www.ijarp.com ISSN 2456-9992 Page: 01-22

International Journal Advanced Research Publications

Review Article

Volume: 02
Issue: 04

ANALYZING PATTERNS OF PARACETAMOL POISONING IN THE OVER- 65 DEMOGRAPHIC

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Article Received: 21 February 2026, Article Revised: 12 March 2026, Published on: 01 April 2026

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DOI: https://doi-doi.org/101555/ijarp.9868

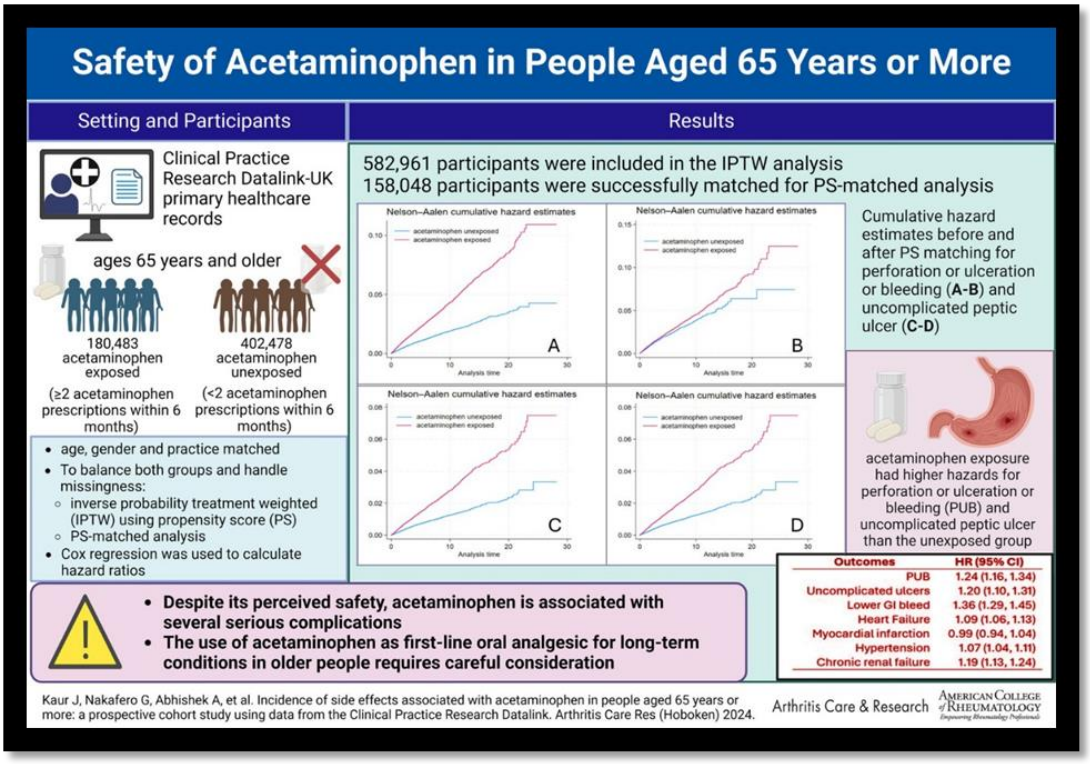
ABSTRACT:

Because of its accessibility and perceived safety, paracetamol (acetaminophen) continues to be one of the most commonly used analgesic and antipyretic medications worldwide. Overdosing on paracetamol remains a major cause of acute liver failure globally, despite its extensive therapeutic use. According to new research, older adults are a clinically vulnerable population where toxicity outcomes may be impacted by pharmacokinetic changes, comorbidities, polypharmacy, and delayed presentation. This review examines clinical risk factors, pharmacological mechanisms, epidemiological trends, and treatment approaches for paracetamol poisoning in people 65 years of age and older. The interaction of comorbid conditions with hepatotoxic pathways, repeated supratherapeutic ingestion, and age-related metabolic changes are all given special attention. To clarify the factors influencing toxicity in this population, recent research from toxicology registries, population cohorts, and clinical pharmacology studies is critically assessed. Comprehending these trends is crucial for enhancing clinical risk assessment, refining therapeutic approaches, and directing preventative measures for senior citizens.

