

Paracetamol and other non-opioid analgesics

The most widely used analgesic and antipyretic in the world, with a mechanism that remains incompletely established and a safety margin defined entirely by the dose: safe just below it, hepatotoxic just above.

Online guide:

<https://www.medguideglobal.com/pharmacology/analgesia-and-anaesthesia/paracetamol-and-other-non-opioid-analgesics>

Content updated: 2026-08-24

Quick revision

One Liner: Paracetamol relieves pain and fever through a mechanism that is still not fully established, and it is safe at licensed doses but hepatotoxic above them because a toxic metabolite overwhelms the liver's capacity to neutralise it.

1. Mechanism: proposed to act through selective inhibition of cyclo-oxygenase within the central nervous system and effects on the hypothalamus, but the exact mechanism is not fully established. [1]
2. Maximum recommended adult daily intake sits around 3 to 4 grams across a day, depending on the product and reference used; OTC labelling states severe liver damage can occur above 4,000 mg of acetaminophen in 24 hours. Exact dosing intervals belong in a prescribing reference and product labelling, not restated here. [1][3]
3. At therapeutic doses only a small fraction is metabolised via CYP2E1 to the toxic intermediate NAPQI, which is normally neutralised by conjugation with hepatic glutathione. [2]
4. In overdose, NAPQI production outpaces glutathione supply; the excess NAPQI binds hepatic macromolecules and causes centrilobular (zone 3) hepatic necrosis. [2]
5. Acetaminophen toxicity is the most common cause of acute liver failure in the United States and the second most common reason for liver transplantation worldwide. [2]
6. N-acetylcysteine is the antidote and is most effective within 8 hours of an acute overdose, working by preventing NAPQI from binding hepatic macromolecules. [2]
7. About half of acetaminophen poisonings are unintentional, often from taking more than one acetaminophen-containing product at once without realising it. [2]
8. Chronic alcohol use, malnutrition and fasting raise hepatotoxicity risk at lower total doses than would otherwise cause harm, by upregulating CYP2E1 or depleting glutathione reserves. [2]

Overview

1. Paracetamol, known as acetaminophen in the United States, is the most widely used analgesic and antipyretic medicine in the world. It is available without a prescription, is a core ingredient in countless combination cold, flu and pain products, and is generally regarded as one of the safest analgesics available when used within its licensed dose - a safety record that makes its narrow margin above that dose easy to underestimate. [1]
2. Unlike NSAIDs, paracetamol's mechanism of action is not fully established. The best-supported explanation involves selective inhibition of cyclo-oxygenase within the central nervous system together with an effect on the hypothalamus, producing analgesia and reduced fever without the significant peripheral anti-inflammatory or antiplatelet action that defines the NSAID class. [1]
3. The defining safety issue is dose-dependent hepatotoxicity. A small fraction of a therapeutic dose is converted by CYP2E1 into the reactive metabolite NAPQI, which the liver's glutathione stores neutralise harmlessly. In overdose, glutathione is overwhelmed, NAPQI accumulates and binds hepatic macromolecules, and the result is centrilobular hepatic necrosis. Acetaminophen toxicity is the most common cause of acute liver failure in the United States and the second most common reason for liver transplantation worldwide - and roughly half of these poisonings are unintentional, commonly from combining more than one acetaminophen-containing product. [2]

Classification and drug examples

Intro: Best learned by exposure pattern, since the toxicity risk that defines this class is driven as much by how the drug is combined and taken as by the drug itself.

1. Name: Paracetamol/acetaminophen as a single-ingredient product

1. Note: The reference form of the drug; risk is governed by total daily dose and individual susceptibility factors.

1. Name: Paracetamol (acetaminophen)

1. APAP

2. N-acetyl-para-aminophenol

1. Route: Oral/IV/rectal

1. Note: Safe and effective at licensed doses; hepatotoxic above them, with risk modified by alcohol use, malnutrition and fasting. [1][2]

2. Name: Extra-strength acetaminophen (Tylenol and store-brand equivalents)

Tylenol

2. Route: Oral

2. Note: Still a single-ingredient acetaminophen product at a higher per-tablet strength; consumer labelling explicitly warns against taking it with any other acetaminophen-containing product, prescription or nonprescription. [3] [1]

2. Name: Combination products containing paracetamol

2. Note: A single largest practical driver of accidental overdose, because a patient can be exposed to acetaminophen from more than one product without realising it - here the paracetamol is combined with a second active ingredient in the same tablet.

