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An Updated Review on the Metabolite (AM404)-Mediated Central Mechanism of Action of Paracetamol (Acetaminophen): Experimental Evidence and Potential Clinical Impact

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Abstract: Paracetamol remains the recommended first-line option for mild-to-moderate acute pain in general population and particularly in vulnerable populations. Despite its wide use, debate exists regarding the analgesic mechanism of action (MoA) of paracetamol. A growing body of evidence challenged the notion that paracetamol exerts its analgesic effect through cyclooxygenase (COX)-dependent inhibitory effect. It is now more evident that paracetamol analgesia has multiple pathways and is mediated by the formation of the bioactive AM404 metabolite in the central nervous system (CNS). AM404 is a potent activator of TRPV₁, a major contributor to neuronal response to pain in the brain and dorsal horn. In the periaqueductal grey, the bioactive metabolite AM404 activated the TRPV₁ channel-mGlu5 receptor-PLC-DAGL-CB1 receptor signaling cascade. The present article provides a comprehensive literature review of the centrally located, COX-independent, analgesic MoA of paracetamol and relates how the current experimental evidence can be translated into clinical practice. The evidence discussed in this review established paracetamol as a central, COX-independent, antinociceptive medication that has a distinct MoA from non-steroidal anti-inflammatory drugs (NSAIDs) and a more tolerable safety profile. With the establishment of the central MoA of paracetamol, we believe that paracetamol remains the preferred first-line option for mild-to-moderate acute pain for healthy adults, children, and patients with health concerns. However, safety concerns remain with the high dose of paracetamol due to the NAPQI-mediated liver necrosis. Centrally acting paracetamol/*p*-aminophenol derivatives could potentiate the analgesic effect of paracetamol without increasing the risk of hepatotoxicity. Moreover, the specific central MoA of paracetamol allows its combination with other analgesics, including NSAIDs, with a different MoA. Future experiments to better explain the central actions of paracetamol could pave the way for discovering new central analgesics with a better benefit-to-risk ratio.

Keywords: paracetamol, acetaminophen, AM404, analgesia, molecular targets

Plain Language Summary

The mechanisms of how paracetamol works are still subject to debate despite its widespread use. Previous scientific research questions the idea that paracetamol relieves pain by inhibiting cyclooxygenases (COX). Now, it is more apparent that paracetamol's pain-relieving effect occurs in the brain and is independent of the COX enzyme. This article reviewed the central paracetamol actions and how the current experimental evidence can be used in clinical practice. Based on the evidence discussed in this review, paracetamol works differently than NSAIDs and has a safer safety profile. With the central MoA for paracetamol in place, we think paracetamol will still be the first choice for acute pain management. When the COX-independent mechanism of action and stable pharmacokinetic properties of paracetamol are considered, it is safe to say that paracetamol should be preferred over NSAIDs for analgesia, especially in special populations. Newer painkillers, based on the central action of paracetamol, are being studied and show promising results in relieving pain without increasing the risk of liver damage.

Introduction

Pain represents substantial healthcare and financial burden despite the available pain management approaches, highlighting the urgent need for innovative medications and, possibly, indications of established analgesics.¹ Non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol (also known as acetaminophen or *N*-acetyl-*p*-aminophenol) are commonly prescribed for pain management in a wide range of conditions. Globally, paracetamol is also at the apex of the most commonly utilized over-the-counter (OTC) analgesic and the preferred first-line option for patients with mild-to-moderate acute pain.² The good tolerability at the recommended dosage (eg, lack of gastrointestinal adverse effects) is a major contributor to the preference for paracetamol by general practitioners, specialists, and pharmacists.³ Although it was introduced in clinics more than 100 years ago,⁴ paracetamol remains the recommended first-line option for pain management by several scientific societies, and particularly in vulnerable populations such as geriatrics, children, patients with peptic ulcers, and pregnant women.^{5,6} Despite its wide use, debate exists regarding the analgesic mechanism of action (MoA) of paracetamol.⁷

Historically, it was believed that the paracetamol-mediated analgesia stems solely from its cyclooxygenase (COX)-dependent inhibitory effect on prostaglandin (PG) synthesis⁸; however, it is now evident that the analgesic MoA of paracetamol is multidimensional and involves several pathways within the central nervous system (CNS), such as the endocannabinoid, serotonergic, and nitric oxide pathways^{9–14} or for some authors opioid pathways.¹⁵ The notion that we already know concerning the metabolic pathways for paracetamol has been challenged in the past two decades following the 2005 study by Högestätt et al; in this report, the authors demonstrated that, following hepatic deacetylation to *p*-aminophenol, this paracetamol metabolite crosses the blood–brain barrier (BBB) and is converted to *N*-arachidonoylphenolamine (AM404).¹⁶ Subsequent experimental evidence found that this new metabolite pathway was involved in its analgesic MoA.^{17–19} Moreover, several molecular actors targeted by the bioactive AM404, including the Cav3.2 calcium channel, the cannabinoid CB1 receptors and TRPV₁ receptors, would participate in the MoA.^{10,20,21}

Paracetamol is generally considered safe for many patients, particularly in comparison with NSAIDs and opioids. The growing evidence of the centrally located COX-independent actions of paracetamol can pave the way for optimizing the use of an old drug in a more widened patients' profile. More importantly, the development of paracetamol-based derivatives can maximize the central effects of paracetamol while reducing the risk of toxicity.^{22–25} The present article provides a comprehensive literature review of the centrally located, COX-independent, analgesic MoA of paracetamol and how the current experimental evidence can be translated into clinical practice. This review highlighted the advantages of the centrally located MoA and the benefit/risk of paracetamol in mild-to-moderate pain conditions. Consequently, we discussed the potential clinical applications of paracetamol analogs. Besides, we review the safety aspects of paracetamol administration and how it can be preferred over NSAIDs due to its more tolerable safety profile.

Review Development

A bibliographic literature search was performed on Medline via PubMed to collect relevant articles from their inception to May 2022. The following keywords were employed during the literature search: (paracetamol[MeSH Terms]) OR (acetaminophen[MeSH Terms]) AND (AM404). The online bibliographic search was complemented by a manual screening of the relevant references.

The Analgesic MoA is Independent of Central COX Inhibition

Historically, Vane and Flower demonstrated that paracetamol reduced brain PGE₂ with a preferred action in the CNS than in the periphery.⁸

PGs are produced by COX enzymes which need to be oxidized by hydroperoxides to be catalytically active. Paracetamol, as reducing agent,²⁶ reduces the hydroperoxide tone and thus inactivates COX.^{27–30} The selectivity of paracetamol for CNS was hypothesized to be based on cellular concentration of peroxide and arachidonic acid. High levels of peroxide (found especially in the periphery, eg, in an inflammatory context) or arachidonic acid, thwart paracetamol COX inhibition.^{30–33}

Another proposed COX-dependent MoA of paracetamol is the involvement of another COX isoenzyme, named COX-3. Flower and Vane demonstrated that the COX inhibitory effect of paracetamol was more potent in the brain than in the spleen, suggesting another COX isoenzyme as a sensitive site for paracetamol action.⁸ COX-3 is an exon splice variant from COX-1 that was identified in the canine cerebral cortex and exhibited selective sensitivity to paracetamol.³⁴ However, further genomic and kinetic studies showed that a full-length, catalytically active form of COX-3 does not exist in humans^{35,36} and that the COX-3 selective interaction is unlikely to be clinically relevant.³¹

However, the question remained whether the analgesic MoA of paracetamol is primarily mediated by COX inhibition. In mice, administering a weekly dose of paracetamol, which induced an analgesic effect, did not reduce PGE2 content in the brain.³⁷ Besides, the antinociceptive profile of paracetamol was found to be different from that of the competitive COX inhibitor, ibuprofen, with no observed antinociceptive action of ibuprofen, in the first phase of the formalin test, despite the proposed shared MoA.³⁷ Altogether, these results indicate that the analgesic action of paracetamol cannot be attributed to the inhibition of central COX, however data from the literature would suggest such an involvement.³⁸ Furthermore, the inhibitory effect of paracetamol on COX observed by some authors seems more closely related to its hypothermic/antipyretic effects than to its analgesic action.^{39–42}

AM404: The Active Metabolite of Paracetamol

Research experiments have shown that the analgesic MoA of paracetamol is primarily COX-independent and mediated by the formation of the bioactive AM404 metabolite in the CNS, highlighting that paracetamol is a pro-drug of a potent analgesic metabolite. The first description of the central conversion of paracetamol was reported in 2005. In this report, Högestätt et al demonstrated that the deacetylated form of paracetamol, the *p*-aminophenol, is converted mainly in the brain to AM404 by the fatty acid amide hydrolase (FAAH) enzyme (Figure 1).¹⁶ These findings were then supported by Muramatsu et al's experiment.²⁰ The first human evidence of central conversion of paracetamol to AM404 was demonstrated by Sharma et al in 2017; 26 patients received 1g of paracetamol, followed by measurement of the