1. INTRODUCTION:

More than half of cases of acute liver failure in high-income countries are caused by the widely used painkiller and antipyretic paracetamol, with older people being disproportionately affected despite having lower incidence rates than younger cohorts [1]. In individuals over 65, poisoning often manifests as an inadvertent overdose brought on by long-term medication use, which is made worse by polypharmacy, poor hepatic clearance, and frailty [2]. According to epidemiological data, fulminant hepatic failure (FHF) and

mortality peak in people over 40, with odds ratios rising to 4.18 for death or transplantation in older ages, while overdoses peak in people between the ages of 15 and 24 [3]. Due to low glutathione levels and CYP2E1 dysregulation, elderly patients present later (more than 24 hours after ingestion), which is linked to a higher risk of hepatotoxicity [4]. Supratherapeutic doses have been linked to occult toxicity, including disorientation, metabolic acidosis, and multi-organ failure, in the frail elderly, according to recent research (2016–2026) [5]. Paracetamol (acetaminophen) is widely regarded as the first-line analgesic for mild to moderate pain and fever management due to its favorable safety profile when used within therapeutic limits. However, overdose of paracetamol remains a major global public health issue and constitutes one of the leading causes of drug-induced liver injury and acute liver failure in many countries. Epidemiological estimates indicate that paracetamol contributes to approximately 56% of severe acute liver injury cases and a substantial proportion of drug-induced hepatotoxicity worldwide



[Fig -1 Despite its perceived safety, acetaminophen is associated with several serious complications. Given its minimal analgesic effectiveness, acetaminophen as the first-line oral analgesic option for long-term conditions in older people requires careful reconsideration. [7].

Although intentional overdose and younger adults have historically been linked to paracetamol poisoning, a growing amount of research indicates that older adults constitute a unique toxicological subgroup. Different patterns of exposure, such as therapeutic mishaps, repeated supratherapeutic dosing, and inadvertent overdoses from combination medications, are frequently seen in older patients. The risk of toxicity is further complicated by physiological changes associated with aging. Frailty, altered drug metabolism, and decreased hepatic reserve may increase vulnerability to hepatotoxic injury. [6]

As the world's population ages, chronic pain conditions that often require analgesic therapy are becoming more common. As a result, the use of paracetamol among people over 65 has significantly increased. The metabolism and toxicity of paracetamol, however, may be impacted by the substantial pharmacokinetic and pharmacodynamic changes linked to aging. These elements emphasize the necessity of focused studies on the prevalence of paracetamol poisoning in this population.

The goal of this review is to thoroughly examine clinical risk factors, mechanistic pathways, epidemiological trends, and management approaches related to paracetamol poisoning in adults over 65. [8]

2. EPIDEMIOLOGY OF PARACETAMOL POISONING IN OLDER ADULTS

One of the most common pharmaceutical toxic exposures reported globally is paracetamol poisoning. Even though overall overdose incidence rates are higher in younger populations, older people typically experience disproportionately higher mortality and severe outcomes. Large observational studies show that older age is linked to a higher risk of serious consequences from paracetamol poisoning, such as death and fulminant hepatic failure. Compared to younger patients, those 40 years of age and older have substantially higher odds of severe hepatic injury and mortality. [9]

Elderly paracetamol poisoning is characterized by a number of epidemiological patterns:

2.1 Intentional vs Unintentional Overdose

Intentional overdoses connected to self-harm are common in younger populations. On the other hand, therapeutic mishaps are more likely to result in inadvertent overdoses in older patients. Cognitive impairment, misinterpreting dosage instructions, and concurrent use of multiple paracetamol-containing medications are factors that contribute to this pattern.

2.2 Repeated Supratherapeutic Ingestion

Older adults who self-medicate for chronic pain are more likely to engage in repeated supratherapeutic ingestion (RSTI). In contrast to acute single-dose overdose, RSTI frequently develops gradually over several days and may show delayed clinical symptoms, making diagnosis more challenging.[10]

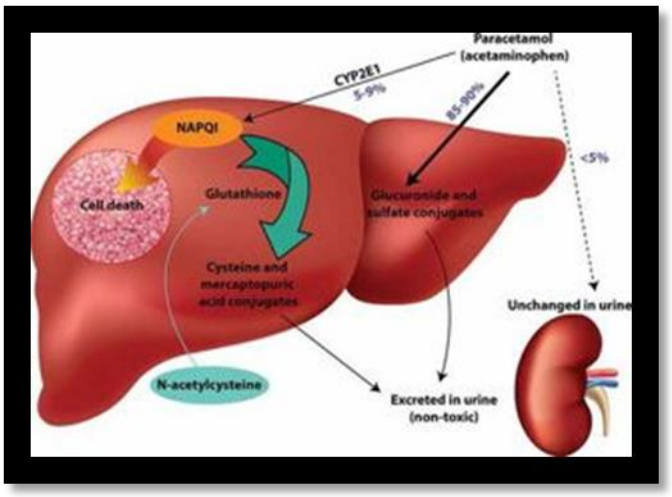
2.3 Hospitalisation and Mortality Trends