Name: Hydrocodone/acetaminophen

Route: Oral

Note: A combination opioid-analgesic/paracetamol product; the paracetamol component still carries the class's hepatotoxicity ceiling regardless of the opioid dose. [2] [2]

Mechanism of action

Summary: Paracetamol's analgesic and antipyretic mechanism is not fully established; the leading proposal is selective inhibition of cyclo-oxygenase within the central nervous system alongside an effect on the hypothalamus. Its toxicity mechanism, by contrast, is well characterised: a minor toxic metabolite, NAPQI, is safely neutralised at normal doses but overwhelms hepatic defences in overdose.

Target: Proposed central cyclo-oxygenase inhibition and hypothalamic modulation (analgesic/antipyretic effect); CYP2E1-generated NAPQI (toxicity pathway)

Cidal Static: Not applicable - this class is an analgesic/antipyretic, not an antimicrobial.

Kill Kinetics: Not applicable in the antimicrobial sense; toxicity is dose-dependent rather than concentration- or time-dependent killing of an organism.

1. Step: 1

1. Title: Central cyclo-oxygenase and hypothalamic effects (proposed analgesic/antipyretic mechanism)

1. Detail: Paracetamol is proposed to selectively inhibit cyclo-oxygenase within the central nervous system and to directly affect the hypothalamus, reducing fever and pain perception without the significant peripheral prostaglandin inhibition that defines NSAIDs. [1]

2. Step: 2

2. Title: Most of the dose follows safe conjugation pathways

2. Detail: At therapeutic doses, most paracetamol is metabolised through glucuronidation and sulfation to inactive, nontoxic metabolites that are renally excreted. [2]

3. Step: 3

3. Title: A small fraction generates NAPQI via CYP2E1

3. Detail: Roughly 8% of a therapeutic dose is oxidised by CYP2E1 into the reactive toxic intermediate N-acetyl-p-benzoquinoneimine (NAPQI). [2]
4. Step: 4
4. Title: Glutathione conjugates NAPQI harmlessly at normal doses
4. Detail: Under normal conditions, NAPQI swiftly conjugates with hepatic glutathione to form nontoxic cysteine and mercaptate compounds, which is why therapeutic dosing does not injure the liver. [2]
5. Step: 5
5. Title: Overdose overwhelms glutathione and causes hepatic necrosis
5. Detail: In overdose, NAPQI production increases and depletes hepatic glutathione stores; the excess NAPQI binds covalently to hepatic macromolecules, particularly mitochondrial proteins, producing centrilobular (zone 3) hepatocellular necrosis. [2]

Major clinical uses

1. Drug: Paracetamol (acetaminophen)
1. Indication: Mild to moderate pain and fever, and as an adjunct analgesic alongside other agents to reduce opioid or NSAID dose requirements
1. Line: first-line for many common types of pain and fever
1. Note: Preferred over NSAIDs in many patients because it lacks significant GI, renal and antiplatelet effects at licensed doses. [1]
2. Drug: Paracetamol (acetaminophen)
2. Indication: Osteoarthritis and other chronic musculoskeletal pain where NSAID risk factors are present
2. Line: alternative when NSAIDs are contraindicated or higher risk
2. Note: Choice depends on hepatic status and total acetaminophen exposure from all sources. [1]
3. Drug: Hydrocodone/acetaminophen
3. Indication: Moderate to moderately severe pain, combining opioid and non-opioid mechanisms
3. Line: targeted, short-course
3. Note: The acetaminophen component still contributes to total daily acetaminophen exposure and its hepatotoxicity ceiling. [2]
4. Drug: Paracetamol (acetaminophen)
4. Indication: Antipyretic use in fever of infectious or inflammatory origin, across paediatric and adult populations
4. Line: first-line antipyretic
4. Note: Weight-based paediatric dosing differs from adult dosing and must come from a current prescribing reference. [1]

