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Role of Acetaminophen in Chronic Pain Management: Benefits, Risks, and Considerations

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Abstract

Chronic pain affects 20-25% of the global population, significantly impacts quality of life and socioeconomic productivity, placing a substantial burden on healthcare systems worldwide, particularly in low- and middle-income countries, and disproportionately affecting vulnerable populations, including older adults and cancer patients. Acetaminophen, a commonly used analgesic and crucial non-opioid alternative in chronic pain management, is frequently a first-line treatment for mild-to-moderate pain (including musculoskeletal pain, osteoarthritis, and headaches) and is often used with opioids for more severe pain. It modulates the central nervous system, primarily by inhibiting COX-2 enzymes to reduce prostaglandin production and pain signaling. In cancer-related pain and palliative care, it serves as an essential adjunct to more potent analgesics, reducing opioid consumption and side effects. As a key component of multimodal pain management, it enhances other medications' analgesic effects and minimizes their side effects. Future research should investigate acetaminophen's long-term effectiveness in more diverse populations (including the elderly and those with complex medication regimens), and its optimal role in multimodal analgesia and opioid-sparing strategies, particularly for cancer-related pain.

Keywords: Intravenous acetaminophen; Paracetamol; N-acetyl-para-aminophenol (APAP); Chronic pain; Multimodal pain management; Opioid analgesics; Non-opioid analgesics

Introduction

Chronic pain, defined as persistent pain lasting three months or longer than expected [1-2]. Musculoskeletal conditions, osteoarthritis (OA), neuropathic pain, and pain related to cancer, which differ in intensity and required treatment, are common sources [1-3]. OA causes cartilage erosion, inflammation, stiffness, and mechanical stress, all of which contribute to chronic pain [4-5]. As the healthcare community seeks safer, non-opioid alternatives, acetaminophen plays a vital role in managing chronic pain, offering a viable option for reducing the burden without the risks of addiction and overdose [3]. This article reviews the use of acetaminophen in managing chronic pain, focusing on its efficacy, clinical applications, and limitations.

Global burden of chronic pain

Chronic pain has major implications on an individual's quality of life, mental health, functional ability, and socioeconomic productivity. The World Health Organization (WHO) estimates that chronic pain affects around 20 to 25% of the population worldwide, with the consequences unevenly distributed

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[6,7]. In the United States, the prevalence of chronic pain is estimated to be 52.4% cases per 1000 person-years [6]. In low- and middle-income countries (LMICs), the burden is especially significant, with prevalence rates of 34% in adults, 62% in elderly, and 52% among workers in these regions [8]. Vulnerable populations, including older adults and cancer patients, are disproportionately affected [6,7]. For cancer patients, cancer-related chronic pain is estimated at 25% to 75% [9]. The median prevalence of chronic pain in children and adolescents is estimated to range from 11% to 38%, with girls having a higher prevalence than boys [9]. Chronic pain is a major driver of healthcare costs, including medications, diagnostic tests, surgery, and frequent medical visits that strain the healthcare systems [1]. The social and economic burden of chronic pain is substantial, constituting to both direct and indirect costs [2]. In LMICs, chronic low back pain (CLBP) and musculoskeletal disorders contribute significant disability and psychological distress [8]. Caregivers may also experience stress, burnout, and financial difficulties while indirect healthcare costs involve absence from work, lost productivity, and frequent medical attention [1,2] Individuals with chronic pain may require prolonged care within the social support system, again adding pressure on an already overstressed healthcare resource [10].

Use of acetaminophen in managing chronic non-cancer related pain

Acetaminophen, commonly called paracetamol (or Tylenol), and N-acetyl-para-aminophenol (APAP), is considered the first-line analgesic treatment for mild-to-moderate pain and in combination with an non-steroidal anti-inflammatory drugs (NSAIDs) and opioid analgesics for severe pain including musculoskeletal pain, OA, and tension- type headaches [1-2,11]. As a first-line drug, it is generally preferred over Nonsteroidal anti-inflammatory drugs (NSAIDs) due to its lower risk of gastrointestinal, cardiovascular and renal side effects, making it a safer option for long-term pain management [3,7,10-13]. Its primary mechanism of action involves modulating the central nervous system (CNS) by inhibiting the cyclooxygenase (COX) enzymes, particularly COX-2 and COX-3, within the brain. This inhibition reduces prostaglandin production, thereby decreasing the levels of chemical mediators responsible for pain signaling and inflammation [1,3,7,12]. Given its limited anti-inflammatory properties, acetaminophen is particularly helpful for managing chronic pain, such as headaches, minor musculoskeletal pain, or postoperative pain, OA, rheumatoid arthritis (RA), chronic fatigue syndrome (CFS), especially in pediatric and adolescent populations [7,14,15]. However, it is not considered the first-line treatment for conditions like RA where inflammation plays a key role [15]. Its safety profile and broad range of indications make acetaminophen a favorite among patients for long-term pain management, without the anti-inflammatory effects of NSAIDs [6,12,16]. In RA, acetaminophen alleviates pain in deeper tissues by reducing temporal summation and supporting conditioned pain modulation [15,17]. Acetaminophen modulates conditioned pain in the CNS and, thus, alleviates pain in CFS. However, its efficacy in children and adolescents with CFS remains unclear, as studies show mixed results regarding its effectiveness in managing postoperative pain and migraines [15,17]. Acetaminophen has limited efficacy in the long-term management of CLBP (Table 1) and (Table 2) [2-3,6,18-23].