Following drug exposure, older adults have worse clinical outcomes and higher hospitalisation rates. According to pharmacovigilance data, people over 65 are much more likely than younger populations to experience severe complications and adverse drug reactions.

3. PHARMACOTHERAPY OF PARACETAMOL POISONING IN ADULTS AGED > 65 YEARS:

3.1. Role of Antidote Therapy in Paracetamol Toxicity:

The timely administration of N-acetylcysteine (NAC), which serves as the main antidote capable of preventing or limiting hepatocellular injury, is the cornerstone of pharmacological management of paracetamol poisoning. The ability of NAC to restore hepatic glutathione stores and aid in the detoxification of the extremely reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI) accounts for its therapeutic effectiveness [10]. Only a small portion of paracetamol is oxidized under physiological conditions by cytochrome P450 enzymes, mainly CYP2E1, to produce NAPQI, which is quickly conjugated with glutathione and eliminated in non-toxic forms. Nevertheless, under overdose circumstances, the glucuronidation and sulfation pathways become saturated, increasing the production of NAPQI and subsequently depleting intracellular glutathione. NAPQI starts to covalently bind to cellular proteins when glutathione stores drop below about 30% of typical hepatic concentrations. causing hepatocyte necrosis, oxidative stress, and mitochondrial malfunction.[12]



[Figure 2. Toxic mechanism of paracetamol and mechanism of action of acetylcysteine. Paracetamol is primarily detoxified by glucuronide and sulfate conjugates which are then excreted in the urine. A small percentage is metabolized by CYP2E1 to the reactive intermediate NAPQI. Under normal conditions, NAPQI can be detoxified by reaction with glutathione to form cysteine and mercaptopuric acid conjugates. If glutathione is depleted (e.g. in paracetamol overdose), NAPQI binds to cell macromolecules causing hepatocyte cell death. The antidote acetylcysteine replenishes cysteine, which is the rate-limiting factor for glutathione synthesis.][13].

By serving as a precursor to cysteine, the rate-limiting substrate for glutathione synthesis, N-acetylcysteine reinstates the hepatic detoxification system. Along with this replenishment effect, NAC has antioxidant qualities and enhances hepatic microcirculatory blood flow, which reduces cellular damage in later stages of toxicity. Numerous clinical studies have shown that the risk of severe hepatotoxicity is significantly decreased when NAC is given within 8–10 hours of ingestion.[14] However, because of its antioxidant and anti-inflammatory qualities, NAC has also been shown to have therapeutic benefits when given later in the course of poisoning, especially in patients with established liver injury.

Early NAC therapy initiation is especially crucial in older adults because hepatic regenerative capacity may be diminished by physiological aging. Moreover, endogenous glutathione reserves may be compromised by comorbid conditions like chronic liver disease or malnutrition, which are common in older patients. Even at relatively lower toxic exposures, these factors may increase susceptibility to hepatotoxic injury. [14]

3.2. Intravenous N-Acetylcysteine Regimens:

Because of its quick onset of action and consistent systemic availability, intravenous NAC administration is frequently used in clinical practice. An initial loading dose is followed by two maintenance infusions as part of a three-stage infusion regimen administered over roughly 21 hours in the conventional intravenous protocol. While the subsequent maintenance infusions sustain protective concentrations of cysteine and facilitate continued detoxification, the loading phase rapidly replenishes glutathione stores and neutralizes circulating NAPQI. [15]

When given early after an overdose, this intravenous regimen has been shown in clinical studies to be very effective in preventing hepatotoxicity. However, during intravenous NAC therapy, side effects like anaphylactoid reactions, which include flushing, rash, bronchospasm, and hypotension, have occasionally been documented. Usually dose-related, these reactions might happen more frequently in the early stages of infusion. The majority of the time, symptoms are temporary and can be controlled by stopping the infusion for a short while or giving antihistamines. [16]

