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PRACTICE

THERAPEUTICS

Paracetamol for pain in adults

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What you need to know

- A trial of paracetamol is reasonable in patients with mild or moderate acute pain from conditions such as migraine, headache, renal colic, and postpartum perineal pain
- The evidence for using paracetamol to treat chronic pain is insufficient
- Caution patients about possible adverse cardiovascular and gastrointestinal effects of paracetamol, the risk of overdose (>3 g/day), and adverse effects from long term use such as liver damage. Dose adjustment may be needed in frail older people and those weighing less than 50 kg

A 65 year old retired engineer has experienced a flare up in the pain he experiences with his osteoarthritic knee. While seeing his general practitioner (GP) about a skin lesion, he mentions the knee problem and asks if he should use paracetamol to manage the pain. The patient is overweight and physically inactive.

What is paracetamol?

Paracetamol (acetaminophen) is one of the most widely used over-the-counter drugs around the world for the treatment of pain.[1] More than 100 different preparations, which contain paracetamol alone or in combination with other substances (eg, non-steroidal anti-inflammatory drugs or NSAIDs, caffeine, and tramadol) are available.[2] Current understanding is that paracetamol acts by inhibiting the cyclooxygenase (COX) enzymes through metabolism of the peroxidase function of these isoenzymes. It is less certain if its action is mediated by inhibition of COX-1, COX-2, or COX-3 enzymes.[2-4]

Paracetamol is inexpensive in most countries and is generally considered safe. This contributes to its widespread use. Paracetamol is available in immediate release (short acting) and modified release (long acting) preparations. In December 2017, the European Medicines Agency recommended suspending the marketing of modified release paracetamol because of concerns about a rise in overdose events and ensuing complications,[5] although the modified release preparations are still widely available in countries such as Australia, New Zealand, and the US.

In this Therapeutics article, we present an overview of the evidence on safety and effectiveness of paracetamol in adults for pain relief in primary care settings. We focus on immediate release preparations and discuss practical considerations for its use.

Search strategy

We searched the Cochrane Library, MEDLINE, and EMBASE from database inception until January 2019 for systematic reviews of randomised controlled trials investigating the effectiveness of paracetamol versus placebo for pain relief in adults, with the terms "paracetamol" OR "acetaminophen" AND "pain." Additionally, we searched for current clinical guidelines, our existing records for relevant publications, and examined the reference lists of studies retrieved by the searches. In this article we mainly rely on Cochrane database systematic reviews.

How well does paracetamol work for adults with pain?

Recent reviews and guidelines report uncertain benefits of paracetamol for pain relief in musculoskeletal conditions, particularly in the long term. Paracetamol is effective for headache and acute renal colic but the effects are smaller compared with other analgesics. Table 1 presents key findings from the Cochrane reviews of paracetamol for pain relief in these conditions.

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This is one of a series of occasional articles on therapeutics for common or serious conditions, covering new drugs and old drugs with important new indications or concerns. The series advisers are Robin Ferner, honorary professor of clinical pharmacology, University of Birmingham and Birmingham City Hospital, and Patricia McGettigan, clinical senior lecturer in clinical pharmacology, Queen Mary's University, London. To suggest a topic, please email us at practice@bmj.com

Musculoskeletal conditions

Paracetamol provides no clinically important improvements in pain in the immediate and short term (up to 12 weeks) compared with placebo in patients with knee or hip osteoarthritis, based on high quality evidence in a recent Cochrane review.[6]

Paracetamol is not effective for acute low back pain in the immediate and short term (up to 12 weeks) as per a Cochrane review.[7] The findings are based on high quality evidence from one large clinical trial (1643 patients). The review found no trials that evaluated its use in chronic low back pain.[6]

A systematic review found weak evidence of benefit of a single dose of paracetamol compared with placebo and an additive benefit of paracetamol in combination with NSAIDs for pain relief in rheumatoid arthritis.[12]

Headache

A single dose of paracetamol (1000 mg) is effective for relief of acute migraine headache at 2 hours as per a Cochrane systematic review.[13] The evidence is of low quality and the effect size is smaller than other commonly used analgesics for migraine. Paracetamol may be a useful option in patients who cannot tolerate other analgesics.

High quality evidence from a Cochrane review[14] shows that paracetamol is effective for tension type headache, with the number needed to treat to achieve pain-free status at 2 hours being 22 (95% confidence interval 15 to 40).

