Journal of the Neurological Sciences 412 (2020) 116778

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Review Article

Ketamine and nitrous oxide: The evolution of NMDA receptor antagonists as antidepressant agents

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ARTICLE INFO

Keywords:
Ketamine
Esketamine
Nitrous oxide
Treatment resistant depression
Major depressive disorder
NMDAR

ABSTRACT

N-methyl-D-aspartate receptor (NMDAR) antagonists, including ketamine and nitrous oxide, are currently intensely studied as rapid-acting antidepressant agents. Interestingly, both of these compounds are also drugs of abuse.

Intravenous ketamine, a dissociative anesthetic that induces complex downstream effects via NMDARs, rapidly reduces depressive and suicidal symptoms in treatment-resistant depression (TRD), as demonstrated by several trials. Recently, the United States Food and Drug Administration (FDA) approved an intranasal version of ketamine (esketamine) for TRD. The United States Drug Enforcement Agency (DEA) lists ketamine as a Class III scheduled drug (moderate-low potential for physical and psychological abuse). The FDA has established a Risk Evaluation and Management Strategy (REMS) program to ensure proper drug storage, handling, dispensing, and monitoring intranasal esketamine to minimize misuse/abuse opportunities.

Nitrous Oxide is a colorless, odorless, gas that has been in medical use for over 150 years. The mechanisms of action of nitrous oxide are not fully understood; however, it is known to act as a non-competitive inhibitor of NMDA-type glutamate receptors. Currently, nitrous oxide is used for inhalational general anesthesia and analgesia for short procedures. Inhaled nitrous oxide is also used recreationally, primarily by teens and young adults, but is not believed to have strong addiction potential. In contrast to ketamine, nitrous oxide is not a controlled substance and can be legally purchased without a prescription. A recent double-blind, prospective, cross-over study demonstrated that nitrous oxide reduced depressive symptoms in a group of severely ill TRD patients. Though this is a promising initial study, further investigation is needed.

1. Introduction

Major Depressive Disorder (MDD) is a clinical syndrome that manifests with persistently low mood and an inability to experience joy, which is often accompanied by suicidal thoughts, sleep disturbance, appetite changes and impaired cognition. Fortunately, most patients with this condition respond to standard antidepressant treatments that act on norepinephrine, serotonin and/or dopamine neurotransmitter systems. However, an estimated 15–20% of MDD patients do not respond to standard antidepressant treatments and are thus categorized as having treatment resistant depression [TRD; [1,2]]. This shortcoming in clinical care has prompted the exploration of alternative antidepressant treatments including neurosteroids, anti-inflammatory agents, and novel neurostimulation treatments (repetitive transcranial magnetic stimulation, transcranial direct current stimulation, deep brain stimulation), among others. Recent data suggest that some novel antidepressant treatments can produce rapid symptomatic response compared to standard oral antidepressant medications, which often take 4 weeks or longer to work.

One promising line of new therapeutic agents are NMDAR antagonists [3–6]. Some compounds, such as AV-101 showed promise in early studies, necessitating ongoing phase 2 investigation [4]. Others, like memantine, were found to have no substantial antidepressant qualities [3]. Some, like lanicemine, showed a positive signal, but remained inferior to ketamine [4]. And finally, others such as traxoprodil are of limited clinical utility due to serious adverse effects, including cardiotoxicity [4]. Additional glutamatergic modulators that remain under active investigation for depression include: d-cycloserine, pioglitazone,

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https://doi.org/10.1016/j.jns.2020.116778
Received 23 August 2019; Received in revised form 20 February 2020; Accepted 14 March 2020
Available online 19 March 2020
0022-510X/

riluzole, GLYX-13, CERC-301 and various combinations of dextromethorphan-quinidine [3–6]. This list is by no means exhaustive, but illustrates that an array of functional NMDA antagonists have been studied as possible rapid-acting antidepressants.

In this review we discuss two of the more prominent agents being studied as therapies for TRD: ketamine and nitrous oxide. For both compounds, we describe existing clinical evidence for their efficacy in TRD, and detail putative mechanisms of action that may explain their antidepressant effects. This article will also explore the addictive and abuse potential inherent to these emerging pharmacotherapies – and strategies for mitigating risk in the medical setting.

