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Ketamine Combined With Dextromethorphan-Bupropion for Depression in the Context of Nitrous Oxide Misuse

Abstract:

Background: Treatment-resistant depression (TRD) affects up to a third of patients with major depressive disorder and remains difficult to manage with conventional therapies. Rapid-acting antidepressants targeting the glutamatergic system, such as ketamine, esketamine, and dextromethorphan-bupropion, have emerged as promising alternatives. Nitrous oxide, also an NMDA receptor antagonist, has demonstrated antidepressant properties in clinical trials but carries significant risks when used recreationally.

Case Presentation: We describe a 27-year-old male with no prior psychiatric history who presented with escalating nitrous oxide use following the suicide of his cousin. He reported compulsive urges to continue use despite associated psychiatric symptoms. The patient endorsed depressive features without suicidal intent or psychosis. Given the limited two-week timeframe prior to his wedding, rapid-acting treatment was initiated with esketamine infusion and dextromethorphan-bupropion (Auvelity), along with naltrexone for craving management. At two-week follow-up, the patient reported abstinence from nitrous oxide, reduced irritability, and symptomatic improvement.

Discussion: This case underscores the clinical overlap between recreational nitrous oxide use and emerging therapeutic applications of NMDA receptor antagonists. esketamine provided rapid symptom reduction, while dextromethorphan-bupropion supported early maintenance of response. The combination highlights a potential therapeutic pathway for patients who self-medicate with nitrous oxide, substituting maladaptive use with evidence-based, clinically supervised interventions.

Conclusion: This report describes a novel treatment strategy combining esketamine and dextromethorphan-bupropion in the context of nitrous oxide misuse. Further research is warranted to explore the biological underpinnings of this approach and to evaluate its generalizability to broader patient populations with comorbid depression and substance misuse.

Introduction

Treatment-resistant depression (TRD) remains one of the most difficult conditions to manage in psychiatry, with up to one-third of patients failing to respond to conventional antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) [1]. In recent years, rapid-acting antidepressants targeting the glutamatergic system, particularly N-methyl-D-aspartate (NMDA) receptor antagonists, have shown promise in addressing this critical gap in care [2,3].

Nitrous oxide, a non-competitive NMDA receptor antagonist long used for anesthesia and analgesia, has been shown in recent studies to produce rapid antidepressant effects [2]. However, its growing prevalence as a recreational substance is concerning, as misuse is associated with significant neurotoxicity and adverse outcomes, including hematologic abnormalities, neurologic deficits, and psychiatric disturbances [3].

Ketamine, another NMDA receptor antagonist, has demonstrated robust efficacy in reducing depressive symptoms and suicidal ideation in TRD, leading to the FDA's 2019 approval of intranasal esketamine, the first antidepressant in decades to act via a novel mechanism [4-6]. More recently, Auvelity, a fixed-dose combination of dextromethorphan and bupropion, was approved in 2022 as another rapid-acting agent targeting the glutamatergic system, with clinical trials confirming its early and sustained antidepressant effects [6].

Here, we present the case of a young adult male with escalating recreational nitrous oxide use in the setting of bereavement-related depression. This report highlights the clinical challenges of replacing maladaptive self-medication with safe, evidence-based alternatives, and describes a novel treatment strategy combining esketamine with dextromethorphan-bupropion.

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Case presentation

We describe the case of a 27-year-old male, with no significant past psychiatric or medical history, presenting for urgent psychiatric evaluation two weeks prior to his scheduled wedding. The referral was prompted by escalating nitrous oxide use ("huffing") following the suicide of his cousin who had been his closest friend and confidant.

The patient reported a six-month history of intermittent nitrous oxide use that intensified after his cousin's death, progressing to three times daily. He described associated symptoms of euphoria, slurred speech, dizziness, headaches, drowsiness, and impaired coordination.

He denied any formal family history of depression and anxiety, though noted that his mother may experience depressive symptoms. The patient endorsed low mood and depressive features but denies manic or psychotic symptoms, delusions, nightmares or suicidal intent. Despite acknowledging compulsive urges to use nitrous oxide, he emphasized a desire to live and build a family. He had previously briefly engaged in psychotherapy, though found it unhelpful.

The patient was initiated on esketamine infusion,in combination with Auvelity (dextromethorphan-bupropion 45/105 mg) for depressive and trauma related symptoms, and naltrexone 50 mg for craving management.

