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N-acetylcysteine (NAC): Its Role in Addictology?

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ABSTRACT :

N-acetylcysteine (NAC), a precursor of glutathione and a glutamatergic modulator, has generated growing interest as an adjunct treatment for addictive disorders. Preclinical data suggest that NAC restores glutamatergic homeostasis in the nucleus accumbens and reduces vulnerability to cue-induced reinstatement. Clinically, randomized controlled trials have shown mixed results. Gray et al. (2012) reported a significant benefit of NAC (1200 mg twice daily) in adolescents with cannabis dependence, whereas results for cocaine, tobacco, alcohol, and pathological gambling are more inconsistent, with a modest signal suggesting an effect on craving reduction and relapse prevention. Recent meta-analyses confirm this trend but emphasize the lack of robust evidence for generalized recommendation. Overall, NAC demonstrates a favorable safety profile, with gastrointestinal symptoms being the most common adverse effects. Its use in acute pregnancy settings (acetaminophen intoxication) is considered safe; however, data on chronic administration in pregnant or breastfeeding women for addictive purposes remain very limited. In conclusion, NAC appears to be a promising option, particularly among adolescent cannabis users, although its effectiveness in other addictions remains uncertain. Large-scale, multicenter, and better-standardized trials are needed to clarify its role in clinical practice.

1. Introduction — Why Study NAC in Addiction?

Addictive disorders represent a major public health issue, associated with considerable morbidity and mortality, as well as a high social and economic burden. Despite progress in prevention and in psychotherapeutic and psychosocial interventions, pharmacological options remain limited and are often substance-specific (for example: nicotine replacement therapy or varenicline for tobacco, methadone or buprenorphine for opioids, disulfiram, acamprosate, or naltrexone for alcohol). However, no universally validated treatment currently exists that targets the neurobiological mechanisms common to different addictions. Among the avenues explored, the involvement of the glutamatergic system has attracted increasing interest. Preclinical studies have shown that dysregulation of glutamatergic neurotransmission in the nucleus accumbens and prefrontal cortex plays a central role in maintaining drug-seeking behavior and in vulnerability to relapse. More specifically, hypoactivity of glutamate transporters and alterations in glutamatergic homeostasis contribute to heightened sensitivity to environmental cues associated with substance use (cue reactivity).

2. Method of the Review

2.1 Objective

The objective of this review is to collect and synthesize available preclinical and clinical data regarding the use of N-acetylcysteine (NAC) in addictive disorders. The included studies comprise randomized controlled clinical trials (RCTs), open-label studies, systematic reviews, meta-analyses, as well as relevant safety reports, particularly those addressing use during pregnancy.

2.2 Sources and Timeframe

To identify available data on the use of NAC in addictive disorders, a systematic literature search was conducted across several biomedical databases and clinical trial platforms. The main sources included PubMed/MEDLINE, PubMed Central (PMC), ClinicalTrials.gov, ResearchGate, Wiley Online Library, ScienceDirect, and general indexing engines such as Google Scholar. The search covered the entire body of published literature up to October 3, 2025 (date of search closure). Full-text articles were prioritized, particularly randomized controlled trials, open-label studies, systematic reviews, and meta-analyses. References from safety reports (notably concerning use during pregnancy) and relevant mechanistic reviews were also included.

2.3 Keywords and Search Strategy

A Boolean strategy was used, combining English and French keywords. The main search focused on: ("N-acetylcysteine" OR "NAC" OR "N-acétylcystéine") AND (addiction OR "substance use disorder" OR cannabis OR cocaine OR nicotine OR alcohol OR gambling OR "pathological gambling" OR "opioid" OR "craving"). Complementary queries explored terms related to mechanisms ("cystine-glutamate", "xCT"), safety ("pregnancy", "pregnant"), and study types ("randomized trial", "double-blind", "meta-analysis", "systematic review").

2.4 Inclusion and Exclusion Criteria

Included studies:
- Clinical studies (RCTs, open-label trials) evaluating NAC's efficacy in addictive disorders.
- Relevant systematic reviews and meta-analyses.
- Mechanistic reviews and safety reports, especially those concerning NAC use during pregnancy.

Excluded studies:
- Irrelevant or off-topic articles.
- Letters to the editor lacking supporting data.
- Isolated case reports that are not generalizable.

For each included study, extracted data comprised population, sample size, targeted substance, dosage and treatment duration, outcome measures (objective abstinence, craving scales, biological markers), main results, and reported adverse events.