2. Methods

A comprehensive literature search of PubMed and Google Scholar was conducted. The search terms and phrases included "nitrous oxide", "ketamine", "esketamine", "treatment resistant depression", "major depressive disorder", "NMDA", "NMDAR". All articles published in English were assessed for relevance. Additional articles were obtained through cross-referencing, searching of citations to identified articles and searching of "similar articles".

3. Ketamine

Ketamine, also known as 2-(2-chlorophenyl)-2-(methylamino) cyclohexan-1-one [7], was first synthesized in 1962. Chemically, ketamine is an arylcyclohexylamine and very closely related to the hallucinogenic drug phencyclidine (PCP). Ketamine exists in two enantiomeric forms, (*S*)-ketamine (esketamine) and (*R*)-ketamine (arketamine). From a mechanistic standpoint, ketamine is a non-competitive NMDAR antagonist, with additional activity via opioid receptors and biogenic amine uptake [7]. Clinically, ketamine has been used as a rapid acting, non-barbiturate general anesthetic [8] since the approval of intravenous (IV) and intramuscular (IM) ketamine hydrochloride in 1970 by the United States Food and Drug Administration. Ketamine's first use was as a battlefield anesthetic during the Vietnam War. Subsequently, ketamine was implemented in hospitals and emergency rooms worldwide for anesthesia, procedural sedation, and analgesia. It produces an anesthetic state referred to as "dissociative anesthesia," which is distinctively different from propofol or inhalational anesthesia. It is particularly valuable due to its unique ability to induce effective anesthesia and analgesia while maintaining cardiorespiratory stability. However, owing to its unique psychoactive properties, ketamine also quickly permeated the realm of recreational drug use by the early 1970's, which has continued through the present.

4. Ketamine use in treating major depressive disorder (MDD)

By the 1990's, preclinical data had emerged suggesting that NMDA antagonists could mitigate depression in animal models [9,10]. Subsequently, numerous studies investigated whether ketamine anesthesia during electroconvulsive therapy (ECT) creates synergistic antidepressant effects with the ECT itself, though results have been a mix of positive [11–14] and negative [15–18]. Based on seminal studies by Krystal and colleagues [19], examining psychotomimetic and cognitive effects of sub-anesthetic doses of ketamine (up to 0.5 mg/kg), it was observed that ketamine alone may have beneficial effects on mood. The first clinical study of IV ketamine for depression in humans was published in 2000 [20] and demonstrated significant reduction in depression scores measured 72 h after a single (0.5 mg/kg) dose.

Over the past 20 years, additional studies demonstrated IV ketamine's rapid and robust antidepressant response after a single dose in patients with MDD [21–23] and bipolar depression [24,25]. Additionally, one study demonstrated a positive antidepressant response to IV ketamine in TRD patients who had previously failed ECT [26]. In several of these studies, ketamine was shown to rapidly reduce or eliminate suicidal ideation [22,27], which remains an area of ongoing intense investigation. Although ketamine quickly and greatly improved symptoms of depression in these early studies, the effects of a single dose were notably short-lived, typically on the order of days.

Subsequent studies have investigated whether a more durable clinical benefit was possible through serial infusions of ketamine. A 2010 pilot study demonstrated not only efficacy of such treatment for TRD, but also safety and feasibility [28]. In that study, ten patients with TRD were treated with six, 40-min IV infusions of ketamine (0.5 mg/kg) over the course of 12 days. Nine of ten participants experienced ≥50% reduction in Montgomery Åsberg Depression Rating Scale (MADRS) scores after the first infusion. Clinical improvement was maintained for the duration of the study, with an average of 19 days to relapse after the final infusion. Several subsequent studies provided additional positive data for serial ketamine infusions [29–34]. A recent dose-finding study compared standard IV ketamine dosing (0.5 mg/kg) to doses slightly lower (0.1–0.2 mg/kg) and slightly higher (1.0 mg/kg); this trial demonstrated that only the standard and high doses were superior to placebo [35]. Following this growing evidence base, off-label use of IV ketamine for depression has become widespread in recent years, through unregulated, in "ketamine clinics."

Up until that point, clinical studies had utilized racemic ketamine hydrochloride, primarily in IV form. However, the (*S*)-ketamine enantiomer was found to have beneficial mood effects and fewer undesirable cognitive effects, compared to the racemic mixtures of S- and R-enantiomers [36]. These findings potentially led to preferential selection of esketamine in subsequent studies in TRD. Drug manufacturers also introduced oral and intranasal (IN) formulations in hopes of creating more user-friendly treatment options.