When oral therapy is not feasible for elderly patients because of nausea, vomiting, altered mental status, or difficulty swallowing, intravenous NAC may be especially helpful. Furthermore, intravenous delivery guarantees consistent drug concentrations, which could be advantageous for weak people with altered gastrointestinal absorption. [17]

3.3. Oral N-Acetylcysteine Therapy:

Oral N-acetylcysteine (NAC) is still a crucial pharmacological intervention, especially in clinical settings where intravenous administration is not readily available. It has long been acknowledged as an effective antidotal therapy for paracetamol poisoning. The amino acid cysteine is the source of NAC, a sulfhydryl-containing compound that is essential for the synthesis of glutathione, the main intracellular antioxidant that detoxifies the toxic metabolite produced during paracetamol metabolism. Oral NAC restores the liver's ability to neutralize the reactive intermediate N-acetyl-p-benzoquinone imine (NAPQI) and replenishes hepatic glutathione stores following an overdose. NAC is essential for halting the development of paracetamol-induced hepatotoxicity by promoting detoxification and lowering oxidative damage in hepatocytes. [18]

Oral NAC's pharmacological mechanism of action goes beyond just replenishing glutathione. After consumption, NAC is deacetylated in the liver and digestive system to create cysteine, which then takes part in the synthesis of glutathione in hepatocytes. Because glutathione is

more readily available, NAPQI can be quickly conjugated and detoxified, avoiding its covalent binding to vital cellular proteins.[19] Because it causes oxidative stress, mitochondrial dysfunction, and eventually cell death, this binding process is thought to be a crucial stage in the pathophysiology of hepatocellular injury. NAC has been demonstrated to have direct antioxidant effects by scavenging reactive oxygen species and lowering the production of free radicals, in addition to its function as a precursor to glutathione. Additionally, by increasing nitric oxide-mediated vasodilation, NAC may enhance hepatic microcirculation and oxygen delivery, facilitating cellular recovery in damaged liver tissue.[20]

The ability of NAC to regulate inflammatory reactions linked to liver damage caused by paracetamol is another significant pharmacodynamic effect. According to experimental research, NAC lessens the activation of cytokines and inflammatory mediators that cause hepatocellular damage in the later stages of toxicity. Even after liver damage has begun, NAC may still have protective effects by reducing oxidative stress and inflammatory signaling pathways. Because NAC therapy may improve survival outcomes even when treatment starts later than the ideal therapeutic window, it is frequently continued in patients with established hepatotoxicity. [21]

In order to maintain sufficient systemic concentrations of glutathione and cysteine for long-term detoxification of harmful metabolites, oral NAC therapy usually entails a prolonged dosing schedule. NAC has a moderate systemic bioavailability after being absorbed through the gastrointestinal tract and going through a lot of first-pass metabolism. [22] When dosage schedules are appropriately adhered to, therapeutic levels are adequate to replenish hepatic glutathione despite this metabolic restriction. The extended course of treatment guarantees ongoing detoxification during the time that paracetamol's continued hepatic metabolism may still be causing NAPQI formation.

Despite the high efficacy of oral NAC, there are a number of potential side effects, chief among them being gastrointestinal intolerance. The medication's disagreeable sulfur-like taste and smell are mostly to blame for the most frequently reported side effects, which include nausea, vomiting, abdominal pain, and diarrhea. Patients who already have nausea and vomiting as symptoms of paracetamol poisoning may find these gastrointestinal reactions especially troublesome. Persistent vomiting may occasionally impair medication absorption and lower treatment compliance, requiring the switch to intravenous therapy. [23]

With oral NAC, hypersensitivity reactions are comparatively uncommon but can happen on occasion. These reactions may show up as mild allergic symptoms, pruritus, or rash. Oral

NAC is typically better tolerated in terms of systemic hypersensitivity than intravenous NAC, which is linked to an increased risk of anaphylactoid reactions. However, close observation is advised throughout treatment, especially for patients who have previously experienced drug allergies. [24]

When giving oral NAC to elderly patients, extra factors need to be taken into account. The pharmacokinetics of drugs taken orally may be impacted by age-related changes in gastrointestinal function, such as delayed gastric emptying and altered drug absorption. Moreover, comorbid conditions like chronic gastrointestinal disorders, hepatic impairment, and renal dysfunction are common in older adults and can impact NAC metabolism and elimination. In this population, polypharmacy is also prevalent, which raises the risk of additive gastrointestinal side effects or drug interactions. [25]

Despite these difficulties, oral NAC is still a useful treatment for paracetamol poisoning in situations where intravenous therapy is either not available or not recommended. When given early after overdose, oral NAC has been shown in numerous clinical studies to have significant hepatoprotective effects. In many clinical settings, its efficacy is comparable to intravenous regimens. Early treatment initiation prior to significant hepatic glutathione depletion is crucial for successful therapy.

