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Review Article

Nitrous Oxide: an emerging novel treatment for treatment-resistant depression

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ABSTRACT

Stemming from the results of the historic STAR-D trial, it is evident that a significant subset of individuals (20–25%) with major depressive disorder (MDD) do not respond to conventional antidepressant medications. As a result, an emphasis has been placed on the development of novel therapeutics for MDD over the last two decades. Recently, substantial research efforts have been focused on the use of ketamine as an antidepressant whose mechanism of action is via the *N*-methyl-D-aspartate (NMDA) receptor. Another potential therapeutic compound of interest is nitrous oxide, which has been utilized for more than a century in multiple fields of medicine for its analgesic and anesthetic properties. Recent clinical studies suggest that nitrous oxide may be effective for treatment-resistant depression. In this review, we will discuss the administration of nitrous oxide as a psychiatric intervention, current use in psychiatry, putative mechanisms of action, and future directions highlighting knowledge gaps and other potential utilities in the field of psychiatry.

1. Antidepressants: past and present

Pharmacological management of depression began in the 1950s with the monoamine hypothesis, which posited that the underlying pathophysiology of depression was related to deficient or aberrant functioning of the "biogenic amines" that include serotonin, dopamine, and norepinephrine [1–4]. Over the subsequent four decades, pharmacotherapies remained focused primarily on these systems. These medications appear to be effective for most individuals with Major Depressive Disorder (MDD); however, a significant subset (estimated 20–25%) of patients do not respond to these standard pharmacotherapies and can be referred to as having "treatment-resistant depression" (TRD) [5]. Though the field has yet to clearly define TRD, evidence does support that patients who fail to respond to two different antidepressant medication trials, with adequate dose and duration (6 to 8 weeks), are less likely to respond to subsequent treatments [6] and some consensus has emerged that failure to respond to two successive treatments defines TRD [7].

Over the last two decades, a concerted effort has been placed on the investigation of novel agents/interventions to treat TRD. These include NMDA antagonists, neurosteroids, neurostimulation treatments, and psychedelics, among others [8–11]. The NMDA receptor antagonists have shown tremendous promise in successfully treating TRD. Early work in ketamine has served as the foundation for exploring other NMDA antagonists as novel antidepressants. In fact, esketamine, which is an enantiomer of ketamine, recently gained FDA approval in 2019 for treatment-resistant depression. Another potential therapeutic that is actively under investigation is nitrous oxide.

2. Nitrous oxide: the basics

Nitrous oxide (N_2O), commonly referred to as laughing gas, is a volatile, colorless gas. It is predominantly used as an anesthetic and analgesic in both hospital and office-based settings, e.g., for dental procedures [12]. N_2O is delivered in an oxygen mixture due to its elevated minimal alveolar concentration and it is commonly administered using a specialized delivery system designed to prevent hypoxia. Mixtures up to inspiratory concentrations of 70% N_2O are considered safe. Another typical safety feature of delivery systems includes scavenging systems to remove excess and residual N_2O in the environment as well as preventing chronic exposure to treating personnel.

N_2O has many potential advantageous properties including: a low side effect profile, rapid onset/recovery due to low blood gas solubility, limited drug interactions, and simple metabolism not influenced by

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other medications as uptake and elimination is solely pulmonary making it a viable option for individuals with hepatic or renal disease. In a large survey of 35,828 patients receiving N_2O in the hospital, side effects were observed in 4.4% of cases [13]. Typically, adverse effects such as mild sedation, mild euphoria, nausea, vomiting, headaches, and dizziness account for a majority of the cases [14]. Most, if not all, of the side effects are noted to be brief in duration and resolve with discontinuation of use. Long term exposure or chronic abuse of N_2O can result in vitamin B12 deficiency and subacute combined degeneration of the spinal cord due to its inactivation of the vitamin [15].

3. Nitrous oxide: another antidepressant option?

In the setting of the recent success of ketamine as a novel antidepressant, work has continued to look at the potential of other NMDA receptor antagonists as targets for MDD treatment. Given that nitrous oxide is thought to work predominantly as an NMDA receptor antagonist (discussed below), Nagele et al., conducted a pilot study to specifically target N_2O's antidepressant potential. In that study, a double-blind, placebo-controlled crossover design was utilized, in which one-hour inhalation treatments of N_2O (50–50% oxygen mixture) vs placebo (50% oxygen 50% room air) were provided to 20 TRD subjects [16]. Treatment resistance in this study was defined as failing at least 2 medication trials in the current depressive episode and at least 3 lifetime trials of adequate dose (based on medication package insert) and duration (8 weeks); although it should be noted, that these subjects were severely treatment-resistant with an average of 8 prior failed antidepressant trials. Confounding diagnoses such as substance use disorders, severe personality disorder, psychotic illnesses, and bipolar disorder were excluded. Treatment with N_2O resulted in significant improvement in depression scale scores compared to placebo as defined by the primary outcome measure, the Hamilton Depression Rating Scale-21 items (HDRS-21). An overall response rate of 20% was observed, and 3 individuals achieved complete remission. In addition, a decrease in depression scores was statistically significant at 2 h and 24 h post-treatment, suggesting rapid onset effects. The most prevalent side effects observed included nausea and vomiting. None of the subjects experienced psychosis or alterations to vitamin B12.