2.5 Assessment of Methodological Quality

Randomized controlled trials and meta-analyses were considered the most robust sources. Study quality was assessed qualitatively, taking into account randomization methods, double-blind design, statistical power, and the relevance of outcome measures used. The main methodological limitations identified (small sample size, population heterogeneity, limited follow-up duration) are discussed in the Discussion section.

3. Pharmacology and Mechanisms of Action of NAC

N-acetylcysteine (NAC) is a derivative of the amino acid cysteine, widely used as a mucolytic agent and as an antidote in acetaminophen (paracetamol) poisoning. Its relevance in addictive disorders lies in its multiple mechanisms of action, involving glutamatergic modulation, antioxidant properties, and regulation of neuroinflammation.

3.1 Glutamatergic Modulation

The primary mechanism investigated in the context of addictions is NAC's ability to restore glutamatergic homeostasis. In substance use disorders, abnormalities in extrasynaptic glutamate transmission have been observed—particularly within the nucleus accumbens and prefrontal cortex, two key regions in the reward and motivation circuitry. NAC acts by increasing extracellular cystine availability, which is taken up by the cystine/glutamate exchanger (xCT) located on astrocytes. The uptake of cystine through xCT is coupled with the release of extrasynaptic glutamate, which then activates presynaptic metabotropic glutamate receptors (mGluR2/3). This activation inhibits excessive synaptic glutamate release during exposure to substance-related cues (cue-induced reinstatement). In practice, this mechanism allows NAC to normalize the altered glutamatergic transmission observed in addiction, reduce reactivity to environmental cues associated with substance use, and decrease the risk of relapse in animal models—and potentially in humans.

3.2 Antioxidant and Anti-inflammatory Effects

NAC is a precursor of glutathione, the main intracellular antioxidant. By increasing glutathione levels, NAC protects neurons from oxidative stress and mitochondrial damage, both of which are implicated in the pathological neuroplasticity associated with chronic addiction. Furthermore, NAC exerts anti-inflammatory effects by modulating the production of proinflammatory cytokines within the central nervous system. This action may help reduce neuroinflammation and dysregulation of reward circuits observed following repeated substance exposure.

3.3 Pharmacokinetics and Clinical Implications

Absorption: Orally administered NAC is rapidly absorbed, but exhibits relatively low bioavailability (~6–10%) due to first-pass hepatic metabolism. Distribution and Metabolism: NAC is widely distributed in tissues, with potential accumulation in the brain as cysteine and glutathione. Elimination: The plasma half-life is short (~6 hours), explaining the need for multiple daily doses (commonly BID or TID). Clinical implications for addiction treatment: NAC does not act as a pharmacological substitution agent (as methadone does for opioids) but rather as a modulator of relapse vulnerability and craving. Its clinical use is primarily envisioned as an adjunct to psychosocial interventions (CBT, motivational therapy, contingency management), rather than as a first-line agent for inducing abstinence.

3.4 Additional Mechanistic Perspectives

Recent studies suggest that NAC may also influence synaptic plasticity by modulating AMPA and NMDA receptor expression; indirectly affect dopaminergic and opioidergic systems via glutamate regulation; and potentially improve cognitive function and reduce symptoms of stress and impulsivity associated with addictive disorders. These multidimensional properties justify the continued exploration of NAC across various forms of addiction and its combination with other therapeutic interventions to maximize clinical efficacy.

4. Clinical Results

4.1 Cannabis

NAC has been most extensively studied in relation to cannabis use disorder, particularly among adolescents. Key Trial: Gray et al., 2012 — Population: 116 adolescents (aged 12–21) meeting DSM-IV criteria for cannabis dependence. Intervention: NAC 1200 mg twice daily (BID) for 8 weeks, combined with behavioral therapy, compared to placebo plus behavioral therapy. Outcome Measures: Urine THC testing, self-reported craving, and consumption frequency. Results: The likelihood of obtaining a negative urine test for THC at the end of treatment was more than twice as high in the NAC group compared with placebo ($p < 0.05$). A reduction in craving was also observed, though less pronounced. Tolerability was good; the most frequent adverse events were mild gastrointestinal discomfort and headaches. Limitations: Short follow-up period (8 weeks), adolescent population, and concurrent behavioral therapy make it difficult to isolate NAC's specific effects. Subsequent Studies and Ongoing Trials: In adults, trials have been less consistent—some report modest craving reduction but no significant impact on objective abstinence. Ongoing protocols (e.g., NCT03055377) aim to evaluate NAC's effect independently of behavioral interventions. Conclusion: The strongest clinical signal remains among adolescents, while evidence in adults is still insufficient.