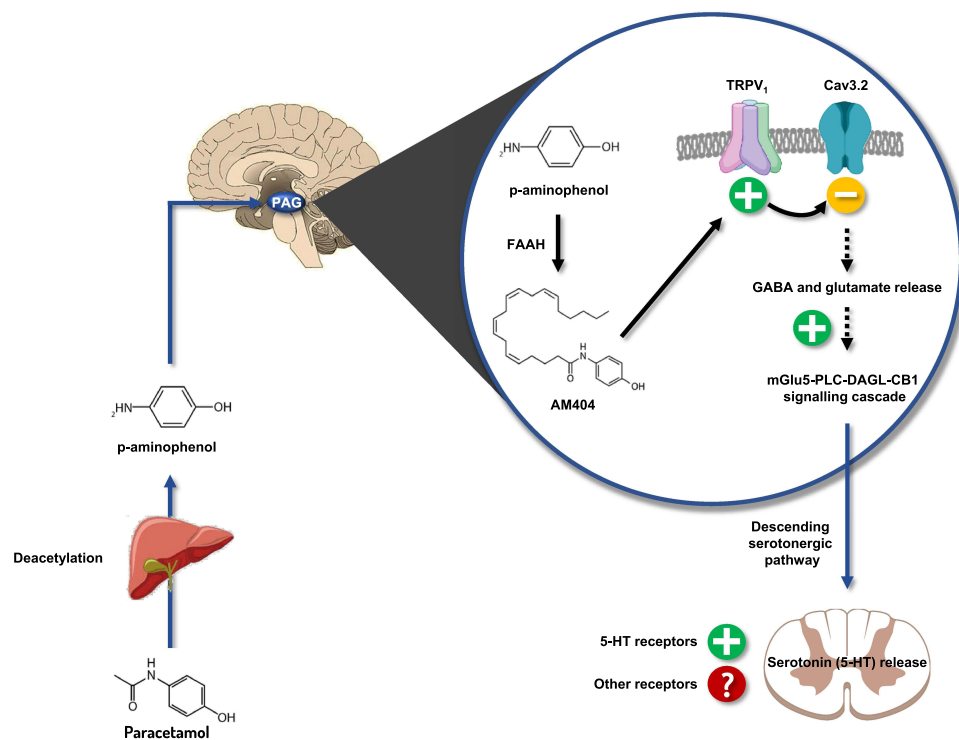


Figure 1 Schematic representation of the central mechanism of action of paracetamol to its antinociceptive activity. Paracetamol is deacetylated in *p*-aminophenol in the liver, then metabolized in the brain by FAAH into AM404. AM404 activates the TRPV1 channel-mGlu5 receptor-PLC-DAGL-CB1 pathway and co-activates the Cav 3.2 T-type calcium channel, which in turn reinforces the activity of the descending serotonergic pathways.

AM404 in the cerebrospinal fluid (CSF) and blood. The study detected AM404 in the CSF of 17 patients, confirming the central conversion of paracetamol to the bioactive AM404 in humans.⁴³

Importantly, it has been shown that 1) centrally injected AM404 induced analgesia^{37,44,45} and 2) the inhibition of FAAH (genetically and pharmacologically) suppressed the analgesic effect of paracetamol (and *p*-aminophenol), demonstrating the involvement of AM404 as the active metabolite in the analgesic effect of paracetamol.^{17,18,37} In the setting of nociceptive pain, Dalmann et al observed the loss of paracetamol analgesic effect after supra-spinal administration of a FAAH inhibitor, which did not occur after peripheral FAAH inhibitor injection. This demonstrated that the FAAH-synthesized AM404 formation occurs mainly at supra-spinal level,¹⁹ even if a study evoked a spinal level.⁴⁶

AM404-Modulated Molecular Targets

TRPV₁ Channels

AM404 is a potent activator of TRPV₁, a major contributor to neuronal response to pain. Contrary to the periphery, where activated TRPV₁ induces nociception, hyperalgesia, and pain transduction modulation,⁴⁷ supraspinal TRPV₁ activation induces anti-nociception.^{37,45,48} In Zygmunt et al's patch-clamp experiment, AM404 activated the vanilloid receptor TRPV₁, an effect that was suppressed after administration of the TRPV₁ antagonist, capsazepine.⁴⁹ Besides, experiments showed diminished analgesic action of paracetamol and *p*-aminophenol in TRPV₁ knockout mice and mice pretreated with capsazepine.^{18,37,45} Notably, a recent report by Barrière et al⁵⁰ demonstrated that paracetamol reduced the connectivity of brain structures in the pain pathway, particularly the periaqueductal grey, where local blockade of TRPV₁ suppressed the analgesic action of paracetamol, this confirms a fully TRPV₁-dependent mechanism and thus tends to exclude a mechanism involving central COX. As a confirmation of the role of TRPV₁ in humans, Pickering et al demonstrated the involvement of a specific TRPV₁ rs224534 variant in paracetamol antinociception in healthy volunteers.⁵¹

Downstream Targets of TRPV₁

The T-type calcium Cav3.2 isoform regulates the neuronal response to pain.^{52,53} Cav3.2 knockout models and mice pretreated with Cav3.2 blockers showed impaired nociceptive response to pain stimuli.⁵⁴ Previous reports indicated that the antinociceptive action of arachidonic compounds involves inhibition of Cav3.2 channels, suggesting a potential interaction between Cav3.2 and AM404.¹¹ In 2014, Kerckhove et al demonstrated that Cav3.2 knockout mice had impaired response to the analgesic effect of a systemic administration of paracetamol or intracerebroventricular injection of AM404.⁵⁵ Interestingly, an experiment aimed to establish the location of Cav3.2 involved in the analgesic effect of paracetamol found that, contrary to supra-spinal channels, spinal Cav3.2 blockade did not affect the analgesic profile of paracetamol, highlighting that the involvement of Cav3.2 in the analgesic activity of paracetamol is mainly supra-spinal.⁴⁵

In Cav3.2 knockout mice, the analgesic effect of the TRPV₁ agonist (capsaicin) was diminished, despite the analgesic action of an inhibitor of Cav3 channels (TTA-A2) persisted in TRPV₁ knockout mice suggesting that Cav3.2 and TRPV₁ support paracetamol's analgesic activity sequentially, Cav3.2 acting downstream of TRPV₁.⁴⁵

In the setting of paracetamol injection, CB1 knockout models or mice pretreated with selective CB1 antagonists showed no analgesic response to paracetamol.^{17,56} The expected synergism between paracetamol and opiates was also attenuated in mice pretreated with selective CB1 antagonist.⁵⁷ Notably, two previous reports showed that paracetamol injection did not alter the brain endocannabinoid content, suggesting that other studies are needed to know how CB1 receptors are involved. Recently, periaqueductal grey-located CB1 receptors were found to be essential for the MoA of paracetamol through a AM404-activated TRPV₁ channel-mGlu5 receptor-PLC-DAGL-CB1 receptor signaling.⁵⁰

Serotonin (5-HT) and norepinephrine are engaged in pathways of physiological nociception, both of which can be produced via descending pain pathways to alter nociceptive transmission in the spinal cord. Serotonin appears to have both inhibitory and facilitative effects on pain.⁵⁸ The involvement of the serotonergic pathway in the analgesic effect of paracetamol was described even before the 2005 work by Högestätt et al.⁵⁹ Earlier reports described the pharmacological blockade of the serotonergic pathway decreased the antinociceptive effect of paracetamol.⁶⁰ The involvement of the

serotonergic pathway in paracetamol action was reported to stem from increasing 5-HT levels in the central structures and activating the spinal 5-HT receptors.^{60–71} Nonetheless, the evidence was not conclusive regarding the contribution of serotonergic receptors to the paracetamol action. As an example, the involvement of 5-HT₃ receptors has been discussed in humans,^{62,70,72–74} and experimental work in rodents with 5-HT₃ receptor antisense oligonucleotides showed that they were not involved in the analgesic effect of paracetamol, while a tropisetron-sensitive receptor was.⁷⁴ However, investigations showed that *p*-aminophenol analgesic action was mediated by the bulbospinal serotonergic system,¹⁸ which may suggest an involvement of this serotonergic system in the AM404 antinociceptive activity, as recently suggested.⁶³ Finally, if bulbospinal serotonergic pathways seem to be involved in the analgesic effect of paracetamol or its metabolites, the exact nature of the spinal tropisetron-sensitive receptor involved in this effect remains to be elucidated.

Altogether, the data collected draw the schematic MoA represented in Figure 1.

Potential Clinical Consequences of the Centrally Located Analgesic Action of Paracetamol

Paracetamol, a COX-Independent, Centrally Acted as the First Choice for a Wide Range of Special Populations

Safety is the primary concern in choosing OTC analgesics, particularly for mild-to-moderate pain conditions in vulnerable groups. Patients with health concerns are frequently reluctant to take the appropriate analgesic dose due to safety concerns, leading to inadequate pain management.⁶ Most NSAIDs have safety concerns related to the development of gastric ulcers and bleeding, bronchial asthma, acute kidney injury, and long-term adverse cardiovascular outcomes.⁷⁵ Initial reports classified paracetamol as a part of the NSAIDs class due to the presumably shared inhibitory effect on PG synthesis. One thing that is already accepted in the scientific community is that paracetamol has almost no anti-inflammatory activity and does not cause the same adverse effects as NSAIDs do.⁵ So, it is sensible to assume that paracetamol is different from NSAIDs. The fact that paracetamol has a limited peripheral COX inhibitory effect and potent centrally located actions can help better understand the benefit–risk ratio of this old drug.