These initial intriguing findings from the pilot study prompted several questions, including what is the optimal antidepressant dose for N_2O and are the effects of N_2O sustained? To begin to answer these questions, further work by Nagele et al. investigated the use of different nitrous oxide dosages [17]. In this phase 2, prospective, randomized, double-blind, crossover trial, antidepressant effects of two different concentrations of N_2O were compared to placebo in a group of 24 TRD subjects. Participants had failed a median of 4.5 antidepressant treatment trials with adequate dose and duration. Treatment arms included one-hour inhalations of 50% N_2O, 25% N_2O vs placebo with study time measurements extending to 2 weeks post inhalations. The primary outcome measure was the HDRS-21. Overall results for this study showed statistically significant reduction in depressive symptoms for both 25% N_2O and 50% N_2O compared to placebo. No significant differences in HDRS-21 scores were seen between the two N_2O concentrations; however, both dosages showed sustained effects as reflected in decreased HDRS-21 scores over the duration of the study (-5.19 points [$P = 0.02$] and -7.00 points [$P = 0.001$] at week 2 for 25% N_2O and 50% N_2O respectively compared to placebo). Of note, adverse effects declined significantly with the lower N_2O dose ($P < 0.0001$). In summary, key findings from this study included: 1) there was similar antidepressant efficacy across the two N_2O dosages; 2) both doses of N_2O were well-tolerated, but the lower dose (25%) was associated with significantly fewer side effects; and 3) antidepressant effects were sustained up to two weeks. Additionally, there was suggestion that some subjects continued to receive benefit beyond two weeks: 8 out of 20 remained in remission following the 3-month study period.

The use of N_2O as an adjunctive therapy in subjects with MDD was recently investigated by Guimaraes et al. In this randomized, placebo-controlled, double-blind, parallel clinical trial, 23 subjects with MDD received either 50% N_2O or placebo (100% O_2) for 60 min twice a week over 4 weeks [18]. At the completion of the study, 21 subjects were included in the final analyses and the primary outcome measure was the Hamilton Depression Rating Scale – 17-item (HDRS-17). There was a statistically significant reduction in depressive symptoms in the N_2O group as compared to placebo. After 4 weeks, the remission and response rates for subjects in the N_2O group were 75% and 91.7%, respectively. In the placebo group, 11.1% and 44.4% were observed to be in remission and response, respectively. The treatment was relatively well-tolerated as 5 out of a total 96 sessions were discontinued prior to the end in the N_2O group. The most common adverse effects reported were somnolence, paresthesia, nausea, and headache. Of note, this study, in contrast to Nagele et al. 2015 and 2021 [16,17], did not attempt to enroll depressed patients with treatment-resistance. Nonetheless, this double-blinded, placebo-controlled study also supports the antidepressant benefits of N_2O.

4. Mechanism of action in TRD

While there is a long history of safe use as an anesthetic and analgesic, the utility of N_2O as an antidepressant is relatively novel and its antidepressant mechanism of action remains largely unknown. Stemming from preclinical tissue culture and rodent models, putative mechanisms have been proposed to account for its activity at the molecular level.

Using a female rat model, Jevtovic-Todorovic et al. demonstrated that excitotoxicity elicited by NMDA agonists, *N*-methyl-D,L aspartic acid, and MK0801, could be abrogated with exogenous nitrous oxide. By taking direct electrophysiologic measurements from cultured hippocampal neurons, they demonstrated that the addition of N_2O inhibited electrical current triggered by NMDA agonism. Dose-response studies performed indicated that saturating concentrations of NMDA receptors inhibited by N_2O were not able to overcome this inhibition. Furthermore, subsequent studies from independent groups showed that the NMDA receptor is required for the behavioral effects of N_2O; these effects were observed both in an invertebrate *Caenorhabditis elegans* and a murine model [19,20]. Taken together, these studies support that some of the effects observed with N_2O occur in conjunction with NMDA antagonism. Further, subsequent studies supported that N_2O acts as non-competitive NMDA antagonist [19,20].

