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Case Report

Acute Olfactory Hypersensitivity to Opium and Cannabis Following Naltrexone Administration: A Rare Case Report

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Abstract

Naltrexone, a long-acting opioid receptor antagonist, is commonly utilized to avert relapse in individuals with opioid or alcohol dependence. While its efficacy in modifying cue-reactivity and lowering desire is well documented, less is known regarding its ability to elicit negative sensory-emotional reactions, particularly in response to olfactory stimulation. We present a rare case of a 16-year-old male with a history of cannabis usage who experienced acute episodes of respiratory distress after starting oral naltrexone (50 mg/day). These episodes were consistently triggered by the smell of opium or cannabis smoke, despite the patient's abstinence. The reactions were severe enough to necessitate multiple emergency medical procedures. The patient had a prior adverse reaction to morphine and a history of multiple drug allergies, suggesting a possible underlying sensitivity to opioid system modulation. The symptoms resolved after discontinuation of naltrexone. This case raises significant clinical and neurobiological concerns about the role of opioid antagonism in modifying olfactory and emotional processing. We propose that naltrexone-induced disinhibition in olfactory-limbic circuits may have contributed to heightened sensory gain and conditioned unpleasant reactions in a sensitized individual. More research is needed to understand the mechanisms driving this unusual yet important reaction.

Keywords: Naltrexone, Substance-related disorders, Olfactory perception, Hypersensitivity, Cannabis, Opium, Case report

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Introduction

Naltrexone is an extended-release, competitive antagonist of opioid receptors predominantly employed in the pharmacotherapeutic management of both opioid and alcohol use disorders.[1,2] Through the selective inhibition of μ-opioid receptors, naltrexone diminishes the reinforcing properties of opioids and mitigates cravings, thereby promoting sustained abstinence in individuals undergoing recovery.[3] Although naltrexone is generally well tolerated, it may occasionally cause adverse psychological or somatic reactions, particularly in susceptible individuals or under certain neurobiological conditions.[4] Common side effects of naltrexone include nausea, headache, dizziness, fatigue, anxiety, and insomnia.[4] Some individuals may also experience abdominal pain, joint or muscle aches, or irritability. While the majority of these adverse effects are mild and transient, they have the potential to influence treatment adherence in certain patients.[5]

Beyond its recognized influence on craving suppression, naltrexone also modulates the brain's response to addiction-related cues, including visual, contextual, and affective stimuli.[6-8] Neuroimaging studies demonstrate that naltrexone alters limbic and prefrontal activation patterns during cue exposure, suggesting broader effects on cognitive-emotional processing beyond receptor blockade.[6,9] This cue-modulatory role raises questions about how opioid antagonism may also influence sensory pathways engaged by addictive cues—not only visual or emotional, but also chemosensory. Indeed, emerging evidence indicates that opioid receptor antagonists can affect gustatory and olfactory perception.[10] Research conducted with healthy participants has revealed that the administration of naltrexone may diminish the subjective pleasantness associated with taste stimuli and modify food consumption behaviors.[11] Moreover, the hedonic experience elicited by highly sweet, calorie-dense tastes appears to be particularly susceptible to manipulation by both opioid agonists and antagonists.[12]

Despite these insights, no prior study has described naltrexone-associated alterations in olfactory sensitivity, particularly in relation to drug-related odors. We report a rare case in which a detoxified adolescent exhibited acute aversive and respiratory reactions specifically to the odors of opium and cannabis shortly after initiating oral naltrexone. This observation highlights a potentially overlooked interface between opioid antagonism and olfactory-limbic processing, with implications for both treatment tolerability and relapse vulnerability in substance use disorders.

Case Presentation

A 16-year-old male high school student from Iran, with a documented history of substantial cannabis consumption, sought our clinic's assistance for consultation regarding cessation of substance use. The patient had successfully refrained from cannabis utilization for a duration of 10 days preceding his visit and indicated an absence of recent opioid consumption. He explicitly denied any recent encounters with either substance, aside from passive exposure, including within his familial setting. After baseline evaluation, oral naltrexone (50 mg/day) was prescribed.

Within 24 hours of initiating treatment with naltrexone, the patient exhibited an abrupt and severe episode of respiratory distress, characterized by pronounced dyspnea, a sensation of constriction in the throat, palpitations, chest discomfort, and significant anxiety, all triggered by exposure to the olfactory stimuli of opium or cannabis smoke. These distressing episodes transpired notwithstanding the patient's complete abstinence from all illicit substances. Each incident was characterized by a rapid onset, reaching its zenith within minutes of exposure to the specific odors, and typically persisted for a duration of 30 to 60 minutes. The patient refuted the presence of any associated rash, wheezing, stridor, or edema indicative of anaphylactic reactions; however, he articulated a subjective experience of impending doom and a profound fear of asphyxiation. These symptoms necessitated multiple presentations to the emergency department (approximately 10 instances within the initial month), with each occasion requiring the provision of oxygen therapy and clinical monitoring for stabilization. The physical examination and vital signs recorded during these episodes reportedly indicated tachypnea and tachycardia; however, there was an absence of hypoxemia, cyanosis, or wheezing. Pulmonary auscultation yielded no remarkable findings. Imaging via chest X-ray and routine laboratory evaluations returned results that fell within normal parameters.

