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Short Report

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Mechanistic Insights into the Potential Central Nervous System Effects of Chronic Analgesic Exposure Beyond Nephrotoxicity

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Abstract

Analgesic medications, particularly non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen, are among the most widely used agents for the management of pain and fever. Their renal adverse effects are well recognized, but potential effects beyond the kidney have received comparatively less integrated attention. This narrative review examines evidence concerning the potential effects of prolonged analgesic exposure on the central nervous system (CNS), with particular emphasis on oxidative stress, mitochondrial disturbances, neuroinflammatory signaling, blood-brain barrier (BBB) considerations, synaptic plasticity, cognitive function, serotonergic adaptation, and medication-overuse headache (MOH). NSAIDs and acetaminophen are considered separately because their pharmacological and toxicological profiles differ substantially. Experimental studies in rodents indicate that prolonged acetaminophen exposure can be associated with altered synaptic structure, glutathione depletion, increased protein oxidation, microglial activation, neuroinflammatory signaling, reduced brain-derived neurotrophic factor, and behavioral changes (Lalert et al., 2020, 2021, 2023). However, these findings arise predominantly from preclinical models, and their relevance to therapeutic exposure in humans remains uncertain. NSAIDs can reach the CNS to varying degrees, but their effects on neural inflammation are complex rather than uniformly neurotoxic. Clinically, medication-overuse headache provides stronger human evidence that repeated exposure to acute pain medications can contribute to maladaptive changes in pain-processing networks. Overall, available evidence supports biological plausibility for CNS effects of prolonged or excessive analgesic exposure but does not establish generalized human CNS neurotoxicity from therapeutic use.

Keywords: analgesics; acetaminophen; NSAIDs; central nervous system; oxidative stress; neuroinflammation; blood-brain barrier; synaptic plasticity; neurotoxicity.

1. Introduction

Analgesics are essential components of modern pain management. Acetaminophen and NSAIDs are widely available and are used for acute and, in some circumstances, recurrent or chronic pain. Their therapeutic benefits are well established, while adverse effects involving the gastrointestinal, cardiovascular, hepatic, and renal systems have received considerable attention.

Renal effects have been particularly important in discussions of prolonged NSAID exposure because inhibition of prostaglandin synthesis can interfere with renal haemodynamic regulation, especially when renal perfusion is dependent on prostaglandin-mediated vasodilation (DiBona, 1986; Whelton, 1999).

The CNS presents a different problem. Analgesics are administered partly to modify pain perception, and several agents or metabolites can reach or influence the CNS. This raises an important question: could prolonged exposure produce neural adaptations or adverse effects that are not adequately captured by conventional organ-toxicity frameworks?

The question should, however, be approached cautiously. Evidence for CNS effects is heterogeneous. Some findings originate from animal studies using doses or exposure periods that cannot be directly equated with human therapeutic exposure. Other findings concern medication-overuse headache, which represents a clinical disorder associated with frequent use of acute headache medications but should not automatically be interpreted as generalized neurotoxicity (Diener et al., 2016; Hird and Sandoe, 2023).

This review therefore examines the available evidence without assuming that chronic analgesic exposure necessarily causes CNS injury.

2. Scope and Conceptual Framework

This article is a **narrative review**, rather than a systematic review. The literature is organized around CNS exposure, oxidative and redox disturbances, mitochondrial function, neuroinflammation, BBB considerations, synaptic plasticity, cognitive function, serotonergic adaptation, and medication-overuse headache.

A critical distinction is made between therapeutic short-term use, prolonged or repeated use, medication overuse, and acute or repeated supratherapeutic exposure. These exposure categories should not be treated as biologically equivalent.

3. Pharmacokinetics and Potential CNS Exposure

3.1 NSAIDs

NSAIDs are chemically diverse compounds with different lipophilicity, protein binding, half-lives, and tissue distribution. Consequently, their penetration into the CNS is not uniform.

Pharmacokinetic investigations demonstrated that NSAIDs can be detected in cerebrospinal fluid, although CNS exposure differs among individual drugs (Bannwarth et al., 1989). Therefore, the presence of an NSAID in the CNS should not itself be interpreted as evidence of CNS toxicity.

3.2 Acetaminophen

Acetaminophen has distinctive central pharmacology. Its metabolites can participate in analgesic mechanisms involving TRPV1, cannabinoid, serotonergic, and cyclooxygenase-related pathways. p-Aminophenol can cross the BBB and contribute to formation of the bioactive metabolite AM404 within neural tissues.