The maximum single dose of paracetamol for pain or fever treatment is 1 g every 4–6 hours as needed, up to a recommended maximum daily dose of 4 g. It is well established that paracetamol is clinically effective under the recommended daily dose and has a well-tolerable safety profile.⁷⁶ Paracetamol-related adverse events are rare in healthy adults receiving a daily dose of ≤ 4 g/day.⁷⁷ Thus, several guidelines recommend paracetamol as an optimal option for mild-to-moderate pain conditions, such as headache and migraine attacks, postoperative pain and chronic osteoarthritis for limited duration of treatment (however, with some discrepancies here, according to guidelines).^{78–81}

Interestingly, the analgesic effect of paracetamol has a distinct dose-response, according to experimental models and consumers' experience.⁸² The French National Agency for Medicines and Health Products Safety (ANSM) recommended initiating paracetamol with the minimum dose. In a recent focus review, studies comparing the analgesic response to higher (1 g) and lower (500–650 mg) doses of paracetamol were retrieved and summarized. Both direct and indirect comparisons demonstrated analgesic superiority of higher single dose compared to lower single doses, highlighting that a higher single dose of paracetamol for a short duration (4–5 days) poses more benefit than lower single doses.⁸⁰ This observation is consistent with the successful experimental demonstration in healthy volunteers of a lack of acetaminophen ceiling effect on R-III nociceptive flexion reflex.⁸³ In terms of safety, a Cochrane review concluded that the rate of adverse events was similar between the higher and lower single doses of paracetamol.⁸⁴ This was in line with another clinical trial showing similar rates of treatment-related adverse events between the higher and lower single doses of paracetamol.⁸⁵

Still, the safety of paracetamol is surrounded by controversy. Of course, hepatotoxicity is well established and remains a major issue. Indeed, paracetamol produces variable amounts of the hepatotoxic compound, NAPQI. Hepatic metabolism of paracetamol via the P450 system (mainly CYP-2E1) leads to the synthesis of NAPQI normally conjugated with glutathione and eliminated in urine. However, when high doses of paracetamol are used or at usual doses, in some patients at risk (malnutrition, alcoholism, some combinations of drugs, etc), glutathione stores can be decreased and/or

CYP activity increased, both leading to a high level of NAPQI and NAPQI-mediated liver necrosis, and thus doses must be adapted in this population. Interestingly, a recent work studying the role of acetaminophen on epitranscriptome suggests that its hepatotoxicity could be reduced by adequate strategy.⁸⁶ Otherwise, although some other safety issues associated with paracetamol remain inconclusive, some patients with comorbidities have concerns with the use of paracetamol for common pain conditions. Thus, it is imperative to consolidate the current literature and appropriately weigh the risk–benefit ratio of paracetamol for pain conditions in special populations until good scientific evidence of safety should prevail. Recently, Alchin et al reviewed the current evidence of paracetamol as the first-option analgesic in patients with kidney disease, cardiovascular diseases, gastrointestinal disorders, asthma, and the elderly.⁶ In another context, a recent work suggests that acetaminophen would be a potential suppressor of antitumor immunity, suggesting that it should be used with caution in patients treated with immune checkpoint blockers.⁸⁷

Regarding kidney function, NSAIDs, inhibitors of COX, should be avoided in patients with renal impairment.⁸⁸ On the contrary, therapeutic doses of paracetamol are generally safe and do not lead to acute renal failure in patients with renal impairment.⁸⁹ It was previously hypothesized that paracetamol may cause renal injury due to the reports of nephropathy after phenacetin overuse; however, this hypothesis was then rejected by further evidence.⁹⁰ Data show no association between paracetamol and acute renal failure in patients with chronic kidney disease.⁹¹ Thus, paracetamol remains the mainstay analgesic option in patients with chronic kidney disease.⁹² It is unnecessary to modify the dose for dialytic patients; however, dose reduction or longer dose interval should be considered in patients with advanced kidney failure.⁶

NSAIDs significantly increase the risk of cardiovascular adverse outcomes.⁹³ No robust evidence supports an association between paracetamol and adverse cardiovascular outcomes (stroke or myocardial infarction) in patients with atherosclerotic heart diseases.^{94–96} On the other hand, the risk of worsening hypertension should be considered, with some observational studies showing an increase in blood pressure among chronic paracetamol users.^{97,98} Still, published studies failed to show an association between elevated blood pressure and the risk of serious cardiovascular events in paracetamol users.⁹⁶ Paracetamol remains probably safer than NSAIDs which showed a significant increase in adverse cardiovascular outcomes amongst patients receiving non-aspirin NSAIDs.⁹⁹ According to an American Heart Association position statement, paracetamol should be preferred over NSAIDs in patients with coronary artery disease.¹⁰⁰

Aspirin and other NSAIDs significantly increase the risk of gastrointestinal ulcers and bleeding. Unlike NSAIDs, paracetamol, which has a minimal peripheral COX inhibitory effect, does not cause damage to the gastrointestinal tract. The current evidence affirms the more tolerable gastrointestinal safety profile of paracetamol than NSAIDs.¹⁰¹ Thus, paracetamol is the recommended first-line option for patients at risk of gastrointestinal ulcers or bleeding.⁶

Finally, paracetamol is considered the preferred analgesic option for the elderly, a challenging group to manage due to the high frequency of comorbidities and polypharmacy. Paracetamol represents an effective and safe analgesic option; however, its use in the elderly with chronic pain is still questionable.¹⁰²

Based on the above, it can be concluded that the centrally acted paracetamol is a compelling first-line analgesic option even for special populations if a low dosage is used, and it should be preferred over NSAIDs due to its very limited COX action and tolerable safety profile.

Paracetamol in Combination with Other Analgesics

Multimodal analgesia has become a principal approach for the management of acute postoperative pain conditions that offers additive or synergistic analgesia and lower opioid dose requirements. Theoretically, combining two analgesics with different mechanisms of action potentiates their analgesic actions without increasing their doses and compromising the safety outcomes.^{103–106} Paracetamol has linear and consistent pharmacokinetics, and its tolerable profile makes it a good option when a combination is required.¹⁰⁷

As previously elucidated, paracetamol has a central, COX-independent, analgesic action that can synergize other analgesics with different central or peripheral MoA. Thus, it can potentiate the analgesic effect of opioids without increasing the risk of adverse events (Table 1). The paracetamol plus opioids combination can benefit from the rapid onset of action of paracetamol and the sustained analgesic effect of opioids.¹⁰⁸ Several reports demonstrated that paracetamol plus opioids led to superior pain relief and lower dose requirements than individual components without

Table I Selected Clinical Studies Using Paracetamol Plus Opioids for Acute Post-Operative Pain

Study, Year	Type of Surgery	Design	N	Treatment Groups, Doses (mg)	Doses/Timing	Outcome
Fricke et al, 2002 ¹³⁰	Oral surgery	Double-blind RCT	200	Tramadol/Paracetamol 37.5 mg/325 mg Tramadol/ Paracetamol 75 mg/650 mg Hydrocodone/Paracetamol 10 mg/650 mg Placebo	Single dose, postoperative	Comparable analgesia, but better tolerability for tramadol/ Paracetamol than hydrocodone/ Paracetamol
MacLeod et al, 2002 ¹³¹	Dental	Double-blind RCT	82	Codeine/Paracetamol 30 mg/1000 mg Paracetamol 1000 mg	3 doses over 8 hours	Better analgesia with combination, with a similar rate of adverse events
Smith et al, 2004 ¹³²	Orthopedic and abdominal surgery	Double-blind RCT	305	Tramadol/Paracetamol 75 mg/650 mg Codeine/Paracetamol 60 mg/600 mg Placebo	1 to 2 tablets every 4 to 6 hours as needed for pain for 6 days.	Both active combinations provided significantly greater pain relief than placebo; scores were similar for tramadol/ Paracetamol and codeine/paracetamol.
Daniels et al, 2011 ¹²²	Dental	Double-blind RCT	678	Ibuprofen/Paracetamol 400 mg/1000 mg Ibuprofen/Paracetamol 200 mg/500 mg Ibuprofen/Codeine 400 mg/25.6 mg Codeine/ Paracetamol 30 mg/1000 mg Placebo	Single dose, postoperative	Ibuprofen/Paracetamol groups were superior in pain reduction to ibuprofen/codeine; ibuprofen/ Paracetamol, and noninferior to ibuprofen/codeine
Rawal et al 2011 ¹³³	Ambulatory hand surgery	Double-blind RCT	462	Tramadol/Paracetamol 37.5 mg/325 mg Tramadol 50 mg	Before and immediately after surgery and every 6 hours thereafter	Comparable analgesic efficacy, fewer adverse events with tramadol/ paracetamol, and reduced tramadol consumption by 24%
Sniezek et al, 2011 ¹²³	Mohs surgery and cutaneous reconstruction	Double-blind RCT	210	Paracetamol 1000 mg Ibuprofen/Paracetamol 400 mg/1000 mg Codeine/Paracetamol 30 mg/ 325 mg	Immediately after surgery and every 4 hours for up to 4 doses	Ibuprofen/paracetamol is superior to other 2 treatments in pain control; Higher rate of AEs under codeine/Paracetamol compared with ibuprofen/Paracetamol and Paracetamol alone
Aweke et al, 2020 ¹³⁴	Abdominal surgery	Single blind RCT	63	Paracetamol 1000 mg Diclofenac /Paracetamol 75 mg/1000 mg Tramadol/Paracetamol 100 mg/1000 mg	Single dose, postoperative	Paracetamol–tramadol and Paracetamol–diclofenac reduce cumulative postoperative analgesic consumption and prolongs the time to first rescue analgesic
Liu et al, 2021 ¹¹²	Arthroscopic knee surgery	Open-label RCT	232	Oxycodone/Paracetamol 10 mg/650 mg Celecoxib	Single dose, postoperative	Oxycodone–Paracetamol increased analgesic efficacy, with comparable safety profiles compared with celecoxib.
Singh et al, 2021 ¹³⁵	Rotator cuff repair	Open-label RCT	57	Oxycodone/Paracetamol 5 mg/1000 mg Oxycodone 5 mg Paracetamol 1000 mg	Combinations every 6 hours postoperative as needed Paracetamol 1000 mg perioperative	Perioperative acetaminophen significantly decreased opioid consumption and improved overall pain control.