Accessibility and affordability are two more benefits of oral NAC therapy, especially in healthcare environments with limited resources. The drug is still a significant choice for treating paracetamol poisoning in rural or low-resource settings since it can be given without the need for specialized tools or infusion systems. To evaluate liver function, identify adverse reactions, and guarantee that therapeutic objectives are met, close patient monitoring is still necessary. [26]

Overall, oral N-acetylcysteine therapy represents a well-established pharmacological intervention that effectively counteracts the toxic mechanisms of paracetamol overdose. NAC is essential for preventing hepatocellular damage and enhancing clinical results because of its combined functions as an antioxidant, glutathione precursor, and modulator of inflammatory processes. When properly administered and closely observed, Oral NAC is still a key treatment for paracetamol poisoning, especially in older adult populations where customized care is crucial.[27]

4. SUPPORTIVE PHARMACOLOGICAL MANAGEMENT:

In order to prevent complications and stabilise patients with severe poisoning, supportive pharmacological therapy is crucial, even though NAC is still the principal treatment for

paracetamol toxicity. Overdosing on paracetamol can cause hepatotoxicity, which can result in severe metabolic problems such hypoglycemia, metabolic acidosis, and coagulopathy. Therefore, pharmacological therapies targeted at rectifying these anomalies are essential parts of all-encompassing treatment [28].

Because of reduced gluconeogenesis and glycogen depletion, hypoglycemia is a frequent consequence of severe hepatic failure. To maintain appropriate blood glucose concentrations and avoid neurological problems, intravenous glucose therapy can be necessary. Similarly, in situations when there is a high risk of bleeding, therapy with vitamin K or plasma products may be required for coagulopathy caused by reduced hepatic synthesis of clotting factors [29].

Advanced stages of paracetamol toxicity may also result in renal failure, either directly from the nephrotoxic effects of NAPQI or as a result of systemic haemodynamic disruptions. Maintaining sufficient renal perfusion and addressing electrolyte imbalances with the right pharmaceutical and supportive measures are the main goals of management in these situations [30].

Comorbid diseases like chronic renal disease or cardiovascular disease can make pharmacological management more difficult for older people. Therefore, while treating elderly patients with paracetamol overdose, careful monitoring of fluid balance, renal function, and metabolic markers is crucial [31].

5. PHARMACOLOGICAL CONSIDERATIONS IN REPEATED SUPRATHERAPEUTIC INGESTION

Among elderly adults, repeated supratherapeutic consumption is a particularly difficult clinical situation. In contrast to acute single-dose overdose, recurrent consumption frequently happens gradually over a few days as patients use excessive amounts of paracetamol as a self-medication for chronic pain issues. Without generating the elevated serum concentrations usually linked to an acute overdose, this pattern may result in the gradual accumulation of harmful metabolites [32].

The Rumack-Matthew nomogram's diagnostic value is restricted in situations of recurrent supratherapeutic intake because it is primarily intended for single-dose exposures. Therefore, while making judgements about pharmacological treatment, clinicians must depend on a mix of hepatic enzyme increases, laboratory results, and clinical history. When there is evidence of hepatic impairment and a history of high paracetamol consumption, NAC therapy is often started experimentally [33].

Because chronic pain issues like osteoarthritis and musculoskeletal illnesses sometimes require long-term analgesic medication, older persons may be especially susceptible to this pattern of toxicity. Additionally, the risk of an unintentional overdose is increased by the widespread availability of combination drugs that contain paracetamol [34].

Advanced treatment strategies for aged patients must be specifically designed to take age-related physiological changes and comorbidities into consideration. Clinicians must weigh the possible advantages of transplantation or extracorporeal support against the dangers of invasive procedures and immunosuppressive medication because older persons may have a lower tolerance to harsh therapies. Determining the best therapeutic approach thus requires a thorough evaluation of functional status, nutritional state, and underlying illnesses [35].