In 2014, Lapidus et al., [37] showed a significant antidepressant response rate (44%) at 24 h after administering IN ketamine (vs 6% for placebo) to depressed patients. A randomized clinical trial of IN esketamine, as an adjunct to oral antidepressant therapy for patients with TRD, showed a rapid and dose-dependent response [38]. Further, Canuso et al., [39] demonstrated that IN esketamine, combined with standard oral antidepressant treatments, helped to reduce symptoms of depression and suicidality in patients at imminent risk for suicide, as compared to placebo. Recent randomized, blinded prospective trials have continued to demonstrate effectiveness of IN ketamine in mildly treatment-resistant depression [40].

On March 6th 2019, the United States FDA approved a drug-device combination for IN esketamine under the brand name Spravato (Janssen Pharmaceuticals). IN esketamine is approved for a single indication: as an adjunct to oral antidepressants for treatment resistant depression in adults. For approval purposes, TRD was defined as a major depressive episode (DSM-V criteria) that had not responded adequately to at least two different antidepressants of adequate dose and duration – which some consider to be a relatively "mild" form of TRD [2].

Despite FDA-approval of the IN esketamine device, use of IV ketamine for depression remains off-label. Likely due to the absence of patentability, there are no plans to pursue FDA-approval of IV ketamine. However, the current expert consensus on the use of ketamine for depression acknowledges that this compound has enormous potential in patients with depression, even for those with mild to moderately resistant cases. It also acknowledges that significant information gaps remain, including evidence for individualized dosing, dosing schedules, duration of treatment, and methods to avoid psychotic/dissociative side effects, among others [41].

Looking beyond depression, ketamine also continues to be investigated for its potential to treat other psychiatric disorders including anxiety [42], social anxiety disorder [43], post traumatic stress disorder [44], and addictions [45], including acute opioid withdrawal [46].

5. Addiction potential of ketamine and efforts to mitigate abuse

In addition to its potential for therapeutic benefit, ketamine has known acute side effects including drowsiness, nausea, vomiting, nystagmus and blood pressure elevation [8]. There is emerging evidence that chronic ketamine use may result in liver and bladder damage [47]. Of particular relevance to this review however, are ketamine's risks of misuse, abuse, and addiction. Specifically, ketamine use has been associated with euphoria, drug-seeking, and reinforcing effects [48,49] that are often attributed to its pharmacologic action at NMDA receptors [50], dopaminergic receptors [48], and possibly opioid receptors. As with other drugs of abuse, when used repeatedly over time, ketamine can cause psychological dependence [51]. Physiological dependence has also been described in persons chronically using high doses of ketamine [50,52].

In recognition of these risks, the DEA has categorized all forms of ketamine as schedule III, which is defined as having "moderate to low potential for physical and psychological dependence." Prescribing of IN esketamine (Spravato) is further managed by its strict, limited distribution through its REMS program [53]. The Spravato REMS program requires individual prescribers, patients, and pharmacies to register with a centralized system before they are eligible to obtain and use esketamine. The program aims to ensure appropriate policies and procedures are in place wherever the drug is used so that clinical staff can competently store, handle, dispense, and dispose of the drug. The REMS program also supports patient education and provides a venue for post-marketing monitoring.

6. Putative mechanisms of ketamine antidepressant effects

The mechanisms of action of ketamine's antidepressant effect are not fully understood. Recently published reviews and commentaries comprehensively discuss the current state of understanding with regard to mechanisms of ketamine's antidepressant activity [54–58]. We present an abbreviated summary of the current knowledge related to ketamine's antidepressant mechanism of action, with an emphasis on a few of the more recent developments that exemplify the evolving landscape of mechanism-related research.

In addition to having antidepressant activity at sub-anesthetic doses, ketamine is a dissociative anesthetic, analgesic, and psychotomimetic. Ketamine also has addictive properties as well as impairing effects on memory and cognition. Some commonalities exist between the mechanisms for each of these activities, but there are notable differences. For example, the antidepressant effects have a slower onset and are longer-lived than the dissociative and psychotomimetic side-effects. The psychotomimetic side-effects parallel the chronology of the short-lived systemic presence of ketamine, but the antidepressant activity persists well beyond the time of blood clearance [59].