Other

A single dose of paracetamol was effective for reducing perineal pain in the early postpartum period following childbirth, as per a Cochrane review.[8]

Paracetamol was also effective for acute renal colic pain compared with placebo at 15 and 30 minutes after drug administration in one trial (152 participants); however, when compared with diclofenac, paracetamol was inferior for pain reduction.[9]

How safe is paracetamol?

Paracetamol is generally considered safe when administered in appropriate doses and for short periods of time.[2] Systematic reviews generally report similar adverse event rates in the paracetamol and placebo arms (supplementary table). However, these trials only studied short term use of paracetamol, in some cases only a single dose of the medicine.

Recent evidence points to increased risks of hospitalisation for perforation, peptic ulceration, and bleeding with paracetamol >3 g/day (hazard ratio=1.20, 95% confidence interval 1.03 to 1.40).[10] A dose response increase in the relative rates of adverse cardiovascular events (including confirmed or probable non-fatal myocardial infarction, non-fatal stroke, fatal coronary heart disease, or fatal stroke) and upper gastrointestinal events (gastroduodenal ulcers and complications such as upper gastrointestinal haemorrhages) is noted in patients prescribed paracetamol compared with those not prescribed in a systematic review of observational studies (eight cohort studies, n=665 789, 2 to 20 years of follow-up).[11] The evidence on safe duration of paracetamol use is inconclusive. Higher risks of cardiovascular and gastrointestinal adverse events have been associated with ≥15 days of use per month, ≥22 days of use per month, and ingestion of ≥15 tablets a week.[15 16]

The quality of evidence for these findings is low.[11] Additionally, large observational studies confirm a favourable side effect profile for paracetamol compared with traditional NSAIDs in older people using the medicine to treat chronic pain conditions.[17]

Dangers of paracetamol overdose

Inadvertent overdose is not uncommon with paracetamol and can result in severe hepatic failure and death. In a Scottish study (663 patients over 15 years), 16.6% of admissions to a liver transplant unit were for unintentional paracetamol overdose.[18] Liver damage can occur with ingestion of 5 g or more of paracetamol.[19] Inadvertent overdose can result from taking additional doses, repeated supra-therapeutic doses of paracetamol, and duplication of therapy (eg, ingesting paracetamol containing cold and flu preparations when already taking the maximum dose of paracetamol for pain). Frail older people and individuals weighing less than 50 kg are at greater risk if appropriate dose adjustment has not been considered.[20] "Medication overuse headache," characterised by headache occurring ≥15 days per month has been reported with overuse of paracetamol beyond maximum recommended doses for more than three months.[21] It is unclear how common this is.

How is paracetamol taken and monitored for treating pain?

Current clinical practice guidelines recommend the regular, time limited use of paracetamol for the treatment of mild to moderate acute and chronic non-malignant pain, except for back pain and some types of osteoarthritis such as hand osteoarthritis.[22 23] Given the evidence on its safety and benefit, a trial of paracetamol is reasonable in patients with mild or moderate acute pain. Evidence to define its place in treating chronic pain is insufficient, although it may be an alternative in older people who are not able to tolerate other analgesics or in whom it is safer compared with NSAIDs.

Paracetamol is taken orally and can be prescribed alone or in combination with other medicines, such as an NSAID or opioid. The usual adult recommended dose is 325 mg to 1000 mg every four or six hours, not exceeding 1000 mg per dose for immediate release formulations or 1330 mg per dose for sustained release formulations. The maximum daily dose is 4000 mg per day,[24] however some recommendations have now reduced the maximum daily dose to up to 3000 mg/day.[25]

Inform patients about the dangers of paracetamol overdose to prevent inappropriate self-medication. Consider dose reduction for frail older people and underweight patients. There is no clear guidance on dose adjustments,[26 27] which must be guided by clinical judgement. Doses up to 500 mg every 4-6 hours, with total daily doses not exceeding 3 g per day may be considered.[28]

Monitor patients, particularly older people, requiring paracetamol for the treatment of chronic pain conditions for upper gastrointestinal and cardiovascular adverse events. Periodic monitoring of liver function tests may be needed in these patients.

How does paracetamol compare with other drugs for common pain conditions?

