the guideline update is published, the original recommendations (from 2008) remain current guidance. However, the evidence review on the effectiveness of paracetamol that was presented in the consultation version of the
The NICE Pathways: osteoarthritis, hip fracture, headaches, low back pain (early management) and postnatal care bring together all related NICE guidance and associated products on these conditions in a set of interactive topic-based diagrams. NICE has also produced a key therapeutic topic on NSAIDs.

New evidence

Systematic review of randomised controlled trials

A systematic review of 13 randomised controlled trials (RCTs) investigated the efficacy and safety of paracetamol compared with placebo in the management of spinal pain (3 RCTs; n=1825) and osteoarthritis of the hip or knee (10 RCTs; n=3541). Paracetamol was taken orally in all but 1 trial in chronic low back pain, where it was given intravenously. The dose varied between trials, with 10 trials using a total dose of 3900 to 4000 mg per day and 3 trials using 3000 mg per day. Washout periods for other drugs, such as simple analgesics, NSAIDs and corticosteroids, also varied between trials. Studies in people with a serious spinal pathology, mixed populations of people with rheumatoid arthritis and osteoarthritis and of analgesia in the immediate post-operative period were excluded from this systematic review.

Meta-analysis of 7 RCTs (n=3153) that included people with osteoarthritis of the hip or knee, with short-term follow-up (more than 2 weeks but 3 months or less) found that paracetamol had a statistically significant benefit on pain compared with placebo (weighted mean difference [WMD] -3.7 on a 100-point scale, 95% confidence interval [CI], -5.5 to -1.9; high quality evidence assessed by GRADE criteria) but this benefit was small and considered unlikely to be clinically significant. Similarly paracetamol was found to have a statistically significant but small, and likely clinically insignificant, short-term reduction in disability compared with placebo (WMD -2.9, 95% CI -4.9 to -0.9; high quality evidence). Pooled analysis of 5 RCTs for immediate effect (2 weeks or less) of paracetamol in people with osteoarthritis of the hip or knee found a small statistically significant benefit in pain reduction (WMD -3.3, 95% CI -5.8 to -0.8; high quality evidence) but not in disability, compared with placebo.

One RCT (n=1692) considered short-term and 2 RCTs considered immediate follow-up of people with low back pain. Pooled analysis in the short-term study found no statistically significant effect of oral paracetamol compared with placebo on pain intensity, disability or quality of life measured by the 12-item short form health survey. The quality of evidence for all 3 outcomes was graded as high quality. The data for immediate follow-up (2 RCTs) of people with spinal pain showed no benefit for paracetamol on pain or disability compared with placebo. (One of these 2 RCTs has recently been retracted from the journal in which it was published.) No studies in people with spinal pain or osteoarthritis had a follow-up longer than 3 months.

Reporting of secondary outcome safety data differed between trials. Pooled analysis from 9 RCTs (n=4846) found no statistically significant difference between paracetamol and placebo in the number of people reporting adverse events (moderate quality evidence). This was also the case for any serious adverse event (7 RCTs, n=4852; moderate quality evidence) and drop outs from adverse events (7 RCTs, n=3023; high quality evidence). Pooled analysis of 3 trials (n=1237) that evaluated liver function tests (LFTs) in people with osteoarthritis found that people taking paracetamol were nearly 4 times more likely to have abnormal LFT results (WMD 3.8, 95% CI 1.9 to 7.4; high quality evidence).
Systematic review of observational studies

Another systematic review that included 8 observational cohort studies in 665,789 adults also considered the safety of paracetamol, but in a non-specific population. Five studies were in healthy female registered nurses or male physicians, 2 were in people prescribed paracetamol and 1 was in adults with chronic kidney disease (CKD). The authors were unable to conduct a meta-analysis for most outcomes because the studies differed in terms of outcomes reported and definitions of paracetamol dosage. Therefore, apart from for hypertension, the results for each study were presented individually.

This systematic review included 2 studies (n=432,294) that reported on mortality, both in people who had been prescribed paracetamol. One study, which followed up 382,404 people in the UK for up to 20 years, reported a dose-response increase in the relative rate (or risk, RR) of all-cause mortality. For those who took paracetamol repeatedly (more than 1 prescription) the all-cause mortality ranged from a RR of 0.95 (95% CI 0.92 to 0.97) with low usage, to a RR of 1.63 (95% CI 1.58 to 1.68) with the highest usage, compared with people who never took paracetamol. The pooled overall RR of all-cause mortality for people taking paracetamol was 1.28 (95% CI 1.26 to 1.30) compared with non-users. The other study (n=49,890 in Denmark) followed up people aged over 16 years for up to 7 years and found that being prescribed paracetamol almost doubled the risk of mortality compared with never being prescribed paracetamol (standardised mortality ratio 1.9, 95% CI 1.88 to 1.94).

Four studies (n=591,330) with UK and USA populations, reported on cardiovascular (CV) adverse events. Maximum follow-up ranged from 2 to 20 years. All 4 studies reported a dose-response increase in CV adverse events. The largest (n=382,404) and longest study (maximum follow-up 20 years), which considered people prescribed paracetamol in the UK, found that greater use of paracetamol was associated with a higher risk of new cases of myocardial infarction (MI) and stroke with paracetamol. For those who took paracetamol repeatedly (more than 1 prescription) the risk of MI compared with no use ranged from a RR of 1.11 (95% CI 1.02 to 1.19) to a RR of 1.17 (95% CI 1.04 to 1.32) for low to high usage, respectively. The RR of stroke ranged from 1.03 (95% CI 0.97 to 1.10, not statistically significant) to 1.30 (95% CI 1.19 to 1.41) for low to high usage, respectively. Meta-analysis of 2 studies carried out in the USA (n=137,955; maximum follow up 2 years) showed a dose-response increase in new cases of hypertension with paracetamol use compared with no use. The pooled relative risk of hypertension ranged from 1.11 (95% CI 1.00 to 1.22, not statistically significant) with paracetamol use on 1 to 4 days per month to 1.40 (95% CI 1.15 to 1.70) with paracetamol use for 15 to 21 days per month. However, the increase in the pooled risk of hypertension was not statistically significant for paracetamol use for at least 22 days per month (RR 1.52, 95% CI 0.92 to 2.51).

