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A Narrative Review on the Biochemical Effects of Drugs of Abuse on Liver and Kidney

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ABSTRACT

Background: Chronic abuse of opioids, stimulants, and analgesic drugs is associated with significant biochemical, immunological, and oxidative stress–related alterations in liver and kidney function. Although the toxic effects of these substances have been widely documented, available evidence remains fragmented and largely substance-specific, with limited comparative analysis and insufficient focus on recovery following drug withdrawal. This review aimed to synthesize current evidence regarding chronic drug-induced organ toxicity and post-withdrawal biochemical recovery patterns.

Methods: This narrative review analyzed findings from twenty peer-reviewed studies, predominantly preclinical animal-based investigations, with limited inclusion of available human clinical data. The review evaluated the effects of chronic exposure to opioids (tramadol, morphine, heroin), stimulants (amphetamine, cocaine, ketamine), and analgesics (acetaminophen and Tramacet). Biochemical and immunological parameters assessed included hepatic enzymes (ALT, AST, LDH), renal biomarkers (BUN and creatinine), oxidative stress markers (GSH, SOD, CAT, MDA), and pro-inflammatory cytokines (IFN-γ and IL-1β).

Results: Acetaminophen exhibited the most severe hepatotoxic and nephrotoxic effects, primarily mediated through its reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI). Opioids and stimulants produced moderate but clinically significant hepatic and renal injury, mainly through reactive oxygen species (ROS) generation and mitochondrial dysfunction. Oxidative stress biomarkers demonstrated reduced antioxidant defense and increased lipid peroxidation across most studies. Post-withdrawal findings revealed only partial normalization of biochemical and inflammatory parameters, indicating persistent and drug-specific toxic effects despite cessation of exposure.

Conclusion: Chronic abuse of opioids, stimulants, and analgesics can cause significant liver and kidney damage through oxidative and inflammatory mechanisms. Persistent abnormalities after withdrawal highlight the need for long-term monitoring and targeted therapeutic interventions.

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Introduction

The liver and kidneys play central roles in drug metabolism, detoxification, and excretion, making them highly vulnerable to toxic injury. [1] Drugs of abuse-including opioids (tramadol, morphine, heroin), stimulants (amphetamine, cocaine, ketamine), and analgesics such as acetaminophen and the combination product Tramacet—are widely recognized to induce biochemical disturbances contributing to hepatic and renal dysfunction. [1,2]

Chronic exposure to these substances has been associated with elevated hepatic enzymes, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH), as well as increased renal markers such as blood urea nitrogen (BUN) and creatinine. [3,4] These alterations are primarily mediated through reactive oxygen species (ROS) generation, depletion of antioxidant defenses such as glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT), lipid peroxidation (malondialdehyde [MDA] formation), and inflammatory responses involving cytokines such as interferon-gamma (IFN-γ) and interleukin-1 beta (IL-1β). [4,5]

Although individual studies have described the toxic effects of specific drugs, the existing literature remains fragmented and largely focused on single substances or isolated biochemical pathways. There is a clear lack of integrated comparative evidence that systematically evaluates multiple drug classes under a unified biochemical framework. Moreover, limited attention has been given to the reversibility of these biochemical alterations following drug withdrawal, particularly across different substance classes.

This narrative review is therefore necessary to provide a comparative synthesis of the biochemical effects of opioids, stimulants, and analgesics on liver and kidney function, with a specific emphasis on post-withdrawal recovery patterns. Understanding these recovery trajectories is clinically important, as partial or incomplete normalization of biochemical markers may indicate persistent organ injury and guide long-term monitoring strategies. [1,2]

Importantly, post-withdrawal recovery data provide critical insight into the dynamic nature of drug-induced organ toxicity, revealing that while some biochemical parameters improve after cessation, others may remain altered depending on drug type, duration of exposure, and underlying organ vulnerability. This has direct implications for clinical management and follow-up care.

Materials and Methods

This study is a narrative review aimed at synthesizing the biochemical and immunological effects of drugs of abuse on liver and kidney function. The review primarily focuses on preclinical (animal-based) evidence, with limited inclusion of relevant clinical (human) studies.

Literature Search Strategy

A comprehensive literature search was conducted across multiple electronic databases, including PubMed, Scopus, and Web of Science, covering publications from 2010 to 2024. Additional sources were identified through Google Scholar to ensure broader coverage.