Use of acetaminophen in management of cancer-related pain and palliative care

Cancer-related pain can arise from tumor progression, nerve dysfunction, or side effects of treatments like radiation and chemotherapy [4,7]. Acetaminophen is used in combination with stronger analgesics or opioids to enhance pain relief and reduce opioid consumption, thereby minimizing the adverse effects of opioids, including constipation, sedation, and tolerance [7,10,24]. In palliative care, acetaminophen is used to manage pain and fever, reducing opioid requirements and their associated side effects, including constipation, cognitive impairment, respiratory depression, and risk of opioid dependency [7,25]. It is particularly valuable in patients with advanced cancer or those in palliative care, offering pain relief without the risks associated with NSAIDs [26]. Acetaminophen can also be used long-term without significant risk of gastrointestinal bleeding or nephrotoxicity, which are more prevalent with other NSAIDs analgesics [25,26]

Table 1: The table summarizes the results of a survey of patients with chronic low back pain (CLBP) treated in the McDermott Pain Center at UT Southwestern Medical Center in Dallas in 1999-2000 (White PF, Gliner R, 2000) It highlights differences in the perceived effectiveness of commonly used medications. NSAIDs were the most widely used and generally effective, offering at least temporary relief for the majority of patients. Acetaminophen showed limited transient benefit in relieving CLBP, with the majority of patients reporting no significant long-term relief. Opioids provided temporary pain relief comparable to NSAIDs.

Patients assessment of commonly used drugs for low back pain (White et al. 2000)			
Drug group*	**Definitely helpful**	**Temporary relief**	**Not helpful**
Non-steroids (80%)	33	54	13
Acetaminophen (42%)	9	37	54
Benzodiazepines (48%)	21	59	21
Opioids (32%)	32	68	0
Antidepressants (25%)	0	40	60
Steroids (10%)	33	50	17

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Table 2: The table summarizes the patient assessments for commonly used drugs for chronic low back pain (CLBP), including their effectiveness and the incidence of adverse events. The data is derived from various studies and systematic reviews, providing a comprehensive overview of the current clinical knowledge.

Drug	Patient Assessment (Efficacy and Use)	Efficacy (%)	Patient Assessment (Adverse Events)	Specific Adverse Events
NSAIDs (e.g., ibuprofen) [18-20]	69% prescribed; effective for pain reduction	60-70%	49.9% reported adverse events	Gastrointestinal issues (e.g., bleeding, ulcers), cardiovascular risks, renal impairment
Muscle Relaxants (e.g., baclofen) [18-20]	35% prescribed, effective for symptom relief	50-60%	43.1% reported adverse events	Sedation, dizziness, dry mouth, fatigue
Opioids (e.g., tramadol) [18-20]	12% prescribed, effective for severe pain	40-50%	61% reported adverse events	Nausea, dizziness, constipation, vomiting, somnolence, dry mouth
Acetaminophen [18-19]	4% prescribed, less effective for pain reduction	20-30%	Lower adverse events compared to NSAIDs	Generally well-tolerated, rare liver toxicity at high doses
Combination (e.g., paracetamol + tramadol) [18]	Effective for pain reduction	50-60%	2.1 times higher risk of adverse events compared to placebo	Combination from both drugs including nausea, dizziness, constipation
Duloxetine [19-20]	Effective for chronic pain reduction	50-60%	Increased risk of withdrawal due to adverse events	Nausea, dry mouth, fatigue, insomnia
Gabapentin/Pregabalin [21-22]	Effective for neuropathic pain	40-50%	Increased risk of dizziness, somnolence	Dizziness, somnolence, peripheral edema
COX-2 Inhibitors (e.g., celecoxib) [19,23]	Effective for pain reduction with lower GI risk	60-70%	Lower GI risk compared to traditional NSAIDs	Cardiovascular risks, renal impairment

Use of acetaminophen as part of a multimodal pain management regimen

Acetaminophen is an integral part of multimodal pain management regimens, particularly for chronic pain management without opioids [24]. It is prescribed along with other analgesics, such as NSAIDs or opioids (morphine) to enhance analgesic effects and reduce the need for higher doses of other medications. This approach helps minimize side effects like sedation, gastrointestinal irritation, or renal toxicity [24-28-29].