As noted earlier, ketamine is a racemic mixture of two enantiomers, (*S*)-ketamine and (*R*)-ketamine, which undergo rapid and extensive metabolism to primary and secondary metabolites, some of which may contribute to clinical outcomes. Although most of the early research on mechanisms of action involved the racemic mixture, differences in activities of the two isomers have been reported in preclinical studies, which are likely a result of mechanistic nuances. Ketamine's activity as a non-selective, non-competitive, glutamatergic antagonist of the NMDAR ion channel is thought to be its primary mode of action, with perhaps preferential effects on NMDARs expressed on interneurons. Ketamine's effects on NMDARs are implicated in its anesthetic, analgesic, and psychotomimetic effects, as well as its antidepressant effects and in the potential for addiction and abuse [59]. Blockage of NMDARs can have downstream effects that include disinhibition of gamma aminobutyric acid (GABA) interneurons, presynaptic release of glutamate, stimulation of postsynaptic AMPARs (alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors), activation of mTOR (mechanistic target of rapamycin), increased levels of brain-derived neurotrophic factor (BDNF), deactivation of glycogen synthase kinase-3 and deactivation of eukaryotic elongation factor 2 kinase [the net result being an increase in BDNF translation [55,57,58]]. The antidepressant benefits of ketamine may result from a convergent combination of these mechanisms that leads to enhancement of brain connectivity and plasticity [55,58]. For example, these downstream NMDAR pathways may partially explain ketamine's inflammation-associated antidepressant effects, particularly BDNF effects through mTOR signaling in mediating neuroplasticity and neurogenesis. While some clinical studies of MDD patients support these mechanisms, clinical studies of ketamine's anti-inflammatory effects overall have been inconsistent, particularly with regard to inflammatory biomarkers [60].

Preclinical studies suggest that NMDAR-blockade and downstream signaling pathways may converge in a common pathway that involves activating neurotrophic factor signaling, increasing synaptic protein synthesis, and promoting dendritic spine formation or restoration [61,62]. It has been further hypothesized that prefrontal cortical (PFC) spine formation may sustain the remission of depression after ketamine treatment by restoring lost spines, thereby rescuing coordinated activity of functional connectivity in PFC microcircuits [61].

Consistent with this preclinical evidence, a recent neuroimaging study [63] showed an increase in functional connectivity between the right lateral PFC and the subgenual anterior cingulate cortex (sgACC) after ketamine treatment of MDD patients. These changes were positively correlated with treatment response, and low baseline functional connectivity between these regions was predictive of treatment outcome [63]. These observations are consistent with a previous report of increased global connectivity in the right lateral PFC of patients with MDD following ketamine treatment [64]. Stronger effects were observed in patients who had responded to antidepressant medications. Earlier, a comprehensive review of clinical neuroimaging literature on ketamine-associated changes in different neural circuits singled out the sgACC as a particularly important region [65]. The review also concluded that neuroimaging research on ketamine has a number of limitations, notably that the majority of studies included only healthy, non-depressed patients. Recent neuroimaging studies of ketamine in the treatment of depressed patients provide evidence of involvement of other neural circuits [e.g. [66,67]]. Other studies have identified potential issues for focus in future neuroimaging and clinical studies of ketamine [68].

Although there is general agreement that NMDARs are likely an initial molecular target of ketamine, recent research has raised questions as to whether NMDAR is the primary mediator of ketamine's rapid and sustained antidepressant effects. For example, ketamine metabolites, including hydroxynorketamines (HNKs) such as (2*R*, 6*R*)-HNK and (2*S*, 6*S*)-HNK induced antidepressant activity in rodent models – wherein, notably, the metabolism of (*R*,*S*)-ketamine to generate these HNKs was necessary for observed antidepressant effects [69]. Strikingly, neither HNK has been shown to effectively antagonize NMDARs at relevant concentrations. In fact, (2*R*,6*R*)-HNK does not have anesthetic effects, nor did it induce side-effects, e.g. psychotic-like behaviors, that would be attributed to NMDAR inhibition [57]. As a result, mood-related benefits of ketamine may be independent of NMDAR blockage. The HNK hypothesis has inspired debate [64,70–72], particularly whether the doses and concentrations of ketamine metabolites that produce in vivo and in vitro effects in rodents are relevant to antidepressant effects in humans [73]. A pilot clinical study did not show a relationship between (2*S*,6*S*; 2*R*,6*R*)-HNK and response to ketamine in MDD patients [74]. More specifically, in contrast to Zanos et al. 2016, other groups have reported (2*R*, 6*R*)-HNK actually does block synaptic NMDARs [71,75], raising questions about the appropriate concentration of (2*R*, 6*R*)-HNK that should be used for these studies [76]. Additionally, antidepressant actions of (2*R*, 6*R*)-HNK reported for in vitro and in vivo rodent studies were observed to involve early and sustained activation of AMPARs [69]. However, at clinically relevant unbound brain concentrations (e.g. 10 μM), neither (2*S*,6*S*)-HNK nor