Abbreviation: RCT, randomized controlled trial.

increasing the risk of adverse events in a wide range of pain conditions, such as osteoarthritis and postoperative pain.^{109,110} However, we do not have good evidence that paracetamol spares the opioid adverse effects when a high dose of opioid is used.¹¹¹ Recently, a comparative trial showed that the oxycodone/paracetamol combination was more effective than celecoxib in terms of reducing postoperative pain and rescue analgesia consumption amongst patients undergoing arthroscopic knee surgery. The oxycodone/paracetamol combination exhibited well tolerable safety profile, with no difference between the two groups.¹¹²

Paracetamol/NSAIDs combinations have regained much attention following the establishment of the COX-independent MoA of paracetamol. Combining paracetamol with NSAIDs can represent an alternative for opioids-

based analgesics in patients with moderate pain and no contraindication for NSAIDs. Paracetamol can theoretically potentiate the analgesic and morphine-sparing effects of NSAIDs in patients with acute pain without the need to increase NSAIDs doses.^{113,114} In a previous systematic review, combining paracetamol and NSAIDs was more effective than either agent alone in acute postoperative pain.¹¹⁵ The antinociceptive effects derived from paracetamol/NSAIDs combinations appear to be additive rather than synergistic; in 2012, Moore et al demonstrated that paracetamol plus NSAIDs led to additive analgesic rather than supra-additive (ie, synergism) effects.¹¹⁶

Previous pharmacokinetic reports demonstrated the lack of significant interactions in the pharmacokinetic profiles of ibuprofen and paracetamol when administered in a fixed-dose combination tablet, highlighting that the effect of this combination is primarily a pharmacodynamic one.^{117,118} Thus, the paracetamol/ibuprofen combination has been studied in several trials over the recent two decades. In a 2013 Cochrane review over three trials (n = 1647 patients), paracetamol/ibuprofen combination demonstrated higher reductions in acute postoperative pain and fewer patients needed rescue analgesia than either drug alone in patients undergoing impacted third molars extraction.¹¹⁹ These findings align with the 2010 systematic review showing that paracetamol/ibuprofen combination achieved superior analgesia than either drug alone.¹¹⁵ Recently, the PANSALID trial showed paracetamol/ibuprofen combination achieved higher analgesia and morphine-sparing effect than paracetamol alone in the first 24 hours after total hip arthroplasty.¹²⁰ The benefit of the paracetamol/ibuprofen combination was not significantly influenced by age, sex, or type of anesthesia.¹²¹ Notably, comparative trials also showed that the non-narcotic paracetamol/ibuprofen combination had a similar or higher analgesic effect compared to the acetaminophen/codeine approach.^{122–124}

According to the abovementioned studies performed in acute pain conditions, the analgesic paracetamol/ibuprofen combination appears to be well tolerable without a significant increase in safety concerns compared to either drug alone. In the PANSALID trial, patients on paracetamol/ibuprofen combination for postoperative pain at the first 24 hours after total hip arthroplasty did not experience a significant increase in the risk of serious adverse events compared to patients on either drug alone.¹²⁰ However, a 13-week trial showed patients on paracetamol/ibuprofen combination had a higher risk of decreases in hemoglobin level (≥ 1 g/dl) than monotherapy, suggesting a potential risk of bleeding on long-term use of paracetamol/ibuprofen combination.¹²² A population-based retrospective cohort study, using data from the government of Quebec health insurance agency databases, suggested that combining traditional NSAIDs with acetaminophen increases the risk of upper GI events beyond that of either agent alone.¹²⁵ Even if one of the limitations of this study pertains to the use of administrative databases in which the indication for which a medication is prescribed and actual drug consumption is not known, the results of these two studies warrant performing further research to establish the beneficial effect of the paracetamol/NSAIDs combinations and to investigate their safety profile for patients in need of chronic therapy.

The combination of paracetamol and gabapentin is another combination that is currently under investigation. Experimental evidence showed that paracetamol had a synergistic effect on gabapentin.¹²⁶ In patients who underwent an abdominal hysterectomy, Durmus et al studied the analgesic effect of the preoperative paracetamol and gabapentin combination compared to gabapentin 1200 mg alone. The results showed that the paracetamol and gabapentin combination was superior to gabapentin alone on pain intensity scores.¹²⁷ Further investigations are warranted.

Paracetamol Perspective: Future Analogs

As we have elucidated in this article, paracetamol itself can be considered as a pro-drug of the active centrally located metabolite, AM404. Nonetheless, paracetamol must first undergo hepatic deacylation into *p*-aminophenol and also produces variable amounts of the hepatotoxic compound NAPQI. Thus, paracetamol analogs were proposed to improve the safety profile of the drug, while keeping the same or even higher analgesic activity.

The development of paracetamol analogs that target the brain TRPV₁ receptors without the production of NAPQI and depletion of glutathione stores is a clinical perspective linked to the central action of paracetamol. It has been recently shown that paracetamol amine analogs undergo FAAH-dependent transformation into TRPV₁ activators without producing hepatotoxicity at the same dose that paracetamol produces clinically relevant hepatotoxicity; these analogs exhibited dose-dependent antinociceptive effects without antipyretic action, liver cell necrosis, or elevation in liver enzyme levels.^{18,128} Adamantyl, a paracetamol analog that selectively inhibits the TRPA₁ receptor, was also proposed.¹²⁹

These findings highlighted that developing centrally acted analgesics is possible; these compounds can exhibit a well-tolerable safety profile without significantly inducing hepatotoxicity.

Conclusion and Expert Opinion

Paracetamol remains among the most commonly prescribed analgesics. Nonetheless, the paracetamol MoA remained complex and not yet fully understood. It is now more evident that paracetamol analgesia has multiple pathways and is mediated by the formation of the bioactive AM404 metabolite in the CNS. The evidence discussed in this review established paracetamol as a central, COX-independent, analgesic medication that has a distinct MoA from NSAIDs and a more tolerable safety profile.

This leads to consider that paracetamol remains the preferred first-line option for mild-to-moderate acute pain management for healthy adults and patients with health concerns, such as the elderly, patients with gastrointestinal, renal impairments and/or cardiovascular disease. Nonetheless, to avoid hepatotoxicity, healthcare practitioners should consider appropriate paracetamol dosing individually in special populations and weigh the potential risk–benefit ratio after considering the patient-specific factors.

The central COX-independent MoA of paracetamol warrants to use it for multimodal analgesic approaches. Paracetamol can potentiate the analgesic effect of opioids without increasing the risk of adverse events; still, the evidence is limited, and further studies are needed on the morphine-sparing effect of combining paracetamol and opioids. Paracetamol/NSAIDs combination resulted in higher analgesia and no increase in the risk of adverse events than NSAIDs alone. Although the interest in paracetamol-based combinations is growing, the evidence is still limited, and further high-quality evidence is warranted.

As our understanding of the AM404-mediated activation of the TRPV₁ channel and CB1 receptor signaling evolves, several investigations are being conducted to test the benefit of paracetamol analogs, with promising results. Paracetamol analogs can activate the TRPV₁ channel signaling without the hepatic production of the toxic metabolite, NAPQI; hence, they can induce a higher analgesic effect than that of paracetamol without increasing the risk of hepatotoxicity. Thus, future experiments to better explain the central actions of paracetamol could pave the way for discovering analgesics with a better benefit-to-risk ratio as genetic studies could help to predict efficacy and tolerability of paracetamol.

Abbreviations

5-HT, serotonin (5-hydroxytryptamine); AM404, *N*-arachidonoylphenolamine; ANSM, Agence Nationale de Sécurité des Médicaments (French national agency for medicines and health products safety); CNS, central nervous system; COX, cyclooxygenase; CSF, cerebrospinal fluid; CYP, cytochrome; DAGL, diacylglycerol lipases; FAAH, fatty acid amide hydrolase; MoA, mechanism of action; NAPQI, *N*-acetyl-*p*-benzoquinone imine; NSAIDs, nonsteroidal anti-inflammatory drugs; OTC, over-the-counter; PG, prostaglandin; PLC, phospholipase C; POX, peroxidase; TRP, transient receptor potential; TRPV₁, transient receptor potential vanilloid.