Pharmacokinetics

- Drug: Paracetamol (acetaminophen)
- Route: Oral/IV/rectal
- Absorption: Rapid and nearly complete oral absorption
- Csf Penetration: Crosses into CNS, consistent with a proposed central mechanism
- Metabolism: Predominantly hepatic glucuronidation and sulfation to inactive metabolites; a minor fraction via CYP2E1 to NAPQI
- Elimination: Renal, as inactive conjugated metabolites
- Half Life: See prescribing reference
- Dose Adjust: Hepatic impairment, chronic alcohol use, malnutrition or fasting - all raise hepatotoxicity risk at a given dose [1][2]
1. This page gives no dose regimens by design. The maximum daily acetaminophen dose, individual dosing interval and paediatric weight-based dosing must come from a current prescribing reference and the treating clinician or

pharmacist.

2. Total daily acetaminophen exposure must be counted across every product a patient is taking, not just the one being newly prescribed, because combination products are the most common real-world route to accidental overdose. [2][3]

Adverse effects

Effect: Generally well tolerated at licensed doses

Detail: At therapeutic doses, paracetamol lacks the GI, renal and antiplatelet effects that limit NSAID use, which is part of why it is favoured as a first-line agent. [1]

1. Effect: Hepatotoxicity and acute liver failure

1. Detail: Acetaminophen toxicity is the most common cause of acute liver failure in the United States and the second most common reason for liver transplantation worldwide; it results from NAPQI overwhelming hepatic glutathione in overdose.

1. Action: Emergency evaluation and N-acetylcysteine, most effective within 8 hours of an acute ingestion. [2]

2. Effect: Severe liver damage from combination-product overdose

2. Detail: Taking a paracetamol-containing product together with another acetaminophen-containing product, or exceeding the maximum daily dose (labelled as above 4,000 mg/24h on US OTC packaging), can cause severe liver damage.

2. Action: Checking every medicine label for acetaminophen content before adding a new product is the standard way to avoid unintentional double-dosing. [3]

1. Drug: Paracetamol (acetaminophen) in chronic alcohol users

1. Effect: Hepatotoxicity risk at lower total doses because CYP2E1 upregulation increases NAPQI generation from a given dose. [2]

2. Drug: Paracetamol (acetaminophen) with malnutrition or fasting

2. Effect: Reduced glucuronidation and lower glutathione reserves raise hepatotoxicity risk at doses that would otherwise be tolerated. [2]

Contraindications, precautions and interactions

1. Known hypersensitivity to acetaminophen. [1]

2. Severe active hepatic impairment or acute liver failure, without specialist direction. [2]

1. Chronic alcohol use, malnutrition, or fasting states, which lower the hepatotoxicity threshold. [2]

2. Concurrent use of any other acetaminophen-containing product, prescription or nonprescription. [3]

3. Pre-existing hepatic disease. [2]

1. With: CYP2E1-inducing medications and chronic alcohol use

1. Effect: Increase NAPQI generation from a given acetaminophen dose, raising hepatotoxicity risk. [2]

2. With: Other acetaminophen-containing products (cold/flu remedies, combination analgesics)

2. Effect: Additive total acetaminophen exposure that can unintentionally exceed the maximum daily dose. [3]

Comparison tables

Title: Why the same drug is 'safe' and 'hepatotoxic'

Caption: The margin between therapeutic and toxic acetaminophen exposure is defined by dose and by host factors, not by a different drug or mechanism. A prescribing reference and the treating clinician govern actual dosing.

1. Key: factor

1. Label: Factor

2. Key: effect_on_risk

2. Label: Effect on hepatotoxicity risk

1. Factor: Total daily dose above the labelled maximum

1. Effect On Risk: Directly raises NAPQI production beyond glutathione capacity [2][3]
2. Factor: Taking more than one acetaminophen-containing product
2. Effect On Risk: Common real-world route to unintentionally exceeding the maximum dose [3]
3. Factor: Chronic alcohol use
3. Effect On Risk: Upregulates CYP2E1, increasing NAPQI generated per dose [2]
4. Factor: Malnutrition or fasting
4. Effect On Risk: Reduces glucuronidation and glutathione reserve, lowering the toxic threshold [2]

