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THERAPEUTIC UTILITY VERSUS TOXICITY: PHARMACOVIGILANCE INSIGHTS INTO PARACETAMOL-ASSOCIATED ADVERSE DRUG REACTIONS

Relli Harshitha[1], Muppidi Pushpa Latha[1], Thollamadugu Naga Siva Saranya[1], G.Manoj Raj[2], Lasini Puvvala[3], Geddam Ratna Priya[4*]

[1]PharmD Scholar, Doctor of Pharmacy, VJ's College of Pharmacy, Diwancheruvu, Rajahmundry - 533296, Andhra Pradesh, India.
[2]Research Intern, Doctor of Pharmacy, Clinilaunch Research Institute, 304, 3rd Floor, Punjagutta Officers Colony, Punjagutta, Hyderabad, Telangana - 500016.
[3]PharmD Scholar, Doctor of Pharmacy, Koringa College of Pharmacy, Korangi, Kakinada, Andhra Pradesh, India.
[4]Assistant Professor, Department of Pharmacy Practice, Koringa College of Pharmacy, Korangi, Kakinada, Andhra Pradesh, India.

***Corresponding Author: Geddam Ratna Priya**

Assistant Professor, Department of Pharmacy Practice, Koringa College of Pharmacy, Korangi, Kakinada, Andhra Pradesh, India. **DOI:** https://doi.org/10.5281/zenodo.18872819

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ABSTRACT

Acetaminophen, often known as paracetamol, is distinguished from conventional non-steroidal anti-inflammatory medications (NSAIDs) by its distinct central mode of action as a non-acidic, non-opioid analgesic agent. Despite being widely used for more than a century. Its central mode of action sets it apart from NSAIDs; it targets several pathways in the Central Nervous System (CNS) as a prodrug. It acts as a vital antipyretic for infectious diseases and is recommended for acute conditions such as migraines, dental pain, and musculoskeletal aches. Intravenous use for postoperative pain and the closure of the patent ductus arteriosus in premature neonates are examples of specialized applications. From the standpoint of a clinical pharmacist, managing paracetamol needs to strike a balance between its broad therapeutic index and its high utility. Although safe at therapeutic levels, an analysis of data from 2016 to 2026 reveals that it is often linked to gastrointestinal distress and, more importantly, "therapeutic misadventure." This happens when patients mix multi-ingredient products and inadvertently overdose. Additionally, recent studies have linked gastrointestinal bleeding and elevated blood pressure to long-term high-dose therapy. Organ-related disorders are rare, but severe hypersensitivity continues to be a major concern. This review highlights the critical role that pharmacists play in patient education, early ADR detection, and multimodal analgesic regimen supervision. Pharmacists make sure paracetamol stays a safe mainstay of contemporary medicine by spotting possible toxicity and stopping careless overdoses. In modern practice, this framework helps physicians balance the drug's significant therapeutic benefits against its changing safety profile.

KEYWORDS: Paracetamol, adverse drug reactions, pharmacovigilance, safety profile, and drug monitoring.

INTRODUCTION

Paracetamol is an aniline derivative. Which is also an active metabolite of phenacetin. Under the category of antipyretics and analgesics. Chemically, it belongs to the class of para-aminophenol derivatives.[1]

Mainly, it is indicated for mild to moderate pain relief, such as treating headaches and migraines and musculoskeletal pain, and in postoperative pain relief. And widely used in fever reduction, which is caused by viral and bacterial infections. i.e., antipyretic. The exact mechanism of action is still undergoing research but primarily works on the central nervous system (CNS) by various pathways, which include

1. Inhibition of prostaglandin synthesis.
2. COX-3 theory.
3. Serotonergic pathways.[2,3]

According to the US FDA review, there were 107 reports of severe skin reactions, the majority of which consisted of the single active ingredient paracetamol and led to the development of severe skin conditions. Clinical pharmacists (PharmDs) play a crucial role in identifying adverse drug reactions (ADRs). To enhance medication safety, they oversee reporting these responses to national pharmacovigilance programs (such as PvPI in India). Changing the safety profile of paracetamol and the pharmacist's proactive role in detecting adverse drug reactions (ADRs) and averting "therapeutic misadventures" to improve patient outcomes in contemporary clinical practice are assessed in this research.[4,5]

Drug Profile

Drug class	Analgesic and antipyretic
Common brands	Calpol, Dolo 650, Pacimol, Sumo L, and Febrinil.
Dosage Forms	Available as tablets, capsules, effervescent tablets, powder, and intravenous injections
Mechanism of action	Primarily work on the CNS system by inhibiting PG's synthesis via COX enzymes and other pathways like serotonergic and cannabinoid pathways.
Uses	Used to relieve mild to moderate pain, reduce fever, and provide multimodal analgesia.
Dosing	Children below 12 years and above can have 500 to 1000 mg every four to six hours with a maximum of 4000 mg in any 24-hour period.
Side effects	Tiredness and fatigue upon long-term use Nausea and vomiting and stomach discomfort are severe, and rare symptoms include Stevens-Johnson syndrome, liver damage,

Adr Overview

a) Reported ADRs

1. Erythema multiforme and paracetamol consumption. Within four days of starting to take paracetamol, she developed skin lesions, and after stopping the medication, there was a noticeable improvement.