For individuals with permanent hepatic failure brought on by paracetamol intoxication, liver transplantation is still the best course of action. What was previously a uniformly fatal condition is now a potentially manageable medical emergency thanks to advancements in transplant medicine and accompanying technology that have greatly increased survival rates. Patients with severe paracetamol-induced liver impairment may have more treatment choices if research into novel therapeutic approaches—such as extracorporeal liver support devices and tailored pharmaceutical agents—continues. These advancements are especially crucial for enhancing clinical outcomes and lowering mortality from paracetamol poisoning in the expanding population of older persons who may have distinct patterns of drug toxicity [36].

7. EMERGING THERAPEUTIC APPROACHES IN PARACETAMOL-INDUCED HEPATOTOXICITY:

The most common and successful treatment for paracetamol poisoning is still N-acetylcysteine (NAC), but during the past ten years, more research has been done to find other therapeutic approaches that can target the intricate molecular mechanisms underlying paracetamol-induced liver damage. Hepatocellular necrosis, inflammatory reactions, metabolic dysregulation, mitochondrial oxidative stress, and other interrelated processes are all part of the pathophysiology of hepatotoxicity, which goes beyond mere glutathione deficiency [37]. Emerging therapeutic techniques therefore seek to address at various phases of this harm cascade, especially in patients who acquire substantial liver damage despite routine NAC therapy or who show late after overdose [38].

Since mitochondrial dysfunction is known to be a key factor in paracetamol-induced hepatotoxicity, one of the main areas of research is mitochondrial protective medicines. Overproduction of the hazardous metabolite N-acetyl-p-benzoquinone imine (NAPQI) causes

oxidative stress in the mitochondria, disruption of electron transport chains, and collapse of the potential of the mitochondrial membrane. These mechanisms intensify liver damage and cause hepatocyte necrosis. Hepatocellular damage may be considerably reduced by substances that can stabilise mitochondrial membranes or lower mitochondrial oxidative stress, according to experimental research [39]. In experimental animals, agents including mitochondrial antioxidants and mitochondrial permeability transition inhibitors have demonstrated encouraging hepatoprotective effects, indicating possible therapeutic roles in severe toxicity where conventional treatment is inadequate [40].

Antioxidant-based treatments intended to mitigate the widespread oxidative damage linked to paracetamol overdose represent another exciting field of study. Through the production of reactive oxygen species and lipid peroxidation, oxidative damage plays a major role in hepatocyte mortality [41]. The potential of a number of pharmacological substances with antioxidant qualities to enhance NAC's detoxifying activities is presently being studied. These substances work by lowering oxidative damage to biological components, strengthening endogenous antioxidant mechanisms, and neutralising free radicals. Many of these medications are still in preclinical phases, but they are promising supplementary therapies that could help patients with severe hepatotoxicity [42].

Another significant therapeutic target is the modification of inflammatory pathways. The activation of inflammatory mediators, such as cytokines, chemokines, and immune cells, which aid in the advancement of tissue damage, is linked to paracetamol-induced liver injury [43]. The ensuing inflammatory reaction increases hepatocyte death and postpones tissue regeneration, even though the initial insult is purely metabolic. Therefore, pharmaceuticals that control immune responses or inhibit excessive inflammatory signalling may help minimise the severity of liver damage. Controlling inflammatory cascades may lessen liver damage and enhance recovery after toxic exposure, according to research on anti-inflammatory drugs and immune-modulating treatments [44].

The investigation of stem cell-based treatments as possible remedies for acute liver failure brought on by paracetamol intoxication has also been prompted by recent developments in regenerative medicine [45]. Through the release of growth factors and regenerative cytokines, stem cells have the capacity to develop into hepatocyte-like cells and may aid in liver regeneration. By promoting cellular regeneration, lowering inflammation, and enhancing tissue recovery, mesenchymal stem cells may improve liver repair, according to experimental research. Stem cell therapy offers a promising way to restore liver function in individuals with significant hepatic injury, even though its therapeutic use is still being studied [46].

The creation of biomarker-guided therapeutic approaches, which enable early identification and focused treatment of paracetamol-induced liver damage, is another new strategy. Conventional clinical indicators such serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) frequently do not increase until substantial liver damage has taken place [47]. Numerous new biomarkers that can identify hepatocellular damage at far earlier stages have been found in recent studies. By using these indicators, doctors may be able to start treatment before irreparable liver damage occurs, which would improve patient outcomes and optimise the timing of pharmaceutical therapies [48].