Similar to the NMDA receptor, alpha-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid (AMPA)/kainite-type receptors are another type of glutamate receptor that are weakly inhibited by N_2O [21]. In preclinical tissue culture and animal models, AMPA receptor activation in tissue culture led to increased brain derived neurotrophic factor (BDNF) and neurogenesis [22,23] while AMPA receptor antagonism attenuated the antidepressant effects of ketamine in mice [24]. In human studies investigating the role of AMPA receptors in depression, treatment with ketamine led to increased glutaminergic signaling in regions with elevated levels of AMPA receptors [25]. Further studies are needed as thus far, the few studies investigating the role of AMPA receptor activity in depression have involved the use of ketamine. It is unknown whether N_2O has similar effects in terms of mediating possible antidepressant effects through the AMPA receptor.

In addition to the NMDA receptor, N_2O has also been shown to target other receptor-mediated pathways. For example, a substantial amount of research has been devoted to understanding the role that opioid receptors play in mediating the analgesic effects of N_2O [26,27]. Given that kappa opioid receptors have been shown to be important for antidepressant effects mediated by buprenorphine and the antidepressant effects of ketamine can be attenuated by naltrexone (an opioid antagonist), it is reasonable to hypothesize that N_2O's antidepressant effects may also be mediated via opioid receptor agonism [28,29].