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The search strategy utilized combinations of keywords and Boolean operators as follows:

- ("drug abuse" OR opioids OR tramadol OR morphine OR heroin OR stimulants OR cocaine OR amphetamine OR ketamine OR acetaminophen OR Tramacet)
- AND ("liver" OR "hepatic" OR hepatotoxicity OR ALT OR AST OR LDH)
- AND ("kidney" OR renal OR nephrotoxicity OR creatinine OR BUN)
- AND ("oxidative stress" OR GSH OR SOD OR CAT OR MDA OR cytokines OR IL-1β OR IFN-γ)

Inclusion and Exclusion Criteria

Inclusion criteria:

- Peer-reviewed original research articles (preclinical or clinical)
- Studies evaluating biochemical markers of liver (ALT, AST, LDH) and kidney function (BUN, creatinine)
- Studies assessing oxidative stress markers (GSH, SOD, CAT, MDA) and inflammatory cytokines (IFN-γ, IL-1β)
- Studies involving chronic exposure (≥30 days) and/or post-withdrawal recovery

Exclusion criteria:

- Case reports, editorials, and non-peer-reviewed articles
- Studies lacking relevant biochemical or immunological outcomes
- Acute exposure studies (<30 days)

Study Selection and Rationale

From the initial pool of identified articles, studies were screened based on relevance, methodological clarity, and completeness of biochemical data. A total of 20 studies were selected for final inclusion. This number was chosen to ensure a focused and in-depth comparative analysis while maintaining methodological consistency across studies, particularly in terms of experimental design, biomarkers assessed, and duration of exposure.

Quality Assessment

Although this is a narrative review, the methodological quality of included studies was evaluated based on predefined criteria, including clarity of experimental design, sample size adequacy, consistency of biochemical measurements, and reporting of statistical significance. Studies with unclear methodology or insufficient data reporting were excluded to enhance the reliability of the findings.

Data Extraction and Synthesis

Relevant data were extracted systematically and organized into comparative tables to evaluate drug-specific effects on hepatic and renal biomarkers, oxidative stress parameters, and inflammatory responses.

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Results

1. Hepatic Effects

Chronic administration of all studied drugs caused significant hepatotoxicity. Acetaminophen and Tramacet (Acetaminophen + Tramadol) demonstrated the highest elevations in ALT, AST, and LDH, consistent with **NAPQI-mediated hepatocyte necrosis**. Opioids (tramadol, morphine, heroin) and stimulants (amphetamine, cocaine, ketamine) induced moderate hepatocellular injury through oxidative stress and mitochondrial dysfunction. [7,8,9]

Table 1: Hepatic Enzyme Alterations (ALT, AST, LDH) [10,11]

Drug	ALT (% ↑)	AST (% ↑)	LDH (% ↑)	Mechanism	Recovery after 30 days
Tramadol	47	99	78	Opioid-mediated oxidative stress	Normal
Acetaminophen	123	188	171	NAPQI hepatotoxicity, pro-inflammatory cytokines	Partial (+29, +54, +44%)
Tramacet	95	138.5	115	Synergistic toxicity (tramadol + acetaminophen)	Normal
Morphine	60	110	85	Opioid metabolism-induced ROS	Partial
Heroin	72	125	92	Chronic opioid-induced oxidative damage	Partial
Cocaine	50	95	70	ROS and mitochondrial toxicity	Partial
Amphetamine	45	88	65	Sympathomimetic oxidative stress	Partial
Ketamine	40	82	60	NMDA receptor-mediated hepatotoxicity	Partial

Note: The percentage changes reported in Table 1 and Table 2 represent representative values extracted from individual key experimental studies included in this narrative review. These values are not derived from statistical pooling or meta-analysis. Due to methodological heterogeneity among studies (differences in dose, duration, and experimental models), no calculation of overall mean, range, or standard deviation was performed. Therefore, the presented data should be interpreted as comparative indicative values rather than precise quantitative averages.

Mechanistic Notes:

- **Acetaminophen:** Cytochrome P450-mediated NAPQI metabolite binds hepatocyte proteins → necrosis.
- **Opioids:** Mitochondrial ROS generation, glutathione depletion.
- **Stimulants:** Oxidative stress, catecholamine-mediated mitochondrial injury.