(2*R*,6*R*)-HNK bound orthosterically to, or directly activated the function of AMPARs [77]. This suggests that *direct* activation of AMPARs by (2*R*, 6*R*)-HNK (at ≤10 μM) may not be an antidepressant mechanism of ketamine. Instead, (2*R*, 6*R*)-HNK may play a role in ketamine's antidepressant effects through *indirect* effects on AMPAR. Continued research on questions related to the HNK hypothesis should broaden the foundation upon which to develop new antidepressant drugs. Ultimately, clinical studies of the HNKs will be required for better understanding of the roles HNKs serve in the antidepressant effects of racemic ketamine and single isomer ketamine. Although results of phase 3 clinical trials of (*S*)-ketamine for treatment of TRD have recently been published [40,78,79], no clinical studies of antidepressant effects of (*R*)-ketamine have been reported to date.

Besides NMDARs and AMPARs, ketamine interacts with a variety of other receptors and ion channels. Although these are typically lower affinity interactions, they nevertheless have potential to be involved in the antidepressant effects of ketamine. These include GABA-A, dopamine, serotonin/5-HT, opioid, and cholinergic receptors, in addition to voltage-gated sodium channels, L-type voltage-dependent calcium channels and hyperpolarization-activated cyclic nucleotide-gated channels. Recent reviews address the current understanding with regard to possible roles of these receptors and ion channels [54–56].

A recent clinical study by Williams et al. [80] has inspired considerable discussion regarding a potential role for the opioid system in ketamine's antidepressant effects. Ketamine is a low-affinity partial agonist of opioid receptors. In a small cross-over study of TRD patients, naltrexone, a high-potency opioid receptor antagonist, blocked the antidepressant effects of ketamine, but not its dissociative effects [80]. Thus, it is suggested that ketamine's antidepressant effects require activation of the opioid system, whereas ketamine's dissociative effects do not [80]. The researchers did not determine whether the effect was a result of binding to opioid receptors or ketamine-induced release of endogenous opioids, as has been reported in a rodent pain study [81]. They suggest that rather than being primarily responsible for the acute antidepressant effects of ketamine, glutamatergic NMDARs may have a greater role in maintenance of the antidepressant response through modulation of brain plasticity. Another possibility is that blockage of NMDARs in acute ketamine antidepressant effects are enabled by co-stimulation of the opioid system. A recently published rodent study [82] concluded that the antidepressant effects are not a result of ketamine having direct agonistic activity on opioid receptors; however, both opioid receptor signaling and NMDAR signaling are required. Interestingly however, animal studies indicate (2*R*,6*R*;2*S*,6*S*)-HNK may *not* interact with the opioid receptor system [56].

An opioid-dependent mechanism of action of ketamine in TRD may have significant unforeseen clinical implications. For example, TRD is a chronic and recurring illness, and ketamine may become a chronic treatment [83]. What are the addictive implications of an activated opioid system in chronic treatment of depression? Interestingly, ketamine treatment is reported to benefit alcohol and opioid use disorders [46,84], as well as cocaine dependency [85], but outcomes for long-term ketamine treatment for these indications are not known. Related concerns were expressed in a commentary about the recently completed phase 3 clinical trials of (*S*)-ketamine for treating TRD [86], questioning whether ketamine's opioid properties may help explain the drug's abuse and potential liability with long-term use. The commentary questions whether discontinuation of (*S*)-ketamine during these clinical studies may have been associated with three suicides, and suggests opioid-like withdrawal as a possible contributing factor. Interestingly, (*S*)-ketamine is reported to have higher affinity than (*R*)-ketamine for binding to opioid receptors and NMDARs, but (*R*)-ketamine is a more potent and longer-lasting antidepressant compared with the (*S*)-ketamine in rodent models [56].