Aside from receptor-mediated signaling pathways, nitrous oxide has

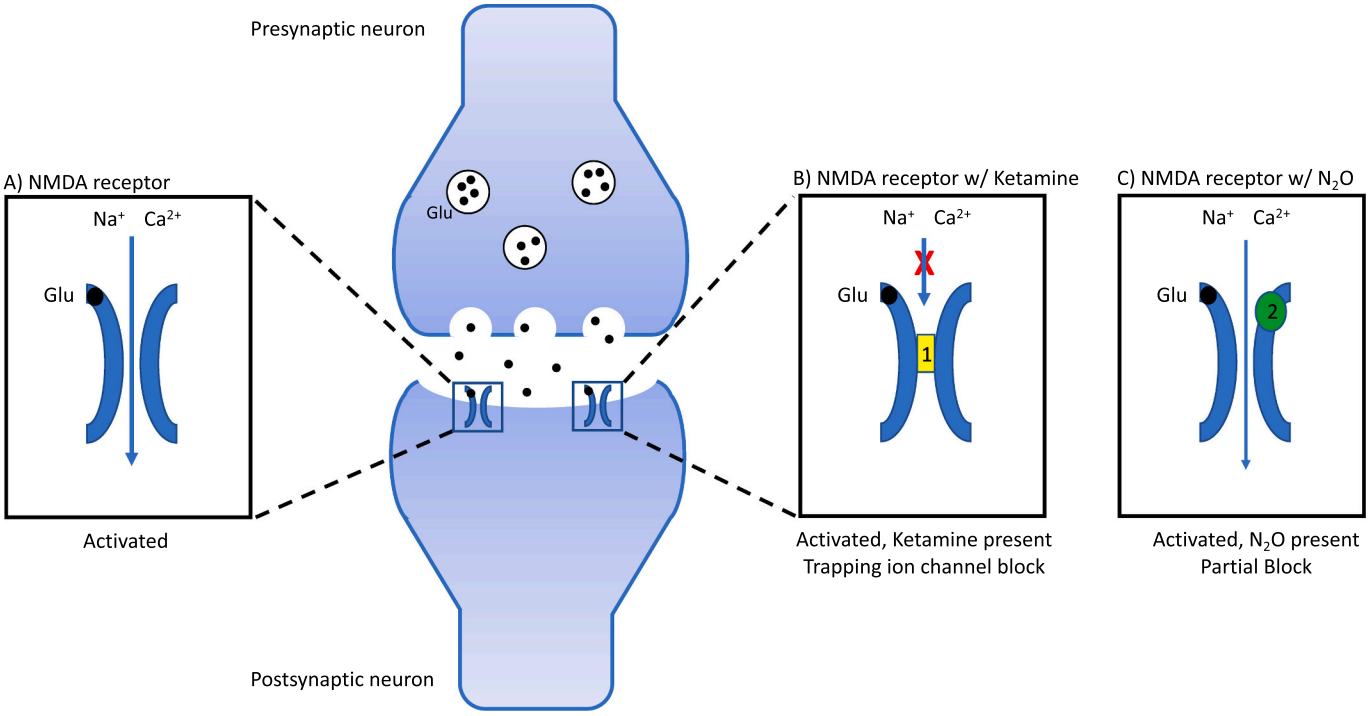

Fig. 1. Putative mechanisms of action for nitrous oxide (N_2O).
Typically, binding of glutamate (Glu) (in the presence of co-agonists glycine or D-serine) to NMDA receptors promotes channel activation and an influx/efflux of cations (A). Ketamine (yellow 1) enters the open channel activated by Glu and acts as a "trapping ion channel block" (B) to prevent ions from flowing through the channel. While ketamine blocks individual NMDA channels completely, its antidepressant effects are observed at submaximal concentrations and involve actions on only a subset of NMDA receptors. Nitrous oxide, like ketamine, is thought to act through the NMDA receptor to exert its antidepressant effects. However, unlike ketamine, its (green 2) effects are thought to be weakly voltage-dependent and is only a partial inhibitor of the NMDA receptor (C) at effective concentrations; thus, akin to ketamine, only a subset of NMDA receptors is inhibited. Its exact mechanism is unknown, but existing studies indicate that it is not an open ion channel blocker like ketamine.

been shown to modulate various ion channels including low voltage activated calcium channels, gamma-aminobutyric acid receptors A and C, glycine receptors, and 5-hydroxytryptamine 3 receptors [21,30–32]. Like other anesthetics, it also changes membrane fluidity [33]. It is unclear, though, if any of these ion channels modulated by N_2O is relevant to its antidepressant activity.

Human studies investigating the mechanism of action of N_2O are limited. To date, studies utilizing electroencephalography have associated N_2O treatment with decreases in functional connectivity in the superficial parietal network and a slowing in frontal slow (delta) wave activity [34,35]. Whether these signaling pathways or changes in brain activity are related to the antidepressant effects of nitrous oxide remains unknown, but they do provide compelling targets to explore in future studies.

5. Comparison between nitrous oxide and ketamine

There are certainly parallels that can be drawn between N_2O and ketamine since they are both non-competitive NMDA receptor antagonists used as analgesic and anesthetic agents, and more recently, as antidepressant agents. However, mechanistically, there are differences at the molecular level. Typically, the binding of glutamate to NMDA receptors, in conjunction with membrane depolarization, promotes opening or activation of the transmembrane ion channel leading to an influx and efflux of cations including Na+, K+, and Ca2+ [36,37]. Ketamine specifically enters this open channel and binds to a site deep within the ion channel pore to occlude ion flow in a phenomenon that is referred to as a "trapping ion channel block" [38,39]. In stark contrast to this, N_2O effects are weakly voltage-dependent and do not appear to exhibit features consistent with an open channel blocker according to electrophysiology measurements [21]. This is depicted in Fig. 1.

Additionally, there have also been some notable differences observed in the clinical trials performed so far. For example, access to ketamine is more tightly regulated due to its abuse potential compared to N_2O. From a safety perspective, there have been no research reports of psychosis with N_2O. Additionally, N_2O has not been associated with hypertension, and the effects of N_2O wear off quickly, making it possible to return back to normal everyday functioning within a short time of use, vis-à-vis ketamine, which requires more extensive monitoring following administration (2 h post-esketamine delivery).

6. Future directions

Recent studies demonstrating the potential utility of N_2O as a novel therapeutic for depression have been extremely promising (Table 1). Additional insight regarding dose, tolerability, and duration of response was gained in a recent Phase 2 trial [17]. However, further studies are needed to determine whether these results can be replicated and to further clarify treatment guidelines (e.g., optimal dosage, dosing schedule, "maintenance" schedule, etc.). Ongoing studies regarding the mechanistic details of ketamine's action have been helpful for conceptualizing potential mechanisms of action for N_2O. Nevertheless, how N_2O works as an antidepressant is currently largely unknown; hence, future studies utilizing nitrous oxide in both preclinical and clinical models will be crucial. Perhaps a clinical study comparing N_2O to ketamine may also be of interest to investigate the context in which each is optimally effective. One possible area of exploration may include attempting to correlate euphoric experiences observed with N_2O inhalation and subsequent antidepressant response. The possibilities of N_2O use in other disorders such as post-traumatic stress disorder or bipolar

Table 1
Clinical study results of nitrous oxide for treatment resistant major depressive disorder.