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References

1. Nagakura Y. The need for fundamental reforms in the pain research field to develop innovative drugs. *Expert Opin Drug Discov.* 2017;12(1):39–46. doi:10.1080/17460441.2017.1261108
2. Ennis ZN, Dideriksen D, Vægter HB, Handberg G, Pottegård A. Acetaminophen for chronic pain: a systematic review on efficacy. *Basic Clin Pharmacol Toxicol.* 2016;118(3):184–189. doi:10.1111/BCPT.12527
3. O'Neil CK, Hanlon JT, Marcum ZA. Adverse effects of analgesics commonly used by older adults with osteoarthritis: focus on non-opioid and opioid analgesics. *Am J Geriatr Pharmacother.* 2012;10(6):331–342. doi:10.1016/j.amjopharm.2012.09.004
4. Mallet C, Eschalier A. The rediscovery of paracetamol, In: Farquhar-Smith P, Beaulieu P, Jaggar S, editors. *Landmark Papers in Pain: Seminal Papers in Pain with Expert Commentaries*. Vol. 1. 1st ed. Oxford University Press; 2018. doi:10.1093/MED/9780198834359.003.0004
5. Freo U, Ruocco C, Valerio A, Scagnol I, Nisoli E. Paracetamol: a review of guideline recommendations. *J Clin Med.* 2021;10(15). doi:10.3390/jcm10153420
6. Alchin J, Dhar A, Siddiqui K, Christo PJ. Why paracetamol (Acetaminophen) is a suitable first choice for treating mild to moderate acute pain in adults with liver, kidney or cardiovascular disease, gastrointestinal disorders, asthma, or who are older. *Curr Med Res Opin.* 2022;1–15. doi:10.1080/03007995.2022.2049551
7. Bertolini A, Ferrari A, Ottani A, Guerzoni S, Tacchi R, Leone S. Paracetamol: new vistas of an old drug. *CNS Drug Rev.* 2006;12(3–4):250–275. doi:10.1111/j.1527-3458.2006.00250.x
8. Flower RJ, Vane JR. Inhibition of prostaglandin synthetase in brain explains the anti-pyretic activity of paracetamol (4-acetamidophenol). *Nature.* 1972;240(5381):410–411. doi:10.1038/240410A0
9. Esh CJ, Christmas BCR, Mauger AR, Taylor L. Pharmacological hypotheses: is Acetaminophen selective in its cyclooxygenase inhibition? *Pharmacol Res Perspect.* 2021;9(4):e00835. doi:10.1002/prp2.835
10. Ohashi N, Kohno T. Analgesic effect of acetaminophen: a review of known and novel mechanisms of action. *Front Pharmacol.* 2020;11:580289. doi:10.3389/fphar.2020.580289
11. Przybyła GW, Szychowski KA, Gmiński J. Paracetamol - An old drug with new mechanisms of action. *Clin Exp Pharmacol Physiol.* 2020. doi:10.1111/1440-1681.13392
12. Mallet C, Eschalier A, Daulhac L. Paracetamol: update on its analgesic mechanism of action. *Pain Reli.* 2017. doi:10.5772/66649
13. 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(3):201–232. doi:10.1007/s10787-013-0172-x
14. Toussaint K, Yang XC, Zielinski MA, et al. What do we (not) know about how paracetamol (acetaminophen) works? *J Clin Pharm Ther.* 2010;35(6):617–638. doi:10.1111/J.1365-2710.2009.01143.X
15. Raffa RB, Walker EA, Sterious SN. Opioid receptors and acetaminophen (paracetamol). *Eur J Pharmacol.* 2004;503(1–3):209–210. doi:10.1016/j.ejphar.2004.08.055
16. Högestätt ED, Jönsson BAG, Ermund A, et al. Conversion of acetaminophen to the bioactive N-acylphenolamine AM404 via fatty acid amide hydrolase-dependent arachidonic acid conjugation in the nervous system*. *J Biol Chem.* 2005;280(36):31405–31412. doi:10.1074/JBC.M501489200
17. Mallet C, Daulhac L, Bonnefont J, et al. Endocannabinoid and serotonergic systems are needed for acetaminophen-induced analgesia. *Pain.* 2008;139(1):190–200. doi:10.1016/J.PAIN.2008.03.030
18. Barrière DA, Mallet C, Blomgren A, et al. Fatty acid amide hydrolase-dependent generation of antinociceptive drug metabolites acting on TRPV1 in the brain. *PLoS One.* 2013;8(8). doi:10.1371/JOURNAL.PONE.0070690
19. Dalmann R, Daulhac L, Antri M, Eschalier A, Mallet C. Supra-spinal FAAH is required for the analgesic action of paracetamol in an inflammatory context. *Neuropharmacology.* 2015;91:63–70. doi:10.1016/J.NEUROPHARM.2014.11.006
20. Muramatsu S, Shiraiishi S, Miyano K, et al. Metabolism of AM404 From Acetaminophen at Human Therapeutic Dosages in the Rat Brain. *Anesthesiol Pain Med.* 2016;6(1). doi:10.5812/AAPM.32873
21. Saliba SW, Marcotegui AR, Fortwängler E, et al. AM404, paracetamol metabolite, prevents prostaglandin synthesis in activated microglia by inhibiting COX activity. *J Neuroinflammation.* 2017;14(1). doi:10.1186/S12974-017-1014-3
22. Sodano F, Lazzarato L, Rolando B, et al. Paracetamol-galactose conjugate: a novel prodrug for an old analgesic drug. *Mol Pharm.* 2019;16(10):4181–4189. doi:10.1021/acs.molpharmaceut.9b00508
23. Parashar A. Pharmacological screening of glycine amino acid prodrug of acetaminophen. *Indian J Pharmacol.* 2015;47(2):202–205. doi:10.4103/0253-7613.153431
24. Wu Z, Patel A, Dave R, Yuan X. Development of acetaminophen proline prodrug. *Bioorg Med Chem Lett.* 2010;20(13):3851–3854. doi:10.1016/J.BMCL.2010.05.050
25. Fadl TA, Omar FA. Paracetamol (acetaminophen) esters of some non-steroidal anti-inflammatory carboxylic acids as mutual prodrugs with improved therapeutic index. *Inflammopharmacology.* 1998;6(2):143–157. doi:10.1007/S10787-998-0031-3
26. Hanel AM, Lands WEM. Modification of anti-inflammatory drug effectiveness by ambient lipid peroxides. *Biochem Pharmacol.* 1982;31(20):3307–3311. doi:10.1016/0006-2952(82)90565-2
27. Schildknecht S, Daiber A, Ghisla S, Cohen RA, Bachschmid MM. Acetaminophen inhibits prostanoid synthesis by scavenging the PGHS-activator peroxynitrite. *FASEB J.* 2008;22(1):215–224. doi:10.1096/FJ.06-8015COM
28. Ouellet M, Percival MD. Mechanism of acetaminophen inhibition of cyclooxygenase isoforms. *Arch Biochem Biophys.* 2001;387(2):273–280. doi:10.1006/ABBI.2000.2232
29. Lucas R, Warner TD, Vojnovic I, Mitchell JA, Mitchell JA. Cellular mechanisms of acetaminophen: role of cyclo-oxygenase. *FASEB J.* 2005;19(6):1–15. doi:10.1096/FJ.04-2437FJE
30. Boutaud O, Aronoff DM, Richardson JH, Marnett LJ, Oates JA. Determinants of the cellular specificity of acetaminophen as an inhibitor of prostaglandin H2 synthases. *Proc Natl Acad Sci U S A.* 2002;99(10):7130–7135. doi:10.1073/PNAS.102588199/ASSET/682AB754-3CF6-4EC9-B4FB-18483C903C21/ASSETS/GRAPHIC/PQ1025881008.JPEG
31. Graham GG, Scott KF. Mechanism of action of paracetamol. *Am J Ther.* 2005;12(1):46–55.
32. Aronoff DM, Oates JA, Boutaud O. New insights into the mechanism of action of acetaminophen: its clinical pharmacologic characteristics reflect its inhibition of the two prostaglandin H2 synthases. *Clin Pharmacol Ther.* 2006;79(1):9–19. doi:10.1016/j.clpt.2005.09.009