In response to recent reports on the potential role of the opioid system in ketamine's MOA for TRD [80], others have described contradictory preclinical and small-sample clinical research [87–89]. A commentary [62] discusses the observations of these other studies, which includes noting that naltrexone also attenuates the effects of other substances of abuse, which may rely on biological mechanisms other than the opioid system. A recent proposal [90] even suggests that naltrexone may block ketamine's antidepressant effects indirectly, without direct opioid agonist activity of ketamine, by antagonism at the mu opioid receptor resulting in increased cAMP, which then interferes with ketamine's activation of mTOR.

7. Nitrous oxide

Nitrous oxide is a colorless, odorless gas that has been in clinical use for over 150 years [91]. Nitrous oxide is among the least potent anesthetic drugs available and as such, it requires concurrent administration of a primary agent to achieve surgical-level anesthesia. To avoid inducing hypoxia, nitrous oxide must be given at concentrations no greater than 70%, with the balance of the inhaled gas being oxygen. Nitrous oxide has a very low blood-gas solubility, which leads to a rapid onset and rapid offset of action, from which patients can easily and quickly recover. Patients typically can drive safely after a short 15-min recovery period. Further, nitrous oxide does not undergo systemic metabolism; hence, it offers potential advantages for patients with severe renal and/or hepatic disease [92]. Currently, the clinical uses of nitrous oxide are primarily for inhalational general anesthesia and for analgesia during short, painful procedures including labor and delivery, dentistry, or emergency medicine procedures [93–95].

8. Nitrous oxide use in treating major depressive disorder

The euphoria-inducing effects of nitrous oxide have long been known and accordingly, it is frequently referred to as “laughing gas”. These properties sparked the hypothesis that nitrous oxide could potentially have clinical antidepressant properties [96]. This awareness, along with the emergence of another NMDAR antagonist, ketamine, as a rapid acting antidepressant, led to the study of inhaled nitrous oxide in MDD.

Nagele and colleagues [97] conducted a pilot, proof of concept clinical trial of inhaled, sub-anesthetic-dose nitrous oxide in a group of 20 patients suffering from TRD. This was a double-blind, prospective, cross-over trial in which TRD patients underwent an hour-long inhalation session with either 50% nitrous oxide, 50% oxygen (active treatment); or 50% nitrogen, 50% oxygen (placebo). Both treatments were separated by 1 week and the order of treatments was randomized. To be enrolled in the trial, patients had to have failed a minimum of two adequate dose-duration antidepressant trials (as confirmed by review of the medical record) and could not have a history of psychotic or bipolar depression, severe personality disorder, or substance use disorder in the past 12 months. Patients were allowed to remain on their existing antidepressant treatments (excluding ECT), but no changes to these treatments were allowed during a 4-week lead-in period, during the trial itself, and for 1 week after the second inhalation session.

The patients enrolled in this trial suffered from severe, refractory, and sustained TRD: patients had a mean age of 48 years, a mean of 19 years of lifetime MDD history, a mean of eight failed antidepressant trials, and four had even failed ECT. A significant improvement in depressive ratings was observed in the TRD patients at 24 h, with a median reduction of 5.5 points on the Hamilton Depression Rating Scale (HDRS; 95 CI −2.5 to 8.5 points), which was the primary endpoint for the trial. Four of the patients were rated as having an antidepressant response (≥ 50% reduction from baseline HDRS score) to the nitrous oxide inhalation at 24 h; whereas, only one placebo patient demonstrated a 24 h antidepressant response. One TRD patient achieved remission (HDRS < 7) at 24 h after active treatment, and there were no remitters in the placebo group.

Of note, this pilot trial determined that certain symptoms appeared to be particularly responsive to nitrous oxide, including: depressed

mood, suicidal ideation, guilt, and psychological symptoms of anxiety. Also noteworthy, and a surprise to the investigative team, was the sustained antidepressant response, which continued to be observed at 1 week post-inhalation. This latter finding confounded the cross-over study design because (active) treatment benefits were still present at the time of the subsequent (placebo) treatment.