There is mixed evidence regarding the comparative effectiveness of paracetamol for osteoarthritis. A recent network meta-analysis (56 randomised controlled trials, 22 128 participants) suggests that paracetamol was least effective for the treatment of knee and or hip osteoarthritis compared with celecoxib (a COX-2 selective NSAID) and the combination of glucosamine and

chondroitin.[29] Another review (29 studies) showed that paracetamol had similar efficacy to NSAIDs for the treatment of osteoarthritis.[30]

One systematic review (seven randomised controlled trials, 2421 participants) has shown that ibuprofen (an NSAID) is superior to paracetamol for pain associated with the surgical removal of wisdom teeth.[31] Paracetamol appears to have similar efficacy to NSAIDs for the treatment of headache[32] (systematic review of six randomised controlled trials, 2162 participants) and similar efficacy to NSAIDs and opioids for the treatment of renal colic (systematic review of 36 randomised controlled trials, 4887 participants).[33]

Case outcome

The GP informed the patient that short term use of paracetamol may provide a small benefit but on its own it may not completely manage the pain exacerbation. She suggested that the patient try paracetamol and consider adding a topical NSAID medicine or a heat pack if there is no relief. The GP advised the patient about the importance of maintaining a healthy weight and physical activity for the long term management of osteoarthritis.[34] The patient shared that he would consider an exercise programme when the exacerbation settled, so the GP arranged a referral to the community physiotherapist to design and monitor a suitable exercise programme.

Tips for patients

- Paracetamol is available in several formulations and is commonly used for short-term relief of pain in the joints, back, teeth and jaw, and head.
- The drug provides only minimal improvement in pain in osteoarthritis of the knee or hip in the short term (less than 12 weeks), and no improvement in acute low back pain. There is no evidence to support its regular use in the long term for these conditions.
- Consult your doctor for these conditions to decide on an appropriate pain management plan, including paracetamol and other pain medications, exercise, and alternative therapies.
- Paracetamol is effective for pain relief within two hours in acute migraine and headaches.
- Prolonged use of paracetamol at high or excessive doses may increase the risk of liver damage or cardiovascular events. Do not exceed the maximum daily dose of 4000 mg.
- Avoid taking cold and flu preparations that contain paracetamol if you are taking a regular regimen of paracetamol for pain, as it is easy to overdose inadvertently.
- Paracetamol overdose is dangerous, complex to manage, and can be fatal.
- If you are using paracetamol regularly for a longer duration for chronic pain, watch for side effects such as fatigue, abdominal pain, or specifically pain under the ribs, anaemia, and breathlessness. Report these to your doctor. Your doctor may advise periodic blood tests to monitor liver function.

Education into practice

- How would you discuss the risks and benefits when prescribing paracetamol for pain relief?
- In what situations is paracetamol overdose likely to occur?
- How would you modify dosing for frail older people or those weighing less than 50 kg?

How patients were involved in the creation of this article

Two patients from a community pharmacy in Sydney reviewed and discussed this paper with one of the authors (during informal patient interviews). These discussions informed the content for the sections “Tips for patients” and “What you need to know.” The patients suggested it was important to caution the public about the dangers of overdose as paracetamol is widely perceived to be a “safe” medicine. Patients also suggested recommendations to prevent inadvertent overdose, and emphasised the need for regular check ups for patients using the medicine long term. We have included these features in the article and revised the sections accordingly. We are grateful for these patients’ input.