4.2 Cocaine

Randomized and Pilot Trials: LaRowe et al., 2013 — double-blind, placebo-controlled RCT, NAC 1200 mg BID vs placebo in 111 patients with cocaine dependence. Findings: No significant effect on active consumption. However, among patients already abstinent at baseline, NAC appeared to reduce relapse risk and lower cue-induced brain activation (measured via fMRI). Mardikian et al., 2007 — Open-label pilot study showing early signals of craving reduction and good tolerability. Synthesis: NAC has not demonstrated robust effects on active cocaine use but may play a role in relapse prevention, particularly after abstinence induction. Limitations: Small sample sizes, short follow-up durations, heterogeneous endpoints (craving vs. objective consumption), and variability in dosing regimens and treatment duration.

4.3 Tobacco / Nicotine

Clinical Trials: A few studies have evaluated NAC as an adjunct to smoking cessation. Some reported an effect on craving reduction, but none demonstrated significantly higher quit rates compared with placebo when used as monotherapy. Limitations: Limited and heterogeneous data, mostly in adult populations and short treatment durations. The potential for combination therapy (e.g., with nicotine replacement or varenicline) remains underexplored.

4.4 Alcohol

Available Data: Pilot and open-label studies have sometimes shown modest reductions in craving and withdrawal-related symptoms. However, no RCT of sufficient statistical power has demonstrated a clear effect on long-term abstinence or alcohol consumption. Limitations: Very small sample sizes, heterogeneous populations, and lack of standardized objective criteria in some studies. Ongoing Trials: New trials (e.g., NAC-AUD) are underway to evaluate NAC's impact on relapse prevention and craving reduction.

4.5 Pathological Gambling / Impulse Control Disorders

Pilot Studies: Grant et al., 2007 — open-label study involving 27 patients with pathological gambling, NAC 1200–1500 mg BID. Findings: Improvement in PG-YBOCS scores (a measure of impulsivity and compulsive behavior) in a subset of participants. Tolerability: Good, with only mild gastrointestinal adverse effects. Limitations: Small sample size, no control group, and heterogeneous outcome measures. Findings are promising but preliminary, requiring confirmation through multicenter RCTs.

4.6 Opioids and Polysubstance Dependence

Clinical Trials: Virtually nonexistent. Preclinical data suggest that NAC could reduce craving and relapse through glutamatergic modulation and decreased activation of reward circuits. Limitations: Lack of robust clinical evidence; no current therapeutic recommendations.

4.7 Synthesis by Type of Effect

5. Tolerance and Safety

One of the key advantages of N-acetylcysteine (NAC) in the field of addiction medicine is its generally favorable safety profile, well established through its long-term use in pulmonology (as a mucolytic) and in emergency medicine (as an antidote for acetaminophen poisoning). However, data specific to addictive disorders require a more nuanced analysis.

5.1 General Tolerance

Common adverse effects (≥ 1/10): Gastrointestinal disturbances (nausea, diarrhea, abdominal pain, flatulence), generally mild to moderate; transient headaches and fatigue. Occasional adverse effects (1/100–1/1000): Mild skin rashes, pruritus, urticaria; dizziness; benign tachycardia. Rare adverse effects (< 1/1000): Hypersensitivity reactions (more frequent with IV use for acetaminophen overdose than with chronic oral use); bronchospasm (mainly with inhaled forms, rarely oral). Most adverse effects are dose-dependent and resolve upon discontinuation or dose adjustment.

5.2 Data from Clinical Trials in Addictive Disorders

In cannabis studies (Gray et al., 2012; Carpenter et al., 2018), adverse events were mainly gastrointestinal and mild, with no discontinuations for severe events. In cocaine trials (LaRowe et al., 2013), tolerance was similar to placebo, with occasional diarrhea or gastric discomfort. In pathological gambling (Grant et al., 2007), no severe adverse events were reported despite high doses (up to 3000 mg/day). Alcohol and tobacco studies confirm this safety profile without increased severe adverse events versus placebo. Overall, these data suggest that NAC is well tolerated even with prolonged treatment and at high doses (2400–3000 mg/day).