The side effects of nitrous oxide were infrequent, minor, and short-lived after terminating nitrous oxide delivery. These side effects included: nausea, vomiting, headache, and paradoxically – increased anxiety in some patients. The next phase of research into nitrous oxide for TRD includes several heretofore unstudied domains including: determination of optimal dose (specifically, attempting nitrous oxide doses lower than 50%), identification of effects on brain network activity, as well as studying its potential anti-suicidal properties.

Nitrous oxide for TRD has significant potential advantages over ketamine. Unlike ketamine, there are no psychotic side effects or blood pressure changes observed with nitrous oxide. Though nitrous oxide has some abuse potential (including adolescents inhaling nitrous oxide from whipped cream containers, also known as “whippets,” to achieve intoxication), it has considerably less addictive potential than ketamine. Further, the rapid on- and off-set of nitrous oxide allows patients receiving this treatment to safely operate motor vehicles within 15 min of delivery, reducing a significant logistical barrier inherent to ketamine.

9. Addiction potential of nitrous oxide and efforts to mitigate abuse

Recreational use of nitrous oxide dates back to at least the Victorian era, when “laughing gas parties,” first became popular [98]. People have continued to use nitrous oxide for non-medical purposes throughout the years since. Today, it is used primarily by teens and young adults, with an estimated prevalence of around 21% within that demographic [92]. Nitrous oxide is also prominent within the so-called “dance culture,” including dance clubs, raves, and music festivals. Nitrous oxide is typically inhaled, either from bulbs or balloons. Acute effects include rapid onset of euphoria, excitement and dissociation, which usually resolve within minutes. However, chronic abuse of nitrous oxide can be associated with neurological damage, such as spinal cord degeneration [99], and, when neurological damage is observed, it is often associated with vitamin B12 deficiency [100]. Contributing to the sustained popularity of nitrous oxide over time are a number of factors including low cost, ease of access, and its relative safety. Reports of psychological dependence and tolerance associated with nitrous oxide first surfaced in the 1960's [101]. Still, such cases are rare, and most recreational nitrous oxide users are not psychologically or physically dependent – over 90% report using monthly or less [98]. Currently, nitrous oxide remains unscheduled by the DEA and otherwise legal to possess for legitimate purposes. However, as investigation continues into its use for TRD, careful thought must be given to how it will be safely stored, dispensed and monitored clinically while remaining vigilant to its abuse potential. In addition, other known safety concerns with inhaled nitrous oxide include adverse effects of dyspnea, headache, impaired judgment, and even impaired fertility with repeated exposure [102].

10. Putative mechanisms of nitrous oxide antidepressant effects

Despite a long history of use as an anesthetic and analgesic, the mechanisms of action of nitrous oxide are still not fully understood. Based on multiple studies over the past 20 years however, it is clear that nitrous oxide acts as a non-competitive inhibitor of NMDARs [59,91]. Inhaled nitrous oxide blocks NMDAR responses with an approximate half-maximal effective concentration of 30–40% [103], but is only a partial NMDAR antagonist at concentrations up to 80%. The effects of nitrous oxide are weakly voltage dependent and do not alter the decay of NMDAR-mediated synaptic currents [104]. Several studies indicate that the effects of nitrous oxide on NMDARs contribute to specific behavioral changes in animal models [105,106]. Nitrous oxide is also a weak inhibitor of AMPA/kainite-type glutamate receptors. Unlike many other anesthetics, nitrous oxide has weak potentiating effects on GABA-A receptors [104] and is a weak inhibitor of GABA-C receptors [107]. Nitrous oxide also affects other ion channels, which could contribute to its various clinical actions. Nitrous oxide inhibits low voltage activated (LVA, T-type) calcium channels, producing about 30% depression of LVA currents at a concentration of 80% nitrous oxide [108], without effect on high voltage activated (L-type) calcium currents [104]. The block of LVA currents involves the $Ca_v3.2$ calcium channel subtype specifically, with no effect on $Ca_v3.1$ isoforms. Mice with deletions of $Ca_v3.2$ genes have dampened analgesic responses to nitrous oxide indicating that effects on LVA currents contribute to certain behavioral effects. Inhibition of $Ca_v3.2$ involves metal catalyzed oxidation at histidine 191 [109,110]. Nitrous oxide generates reactive oxygen species (ROS) in the presence of iron, and both scavengers of iron and ROS can dampen effects on LVA channels [110].