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1 Blieden M, Paramore LC, Shah D, Ben-Joseph R. A perspective on the epidemiology of acetaminophen exposure and toxicity in the United States. *Expert Rev Clin Pharmacol* 2014;7:341-8. 10.1586/17512433.2014.904744 24678654
2 Jóźwiak-Bebenista M, Nowak JZ. Paracetamol: mechanism of action, applications and safety concern. *Acta Pol Pharm* 2014;71:11-23.24779190
3 Botting R, Ayoub SS. COX-3 and the mechanism of action of paracetamol/acetaminophen. *Prostaglandins Leukot Essent Fatty Acids* 2005;72:85-7. 10.1016/j.plefa.2004.10.005 15626590
4 Graham GG, Davies MJ, Day RO, Mohamudally A, Scott KF. The modern pharmacology of paracetamol: therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings. *Inflammopharmacology* 2013;21:201-32. 10.1007/s10787-013-0172-x 23719833
5 Cairns R, Brown JA, Wylie CE, Dawson AH, Isbister GK, Buckley NA. Paracetamol poisoning-related hospital admissions and deaths in Australia, 2004-2017. *Med J Aust* 2019;211:218-23. 10.5694/mja2.50296 31389025
6 Leopoldino AO, Machado GC, Ferreira PH, etal . Paracetamol versus placebo for knee and hip osteoarthritis. *Cochrane Database Syst Rev* 2019;2:CD013273. 10.1002/14651858.CD013273 30801133
7 Saragiotto BT, Machado GC, Ferreira ML, Pinheiro MB, Abdel Shaheed C, Maher CG. Paracetamol for low back pain. *Cochrane Database Syst Rev* 2016;6:CD012230.27271789
8 Chou D, Abalos E, Gyte GM, Gülmezoglu AM. Paracetamol/acetaminophen (single administration) for perineal pain in the early postpartum period. *Cochrane Database Syst Rev* 2013;1:CD008407. 10.1002/14651858.CD008407.pub2 23440827
9 García-Perdomo HA, Echeverría-García F, López H, Fernández N, Manzano-Nunez R. Pharmacologic interventions to treat renal colic pain in acute stone episodes: systematic review and meta-analysis. *Prog Urol* 2017;27:654-65. 10.1016/j.purol.2017.05.011 28651994
10 Zhang W, Nuki G, Moskowitz RW, etal . OARSI recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthritis Cartilage* 2010;18:476-99. 10.1016/j.joca.2010.01.013 20170770
11 Roberts E, Delgado Nunes V, Buckner S, etal . Paracetamol: not as safe as we thought? A systematic literature review of observational studies. *Ann Rheum Dis* 2016;75:552-9. 10.1136/annrheumdis-2014-206914 25732175
12 Hazlewood G, van der Heijde DM, Bombardier C. Paracetamol for the management of pain in inflammatory arthritis: a systematic literature review. *J Rheumatol Suppl* 2012;90:11-6. 10.3899/jrheum.120336 22942323
13 Derry S, Moore RA. Paracetamol (acetaminophen) with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database Syst Rev* 2013;4:CD008040. 10.1002/14651858.CD008040.pub3 23633349
14 Stephens G, Derry S, Moore RA. Paracetamol (acetaminophen) for acute treatment of episodic tension-type headache in adults. *Cochrane Database Syst Rev* 2016;6:CD011889. 10.1002/14651858.CD011889.pub2 27306653
15 Curhan GC, Willett WC, Rosner B, Stampfer MJ. Frequency of analgesic use and risk of hypertension in younger women. *Arch Intern Med* 2002;162:2204-8. 10.1001/archinte.162.19.2204 12390063
16 Chan AT, Manson JE, Albert CM, etal . Nonsteroidal antiinflammatory drugs, acetaminophen, and the risk of cardiovascular events. *Circulation* 2006;113:1578-87. 10.1161/CIRCULATIONAHA.105.595793 16534006

17 Rahme E, Barkun A, Nedjar H, Gaugris S, Watson D. Hospitalizations for upper and lower GI events associated with traditional NSAIDs and acetaminophen among the elderly in Quebec, Canada. *Am J Gastroenterol* 2008;103:872-82. 10.1111/j.1572-0241.2008.01811.x 18371130
18 Craig DG, Bates CM, Davidson JS, Martin KG, Hayes PC, Simpson KJ. Overdose pattern and outcome in paracetamol-induced acute severe hepatotoxicity. *Br J Clin Pharmacol* 2011;71:273-82. 10.1111/j.1365-2125.2010.03819.x 21219409
19 What dose of paracetamol for older people?*Drug Ther Bull* 2018;56:69-72. 10.1136/dtb.2018.6.0636 29903753
20 Hayward KL, Powell EE, Irvine KM, Martin JH. Can paracetamol (acetaminophen) be administered to patients with liver impairment?*Br J Clin Pharmacol* 2016;81:210-22. 10.1111/bcp.12802 26460177
21 Aleksenko D, Sanchez-Manso JC. *Medication overuse induced headache (MOH).* StatPearls, 2019.
22 Blondell RD, Azadfard M, Wisniewski AM. Pharmacologic therapy for acute pain. *Am Fam Physician* 2013;87:766-72.23939498
23 NHS. The pharmacological management of adults with chronic non-cancer pain 2015. https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&cad=rja&uact=8&ved=2ahUKEwjo16XF7Z3dAhWOQN4KHQZSD1cQFjAAegQIABAC&url=http%3A%2F%2Fwww.lancsmmg.nhs.uk%2Fwp-content%2Fuploads%2Fsites%2F3%2F2013%2F04%2FChronic-Non-cancer-Pain-Guidelines-V1.1.pdf&usg=AOvVaw26_Ux-v_AUPP9OG-9AKE3s
24 Amar PJ, Schiff ER. Acetaminophen safety and hepatotoxicity–where do we go from here?*Expert Opin Drug Saf* 2007;6:341-55. 10.1517/14740338.6.4.341 17688378
25 McNeil Consumer Helthcare. TYLENOL. Dosage for adults 2016. https://www.tylenol.com/safety-dosing/usage/dosage-for-adults
26 Joint Formulary Committee. *British National Formulary.* 75th ed. BMJ Group and Pharmaceutical Press, 2018.
27 Panadol original tablets. Summary of product characteristics. UK: GlaxoSmithKline Consumer Healthcare (UK) Trading Limited January 2018.
28 Mian P, Allegaert K, Spriet I, Tibboel D, Petrovic M. Paracetamol in older people: towards evidence-based dosing?*Drugs Aging* 2018;35:603-24. 10.1007/s40266-018-0559-x 29916138
29 Zhu X, Wu D, Sang L, etal . Comparative effectiveness of glucosamine, chondroitin, acetaminophen or celecoxib for the treatment of knee and/or hip osteoarthritis: a network meta-analysis. *Clin Exp Rheumatol* 2018;36:595-602.29465368
30 Stewart M, Cibere J, Sayre EC, Kopec JA. Efficacy of commonly prescribed analgesics in the management of osteoarthritis: a systematic review and meta-analysis. *Rheumatol Int* 2018;38:1985-97. 10.1007/s00296-018-4132-z 30120508
31 Bailey E, Worthington HV, van Wijk A, Yates JM, Coulthard P, Afzal Z. Ibuprofen and/or paracetamol (acetaminophen) for pain relief after surgical removal of lower wisdom teeth. *Cochrane Database Syst Rev* 2013;12:CD004624. 10.1002/14651858.CD004624.pub2 24338830
32 Yoon YJ, Kim JH, Kim SY, Hwang IH, Kim MR. A comparison of efficacy and safety of non-steroidal anti-inflammatory drugs versus acetaminophen in the treatment of episodic tension-type headache: a meta-analysis of randomised placebo-controlled trial studies. *Korean J Fam Med* 2012;33:262-71. 10.4082/kjfm.2012.33.5.262 23115700
33 Pathan SA, Mitra B, Cameron PA. A systematic review and meta-analysis comparing the efficacy of nonsteroidal anti-inflammatory drugs, opioids, and paracetamol in the treatment of acute renal colic. *Eur Urol* 2018;73:583-95. 10.1016/j.eururo.2017.11.001 29174580
34 The Royal Australian College of General Practitioners. *Guideline for the management of knee and hip osteoarthritis.* 2nd ed. East Melbourne, 2018.