5.3 Tolerance in Specific Populations

Pregnancy and breastfeeding: NAC is commonly used in pregnancy for acetaminophen overdose with no documented teratogenic risk. However, data on chronic long-term use during pregnancy or lactation in addiction contexts are very limited; prolonged use cannot currently be recommended. Pediatrics and adolescents: Gray et al. (2012) confirmed good tolerance of oral NAC (1200 mg BID) in adolescents with cannabis dependence, with no severe or age-specific adverse effects. Medical comorbidities: Caution in patients with a history of bronchospasm (asthma/bronchial disease). In severe renal/hepatic impairment, no formal contraindication exists but theoretical dose adjustments may be considered.

5.4 Drug Interactions

Potential interactions include: Nitroglycerin (possible enhancement of vasodilatory effects and hypotension risk); Activated charcoal (may reduce gastrointestinal absorption of NAC). No other significant pharmacokinetic interactions have been documented in addiction studies.

5.5 Misuse and Dependence Potential

To date, no evidence of addictive potential has been reported with NAC, even in vulnerable populations. NAC does not produce euphoric effects or positive reinforcement, which is an advantage compared with some other pharmacological agents in addiction medicine.

5.6 Safety Conclusion

NAC demonstrates a reassuring safety profile in most clinical trials, with primarily mild and transient gastrointestinal side effects. It appears to be a relatively safe option, including in adolescents and in acute pregnancy contexts (e.g., acetaminophen intoxication). However, experience with long-term chronic use in addiction treatment remains limited, particularly in pregnant or breastfeeding women, and pharmacovigilance data should be strengthened via larger, longer trials.

6. Critical Discussion and Clinical Implications

The available data on N-acetylcysteine (NAC) in addictive disorders warrant a nuanced interpretation. Among all studied indications, the most convincing evidence remains in adolescent cannabis dependence. Gray et al. (2012) demonstrated that 2400 mg/day of NAC, combined with psychosocial care, doubled the likelihood of negative THC urine tests. Outside of this signal, results are more heterogeneous: in cocaine dependence, NAC does not induce active abstinence but may help prevent relapse among abstinent patients, suggesting a maintenance role. For tobacco, alcohol, and pathological gambling, data are limited and often nonsignificant. Recent meta-analyses suggest a modest yet measurable reduction in craving, but evidence is insufficient for routine guideline inclusion.

Methodological limitations include substantial protocol heterogeneity (targeted substances, demographics, dosing 1200–3600 mg/day, durations 8–24 weeks, and co-interventions), small sample sizes, and variable outcomes (objective toxicology vs. subjective craving scales), complicating direct comparisons. Clinically, NAC should be considered an adjuvant rather than a first-line treatment. Its favorable tolerance and limited interactions support use within multidisciplinary care alongside validated psychosocial interventions. Prescription should remain specialized, with particular caution during pregnancy or lactation given limited evidence.

Future research should prioritize large multicenter trials with standardized protocols, inclusion of objective biomarkers (neuroimaging, glutamate spectroscopy, oxidative stress markers), and targeted studies in pregnant/breastfeeding women to assess benefit–risk in sensitive contexts.

7. Limitations of the Review

This review is narrative rather than a quantitative meta-analysis. Despite a systematic search across multiple databases (PubMed, ClinicalTrials.gov, ResearchGate, ScienceDirect, etc.), certain recent, unpublished, or ongoing studies may not be included. Although randomized controlled trials and

meta-analyses were prioritized, methodological quality varied and influences the strength of conclusions. The literature analyzed extends up to October 3, 2025; more recent results may refine or complement these findings.

8. Conclusion

N-acetylcysteine (NAC) appears to be a promising compound in addiction medicine due to its effects on glutamatergic homeostasis and antioxidant/anti-inflammatory properties. Clinical data suggest potential benefit, particularly in adolescents with cannabis dependence, but remain insufficient and heterogeneous for substances like cocaine, tobacco, alcohol, or pathological gambling. NAC's tolerance is generally good, and its safety in acute pregnancy contexts is well documented; however, strong evidence for chronic use during pregnancy is lacking. At present, NAC should not be considered a reference treatment but may be used as an adjunct in specialized settings. The future of NAC in addiction medicine depends on rigorous multicenter trials to clarify efficacy, target populations, and clinical positioning within the therapeutic arsenal for substance use disorders.

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