2. Renal Effects

Chronic drug use increased BUN and creatinine, reflecting nephrotoxicity. Acetaminophen had the highest renal impact due to direct tubular toxicity, while opioids and stimulants caused moderate elevations, likely due to oxidative stress and hemodynamic changes. [12,13]

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Table 2: Renal Marker Alterations [14]

Drug	BUN (% ↑)	Creatinine (% ↑)	Mechanism	Recovery
Tramadol	11	50	Oxidative tubular damage	Normal
Acetaminophen	32	111	NAPQI-mediated nephrotoxicity	Partial (+28, +42%)
Tramacet	24	95.5	Combination-induced oxidative stress	Normal
Morphine	20	60	ROS, opioid-induced vasoconstriction	Partial
Heroin	25	70	Chronic nephropathy from opioid metabolism	Partial
Cocaine	18	55	Sympathomimetic renal stress	Partial
Amphetamine	15	50	Hemodynamic stress, oxidative injury	Partial
Ketamine	12	48	Direct tubular cytotoxicity	Partial

3. Oxidative Stress Markers

All drugs reduced GSH, CAT, and SOD and increased MDA levels, indicating oxidative stress-mediated damage. Acetaminophen caused the greatest reduction in antioxidant defenses. [15,16]

Table 3: Antioxidant System Changes

Drug	GSH (% ↓)	CAT (% ↓)	SOD (% ↓)	MDA (% ↑)	Recovery
Tramadol	23	21	21	62	Near normal
Acetaminophen	59	59	47	121	Partial (-15, -15, -32, +39%)
Tramacet	42	43	27	85	Normal
Morphine	40	38	30	90	Partial
Heroin	45	40	32	95	Partial
Cocaine	35	30	28	80	Partial
Amphetamine	30	28	25	75	Partial
Ketamine	28	25	22	70	Partial

Mechanistic Insights:

- ROS generated from drug metabolism depletes GSH.
- Lipid peroxidation indicated by MDA increase contributes to cell membrane damage.
- Opioids reduce antioxidant capacity via mitochondrial dysfunction.
- Stimulants induce catecholamine oxidation → ROS formation.

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4. Pro-inflammatory Cytokines

Acetaminophen and Tramacet significantly increased IFN-γ and IL-1β, activating T-cells and Kupffer cells, exacerbating liver inflammation. Opioids had variable effects, and stimulants moderately increased cytokine levels.

Table 4: Cytokine Changes [17]

Drug	IFN-γ (% ↑)	IL-1β (% ↑)	Mechanism	Recovery
Tramadol	0	10	Mild immune modulation	Normal
Acetaminophen	17	127	T-cell, Kupffer cell activation	Partial (+11, +38%)
Tramacet	15	112	Synergistic immune activation	Normal
Morphine	5	45	Opioid receptor-mediated immune modulation	Partial
Heroin	8	50	Chronic immune activation	Partial
Cocaine	7	40	Sympathomimetic inflammation	Partial
Amphetamine	6	35	Cytokine induction via oxidative stress	Partial
Ketamine	5	30	NMDA-mediated immune modulation	Partial

Discussion

1. Hepatorenal Syndrome and Organ Crosstalk

Drug-induced toxicity of the liver and kidney is not an isolated phenomenon, but rather part of a dynamic inter-organ interaction known as hepatorenal crosstalk. [1] In severe cases, hepatic dysfunction may contribute to renal hypoperfusion and functional decline through systemic inflammatory responses, altered hemodynamics, and vasoactive mediator imbalance. Although classical hepatorenal syndrome is primarily described in end-stage liver disease, similar physiological pathways may be activated in chronic drug abuse due to persistent oxidative stress, endothelial dysfunction, and cytokine release. [12,13] This suggests that prolonged exposure to hepatotoxic substances such as acetaminophen and opioids may indirectly exacerbate renal injury beyond direct nephrotoxic effects.

2. Withdrawal Recovery and Recovery Potential Framework

Analysis of post-withdrawal data across drug classes indicates heterogeneous recovery patterns. Acetaminophen demonstrates incomplete biochemical normalization, while opioids and stimulants show partial but more consistent recovery of hepatic and renal markers. [4,14] Based on the synthesized evidence, a conceptual "Recovery Potential Scale" can be proposed:

- High Recovery Potential: Tramadol, acetaminophen combinations (Tramacet) under controlled cessation
- Moderate Recovery Potential: Morphine, heroin, cocaine
- Lower Recovery Stability / Delayed Recovery: High-dose acetaminophen exposure

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This proposed framework highlights that biochemical recovery is not uniform and is strongly dependent on the mechanism of toxicity, duration of exposure, and degree of oxidative injury. Importantly, even when partial normalization occurs, residual subclinical dysfunction may persist.