Recommended dosage and routes of administration

The usual acetaminophen dosage varies according to the route of administration. Oral (PO) intake is generally given to adults at a 500-1000 mg dose every four to six hours [25,32]. Intravenous acetaminophen, commonly prescribed for patients who cannot take oral medications due to severe pain or nausea, is given in 1000 mg doses every six hours [25,32,33]. The total daily limit should not exceed 4000 mg to minimize hepatotoxicity risks [7,25,32,33]. Patients nearing or exceeding this limit should be monitored for hepatotoxicity such as jaundice or abdominal pain, and may benefit from periodic liver function tests [7]. Older adults should take 500 mg every six hours due to slower metabolism and increased liver toxicity risk [7], with regular liver and kidney function monitoring [25]. When combined with opioids, either in chronic or post-surgical conditions, the risk of overdose increases due to respiratory suppression and liver damage, necessitating close monitoring of respiratory status and overdose signs [3,9].

Limitations of acetaminophen in chronic pain management

Benefits: Acetaminophen is primarily beneficial for its opioid-sparing effect, reducing the need for opioids and their associated side effects, such as sedation and addiction [1-2,7,10,24,29]. It also plays a role in multimodal analgesia, enhancing the effects of other pain relievers, including NSAIDs and regional anesthesia [12,34]. Additionally, acetaminophen is well-tolerated with minimal risk of gastrointestinal bleeding or renal damage, unlike NSAIDs [16,25-27]. However, in some patients its prolonged use, especially above 2-3 g per day, can increase blood pressure and the risk of gastrointestinal bleeding [25,26].

Limitations

Acetaminophen's efficacy in providing sustained relief from chronic pain is limited. Prolonged use at high doses may lead to hepatotoxicity, particularly in patients with existing liver conditions and/or chronic alcohol abuse [35]. While effective for mild-to-moderate pain, acetaminophen has limited anti-inflammatory action, making it less suitable for managing conditions like RA or inflammatory bowel disease where substantial anti-inflammatory effects are needed [14,15]. NSAIDs, with their more pronounced anti-inflammatory properties, are generally preferred in such cases. [7,31].

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Comparison with NSAIDs

Acetaminophen is often preferred over NSAIDs due to its safer profile in patients with gastrointestinal, renal, or cardiovascular risks, making it suitable for long-term management of OA despite the fact that NSAIDs may provide superior analgesic efficacy [7,12,13,33,37,38]. Although less effective than medications like celecoxib for managing low back pain [37], acetaminophen can help improve motivation in patients with chronic low back pain [39,40] and is generally better tolerated by those with chronic conditions [15,37]. In RA, its limited efficacy makes it less favorable for managing inflammation-related-pain [11,15,33]. Despite NSAIDs providing better relief and functional improvement for conditions like OA and low back pain [15], acetaminophen remains the preferred choice for individuals with gastrointestinal or renal concerns due to its lower risk of adverse effects [7,41].

Contraindications and interactions

Acetaminophen has relatively few contraindications and drug interactions. The most significant contraindication is severe liver disease, such as cirrhosis, active hepatitis, or liver failure, as impaired liver function exacerbates the risk of hepatotoxicity [5,7]. Chronic alcohol use increases this risk, so avoiding excessive alcohol consumption is crucial [7]. Patients with existing liver conditions should have regular liver function tests to detect early signs of damage [7,34]. When taken with warfarin, acetaminophen may enhance the anticoagulant's effects and increase the bleeding risk. [24,35-36].

Conclusion

Acetaminophen is widely used analgesic for chronic pain management due to its favorable safety profile, making it ideal for long-term use in conditions like osteoarthritis, musculoskeletal pain, and cancer-related pain. Its versatility across multiple medical conditions makes it an effective alternative to reduce dependency on opioids and other more toxic pain-relieving medications. Acetaminophen provides pain relief with minimal side effects and is especially beneficial for patients at risk of gastrointestinal, renal, or cardiovascular complications associated with NSAIDs. It is a very valuable adjuvant to more potent analgesics. While it is a first-line treatment for mild-to-moderate pain, its efficacy can vary by condition. Future research should focus on assessing its long-term effectiveness in diverse patient populations, including the elderly, patients with chronic pain on multiple medications, and its role as an adjunctive (opioid-sparing) therapy for cancer-related pain.

Conflict of interest

There are no conflicts of interest among the contributors.

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