33. Murakami M, Naraba H, Tanioka T, et al. Regulation of prostaglandin E2 biosynthesis by inducible membrane-associated prostaglandin E2 synthase that acts in concert with cyclooxygenase-2. *J Biol Chem.* 2000;275(42):32783–32792. doi:10.1074/JBC.M003505200
34. Chandrasekharan NV, Dai H, Roos KLT, et al. COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure, and expression. *Proc Natl Acad Sci U S A.* 2002;99(21):13926–13931. doi:10.1073/pnas.162468699
35. Schwab JM, Beiter T, Linder JU, et al. COX-3—A virtual pain target in humans? *FASEB J.* 2003;17(15):2174–2175. doi:10.1096/FJ.03-0595LTE
36. Dinchuk JE, Liu RQ, Trzaskos JM. COX-3: in the wrong frame in mind. *Immunol Lett.* 2003;86(1):121. doi:10.1016/S0165-2478(02)00268-7
37. Mallet C, Barrière DA, Ermund A, et al. TRPV1 in brain is involved in acetaminophen-induced antinociception. *PLoS One.* 2010;5(9):1–11. doi:10.1371/journal.pone.0012748
38. Ayoub SS. Paracetamol (acetaminophen): A familiar drug with an unexplained mechanism of action. *Temperature.* 2021;8(4): 351–371. doi:10.1080/23328940.2021.1886392
39. Engström Ruud L, Wilhelms DB, Eskilsson A, et al. Acetaminophen reduces lipopolysaccharide-induced fever by inhibiting cyclooxygenase-2. *Neuropharmacology.* 2013;71:124–129. doi:10.1016/J.NEUROPHARM.2013.03.012
40. Feldberg W, Gupta KP. Pyrogen fever and prostaglandin-like activity in cerebrospinal fluid. *J Physiol.* 1973;228(1):41–53. doi:10.1113/JPHYSIOL.1973.SP010071
41. Ayoub SS, Botting RM, Goorha S, Colville-Nash PR, Willoughby DA, Ballou LR. Acetaminophen-induced hypothermia in mice is mediated by a prostaglandin endoperoxide synthase 1 gene-derived protein. *Proc Natl Acad Sci U S A.* 2004;101(30):11165–11169. doi:10.1073/PNAS.0404185101
42. Mirrasekhian E, Nilsson JLÅ, Shionoya K, et al. The antipyretic effect of paracetamol occurs independent of transient receptor potential ankyrin 1-mediated hypothermia and is associated with prostaglandin inhibition in the brain. *FASEB J.* 2018;32(10):5751–5759. doi:10.1096/fj.201800272R
43. Sharma CV, Long JH, Shah S, et al. First evidence of the conversion of paracetamol to AM404 in human cerebrospinal fluid. *J Pain Res.* 2017;10:2703–2709. doi:10.2147/JPR.S143500
44. Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: updates of national surgical adjuvant breast and bowel project protocols B-18 and B-27. *J Clin Oncol.* 2008;26(5):778–785. doi:10.1200/JCO.2007.15.0235
45. Kerckhove N, Mallet C, François A, et al. Ca(v)3.2 calcium channels: the key protagonist in the supraspinal effect of paracetamol. *Pain.* 2014;155(4):764–772. doi:10.1016/J.PAIN.2014.01.015
46. Ohashi N, Uta D, Sasaki M, Ohashi M, Kamiya Y, Kohno T. Acetaminophen metabolite N-acylphenolamine induces analgesia via transient receptor potential vanilloid 1 receptors expressed on the primary afferent terminals of C-fibers in the spinal dorsal horn. *Anesthesiology.* 2017;127(2):355–371. doi:10.1097/ALN.0000000000001700
47. Ryskamp DA, Redmon S, Jo AO, Križaj D. TRPV1 and endocannabinoids: emerging molecular signals that modulate mammalian vision. *Cells.* 2014;3(3):914. doi:10.3390/CELLS3030914
48. Liao HT, Lee HJ, Ho YC, Chiou LC. Capsaicin in the periaqueductal gray induces analgesia via metabotropic glutamate receptor-mediated endocannabinoid retrograde disinhibition. *Br J Pharmacol.* 2011;163(2):330. doi:10.1111/J.1476-5381.2011.01214.X
49. Zygmunt PM, Chuang HH, Movahed P, Julius D, Högestätt ED. The anandamide transport inhibitor AM404 activates vanilloid receptors. *Eur J Pharmacol.* 2000;396:1. 39–42. doi:10.1016/S0014-2999(00)00207-7
50. Barrière DA, Boumezbeur F, Dalmann R, et al. Paracetamol is a centrally acting analgesic using mechanisms located in the periaqueductal grey. *Br J Pharmacol.* 2020;177(8):1773–1792. doi:10.1111/bph.14934
51. Pickering G, Creveaux I, Macian N, Pereira B. Paracetamol and pain modulation by TRPV1, UGT2B15, SULT1A1 genotypes: a randomized clinical trial in healthy volunteers. *Pain Med.* 2020;21(4):661–669. doi:10.1093/PM/PNZ037
52. Bourinet E, Francois A, Laffray S. T-type calcium channels in neuropathic pain. *Pain.* 2016;157:S15–S22. doi:10.1097/J.PAIN.0000000000000469
53. Harding EK, Zamponi GW. Central and peripheral contributions of T-type calcium channels in pain. *Mol Brain.* 2022;15(1):1–13. doi:10.1186/S13041-022-00923-W
54. Francois A, Kerckhove N, Meleine M, et al. State-dependent properties of a new T-type calcium channel blocker enhance Ca(V)3.2 selectivity and support analgesic effects. *Pain.* 2013;154(2):283–293. doi:10.1016/J.PAIN.2012.10.023
55. Barbara G, Alloui A, Nargeot J, et al. T-type calcium channel inhibition underlies the analgesic effects of the endogenous lipoamino acids. *J Neurosci.* 2009;29(42):13106–13114. doi:10.1523/JNEUROSCI.2919-09.2009
56. Ottani A, Leone S, Sandrini M, Ferrari A, Bertolini A. The analgesic activity of paracetamol is prevented by the blockade of cannabinoid CB1 receptors. *Eur J Pharmacol.* 2006;531(1–3):280–281. doi:10.1016/J.EJPHAR.2005.12.015
57. Hama AT, Sagen J. Cannabinoid receptor-mediated antinociception with acetaminophen drug combinations in rats with neuropathic spinal cord injury pain. *Neuropharmacology.* 2010;58(4–5):758–766. doi:10.1016/J.NEUROPHARM.2009.12.010
58. Heinricher MM, Tavares I, Leith JL, Lumb BM. Descending control of nociception: specificity, recruitment and plasticity. *Brain Res Rev.* 2009;60(1):214–225. doi:10.1016/j.brainresrev.2008.12.009
59. Tjølsen A, Lund A, Hole K. Antinociceptive effect of paracetamol in rats is partly dependent on spinal serotonergic systems. *Eur J Pharmacol.* 1991;193(2):193–201. doi:10.1016/0014-2999(91)90036-P
60. Dogrul A, Seyrek M, Akgul EO, Cayci T, Kahraman S, Bolay H. Systemic paracetamol-induced analgesic and antihyperalgesic effects through activation of descending serotonergic pathways involving spinal 5-HT 7 receptors. *Eur J Pharmacol.* 2012;677(1–3):93–101. doi:10.1016/j.ejphar.2011.12.016
61. Courade JP, Caussade F, Martin K, et al. Effects of Acetaminophen on monoaminergic systems in the rat central nervous system. *Naunyn Schmiedeberg's Arch Pharmacol.* 2001;364(6):534–537. doi:10.1007/s002100100484
62. Pickering G, Loriot MA, Libert F, Eschalié A, Beaune P, Dubray C. Analgesic effect of acetaminophen in humans: first evidence of a central serotonergic mechanism. *Clin Pharmacol Ther.* 2006;79(4):371–378. doi:10.1016/J.CLPT.2005.12.307
63. Nakamura S, Nonaka T, Komatsu S, Yamada T, Yamamoto T. Oral Acetaminophen-induced spinal 5-hydroxytryptamine release produces analgesic effects in the rat formalin test. *Biomed Pharmacother.* 2022;146. doi:10.1016/J.BIOPHA.2021.112578
64. Alloui A, Pelissier T, Dubray C, Lavarenne J, Eschalié A. Tropicisetron inhibits the antinociceptive effect of intrathecally administered paracetamol and serotonin. *Fundam Clin Pharmacol.* 1996;10(4):406–407. doi:10.1111/J.1472-8206.1996.TB00593.X
65. Alloui A, Chassaing C, Schmidt J, et al. Paracetamol exerts a spinal, tropisetron-reversible, antinociceptive effect in an inflammatory pain model in rats. *Eur J Pharmacol.* 2002;443(1–3):71–77. doi:10.1016/S0014-2999(02)01578-9