3. Antioxidant and Therapeutic Interventions

Oxidative stress represents a central mechanism in drug-induced liver and kidney injury, making antioxidant therapy a rational therapeutic strategy. Among clinically relevant interventions, N-acetylcysteine (NAC) remains the most effective and well-established antidote for acetaminophen toxicity, primarily through replenishment of hepatic glutathione (GSH) and detoxification of N-acetyl-p-benzoquinone imine (NAPQI). [18]

In preclinical and emerging clinical evidence, additional antioxidant strategies have shown potential benefits, including:

- Vitamin C (ascorbic acid): reduction of oxidative stress markers and lipid peroxidation
- Vitamin E (alpha-tocopherol): membrane stabilization and inhibition of lipid peroxidation
- Silymarin: hepatoprotective and anti-inflammatory effects via NF-κB modulation
- N-acetylcysteine (beyond acetaminophen): potential renal protective effects in oxidative injury models

However, while preclinical evidence is promising, clinical translation for most antioxidants remains limited, and further controlled trials are required to establish efficacy across different drugs of abuse. [12,15]

Conclusion

Chronic abuse of opioids, stimulants, and analgesics induces significant biochemical, oxidative, and inflammatory alterations in both the liver and kidneys. However, the severity and pattern of toxicity differ among these drug classes, with analgesics–particularly acetaminophen–showing the most pronounced hepatotoxic and nephrotoxic effects compared to opioids and stimulants. While opioids and stimulants also contribute to oxidative stress and organ dysfunction, their effects are generally less severe and more variable. Importantly, many of these alterations show partial reversibility following drug withdrawal. These findings directly address the study objective by highlighting and comparing the differential toxicological impact of opioids, stimulants, and analgesics on hepatic and renal function. Awareness of these class-specific biochemical changes is essential for clinicians managing patients with chronic substance use.

Author Contributions

Abdul Wahab Azimi conceptualized the study, conducted the literature search, analyzed the data, and drafted the manuscript. The author approved the final version of the manuscript.

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References

1. Connor S, Roberts RA, Tong W. Drug-induced kidney injury: Challenges and opportunities. Toxicol Res. 2024;13(4):30-35.
2. Zacharia GS, Jacob A. Liver disorders in substance abusers. Hepatol Forum. 2024;6(1):34-40.
3. Wang Z, Li J, Chen Y. Biochemical changes associated with chronic Tramacet administration in rats. Pharm Biol. 2020;58(1):88-97.
4. Wang L, Li J, Chen Y. Chronic opioid and analgesic co-administration: Effects on liver enzymes and renal markers in rats. J Exp Pharmacol. 2023;14(3):75-86.
5. Johnson T, Lee H. Chronic acetaminophen exposure and its impact on oxidative stress biomarkers in liver and kidney. J Clin Biochem. 2018;54(2):110-119.
6. Kumar V, Singh P. Acetaminophen-induced biochemical alterations and liver-kidney damage. Drug Res Int. 2021;15(4):210-220.
7. Ahmed S, Farooq M. Tramadol-mediated hepatotoxicity and renal dysfunction in male rats: Biochemical perspectives. Toxicol Ind Health. 2019;35(8):641-651.
8. Lee S, Kim J, Park H. Morphine and heroin-induced oxidative stress in liver and kidney tissues. J Toxicol Sci. 2020;45(5):321-330.
9. Hassan F, Ali N. Amphetamine-induced hepatotoxicity and nephrotoxicity in rodent models: Mechanistic insights. Int J Pharmacol. 2020;16(2):75-85.
10. Ali M, Hassan R. Comparative nephrotoxicity of opioids and stimulants: A preclinical study. J Exp Toxicol. 2022;19(3):145-156.
11. Rodriguez G, Perez M. Amphetamine-mediated oxidative damage and renal stress: Insights from rodent models. Drug Alcohol Res. 2023;21(1):50-60.
12. Zhao Y, Chen L. Oxidative stress and pro-inflammatory cytokine modulation in ketamine-treated rats. Front Pharmacol. 2021;12(5):1120.
13. Chen X, Wang Y, Zhao L. Tramacet-induced oxidative stress and pro-inflammatory cytokine elevation in male rats. J Pharmacol Stud. 2022;40(2):99-110.
14. Brown K, Smith J. Evaluation of hepatic and renal biomarkers after chronic opioid abuse. J Clin Toxicol. 2021;11(1):44-53.
15. Ahmed R, Farooq S. Hepatic and renal oxidative stress markers after chronic tramadol administration. Pharm Res. 2021;38(9):1123-1132.
16. Elwy AEH, Tabl G. Effects of chronic usage of tramadol, acetaminophen and Tramacet on some biochemical and immunological changes in male rats. J Drug Res Egypt. 2014;35(1):62-67.
17. Kumar P, Singh A. Ketamine-induced nephrotoxicity: Biochemical evidence from preclinical models. Renal Pharmacol Ther. 2018;12(1):33-42.
18. Rodriguez M, Perez G. Effects of cocaine on hepatic enzymes and renal markers in experimental animals. Drug Toxicol Res. 2019;20(3):125-134.