An increase in the relative risk of upper gastrointestinal (GI) adverse events (gastroduodenal ulcers and complications such as upper GI haemorrhages) with increasing paracetamol use was reported in the large UK study compared with no use. For those who took paracetamol repeatedly, upper GI adverse events ranged from a RR of 1.11 (95% CI 1.04 to 1.21) to 1.49 (95% CI 1.34 to 1.66) for low to highest usage, respectively. This study also reported a dose-response increased risk of new cases of acute renal failure ranging from a RR of 1.16 (95% CI 1.04 to 1.29) to 1.34 (95% CI 1.15 to 1.57) for low to highest usage. Two out of a further 3 studies that considered renal adverse events (n=23,768; maximum follow up 11 to 14 weeks in the USA) also found dose-response reductions in estimated glomerular filtration rate. However, a smaller Swedish study in 801 people with chronic kidney disease (CKD; maximum follow up 7 weeks) did not find a dosage-related increase in estimated rates of progression of CKD or in time to renal replacement therapy between those who took paracetamol and those who did not.

The authors of the systematic review of placebo-controlled RCTs in spinal pain and osteoarthritis, with short-term follow up, commented that the quality of evidence was considered to be high quality. The
authors of the systematic review carried out in a non-specific population, but with longer follow-up, commented that all the studies included were considered low quality because they were observational\(^2\).

**Commentary**

**Commentary provided by the Medicines and Prescribing Centre**

The systematic review of RCTs\(^1\) suggests that paracetamol does not have any clinically significant benefits in adults with low back pain or osteoarthritis of the hip or knee in the short-term. This evidence came from placebo-controlled RCTs and so was considered high quality. This review supports an earlier Cochrane Review\(^3\) in people with osteoarthritis that found a statistically significant but clinically insignificant reduction in pain when paracetamol was compared with placebo. The more recent systematic review of RCTs is reassuring in that there was no difference between paracetamol and placebo in the number of people reporting adverse events. However, it is still limited by the small number of RCTs included (only 1 RCT in low-back pain for short-term follow-up) and, in particular, by the lack of long-term data beyond 3 months. Also, no studies were available on people with neck pain. The investigators acknowledge although the effect of paracetamol on hepatic enzymes is well-known, the clinical significance of the increase in LFTs seen in these short-term studies is uncertain.

Although the systematic review of observational studies\(^2\) included a large number of people from European and US populations, some of whom were followed up for up to 20 years (longer than in the systematic review of RCTs\(^1\)), the authors highlight several important limitations. For example, only a small number of studies were suitable for inclusion, with several differences between them, including how the outcomes were reported and the dosages of paracetamol taken. Therefore, pooling of the results was difficult in most cases.

Only observational studies were included in this meta-analysis\(^5\) and, therefore, it is prone to confounding and bias. For example, 4 studies did not adjust for concomitant use of NSAIDs, which are already associated with increased adverse events. There might also have been some confounding by indication; for example, people considered unsuitable for NSAIDs and, therefore, more prone to adverse events, receiving paracetamol as a safer alternative. It is possible that people who take paracetamol regularly already have an increased baseline risk of adverse events than the general population. The UK study (which was the largest study) and 1 other Danish study provided all the mortality data and were conducted in people who were prescribed paracetamol. These people might also be ‘sicker’ than people who self-medicate with paracetamol and so the results from these 2 studies may not be generalisable to the population who buy paracetamol over the counter. Conversely, the results from the other 6 studies may not be generalisable to people prescribed paracetamol. These 6 studies looked at self-reported medication use, which in itself may be subject to error. None of the included studies may reflect the safety of paracetamol in particular groups of people, such as those taking paracetamol for osteoarthritis. The systematic review of RCTs\(^1\) did not find any difference between paracetamol and placebo in the numbers of serious adverse events in people with osteoarthritis or low back pain in the short-term.

One of the most important limitations of both of these systematic reviews\(^1,2\) is that they do not compare the safety of paracetamol treatment with other commonly used analgesics, such as NSAIDs, which already have a well-established association with GI, renal and CV adverse events. The limited effectiveness of paracetamol demonstrated by the systematic review of RCTs\(^1\) highlights the importance of following the NICE guidelines on osteoarthritis and low back pain (being updated) that recommend non-pharmacological measures, such as exercise, as core treatments for all people with these conditions. Until good-quality comparative data are available it seems sensible to continue to follow current NICE guidance. NICE recommends paracetamol as a first-choice analgesic in several
clinical situations (see Overview and current advice for more details). The risks and benefits of each analgesic should be considered on an individualised basis.

**Study sponsorship**

The systematic review of RCTs in osteoarthritis and spinal pain received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. Sponsorship information for the individual studies included in this systematic review was not specified, but the authors commented that 8 RCTs were funded by manufacturers of paracetamol. The systematic review of observational studies was funded by the National Clinical Guidelines Centre, UK. Sponsorship information for the individual studies included in this systematic review was not specified.

**References**


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