Table

Table 1| Effectiveness of paracetamol compared with placebo for short term pain relief in adults

Condition	Evidence	RCTs included (n)	Outcome measure	Effect (95% CI)	Quality of evidence	Uncertainty
Pain control for musculoskeletal conditions						
Knee and hip OA	Cochrane review[5] Dose 1.95 g/day – 4 g/day	7 (2355)	Pain 0-100	MD –3.3 (–5.4 to –1.0)*	High	Effect may be too small to be clinically worthwhile. All studies follow up patients for up to 12 weeks (3 months), except one which went up to 24 weeks. Long term benefit and risks are not reported.
Acute low back pain	Cochrane review[6]	1 (1643)	Pain 0-100	MD 1.5 (–1.3 to 4.3)	High	Based on one trial
Rheumatoid arthritis	Systematic review[7]	3 (85)	Mean pain intensity	N/R	N/R	Non-Cochrane review, pooling was not undertaken, no quality rating
Headache						
Acute migraine headache	Cochrane review[8] Single dose (1000 mg paracetamol)	3 (717)	Complete pain relief at two hours	NNT 12 (7.5 to 32)*	Low	Effect size is smaller than other commonly used analgesics reported in the same review
			Some pain relief at two hours	NNT 5.0 (3.7 to 7.7)*		
Episodic tension type headache	Cochrane review[9] Single dose (1000 mg paracetamol)	8 (5890)	Pain-free at two hours	NNT 22 (15 to 4)*	High	Small effect size
Other						
Perineal pain postpartum	Cochrane review[10] Single dose of paracetamol (500-650 mg, and 1000 mg)	19 (1279)	>50% pain relief	RR 2.1 (1.6 to 2.9)*	Moderate	-
Renal colic	Systematic review[11]	1 (152)	Pain 0-100	15 minutes after drug administration* MD –25.0, (95% CI –33.2 to –16.4) 30 min after drug administration* MD –16.0 (95% CI –29.0 to –3.0)	N/R	Non-Cochrane review of one trial, no quality rating

OA=osteoarthritis; **RCT=**randomised controlled trial; **MD**=mean difference; **RR=**risk ratio; **NNT**=number needed to treat; **CI=**confidence interval; **N/R**=not reported. The number of RCTs and the sample size reported are related to the comparison in which paracetamol was included, not the total number of RCTs and sample size included in the systematic review

* Statistically significant effect