The WHO UMC system also suggests a "possible" relationship, and the Naranjo algorithm was used for the causality assessment, yielding a score of +4. Because of its mild anti-inflammatory properties, paracetamol, a para-amino phenol derivative sometimes referred to as acetaminophen, is not frequently classified as an NSAID. It is the most widely used antipyretic medication worldwide and is usually well tolerated. In the literature, paracetamol-induced erythema multiforme major is uncommon.[5]

2. Just 1.2% (55 instances) of all hypotension cases were linked to paracetamol

The most frequent adverse drug response (ADR) linked to propacetamol use was hypotension (37.1%), while the most common adverse drug reaction (ADR) linked to paracetamol was cutaneous rashes. In senior individuals (≥54 years), propacetamol/paracetamol-associated hypotension was commonly observed.[6–8]

3. Severe hypersensitivity reactions to paracetamol are uncommon

According to the article, paracetamol can cause Stevens-Johnson Syndrome (SJS): crusty lips and painful oral sores. Lesions on the skin that resemble targets. Genital ulcers and inflamed eyes.

Leukocytosis and increased C-reactive protein were among the laboratory results that were indicative of systemic inflammation. The ADR was severe enough to necessitate supportive care, corticosteroid therapy, and hospitalization.[9]

b) Classification of ADRs based on their severity.[10–14]

MILD	MODERATE	SEVERE
Nausea and vomiting	Hypertension	hepatotoxicity
loss of appetite	Gastrointestinal issues	Severe allergic reactions
Increased sweating, fatigue	Renal complications	Stevens-Johnson syndrome (SJS)
mild fever or headache	Abnormal liver function	Acute Generalized Exanthematous Pustulosis (AGEP).

c) Incidence and frequency[15,16]

Incidence	Findings	Frequency
Mild	mostly headache, rash, and nausea. According to retrospective hospital investigations, this group accounted for 60.97% of	~61% of ADRs
	All reported adverse drug reactions.	
Moderate	Includes situations requiring medical attention, such as face puffiness or increased liver enzymes. Hospital settings made up 39.02% of reports.	~39% of ADRs
Severe	includes situations that need medical attention, such as face puffiness or high liver enzymes. In certain hospital settings, these made up 39.02% of the reports.	<5% of total patients

Mechanism Behind ADRs of Paracetamol

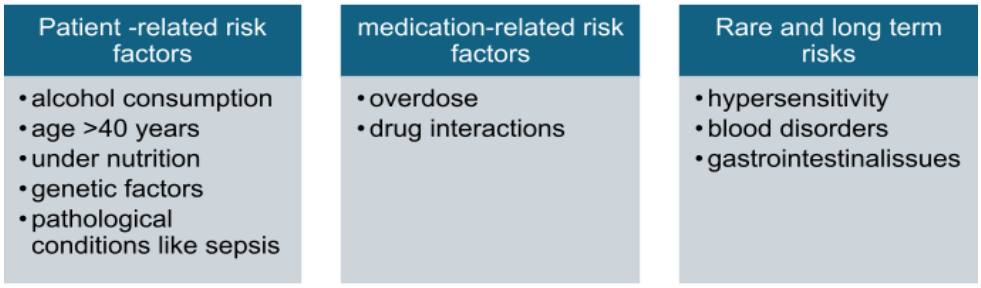
The enzyme known as cyclooxygenase, which is responsible for the metabolism of arachidonic acid to the prostanoids (including prostaglandins and thromboxane's), is also more appropriately called prostaglandin H2 synthetase. Prostaglandin's G2 (PGG2), an unstable intermediate hydroperoxide, must first be produced by activity at the COX site for arachidonic acid to be transformed to prostanoids. Prostaglandin H2 (PGH2) is subsequently produced.

By functioning as a reducing co-substrate at the POX site, paracetamol is thought to indirectly interfere with COX's enzymatic activity, which depends on it being in the oxidized form. By preventing the natural regeneration of POX, paracetamol is a powerful inhibitor of PG production in intact cells when arachidonic acid levels are low.[17,18]

The reason paracetamol is more effective in lowering conditions with low peroxide concentration is because it has no affinity for the active site of COXs and instead inhibits their activity by decreasing the conversion of the active oxidized form of the enzymes to an inactive form.[19] After being administered centrally, paracetamol is beneficial in rat pain models.