Ohashi and Kohno (2020) emphasized that acetaminophen's analgesic activity cannot be adequately explained by simple peripheral COX inhibition. Its central and spinal actions involve multiple signaling pathways.

Recent synthesis of the literature similarly suggests that acetaminophen's effects on neuroplasticity may depend strongly on dose and exposure duration (Lashgari et al., 2026).

4. Oxidative Stress and Redox Homeostasis

The CNS is particularly vulnerable to disturbances in redox homeostasis because of its high oxygen consumption and lipid-rich cellular membranes.

Acetaminophen toxicity is classically associated with hepatic formation of N-acetyl-p-benzoquinone imine (NAPQI), particularly during overdose. However, mechanisms demonstrated during severe hepatic toxicity should not automatically be transferred to the brain.

Experimental evidence provides some support for CNS redox effects. Lalert et al. (2020) reported glutathione depletion and increased protein carbonylation following long-term paracetamol treatment in rat brain, accompanied by alterations in synaptic structure and proteins.

These findings should be interpreted as preclinical evidence rather than proof of clinically significant oxidative brain injury in humans.

5. Mitochondrial Function

Mitochondria regulate ATP production, calcium homeostasis, redox balance, and cell survival. Persistent oxidative stress can impair mitochondrial function and increase reactive oxygen species. Mitochondrial dysfunction is well established in severe acetaminophen hepatotoxicity, but whether comparable processes occur in the CNS during prolonged non-overdose exposure remains incompletely established. This distinction is important because mechanisms identified during severe systemic toxicity cannot automatically be extrapolated to routine chronic analgesic use.

6. Neuroinflammation and Microglial Responses

Microglia participate in immune surveillance, synaptic remodeling, and inflammatory responses. Their activation can be protective or detrimental depending on intensity and duration.

The literature concerning NSAIDs is complex because these drugs are themselves anti-inflammatory agents and have been investigated for potentially neuroprotective effects. Therefore, NSAIDs should not be characterized as uniformly microglia-activating or neurotoxic.

Acetaminophen provides a different experimental signal. Lalert et al. (2021) reported increased TNF-α, IL-1β and Iba-1 expression in the hippocampus of rats receiving 200 mg/kg acetaminophen daily for 30 days, consistent with neuroinflammatory and microglial responses.

Conversely, Králová et al. (2025) demonstrated that a brain-targeted paracetamol derivative reduced inflammatory signaling in experimental models, illustrating that acetaminophen-related CNS pharmacology may involve both potentially harmful and potentially protective effects depending on exposure and molecular context.

The appropriate interpretation is therefore one of **context-dependent CNS modulation**, rather than a simple toxic/non-toxic classification.

7. Blood-Brain Barrier and Neurovascular Considerations

The BBB regulates movement between the circulation and CNS and is central to drug distribution and neural protection.

Analgesic CNS exposure depends on physicochemical properties, protein binding, transport mechanisms, and BBB characteristics. Pain states themselves may also influence neurovascular and glial signaling.

BBB disruption should therefore be regarded as a potential mechanistic interface rather than an established consequence of chronic NSAID or acetaminophen use.

Future work should determine whether prolonged exposure produces measurable changes in tight-junction proteins, endothelial function, transporter activity, or BBB permeability.

8. Synaptic Plasticity and Cognitive Function

Synaptic plasticity provides another possible link between prolonged drug exposure and CNS function.

Lalert et al. (2020) reported alterations in synaptic ultrastructure and reductions in synaptophysin and PSD-95 following prolonged acetaminophen exposure in adult rats. Lalert et al. (2023) subsequently reported behavioral changes involving learning and memory together with reduced BDNF expression in frontal cortex and hippocampus. These studies provide a coherent experimental signal involving synaptic structure, neurotrophic signaling, and behavior. Nevertheless, their doses, exposure conditions, and animal models limit direct extrapolation to human therapeutic use.

Recent systematic synthesis also emphasizes substantial heterogeneity in acetaminophen exposure paradigms and argues for standardized preclinical and clinical studies before firm conclusions about human neurological effects can be made (Lashgari et al., 2026).

9. Serotonergic Adaptation and Central Pain Processing

Serotonin participates extensively in nociception, mood regulation, sensory processing, and descending pain modulation.

Earlier experimental work found changes in components of the central serotonin system following chronic analgesic exposure, suggesting that repeated exposure may interact with neural circuits involved in pain modulation (Srikiatkhachorn et al., 2000).