At two week follow up, patient had been compliant with pharmacotherapy and had received 2 infusions of Ketamine. He demonstrated reduced irritability and agitation, with self-reported maintenance of abstinence from nitrous oxide use.

Discussion

Nitrous oxide and ketamine share overlapping neurobiologic effects through their non-competitive inhibitory nature of the NMDA receptor [1,2]. Both agents have demonstrated rapid antidepressant effects in patients with TRD, with ketamine showing particular efficacy by enhancing glutamate-mediated synaptic transmission in the hippocampus and prefrontal cortex [1]. At subanesthetic, but therapeutically significant concentrations, nitrous oxide produces ketamine-like effects on hippocampal synaptic function, further suggesting convergence in their mechanism of action [1].

Despite these similarities, the clinical and recreational contexts differ significantly. While nitrous oxide has been in medical use for more than 150 years, recreational misuse has been associated with severe adverse outcomes including hematologic abnormalities, frostbite, impaired bowel and bladder function, paralysis, heart palpitations, and psychiatric disturbances such as psychosis [3]. In contrast, ketamine, when administered in a controlled clinical setting, is associated with a more favorable risk-benefit profile and is recognized as a rapid-acting antidepressant [5-7]. esketamine, the S-enantiomer of ketamine, received FDA fast-track and breakthrough therapy designations, reflecting both its novel mechanism beyond traditional monoaminergic agents and efficacy in reducing both depressive symptoms and suicidal ideation [4,5].

At the cellular level, NMDA receptor antagonism triggers downstream glutaminergic signaling, including transient glutamate release, stimulation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, and activation of neurotrophic factor pathways. These changes ultimately promote

synaptogenesis in brain regions critical to mood regulation [7]. Ketamine's rapid effects may also involve stimulations of the mammalian target of rapamycin complex 1 (mTORC1) pathway, which enhances brain-derived brain-derived neurotrophic factor (BDNF) production and restores dopaminergic neurotransmission [7]. These effects contrast with the delayed onset of SSRIs and SNRIs, making esketamine particularly useful in acute or time-sensitive clinical scenarios such as suicidality or major psychosocial stressors [4,5].

In this case, the patient's reliance on nitrous oxide to self-manage his depressive symptoms necessitated substitution with a safer, evidence-based alternative. The limited two-week timeframe before his wedding justified the use of a rapid-acting intervention. esketamine provided a clinically meaningful reduction in depressive and trauma-related symptoms, while Auvelity (dextromethorphan-bupropion) was initiated to sustain this early response. Dextromethorphan acts as both an NMDA receptor antagonist and sigma-1 receptor agonist; when combined with bupropion, which prolongs its half-life through CYP2D6 inhibition, the combination produces rapid and robust antidepressant effects. Clinical trials have demonstrated reductions in Montgomery-Åsberg Depression Rating Scale (MADRS) scores within two weeks of treatment initiation [6].

Importantly, recent research suggests that dextromethorphan-based therapy may also help maintain the antidepressant effects of ketamine over time [8]. Given their shared pharmacologic properties, including modulation of NMDA receptors, sigma-1 receptors, and mu-opioid receptors, a synergistic effect in sustaining mood stabilization is biologically plausible [8]. This raises the possibility that dextromethorphan-bupropion may function not only as a rapid-acting antidepressant, but also as a maintenance strategy following ketamine treatment.

To our knowledge, this is the first reported case describing combined esketamine and dextromethorphan-bupropion in the context of nitrous oxide misuse. It highlights a potential therapeutic pathway in which clinically supervised NMDA receptor antagonists can substitute for maladaptive self-medication, providing both acute symptom relief and sustained stabilization. Further studies are warranted to clarify the biological underpinnings of this approach and to evaluate its broader applicability in patients with comorbid depression and substance misuse.

Conclusion

This case illustrates a novel therapeutic strategy in which rapid-acting glutamatergic agents, esketamine and dextromethorphan-bupropion, were successfully employed to treat depressive symptoms in a patient with maladaptive nitrous oxide use. By substituting recreational NMDA receptor antagonism with clinically supervised, evidence-based interventions, the approach provided rapid symptom relief within a time-sensitive context and facilitated abstinence from nitrous oxide. Future research should investigate the biological rationale and clinical utility of this combination, particularly in patients with comorbid depression and substance misuse.

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