The idea that paracetamol interacts with serotonergic descending pain pathways and that spinal 5-hydroxytryptamine type 3 (5-HT3) receptors are involved in the antinociceptive impact of the drug is supported by animal studies. When the analgesic effects of acetaminophen were totally inhibited in volunteers when tropisetron or granisetron (5-HT3 receptor antagonists) were administered with paracetamol. when measured by median nerve electrical stimulation-induced pain. Granisetron, a more selective antagonist, caused more pain in volunteers than tropisetron (as seen by the area under the time-pain curve). Paracetamol is thought to strengthen descending inhibitory pain pathways.[3,20]

Risk Factors[4,21,22]



Management and monitoring

In 2026, standardized, evidence-based methods that prioritize accuracy in antidote administration and multidisciplinary surveillance have taken over clinical care and monitoring of adverse drug reactions (ADRs) related to paracetamol (acetaminophen).[23,24] Early risk assessment and N-acetylcysteine (NAC) treatment are the main strategies for managing paracetamol-induced hepatotoxicity.[25]

Protocols for Stratified Infusion: A systematic NAC regimen is frequently advised by current clinical guidelines. This strategy seeks to reduce the possibility of non-allergic responses while offering an adequate antidote. To successfully neutralize the hazardous metabolite NAPQI, the typical NAC method may need to be modified in cases of substantial overdose. The use of instruments such as the Naranjo Scale for systematic causality assessment. To detect possible drug-induced liver injury (DILI) at an earlier stage, future systems are anticipated to integrate artificial intelligence (AI) and real-world evidence.[26,27] Many people are unaware that their prescription painkiller, sleep aid, and cold remedy all include paracetamol. These "double doses" are

discovered by pharmacists before the patient even leaves the pharmacy.[28,29]

A pharmacist sees more than simply a "standard dose." They consider the patient's age, weight, and other prescription drugs. The pharmacist steps in to reduce the dosage if the patient is taking a medication that increases the toxicity of paracetamol, such as several seizure medications. Pharmacist's take the time to explain the significance of the daily dosage limit. They stop "accidental overdoses" that result in hospital stays by educating patients on how to read labels. The pharmacist is typically the one who formally notifies health authorities (such as PVPI) when a patient experiences a negative reaction.[30]

DISCUSSION

From the perspective of a clinical pharmacist in 2026, paracetamol is a "double-edged sword." Although it is perhaps the most dependable drug on the planet, its familiarity frequently breeds a risky degree of complacency. This review emphasizes the clinical pharmacist's viewpoint to learn more about the drug's side effects before administering it to a patient and to draw attention to the growing trend of "therapeutic misadventure." This is not just a medical phrase; it is a real-life scenario in which a patient unintentionally overlaps many pills while attempting to treat a backache or the flu, endangering their liver. However, it is impossible to overstate the uncommon and serious reactions like Stevens-Johnson Syndrome (SJS).[31] Pharmacists must be extremely careful in identifying early warning symptoms, such as painful mouth sores or target-shaped skin lesions, because these are life-altering occurrences, not just statistics. A dose that is safe for one individual may be dangerous for another due to the science underlying these processes, which explains how paracetamol interacts with enzymes and weakens the body's natural defenses.[32] A patient's liver does not have the same "protective shield" if they are undernourished or have alcoholism. The clinical pharmacist serves as the last line of defense in this situation. We are examining the individual's entire life, including their nutrition, other medicines, and routines, rather than merely marking boxes in the forms.[33,34]

CONCLUSION

Proactive risk assessment must replace reactive treatment in the management of paracetamol adverse drug reactions. Pharmacists are crucial gatekeepers who use patient education and kinetic monitoring to reduce the increased occurrence of organ-related illnesses and severe hypersensitivity. They are more than just reporters to pharmacovigilance programs like PvPI or FDA. By balancing the drug's central mode of action with its potential for systemic harm, clinical pharmacists ensure that paracetamol remains a safe pillar of modern medicine.

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Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

Authors' Contributions

R.H, M.P.L., and T.N.S.S. conducted the literature review, performed data collection, and contributed to drafting the manuscript. G.M.R and L.P. assisted with reference compilation, formatting, and preliminary revisions. G.R.P. provided critical academic guidance, supervision, and clinical content validation. G.R.P. also conceptualized the study, coordinated the review process, finalized the manuscript, and ensured its overall intellectual integrity. All authors read, reviewed, and approved the final version of the manuscript.

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