Katie McMahon
BMedSci, MBBS(Hons), FRACGP, is Clinical Lecturer, Discipline of General Practice, University of Tasmania.

Mark Nelson
MBBS(Hons), MFM, FRACGP, FAFPHM, PhD, is Chair, Discipline of General Practice, School of Medicine, University of Tasmania, and Senior Fellow, Menzies Research Institute, Tasmania.
mrnelson@utas.edu.au

Graeme Jones
MBBS(Hons), FRACP, MMedSc, MD, FAFPHM, is Head, Musculoskeletal Unit, Menzies Research Institute, Tasmania.

Treating the symptoms of osteoarthritis

Oral treatments

This series of articles facilitated by the Australian Cochrane Musculoskeletal Group aims to place the findings of recent Cochrane musculoskeletal reviews in a context immediately relevant to general practitioners. This article looks at treatment options for osteoarthritis.

In 2004–2005, 15% of Australians reported having arthritis.[1] Osteoarthritis (OA) is by far the most common form, and is a leading cause of pain and disability among people over 65 years of age.[2]

Nonsteroidal anti-inflammatory drugs (NSAIDs), while not first line, have long been a mainstay of OA treatment but may be associated with adverse effects, particularly in the elderly. COX-2 inhibitors (C2I) were developed as it was considered theoretically plausible that they wouldn't cause gastrointestinal side effects such as gastric erosion.[3] This was borne out by multiple large randomised controlled trials (*Table 1*).

Table 2. Summary of Cochrane review on tramadol for osteoarthritis[10]

- The review included 11 RCTs, in which 1019 adults with OA of hip and/or knee received tramadol or tramadol/paracetamol and 920 received placebo or active control. Average length of follow up was 35 days (range 7–91 days)
- Tramadol rated slightly better than placebo for pain control as measured by a pain scale, but the clinical significance of the measured difference is doubtful
- One trial of 20 participants found paracetamol 1500 mg/day was more effective than 150 mg/day of tramadol for pain control and had fewer side effects
- One trial compared tramadol with an NSAID (diclofenac). The two drugs had similar effects on function with roughly half of participants in both groups reporting at least moderate overall improvement. Over the 2 month follow up period there were significantly more minor adverse events with tramadol than with diclofenac
- Compared with placebo, tramadol increased the likelihood of at least moderate overall improvement with a NNTB of 6. However, people taking tramadol were more than twice as likely as those taking placebo to have a minor adverse event such as vomiting, headache or constipation – NNTH is 5

NNTB = number needed to treat to benefit, NNTH = number needed to treat to harm

Table 1. Key trials: ulcer complications with nonselective NSAIDs vs. selective C2Is

Trial	Drugs and doses	Total number of participants	Key results
SUCCESS[8]	Celecoxib 100 mg twice per day, or Celecoxib 200 mg twice per day, or Diclofenac 50 mg twice per day, or Naproxen 500 mg twice per day	13 274	•Odds of ulcer complication >7 times greater in NSAID than celecoxib group •No significant difference if participants also on aspirin •Not powered to detect cardiovascular differences •Celecoxib 100 mg twice per day and 200 mg twice per day equally efficacious for OA
VIGOR[9]	Rofecoxib (Vioxx) 50 mg/day, or Naproxen 500 mg twice per day	8076	•Relative risk of a complicated gastrointestinal event on rofecoxib compared with naproxen is 0.4 •Patients had rheumatoid arthritis

In 2004, the C2I rofecoxib (Vioxx) was withdrawn from the market after it was found that the relative risk of a cardiovascular event compared with placebo after 18 months of therapy was 1.8.[4] Concern was raised about celecoxib's safety, particularly in higher doses.[5] A recent meta-analysis found the risk of a cardiovascular event to be the same with celecoxib as with placebo.[6] Nonetheless, concern about the safety of NSAIDs as a whole persists, as diclofenac and others have been linked to adverse cardiovascular outcomes.[7]

In this setting, the need for a safe, effective oral treatment for OA is pressing. Two possibilities – apart from paracetamol – include tramadol and glucosamine. The results are summarised in *Table 2* and *3* and how these results might affect practice are shown in *Table 4*.