66. Bonnefont J, Alloui A, Chapuy E, Clottes E, Eschalié A. Orally administered paracetamol does not act locally in the rat formalin test: evidence for a supraspinal, serotonin-dependent antinociceptive mechanism. *Anesthesiology*. 2003;99(4):976–981. doi:10.1097/0000542-200310000-00034
67. Bonnefont J, Chapuy E, Clottes E, Alloui A, Eschalié A. Spinal 5-HT_{1A} receptors differentially influence nociceptive processing according to the nature of the noxious stimulus in rats: effect of WAY-100635 on the antinociceptive activities of paracetamol, venlafaxine and 5-HT. *Pain*. 2005;114(3):482–490. doi:10.1016/J.PAIN.2005.01.019
68. Bonnefont J, Daulhac L, Etienne M, et al. Acetaminophen recruits spinal p42/p44 MAPKs and GH/IGF-1 receptors to produce analgesia via the serotonergic system. *Mol Pharmacol*. 2007;71(2):407–415. doi:10.1124/MOL.106.025775
69. Liu J, Reid AR, Sawynok J. Antinociception by systemically-administered acetaminophen (paracetamol) involves spinal serotonin 5-HT₇ and adenosine A₁ receptors, as well as peripheral adenosine A₁ receptors. *Neurosci Lett*. 2013;536(1):64–68. doi:10.1016/J.NEULET.2012.12.052
70. Pickering G, Estève V, Lorient MA, Eschalié A, Dubray C. Acetaminophen reinforces descending inhibitory pain pathways. *Clin Pharmacol Ther*. 2008;84(1):47–51. doi:10.1038/SJ.CLPT.6100403
71. Yamaguchi C, Yamamoto D, Fujimaru Y, Asano T, Takaoka A. Acetaminophen exerts an analgesic effect on muscular hyperalgesia in repeated cold-stressed rats through the enhancing of the descending pain inhibitory system involving spinal 5-HT₃ and noradrenergic α₂ receptors. *Biol Pharm Bull*. 2021;44(8):1067–1074. doi:10.1248/BPB.B21-00178
72. Pickering G, Faure M, Commun F, et al. Tropicisetron and paracetamol association in post-operative patients. *Fundam Clin Pharmacol*. 2012;26(3):432–437. doi:10.1111/J.1472-8206.2011.00933.X
73. Bandschapp O, Filitz J, Urwyler A, Koppert W, Ruppen W. Tropicisetron blocks analgesic action of acetaminophen: a human pain model study. *Pain*. 2011;152(6):1304–1310. doi:10.1016/J.PAIN.2011.02.003
74. Hamurtekin Y, Nouilati A, Demirbatir C, Hamurtekin E. The contribution of serotonergic receptors and nitric oxide systems in the analgesic effect of acetaminophen: an overview of the last decade. *Turkish J Pharm Sci*. 2020;17(1):119. doi:10.4274/TJPS.GALENOS.2018.35403
75. Danelich IM, Wright SS, Lose JM, Tefft BJ, Cicci JD, Reed BN. Safety of nonsteroidal antiinflammatory drugs in patients with cardiovascular disease. *Pharmacother J Hum Pharmacol Drug Ther*. 2015;35(5):520–535. doi:10.1002/PHAR.1584
76. Jozwiak-Bebenista M, Nowak JZ. Paracetamol: mechanism of action, applications and safety concern. *Acta Pol Pharm Drug Res*. 2014;71(1):11–23.
77. Hayward KL, Powell EE, Irvine KM, Martin JH. Can paracetamol (Acetaminophen) be administered to patients with liver impairment? *Br J Clin Pharmacol*. 2016;81(2):210–222. doi:10.1111/bcp.12802
78. Richette P, Doherty M, Pascual E, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. *Ann Rheum Dis*. 2017;76(1):29–42. doi:10.1136/annrheumdis-2016-209707
79. Haag G, Diener HC, May A, et al. Self-medication of migraine and tension-type headache: summary of the evidence-based recommendations of the Deutsche Migräne und Kopfschmerzgesellschaft (DMKG), the Deutsche Gesellschaft für Neurologie (DGN), the Österreichische Kopfschmerzgesellschaft (Ö). *J Headache Pain*. 2011;12(2):201–217. doi:10.1007/s10194-010-0266-4
80. Gaul C, Eschalié A. Dose can help to achieve effective pain relief for acute mild to moderate pain with over-the-counter paracetamol. *Open Pain J*. 2018;11(1):12–20. doi:10.2174/1876386301811010012
81. Perrot S, Eschalié A, Desmeules J, Lanteri-Minet M, Attal N. Practice guidelines for the treatment of acute migraine and chronic knee osteoarthritis with paracetamol: an expert appraisal on evolution over time between scientific societies. *Curr Med Res Opin*. 2022. doi:10.1080/03007995.2022.2076475
82. McQuay HJ, Moore RA. Dose-response in direct comparisons of different doses of aspirin, ibuprofen and paracetamol (acetaminophen) in analgesic studies. *Br J Clin Pharmacol*. 2007;63(3):271–278. doi:10.1111/j.1365-2125.2006.02723.x
83. Piguet V, Desmeules J, Dayer P. Lack of Acetaminophen ceiling effect on R-III nociceptive flexion reflex. *Eur J Clin Pharmacol*. 1998;53(5):321–324. doi:10.1007/S002280050386
84. Moore RA, Wiffen PJ, Derry S, Maguire T, Roy YM, Tyrrell L. Non-prescription (OTC) oral analgesics for acute pain - an overview of Cochrane reviews. *Cochrane Database Syst Rev*. 2015;2017(10). doi:10.1002/14651858.CD010794.pub2
85. Qi DS, May LG, Zimmerman B, et al. A randomized, double-blind, placebo-controlled study of acetaminophen 1000 mg versus acetaminophen 650 mg for the treatment of postsurgical dental pain. *Clin Ther*. 2012;34(12). doi:10.1016/j.clinthera.2012.11.003
86. Evke S, Lin Q, Melendez JA, Begley TJ. Epitranscriptomic reprogramming is required to prevent stress and damage from Acetaminophen. *Genes*. 2022;13(3). doi:10.3390/GENES13030421/S1
87. Bessede A, Marabelle A, Guégan JP, et al. Impact of Acetaminophen on the efficacy of immunotherapy in cancer patients. *Ann Oncol off J Eur Soc Med Oncol*. 2022;33(9):909–915. doi:10.1016/J.ANNONC.2022.05.010
88. Davison SN. Clinical pharmacology considerations in pain management in patients with advanced kidney failure. *Clin J Am Soc Nephrol*. 2019;14(6):917–931. doi:10.2215/CJN.05180418
89. Hiragi S, Yamada H, Tsukamoto T, et al. Acetaminophen administration and the risk of acute kidney injury: a self-controlled case series study. *Clin Epidemiol*. 2018;10:265–276. doi:10.2147/CLEP.S158110
90. Evans M, Fore D, Bellocco R, et al. Acetaminophen, aspirin and progression of advanced chronic kidney disease. *Nephrol Dial Transplant*. 2009;24(6):1908–1918. doi:10.1093/ndt/gfn745
91. Graham G, Graham R, Day R. Comparative analgesia, cardiovascular and renal effects of celecoxib, rofecoxib and acetaminophen (paracetamol). *Curr Pharm Des*. 2005;8(12):1063–1075. doi:10.2174/1381612023394917
92. Davison SN, Rathwell S, George C, Hussain ST, Grundy K, Dennett L. Analgesic use in patients with advanced chronic kidney disease: a systematic review and meta-analysis. *Can J Kidney Heal Dis*. 2020;(7). doi:10.1177/2054358120910329
93. Martín Arias LH, Martín González A, Sanz Fadrique R, Vazquez ES. Cardiovascular risk of nonsteroidal anti-inflammatory drugs and classical and selective cyclooxygenase-2 inhibitors: a meta-analysis of observational studies. *J Clin Pharmacol*. 2019;59(1):55–73. doi:10.1002/JCPH.1302
94. White WB, Kloner RA, Angiolillo DJ, Davidson MH. Cardiorenal Safety of OTC Analgesics. *J Cardiovasc Pharmacol Ther*. 2018;23(2):103–118. doi:10.1177/1074248417751070
95. Dawson J, Fulton R, McInnes GT, et al. Acetaminophen use and change in blood pressure in a hypertensive population. *J Hypertens*. 2013;31(7):1485–1490. doi:10.1097/HJH.0b013e328360f6f8
96. Fulton RL, Walters MR, Morton R, et al. Acetaminophen use and risk of myocardial infarction and stroke in a hypertensive cohort. *Hypertension*. 2015;65(5):1008–1014. doi:10.1161/HYPERTENSIONAHA.114.04945