In addition to these pharmacological developments, breakthroughs in pharmacogenomics and precision medicine are offering fresh perspectives on each person's vulnerability to paracetamol toxicity [49]. The rate of NAPQI production and detoxification may be influenced by genetic polymorphisms in drug metabolism-related enzymes, including cytochrome P450 isoforms and glutathione-related pathways. Clinicians may be able to identify high-risk patients and tailor treatment plans based on metabolic profiles if they are aware of these genetic variations. In elderly populations, where medication metabolic variability and concomitant diseases may greatly impact toxicity risk, these strategies are especially pertinent [50].

Even though these new therapeutic modalities show promise, the majority are still being studied and have not yet supplanted well-established therapies like supportive care and NAC therapy [51]. However, continuing studies continue to deepen our understanding of the molecular mechanisms behind the hepatotoxicity caused by paracetamol, opening the door to the creation of more focused and potent treatments [52]. These innovative approaches may potentially supplement current treatments and enhance survival rates as scientific understanding grows, especially in patients with severe poisoning or delayed clinical manifestation [53].

All things considered, new therapeutic strategies reflect a developing field in the treatment of paracetamol toxicity. These approaches seek to address the many molecular mechanisms underlying liver damage by focusing on oxidative stress, inflammatory reactions, mitochondrial malfunction, and regeneration pathways. Determining the safety, effectiveness, and practical applicability of these therapies in actual clinical settings will require ongoing clinical research and translational studies, particularly for vulnerable populations like older adults who may experience distinct patterns of paracetamol toxicity [54].

8. CLINICAL IMPLICATIONS FOR THE ELDERLY POPULATION:

The clinical difficulties associated with paracetamol toxicity in older persons are distinct from those seen in younger populations. People 65 years of age and older may have unique exposure patterns, physiological vulnerabilities, and concomitant diseases that affect the degree of toxicity as well as the efficacy of therapeutic approaches [55]. As the world's population ages and chronic pain disorders become more frequent, paracetamol continues to be one of the most popular analgesics among senior citizens [56]. Even in situations involving relatively minor dosage errors or recurrent supratherapeutic consumption, age-related physiological changes and clinical complexity may enhance vulnerability to hepatotoxicity, even though the medicine is typically regarded as safe at therapeutic levels [57].

The existence of age-related pharmacokinetic changes that affect the metabolism and excretion of paracetamol is one of the most significant clinical factors in older individuals. Drug metabolism may be impacted by changes in enzyme activity, decreased liver mass, and decreased hepatic blood flow, all of which are linked to ageing [58]. These modifications may result in longer exposure to the hazardous metabolite of paracetamol, N-acetyl-p-benzoquinone imine (NAPQI), and slower clearance of the drug. Additionally, the detoxification of this reactive metabolite may be hampered by lower glutathione reserves in older people, raising the risk of hepatocellular damage [59]. When giving paracetamol to senior individuals, these physiological changes emphasise the significance of judicious dosage and thorough monitoring [60].

The high incidence of polypharmacy in older persons has another important therapeutic implication. For long-term ailments such hypertension, diabetes, arthritis, and cardiovascular disease, many older people need several drugs [61]. When many drugs are taken at the same time, there is a greater chance of drug-drug interactions that could change how paracetamol is metabolised or raise hepatic susceptibility. Certain drugs may enhance the production of NAPQI and worsen the risk of hepatotoxicity, especially those that activate cytochrome P450 enzymes like CYP2E1. Additionally, older persons may unintentionally overdose on paracetamol due to the widespread availability of combination drugs that include the same active component [62].

The therapeutic treatment of paracetamol poisoning in the elderly is made more difficult by the existence of coexisting medical problems. This demographic is relatively prone to chronic liver disease, renal impairment, malnutrition, and alcohol use disorders, all of which can have a substantial impact on medication metabolism and toxicity effects [63]. For example, the

body's ability to detoxify NAPQI may be compromised by malnutrition and frailty, which can lower hepatic glutathione reserves. In a similar vein, long-term alcohol use may trigger liver enzymes that boost the generation of harmful metabolites, hence increasing the risk of hepatocellular damage. Therefore, while determining the risk and severity of paracetamol toxicity in elderly individuals, clinicians must carefully consider underlying medical problems [64].