Table 3. Summary of Cochrane review on glucosamine for osteoarthritis[11]

- The review included 2592 adults in 20 RCTs. The mean age of participants was generally 50–70 years. RCT duration was 3 weeks to 3 years
- Participants received glucosamine or placebo/active control. In all but one trial, glucosamine sulfate (as opposed to glucosamine hydrochloride) was used
- The results were mixed
- Glucosamine outperformed NSAIDs ibuprofen and piroxicam for pain in three trials, including one top quality trial that followed 319 participants for 20 weeks
- Overall, glucosamine helped pain more than placebo. However, concealment allocation was adequate in only eight of the 15 relevant trials, and seven out of these 8 trials found no difference between glucosamine and placebo
- It was unclear whether glucosamine improved function more than placebo
- Glucosamine was as safe as placebo
- After the Cochrane review was completed, a large RCT found glucosamine hydrochloride and chondroitin in combination but not individually to be effective for moderate to severe knee pain and to have no effect on mild pain. In half of patients on this combination, significant improvement occurred at 4 weeks. A further 15% of patients had improved significantly at 24 weeks[12]
- A subsequent large RCT found 4–24 weeks of glucosamine sulphate 1500 mg/day was highly effective for relieving pain and improving function in knee OA[13]

Conclusion

Glucosamine seems safe but it is controversial whether it benefits pain or function. Emerging evidence suggests that it may help both alone and when combined with chondroitin in the group that has moderate to severe knee symptoms. The optimum dose seems to be 1500 mg once daily. Tramadol has marginal effects on OA pain and can bring about functional improvement. It has a higher rate of unpleasant side effects in the short term than diclofenac and placebo, but its long term effects (vs. those associated with NSAIDs) are unknown.

Conflict of interest: none declared.

Table 4. Putting evidence into practice

Case study

Mrs Jones, 55 years of age, is a teacher with moderate left knee OA and borderline hypertension. She is increasingly uncomfortable about taking Celebrex. She already takes paracetamol regularly and didn't tolerate diclofenac or ibuprofen. What can you advise her?

You can advise her that while celecoxib in high dose (800 mg/day and 200 mg twice daily, but not 400 mg once daily) does appear to increase the risk of cardiovascular events, 200 mg once daily has not been linked to heart disease.

Her brother has been prescribed tramadol for knee pain. Would it be worth trying that?

You can tell Mrs Jones that tramadol was only very slightly better than a placebo for OA pain, and about the same as diclofenac for its ability to bring about overall improvement. However, in the short term tramadol was much more likely to cause side effects such as vomiting, headache, constipation and dizziness than diclofenac. One in 6 people who take tramadol will get unpleasant minor side effects, and one in 5 will get a sense of at least moderate improvement. There may be specific patients who have trouble with other medication who may benefit from tramadol. She decides not to try tramadol at the moment.

What about the glucosamine she's noticed in the pharmacy?

You can tell her that while the jury is still out overall, a considerable body of evidence shows that glucosamine sulphate 1500 mg/day is more effective for pain control than ibuprofen, and that studies have found glucosamine to benefit function. Also, glucosamine may slow disease progression and the need for knee replacement and is safe (except in patients with shellfish allergy).

You decide to advise her that taking glucosamine at the recommended dose for at least 2 months is worthwhile. She needs to be aware that because glucosamine is sold as a supplement rather than a therapeutic drug, it is not subject to the same type of quality control measures as celecoxib. That said, Therapeutic Goods Administration data has suggested there is no problem with glucosamine available in Australia.

References

1. Australian Bureau of Statistics. Musculoskeletal conditions in Australia: a snapshot, 2004–05.
2. Reginster JY. The prevalence and burden of arthritis. Rheumatology (Oxford) 2002;41(Suppl 1):3–6.
3. Drazen JM. COX-2 inhibitors: a lesson in unexpected problems. N Engl J Med 2005;352:1131–2.
4. Bresalier RS, Sandler R, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med 2005;352:1092–102.
5. Solomon SD, McMurray JJ, Pfeffer MA, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med 2005;352:1071–80.
6. White WB, West CR, Borer JS, et al. Risk of cardiovascular events in patients receiving celecoxib: a meta-analysis of randomized clinical trials. Am J Cardiol 2007;99:91–8.
7. McGettigan P, Henry.D, Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. JAMA 2006;296:1633–44.
8. Singh G, Fort JG, Goldstein JL, et al. Celecoxib versus naproxen and diclofenac in osteoarthritis patients: SUCCESS-I Study. Am J Med 2006;119:255–66.
9. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. N Engl J Med 2000;343:1520–8.
10. Cepeda M, Camargo F, Zea C, Valencia L. Tramadol for osteoarthritis. Cochrane Database Syst Rev 2006; Art. No.: CD005522 DOI:10.1002/14651858.CD005522.pub2.
11. Towheed T, Maxwell L, Anastassiades T, et al. Glucosamine therapy for treating osteoarthritis. Cochrane Database Syst Rev 2005 Issue 2; Art. No.:CD002946 DOI: 10.1002/14651858.CD002946.pub2.
12. Clegg DO, Reda DJ, Harris CL, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. N Engl J Med 2006;354:795–808.
13. Herrero-Beaumont G, Del Carmen IJ, Trabado M, et al. Glucosamine sulfate in the treatment of knee osteoarthritis symptoms: A randomized, double-blind, placebo-controlled study using acetaminophen as a side comparator. Arthritis Rheum 2007;56:555–67.

AFP CORRESPONDENCE afp@racgp.org.au