High-yield exam pearls

1. Pearl: Paracetamol is the analgesic whose exact mechanism is still debated.
1. Why: Unlike NSAIDs, whose COX mechanism is well characterised, paracetamol's mechanism is only proposed - central COX inhibition and hypothalamic effects - and remains incompletely established despite the drug's universal use. [1]
2. Pearl: One metabolite explains the whole toxicity story.
2. Why: NAPQI is produced in tiny amounts at normal doses and safely neutralised by glutathione. Overdose does not introduce a new toxic pathway - it simply produces more NAPQI than glutathione can conjugate, and the excess destroys hepatocytes. [2]
3. Pearl: The most dangerous overdoses are often accidental.
3. Why: About half of acetaminophen poisonings are unintentional, typically from a patient taking more than one acetaminophen-containing product - for example a cold remedy plus a separate pain reliever - without realising both contain the same drug. [2]
4. Pearl: The antidote has a clock attached.
4. Why: N-acetylcysteine is most effective within 8 hours of an acute overdose. This time-dependence is why acetaminophen overdose is treated as time-critical even when the patient looks well initially. [2]
5. Pearl: Chronic drinkers and malnourished patients need a lower threshold of suspicion.
5. Why: Chronic alcohol use upregulates CYP2E1, generating more NAPQI from the same dose, while malnutrition and fasting reduce glucuronidation and glutathione reserves - both lower the dose at which hepatotoxicity becomes possible. [2]

Common exam traps

1. Trap: "Paracetamol works the same way as NSAIDs, just weaker."
1. Correction: Paracetamol's mechanism is not the same well-established peripheral COX inhibition seen with NSAIDs. It is proposed to act more centrally, and the exact mechanism remains incompletely established - a genuinely different, less certain pharmacology, not simply a weaker NSAID. [1]
2. Trap: "Acetaminophen overdose only matters if it was taken intentionally in one large dose."
2. Correction: About half of poisonings are unintentional, frequently from combining multiple acetaminophen-containing products, and chronic low-margin dosing in a patient with alcohol use or malnutrition can also cause hepatotoxicity without any single large overdose. [2]
3. Trap: "If the patient feels fine hours after an overdose, no treatment is needed."
3. Correction: Acetaminophen hepatotoxicity is often clinically silent early on; N-acetylcysteine is most effective within 8 hours of ingestion, so treatment decisions are based on ingested dose and timing, not on how the patient currently feels. [2]

Self-test questions

1. Question: What is the current understanding of paracetamol's mechanism of action?
1. It is a well-characterised peripheral COX-1 inhibitor identical in mechanism to ibuprofen

2. It is proposed to act through selective central cyclo-oxygenase inhibition and hypothalamic effects, but the exact mechanism is not fully established

3. It works exclusively through mu-opioid receptor agonism

4. It blocks voltage-gated sodium channels in peripheral nerves

1. Explanation: Paracetamol's mechanism is incompletely established. The best-supported proposal involves selective inhibition of cyclo-oxygenase within the central nervous system and an effect on the hypothalamus, which is a materially different and less certain picture than the well-defined peripheral COX mechanism of NSAIDs. [1]

2. Question: At therapeutic doses, how does the body handle the toxic metabolite NAPQI?

1. NAPQI is not produced at therapeutic doses at all

2. A small amount of NAPQI is produced via CYP2E1 and swiftly conjugated with hepatic glutathione into nontoxic compounds

3. NAPQI is excreted unchanged by the kidney before it can cause harm

4. NAPQI is converted back into paracetamol by the liver

2. Explanation: At therapeutic doses, only a small fraction of paracetamol is metabolised via CYP2E1 into NAPQI, which is rapidly conjugated with hepatic glutathione to form nontoxic cysteine and mercaptate compounds - this is the normal, safe pathway. [2]

3. Question: What actually causes liver injury in paracetamol overdose?

1. Paracetamol itself directly destroys hepatocytes

2. Increased NAPQI production depletes glutathione stores, and the excess NAPQI binds hepatic macromolecules, causing centrilobular necrosis