His past medical history was predominantly unremarkable, with the exception of enduring chronic functional constipation and a historical occurrence of nephrolithiasis, during which he received intravenous morphine and subsequently experienced acute respiratory distress necessitating urgent intervention, which included the administration of oxygen and antihistamines. There was no documented personal or familial history of asthma, atopy, or any chronic respiratory ailments. The patient additionally disclosed a record of pharmacological hypersensitivities, which included urticarial rashes and facial edema following administration of azithromycin syrup during childhood, gastrointestinal intolerance to tetracycline, and a suspected allergic response to cefazolin (characterized by a rash without systemic involvement).

He refuted the assertion of any habitual pharmacological intervention, with the exception of a brief regimen involving naltrexone. Furthermore, there was an absence of simultaneous consumption of ethanol, benzodiazepines, or any additional psychoactive agents. At the conclusion of the most recent follow-up, the patient had autonomously ceased the use of naltrexone following a dialogue with his healthcare provider, and reported a complete alleviation of hypersensitivity manifestations. A detailed clinical timeline summarizing the temporal relationship between naltrexone initiation, symptom onset, and subsequent recovery is illustrated in Figure 1. He maintained abstinence from cannabis, reported only occasional cigarette smoking, and exhibited satisfactory performance in his academic pursuits and part-time employment. No subsequent incidents of respiratory distress were documented following the discontinuation of naltrexone, even when subjected to passive exposure to the identical olfactory stimuli. A formal causality assessment using the Naranjo scale was performed subsequently (see Supplementary File 1).

Discussion

This case report suggests a previously unrecorded possible adverse reaction potentially associated with naltrexone therapy: Acute hypersensitivity to drug-associated olfactory stimuli in an adolescent with a documented history of cannabis consumption. The patient developed recurrent

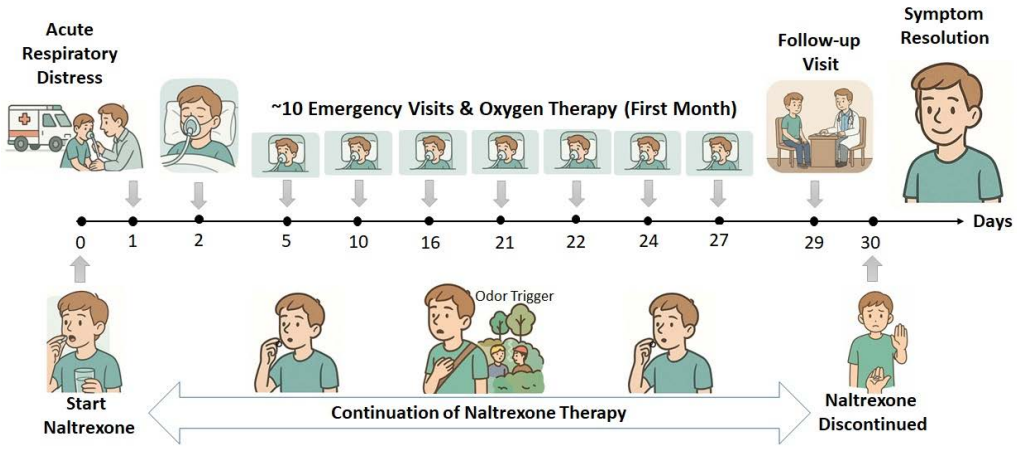

Figure 1. Clinical timeline depicting the sequence of events following initiation of oral naltrexone therapy, including acute respiratory distress triggered by the exposure to opium or cannabis smoke, multiple emergency visits with oxygen therapy, continuation and discontinuation of treatment, and complete symptom resolution

episodes of respiratory distress exclusively triggered by the smell of opium or cannabis, an unusual presentation that raises important questions about the interaction between opioid receptor antagonism and sensory-limbic processing within the context of substance use disorders. Given that this observation is based on a single case, no causal inference can be drawn, and further studies are warranted to verify this association.

To further assess the causal relationship between naltrexone intake and the observed reaction, the Naranjo Adverse Drug Reaction Probability Scale was applied.[13] The total score was 5, indicating a *probable* association between naltrexone administration and the observed olfactory hypersensitivity accompanied by respiratory distress. Despite the absence of physiological or imaging data confirming an underlying mechanism, the strong temporal association, full resolution of symptoms following drug discontinuation, and the patient's prior opioid-related respiratory reaction (post-morphine administration) collectively support a pharmacological contribution. Detailed scoring is presented in Supplementary 1.