97. Turtle EJ, Dear JW, Webb DJ. A systematic review of the effect of paracetamol on blood pressure in hypertensive and non-hypertensive subjects. *Br J Clin Pharmacol*. 2013;75(6):1396–1405. doi:10.1111/BCP.12032
98. MacIntyre IM, Turtle EJ, Farrah TE, Graham C, Dear JW, Webb DJ. Regular acetaminophen use and blood pressure in people with hypertension: the PATH-BP trial. *Circulation*. 2022;145(6):416–423. doi:10.1161/CIRCULATIONAHA.121.056015
99. Schjerning AM, McGettigan P, Gislason G. Cardiovascular effects and safety of (non-aspirin) NSAIDs. *Nat Rev Cardiol*. 2020;17(9):574–584. doi:10.1038/s41569-020-0366-z
100. Antman EM, Bennett JS, Daugherty A, Furberg C, Roberts H, Taubert KA. Use of nonsteroidal antiinflammatory drugs: an update for clinicians: a scientific statement from the American Heart Association. *Circulation*. 2007;115(12):1634–1642. doi:10.1161/CIRCULATIONAHA.106.181424
101. Ishitsuka Y, Kondo Y, Kadowaki D. Toxicological property of acetaminophen: the dark side of a safe antipyretic/analgesic drug? *Biol Pharm Bull*. 2020;43(2):195–206. doi:10.1248/bpb.b19-00722
102. BMJ Publishing Group Limited. What dose of paracetamol for older people? *Drug Ther Bull*. 2018;56(6):69–72. doi:10.1136/dtb.2018.6.0636
103. Wu CL, Raja SN. Treatment of acute postoperative pain. *Lancet*. 2011;377(9784):2215–2225. doi:10.1016/S0140-6736(11)60245-6
104. Raffa RB. Pharmacology of oral combination analgesics: rational therapy for pain. *J Clin Pharm Ther*. 2001;26(4):257–264. doi:10.1046/j.1365-2710.2001.00355.x
105. Patel R, Dickenson AH. Neuropharmacological basis for multimodal analgesia in chronic pain. *Postgrad Med*. 2022;134(3):245–259. doi:10.1080/00325481.2021.1985351
106. Gilron I, Jensen TS, Dickenson AH. Combination pharmacotherapy for management of chronic pain: from bench to bedside. *Lancet Neurol*. 2013;12(11):1084–1095. doi:10.1016/S1474-4422(13)70193-5
107. Bannwarth B, Péhourcq F. [Pharmacologic basis for using paracetamol: pharmacokinetic and pharmacodynamic issues]. *Drugs*. 2003;63 (Special Issue 2):5–13. French. doi:10.2165/00003495-200363992-00003
108. Schug SA. Combination analgesia in 2005—a rational approach: focus on paracetamol–tramadol. *Clin Rheumatol*. 2006;25(SUPPL 7):16–21. doi:10.1007/S10067-006-0202-9/FIGURES/5
109. Dhillon S. Tramadol/paracetamol fixed-dose combination: a review of its use in the management of moderate to severe pain. *Clin Drug Investig*. 2010;30(10):711–738. doi:10.2165/11205830-000000000-00000
110. Jebaraj B, Maitra S, Baidya DK, Khanna P. Intravenous paracetamol reduces postoperative opioid consumption after orthopedic surgery: a systematic review of clinical trials. *Pain Res Treat*. 2013;2013. doi:10.1155/2013/402510
111. Freo U. Paracetamol for multimodal analgesia. *Pain Manag*. 2022;12(6):737–750. doi:10.2217/pmt-2021-0116
112. Liu J, Di J, Zhang Y, Xing E. Oxycodone–paracetamol tablet exhibits increased analgesic efficacy for acute postoperative pain, higher satisfaction and comparable safety profiles compared with celecoxib in patients underwent arthroscopic knee surgery. *Inflammopharmacology*. 2021;29(4):1091–1099. doi:10.1007/s10787-021-00828-5
113. Dahl JB, Nielsen RV, Wetterslev J, et al. Post-operative analgesic effects of paracetamol, NSAIDs, glucocorticoids, gabapentinoids and their combinations: a topical review. *Acta Anaesthesiol Scand*. 2014;58(10):1165–1181. doi:10.1111/AAS.12382
114. Miranda HF, Puig MM, Prieto JC, Pinardi G. Synergism between paracetamol and nonsteroidal anti-inflammatory drugs in experimental acute pain. *Pain*. 2006;121(1–2):22–28. doi:10.1016/J.PAIN.2005.11.012
115. Ong CKS, Seymour RA, Lirk P, Merry AF. Combining paracetamol (acetaminophen) with nonsteroidal antiinflammatory drugs: a qualitative systematic review of analgesic efficacy for acute postoperative pain. *Anesth Analg*. 2010;110(4):1170–1179. doi:10.1213/ANE.0B013E3181CF9281
116. Moore RA, Derry CJ, Derry S, Straube S, McQuay HJ. A conservative method of testing whether combination analgesics produce additive or synergistic effects using evidence from acute pain and migraine. *Eur J Pain*. 2012;16(4):585–591. doi:10.1016/J.EJPAIN.2011.08.009
117. Tanner T, Aspley S, Munn A, Thomas T. The pharmacokinetic profile of a novel fixed-dose combination tablet of ibuprofen and paracetamol. *BMC Clin Pharmacol*. 2010;10(1):10. doi:10.1186/1472-6904-10-10
118. Atkinson HC. A pharmacokinetic analysis of a novel fixed dose oral combination of paracetamol and ibuprofen, with emphasis on food effect. *J Bioequiv Availab*. 2015;7(3). doi:10.4172/JBB.1000230
119. Derry CJ, Derry S, Moore RA. Single dose oral ibuprofen plus paracetamol (Acetaminophen) for acute postoperative pain. *Cochrane Database Syst Rev*. 2013;2013(6). doi:10.1002/14651858.CD010210.PUB2
120. Thybo KH, Hägi-Pedersen D, Dahl JB, et al. Effect of combination of paracetamol (acetaminophen) and ibuprofen vs either alone on patient-controlled morphine consumption in the first 24 hours after total hip arthroplasty: the PANSALID randomized clinical trial. *JAMA*. 2019;321(6):562–571. doi:10.1001/JAMA.2018.22039
121. Thybo KH, Hägi-Pedersen D, Wetterslev J, et al. Benefits and harm of paracetamol and ibuprofen in combination for post-operative pain: pre-planned subgroup analyses of the multicenter, randomized PANSALID trial. *Acta Anaesthesiol Scand*. 2020;64(2):245–253. doi:10.1111/AAS.13496
122. Daniels SE, Goulder MA, Aspley S, Reader S. A randomised, five-parallel-group, placebo-controlled trial comparing the efficacy and tolerability of analgesic combinations including a novel single-tablet combination of ibuprofen/paracetamol for postoperative dental pain. *Pain*. 2011;152(3):632–642. doi:10.1016/J.PAIN.2010.12.012
123. Sniezek PJ, Brodland DG, Zitelli JA. A randomized controlled trial comparing acetaminophen, acetaminophen and ibuprofen, and acetaminophen and codeine for postoperative pain relief after Mohs surgery and cutaneous reconstruction. *Dermatol Surg*. 2011;37(7):1007–1013. doi:10.1111/J.1524-4725.2011.02022.X
124. Mitchell A, McCrea P, Inglis K, Porter G. A randomized, controlled trial comparing acetaminophen plus ibuprofen versus acetaminophen plus codeine plus caffeine (Tylenol 3) after outpatient breast surgery. *Ann Surg Oncol*. 2012;19(12):3792–3800. doi:10.1245/S10434-012-2447-7
125. 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(4):872–882. doi:10.1111/j.1572-0241.2008.01811.x
126. Mititelu Tartau L, Popa EG, Lupusoru RV, Lupusoru CE, Stoleriu I, Ochiuz L. Synergic effects of pregabalin-acetaminophen combination in somatic and visceral nociceptive reactivity. *Pharmacology*. 2014;93(5–6):253–259. doi:10.1159/000362649
127. Durmus M, But AK, Saricicek V, Toprak HI, Ersoy MO. The post-operative analgesic effects of a combination of gabapentin and paracetamol in patients undergoing abdominal hysterectomy: a randomized clinical trial. *Acta Anaesthesiol Scand*. 2007;51(3):299–304. doi:10.1111/J.1399-6576.2006.01237.X

128. Johan JL, Mallet C, Shionoya K, et al. Paracetamol analogues conjugated by FAAH induce TRPV1-mediated antinociception without causing acute liver toxicity. *Eur J Med Chem.* 2021;213. doi:10.1016/J.EJMECH.2020.113042
129. Fresno N, Pérez-Fernández R, Goicoechea C, et al. Adamantyl analogues of paracetamol as potent analgesic drugs via inhibition of TRPA1. *PLoS One.* 2014;9(12):e113841. doi:10.1371/journal.pone.0113841
130. Fricke JR, Karim R, Jordan D, Rosenthal N. A double-blind, single-dose comparison of the analgesic efficacy of tramadol/acetaminophen combination tablets, hydrocodone/acetaminophen combination tablets, and placebo after oral surgery. *Clin Ther.* 2002;24(6):953–968. doi:10.1016/S0149-2918(02)80010-8
131. Macleod AG, Ashford B, Voltz M, et al. Paracetamol versus paracetamol-codeine in the treatment of post-operative dental pain: a randomized, double-blind, prospective trial. *Aust Dent J.* 2002;47(2):147–151. doi:10.1111/J.1834-7819.2002.TB00319.X
132. Smith AB, Ravikumar TS, Kamin M, Jordan D, Xiang J, Rosenthal N. Combination tramadol plus acetaminophen for postsurgical pain. *Am J Surg.* 2004;187(4):521–527. doi:10.1016/j.amjsurg.2003.12.038
133. Rawal N, Macquaire V, Catalá E, Berti M, Costa R, Wietlisbach M. Tramadol/paracetamol combination tablet for postoperative pain following ambulatory hand surgery: a double-blind, double-dummy, randomized, parallel-group trial. *J Pain Res.* 2011;4:103. doi:10.2147/JPR.S16760
134. Aweke Z, Seyoum F, Shitemaw T, Doba DN. Comparison of preemptive paracetamol, paracetamol-diclofenac & paracetamol-tramadol combination on postoperative pain after elective abdominal surgery under general anesthesia, Ethiopia: a randomized control trial study, 2018. *BMC Anesthesiol.* 2020;20(1). doi:10.1186/S12871-020-01115-6
135. Singh AM, Kirsch JM, Patel MS, et al. Effect of perioperative acetaminophen on pain management in patients undergoing rotator cuff repair: a prospective randomized study. *J Shoulder Elb Surg.* 2021;30(9):2014–2021. doi:10.1016/J.JSE.2021.03.132

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