Other potentially important effects of nitrous oxide include activation of a two-pore-domain potassium channel expressed throughout the central nervous system, called TREK-1 [111]. Nitrous oxide is also a weak antagonist of serotonin-type 3 receptors, and is a partial inhibitor of certain nicotinic acetylcholine receptors [107]. Nitrous oxide has effects on the endogenous opioid system that could contribute to analgesia and perhaps, to psychotropic effects [112–115]. Some evidence indicates that nitrous oxide exerts preferential effects on kappa-type opiate receptors over mu-type receptors [116,117]. Modulation of the opiate system may be important for antidepressant effects given recent evidence suggesting that an opiate receptor antagonist dampens the antidepressant effects of ketamine [80]. Nitrous oxide also has effects on brainstem adrenergic neurons; activation of α-adrenoceptors in the brainstem and spinal cord contribute to anti-nociceptive effects in rats [118,119].

Studies examining effects of nitrous oxide on brain networks remain a work in progress. In hippocampal circuits, nitrous oxide confers disinhibition on network-driven spike firing [120]. It also appears that nitrous oxide can increase cellular proliferation in the dentate gyrus, and possibly result in increased neurogenesis [121] – effects that could contribute to antidepressant actions. Studies in humans using electroencephalography (EEG) indicate that nitrous oxide dampens functional connectivity in superficial parietal networks [122] and acutely decreases frontal slow wave (delta) activity with an increase in theta activity following drug discontinuation [123]. When given in high doses during the emergence from ether-based general anesthesia, nitrous oxide can induce large amplitude slow-delta oscillations [124]. Precisely how these changes in networks and brain rhythms contribute to behavioral effects of nitrous oxide remains uncertain.

11. Conclusion

NMDAR antagonists, including ketamine and nitrous oxide, have demonstrated antidepressant properties and continue to be under clinical investigation and development. Ketamine, a dissociative anesthetic that induces complex downstream effects via NMDARs, has been shown to induce rapid onset of antidepressant effects as well as anti-suicide effects in patients with major depression. These antidepressant effects of ketamine appear to be sustained with repeated dosing; however, significant questions remain unanswered with regard to optimal treatment protocols, treatment duration, and discontinuation of therapy. Furthermore, ketamine is liable to abuse and addiction, particularly when used over long periods of time. Hence, therapeutic use of the newly approved intranasal esketamine for TRD requires special regulations and monitoring, including a REMS program. The long-term consequences, with regard to emergence of abuse or addiction in TRD patients receiving chronic ketamine are yet to be determined. Nitrous oxide, another non-competitive NMDAR antagonist initially used as an

anesthetic, has also recently been shown to have rapid-acting antidepressant effects in treatment-resistant depression. Like ketamine, nitrous oxide has long been used for recreational purposes; however, it is believed to have considerably lower addictive potential than ketamine.

Although ketamine has therapeutic benefits for patients with depression, its prescription and dispensing are tightly controlled by the United States government due to concerns of potential misuse and abuse. Although nitrous oxide is currently legal, concerns about its recreational use and abuse may ultimately hinder its clinical development. Interestingly, by way of comparison, marijuana is another widespread and longstanding substance of abuse, which has recently entered the commercial and medical-pharmaceutical markets without similarly stringent regulations or opposition. Moving forward, new (and old) therapeutic agents will continue to be considered for treatment of illnesses like depression. Investigators and clinicians alike must continue to weigh the benefits and risks of potential treatment modalities as they become available.

Declaration of competing interest

CFZ serves on the Scientific Advisory Board of Sage Therapeutics and owns stock in Sage Therapeutics. Sage Therapeutics was not involved in this manuscript. He has also previously served as a consultant for Takeda Pharmaceuticals. CRC receives fees for research and received speaking fees from LivaNova, and research grants from LivaNova, NeoSync, Inc. and Myriad Genetics, all unrelated to this manuscript. CRC, PN and BJP receive research grant support for studying nitrous oxide from The National Institute of Mental Health, Brain and Behavior Research Foundation, and The American Foundation for Suicide Prevention. All other authors have nothing to disclose.

Acknowledgments

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No funding source is associated with this work.

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