In this population, diagnostic difficulties also constitute a major clinical problem. It might be challenging to identify paracetamol toxicity in older people because they may exhibit unusual or delayed symptoms. Mild, nonspecific symptoms like nausea, exhaustion, or stomach discomfort are frequently present in the early stages of poisoning and can be readily mistaken for other illnesses that older persons frequently suffer [65]. Serum paracetamol concentrations may not adequately reflect the level of hepatotoxic risk in cases of recurrent supratherapeutic intake, which further complicates clinical assessment. Therefore, when assessing older patients with nonspecific gastrointestinal symptoms or unexplained hepatic enzyme increases, doctors need to use extreme caution [66].

The possibility of delayed presentation to medical treatment must also be considered in management options for paracetamol poisoning in older persons. Elderly people may be less inclined to seek emergency care after overdosing, especially if they were accidentally exposed or had a therapeutic mishap [67]. Because antidotal medication, especially N-acetylcysteine, is most effective when given in the early hours after ingestion, delaying treatment might greatly raise the risk of serious liver damage. Therefore, anytime there is a suspicion of excessive paracetamol use, healthcare providers should prioritise early screening and fast beginning of treatment [68].

Carefully monitoring treatment tolerance and side effects is also necessary for the therapeutic management of paracetamol toxicity in the elderly. Elderly patients may be more vulnerable to problems related to intravenous infusions, fluid overload, or medication hypersensitivity reactions, despite the fact that N-acetylcysteine is normally safe and very effective [69]. Therefore, it is crucial to closely evaluate coagulation profiles, metabolic state, liver function, and renal parameters throughout treatment. Additionally, to account for the physiological constraints brought on by ageing, customised dosage plans and supportive care measures can be necessary [70].

In order to lessen the incidence of paracetamol poisoning among older persons, prevention is essential. Reducing the risk of inadvertent overdose requires education on proper dosage, identification of combination drugs, and adherence to suggested daily limits. In order to find

possible sources of duplicate paracetamol exposure, healthcare providers should regularly check medications for older patients. Medication safety in this susceptible group can be further improved with better labelling, precise dosage guidelines, and pharmacist-led counselling [71].

In conclusion, polypharmacy, concomitant conditions, age-related physiological changes, and diagnostic difficulties all contribute to the complicated clinical problem of paracetamol poisoning in the elderly [72]. These characteristics affect clinical management and treatment outcomes in addition to increasing vulnerability to hepatotoxic damage. Optimising patient care requires a comprehensive strategy that incorporates meticulous risk assessment, early diagnosis, timely pharmaceutical intervention, and preventative measures. In order to lower the morbidity and mortality linked to paracetamol overdose in this susceptible demographic, more focus on these clinical consequences will be essential as the world's old population continues to expand [73].

9. CONCLUSION:

Worldwide, paracetamol overdose is still a major cause of drug-induced liver damage, and its clinical effects on those 65 years of age and older need special consideration. Elderly patients are more susceptible to hepatotoxicity due to age-related physiological changes, polypharmacy, comorbid medical conditions, and patterns of repeated supratherapeutic ingestion, even though paracetamol is generally regarded as a safe and effective analgesic when used within recommended doses [74]. These variables may change how drugs are metabolised, lower the liver's ability to detoxify, and delay the detection of toxicity, all of which raise the possibility of serious clinical consequences [75].

The cornerstone of treatment continues to be early diagnosis and rapid beginning of antidotal therapy with N-acetylcysteine, which, when given promptly, dramatically reduces the risk of liver damage. Advanced treatment procedures, such as extracorporeal liver support and liver transplantation, may be required to enhance survival results in cases of severe toxicity leading to acute liver failure. However, other therapy options may be available in the future due to continuing research into novel therapeutic approaches that target oxidative stress, mitochondrial dysfunction, and inflammatory pathways [76].

All things considered, increasing knowledge of paracetamol toxicity patterns in the senior population is crucial for maximising therapeutic care and averting negative consequences. Reducing the prevalence of paracetamol poisoning in older individuals requires careful prescription practices, patient education, medication monitoring, and early clinical

intervention. The safe use of paracetamol in this expanding population will be further improved by ongoing research on age-specific pharmacological reactions and therapeutic approaches [77].

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