However, serotonergic adaptation is not equivalent to neuronal injury. Changes in receptor expression or transporter activity may represent compensatory plasticity rather than toxic degeneration.

10. Medication-Overuse Headache and Central Sensitization

Medication-overuse headache is one of the clearest clinical examples of a disorder associated with frequent use of acute headache medications.

Diener et al. (2016) described MOH as involving complex interactions among medication exposure, headache susceptibility, and altered pain-processing mechanisms. More recent reviews continue to emphasize the multifactorial pathophysiology and management challenges associated with MOH (Hird and Sandoe, 2023).

The condition is relevant because repeated medication exposure may interact with pain-processing networks and contribute to headache chronification.

However, MOH should not be described simply as "analgesic neurotoxicity." It is better understood as a disorder involving maladaptive neural adaptation and altered nociceptive processing.

11. Comparative Perspective: Kidney and CNS

Domain	Kidney	CNS
Evidence base	Relatively well established for several NSAID-related effects	More heterogeneous
Main mechanisms	Prostaglandin inhibition and altered renal haemodynamics	Oxidative stress, synaptic changes, neuroinflammation and neural adaptation
Acetaminophen	Renal effects less clearly established than hepatic toxicity	Experimental evidence of CNS effects
NSAIDs	Well-established renal haemodynamic effects	CNS actions vary according to drug and context

Domain	Kidney	CNS
Human evidence	Substantial clinical literature	More limited for direct toxicity
Animal evidence	Extensive	Increasing but heterogeneous
Key clinical manifestation	Acute kidney injury and other renal complications	Medication-overuse headache and altered pain processing
Major knowledge gap	Individual susceptibility and long-term exposure	Human dose-response relationship and clinical relevance

12. Evidence Strength and Major Knowledge Gaps

The evidence can be divided into four broad categories.

Established: analgesics can act within or influence CNS pathways, and frequent acute medication use is clinically associated with MOH.

Supported experimentally: prolonged acetaminophen exposure has produced oxidative, inflammatory, synaptic, and behavioral changes in animal models (Lalert et al., 2020, 2021, 2023).

Plausible but incompletely established: prolonged exposure may influence mitochondrial function, BBB integrity, and neurovascular signaling.

Unresolved: whether therapeutic long-term exposure to commonly used analgesics produces clinically meaningful CNS injury in humans.

Future studies should characterize dose, duration, frequency, indication, co-medications, plasma exposure and CNS exposure rather than using the broad term “chronic use” alone.

13. Future Experimental Directions

Future investigations should combine:

- pharmacokinetic measurements of plasma and CNS drug concentrations;
- brain-region-specific oxidative-stress measurements;
- mitochondrial respiration and membrane-potential assays;
- glutathione and antioxidant profiling;

- microglial and astrocytic markers;
- BBB permeability and tight-junction measurements;
- synaptophysin, PSD-95 and BDNF assessment;
- behavioral tests of learning, memory and pain sensitivity;
- electrophysiological measurements of neural excitability; and
- longitudinal assessment following drug withdrawal.

A particularly valuable experimental approach would compare acetaminophen and individual NSAIDs under matched exposure conditions rather than treating analgesics as a single pharmacological category.

14. Conclusion

Analgesics have well-established therapeutic roles, but their effects cannot be understood solely through their intended peripheral targets. Experimental evidence indicates that prolonged acetaminophen exposure can influence oxidative balance, synaptic structure, neuroinflammatory signaling, neurotrophic pathways, and behavior in animal models (Lalert et al., 2020, 2021, 2023). At the same time, newer experimental work demonstrates potentially anti-inflammatory effects of paracetamol-related compounds, highlighting the context-dependent nature of CNS pharmacology (Králová et al., 2025).

The current evidence does not justify describing routine therapeutic analgesic use as established human CNS neurotoxicity. Rather, it supports a cautious interpretation: prolonged or excessive exposure may influence CNS homeostasis through multiple interacting pathways, while the clinical significance of these changes remains incompletely defined.

Medication-overuse headache provides the strongest clinically recognizable example of maladaptive neural consequences associated with repeated acute-medication exposure. However, it represents a disorder of pain processing and neural adaptation rather than proof of generalized neuronal toxicity.

Clarifying the relationship between exposure, neural adaptation and toxicity will require carefully controlled experimental studies and longitudinal human research.

DECLARATION

Ethical Approval - not applicable

Consent to participate - not applicable

Consent to publish - not applicable

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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