3. Paracetamol overdose causes an allergic hypersensitivity reaction in the liver

4. The kidney fails first, and liver injury is a secondary consequence

3. Explanation: In overdose, increased NAPQI production outpaces the liver's glutathione supply. The unconjugated NAPQI binds covalently to hepatic macromolecules, particularly mitochondrial proteins, producing centrilobular (zone 3) hepatocellular necrosis. [2]

4. Question: Why is N-acetylcysteine most effective when given within 8 hours of an acute paracetamol overdose?

1. It has no time-dependence and works equally well at any interval

2. It works by replenishing/mimicking glutathione to prevent NAPQI from binding hepatic macromolecules, before that binding and the resulting necrosis have already occurred

3. It only works if given before the drug is absorbed

4. It directly reverses hepatic necrosis that has already occurred

4. Explanation: N-acetylcysteine acts by preventing NAPQI from binding to hepatic macromolecules. Once that binding has already happened and hepatocyte injury is underway, the drug's benefit diminishes, which is why early administration, ideally within 8 hours, matters so much. [2]

5. Question: Why are chronic alcohol users at higher hepatotoxicity risk from the same paracetamol dose as other patients?

1. Alcohol has no effect on paracetamol metabolism

2. Chronic alcohol use upregulates CYP2E1, increasing NAPQI production from a given dose, and can also affect glutathione reserves

3. Alcohol blocks paracetamol absorption entirely, so more must be taken to reach the same effect

4. Chronic alcohol users metabolise paracetamol entirely through a nontoxic pathway

5. Explanation: Chronic alcohol ingestion is a documented risk factor because it upregulates CYP2E1, the enzyme that produces NAPQI, meaning more toxic metabolite is generated from the same paracetamol dose than in a person without that enzyme induction. [2]

6. Question: Why does the FDA-approved consumer label warn against taking a paracetamol-containing product together with another acetaminophen-containing product?

1. Because the two drugs interact pharmacodynamically to increase pain

2. Because doing so risks unknowingly exceeding the maximum daily acetaminophen dose and causing severe liver damage
3. Because it voids the product warranty
4. Because acetaminophen from two products cancels out and neither works
6. Explanation: Multiple over-the-counter and prescription products contain acetaminophen (for example combination cold remedies and combination analgesics). Taking more than one at a time is a common, real route to accidental overdose and severe liver damage, which is exactly what the label warning is designed to prevent. [3]

Frequently asked questions

1. Question: Is paracetamol/acetaminophen safe to take every day?
1. Answer: At the licensed dose it is one of the safest widely used analgesics, but 'safe' depends entirely on staying within the maximum daily dose and not combining it with other acetaminophen-containing products. Discuss regular, ongoing use with a clinician or pharmacist, especially with chronic alcohol use or liver disease. [1][3]
2. Question: Why is acetaminophen overdose so often accidental?
2. Answer: Because it is an ingredient in many different products - pain relievers, cold and flu remedies, and combination opioid/acetaminophen products - a patient can take more than one without realising each contains acetaminophen, and about half of poisonings happen this way. [2]
3. Question: What treats a paracetamol overdose?
3. Answer: N-acetylcysteine is the antidote and works by preventing the toxic metabolite NAPQI from binding hepatic proteins; it is most effective when given within 8 hours of an acute overdose. Anyone who may have taken too much acetaminophen should seek emergency medical care immediately rather than wait to see if symptoms develop. [2]
4. Question: Does drinking alcohol make paracetamol more dangerous?
4. Answer: Chronic alcohol use is a documented risk factor because it increases the enzyme activity that generates the toxic metabolite NAPQI, lowering the dose at which liver injury becomes possible. This is different from a single social drink, but anyone with regular alcohol use should discuss acetaminophen use with a clinician. [2]

References

- [1] Acetaminophen (StatPearls). StatPearls Publishing / NCBI Bookshelf 2025. <https://www.ncbi.nlm.nih.gov/books/NBK482369/>
- [2] Acetaminophen Toxicity (StatPearls). StatPearls Publishing / NCBI Bookshelf 2025. <https://www.ncbi.nlm.nih.gov/books/NBK441917/>
- [3] Tylenol Extra Strength (acetaminophen) - FDA-approved consumer label (DailyMed). DailyMed, U.S. National Library of Medicine 2026. <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8ed90757-833e-f4d9-e053-2995a90a29db>

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