Naltrexone, a non-selective opioid receptor antagonist with substantial affinity for μ-receptors, is primarily used to mitigate cravings and prevent relapse in opioid and alcohol use disorders.[14,15] Beyond its receptor-blocking function, converging evidence indicates that naltrexone influences cue reactivity, emotional regulation, and attentional biases through its actions on cortico-limbic circuitry.[6,16] Neuroimaging data demonstrate attenuated activation of the amygdala, ventral striatum, and prefrontal cortex during cue exposure, implying a generalized dampening of motivational salience.[17] However, in contrast to this expected cue-attenuating effect, the present case manifested a paradoxical enhancement of emotional and somatic reactivity specifically to olfactory drug cues. The odor-specific nature of this reaction, in the absence of direct substance exposure, indicates a distinctive interaction between opioid antagonism and the neural systems mediating odor perception, affective valuation, and conditioned responses.

A plausible mechanistic explanation involves naltrexone's modulation of endogenous opioid tone within the olfactory-limbic network.[18] Endogenous opioids act as modulators in the olfactory bulb and related structures such as the piriform cortex and amygdala.[18] Blockade of these inhibitory pathways may inadvertently enhance sensory reinforcement or reduce inhibitory control, eliciting an exaggerated aversive response to previously conditioned odors. In individuals with heightened interoceptive sensitivity or prior negative opioid experiences, as exemplified by this patient's earlier morphine-induced respiratory distress, such disinhibition could manifest as panic-like somatic symptoms. Additional mechanisms of sensory sensitization and classical conditioning through negative reinforcement may also contribute: The repeated pairing of drug cues with distress during naltrexone exposure might have consolidated a reflexive aversive reaction even to minimal odor exposure. This mechanism resembles conditioned aversion phenomena described in aversive addiction therapies, albeit with greater physiological intensity in the present instance.[19,20]

Although anxiety is a well-documented side effect of naltrexone,[21] several clinical features in this case argue against a primary pharmacologic anxiety reaction. The distress episodes were not spontaneous or temporally linked to medication intake but were exclusively triggered by the olfactory cues of opium or cannabis, while neutral odors or odor-free contexts remained asymptomatic. Furthermore, each episode resolved promptly upon removal of the odor stimulus and did not occur during rest or at night, which is atypical for spontaneous panic attacks. The absence of generalized anxiety, avoidance behavior, or anticipatory fear between exposures supports the interpretation of a stimulus-bound, olfactory-related hypersensitivity reaction rather than a generalized anxiety or panic disorder.

Taken together, these observations suggest a tentative mechanism in which opioid receptor blockade disrupts inhibitory modulation within the olfactory-limbic circuitry, amplifying conditioned aversive responses to drug-related stimuli. To date, no documented case has reported olfactory hypersensitivity or dyspnea induced by naltrexone, particularly confined to drug-related odors. This case therefore contributes novel clinical insight into a potentially overlooked sensory-emotional adverse effect of naltrexone, highlighting the need for heightened awareness in patients with prior hypersensitivity or adverse opioid experiences.

From a clinical perspective, this case emphasizes the importance of close observation for atypical sensory or affective reactions to naltrexone, especially in adolescents or individuals with allergic or interoceptive vulnerability. Further studies incorporating multimodal physiological and neurobiological assessments are warranted to determine whether naltrexone unmasks latent hypersensitivities within sensory-limbic pathways.

It should be acknowledged that no standardized psychometric or physiological testing, such as anxiety scales, olfactory threshold measures, autonomic monitoring, serum naltrexone levels, or neuroimaging was performed in this case. The absence of these data limits the objective mechanistic inference. Future research employing integrative psychophysiological and imaging methods may clarify the complex interactions between opioid antagonism and sensory-limbic processing in predisposed individuals.

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Authors' Contribution
Conceptualization: Seyed Hamzeh Hosseini.
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Writing–Original Draft: Raheleh Rafaiee.
Writing–Review & Editing: Seyed Hamzeh Hosseini, Raheleh Rafaiee.

Competing Interests
The authors declare that they have no conflict of interest.

Ethical Approval

This study was designed based on the ethical principles of the Declaration of Helsinki (2008) for medical studies involving humans. The local Ethics Committee affiliated with the Mazandaran University of Medical Sciences approved this study (Ethical Approval code: IR.MAZUMS.REC.1404.230). Informed consent was obtained from the patient before publication.

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Intelligence Use Disclosure

We confirm that the conception, design of the review framework, literature search, selection and interpretation of sources, and drafting of the manuscript were entirely performed by the authors. During the writing process, AI tools (ChatGPT and Grammarly) were used solely to enhance clarity, style, grammar, and punctuation. All cartoon-style illustrations in the figure were generated using OpenAI's ChatGPT (free version) image creation tools. Following this assistance, all authors critically reviewed and refined the text and take full responsibility for the accuracy, originality, and integrity of the scientific interpretations presented in this paper.

Supplementary Files

Table S1. Naranjo Adverse Drug Reaction Probability Scale Assessment

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