Citation	Study Design	TRD	N	# failed	Results
Nagele et al. 2015	Randomized, placebo-controlled crossover (clinicaltrials.gov: NCT02139540)	Y	20	8	20% of subjects receiving 50% nitrous oxide with treatment response compared to 5% in the placebo group. Depressive symptoms improved at 2 and 24 h based on HDRS-21 with mean differences of 4.8 and 5.5 points, respectively.
Nagele et al. 2021	Double-blind, randomized placebo-controlled crossover (clinicaltrials.gov: NCT03283670)	Y	24	4.5	33% of subjects receiving 25% nitrous oxide with treatment response and 41% of subjects receiving 50% nitrous oxide with treatment response compared to 11% in the placebo group. Depressive symptoms improved based on HDRS-21 after the 3-month study period with a median change of 11 points.

TRD: treatment-resistant depression; N: number of subjects in the study; # failed: number of failed adequate dose-duration antidepressant trials; HDRS-21: Hamilton Depression Rating Scale.

disorder are currently under investigation [40,41]. Another area of interest may be studying the impact of N_2O on suicidality, especially given the rapid anti-suicidal effect of ketamine in previous studies [42].

Considering its overall safety and tolerability, relative ease of use, and favorable results from initial studies in the treatment of both TRD and MDD, it is reasonable to propose the eventual potential use of N_2O as an adjunctive treatment modality in addition to oral antidepressant therapy. At this stage of development, a larger, multi-center trial of inhaled nitrous oxide is warranted. If this trial is successful, one could envision the eventual development of a specialty clinic for delivery of N_2O or perhaps eventual incorporation into a private practice setting under medical supervision similar to many dental practices.

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Declaration of Competing Interest

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References

[1] P.L. Delgado, Serotonin and the neurobiology of depression, Arch. Gen. Psychiatry 51 (1994) 865, https://doi.org/10.1001/archpsyc.1994.03950110025005.
[2] M. Hirschfeld Robert, History and evolution of the monoamine hypothesis of depression, J. Clin. Psychiatry. 61 (2000) 4–6.
[3] J.J. Schildkraut, The catecholamine hypothesis of affective disorders: a review of supporting evidence, Am. J. Psychiatr. 122 (1965) 509–522, https://doi.org/10.1176/ajp.122.5.509.
[4] L. Delgado Pedro, Depression: the case for a monoamine deficiency, J. Clin. Psychiatry. 61 (2000) 7–11.
[5] A. John Rush, M.H. Trivedi, S.R. Wisniewski, A.A. Nierenberg, J.W. Stewart, D. Warden, M. George Niederehe, M.E. Thase, P.W. Lavori, B.D. Lebowitz, P. J. McGrath, J.F. Rosenbaum, H.A. Sackeim, D.J. Kupfer, J. Luther, M. Maurizio Fava, STAR-D (2006; AjPsych) Tiered approach for depression, Am. J. Psychiatry 16311 (2006) 1905–1917, https://doi.org/10.1176/ajp.2006.163.11.1905.
[6] C.R. Conway, M.S. George, H.A. Sackeim, Toward an evidence-based, operational definition of treatment-resistant depression: when enough is enough, JAMA Psychiatry. 74 (2017) 9–10, https://doi.org/10.1001/jamapsychiatry.2016.2586.
[7] B.N. Gaynes, L. Lux, G. Gartlehner, G. Asher, V. Forman-Hoffman, J. Green, E. Boland, R.P. Weber, C. Randolph, C. Bann, E. Coker-Schwimmer, M. Viswanathan, K.N. Lohr, Defining treatment-resistant depression, Depress. Anxiety 37 (2020) 134–145, https://doi.org/10.1002/da.22968.
[8] A. Garcia-Romeu, B. Kersgaard, P.H. Addy, Clinical applications of hallucinogens: a review, Exp. Clin. Psychopharmacol. 24 (2016) 229–268, https://doi.org/10.1037/pha0000084.
[9] H. Akhtar, F. Bukhari, M. Nazir, M.N. Anwar, A. Shahzad, Therapeutic efficacy of neurostimulation for depression: techniques, current modalities, and future challenges, Neurosci. Bull. 32 (2016) 115–126, https://doi.org/10.1007/s12264-015-0009-2.
[10] C.F. Zorumski, S.M. Paul, D.F. Covey, S. Mennerick, Neurosteroids as novel antidepressants and anxiolytics: GABA-A receptors and beyond, Neurobiol. Stress. 11 (2019), https://doi.org/10.1016/j.ynstr.2019.100196.
[11] M. Ghasemi, C. Phillips, L. Trillo, Z. de Miguel, D. Das, A. Salehi, The role of NMDA receptors in the pathophysiology and treatment of mood disorders, Neurosci. Biobehav. Rev. 47 (2014) 336–358, https://doi.org/10.1016/j.neubiorev.2014.08.017.
[12] D.E. Becker, M. Rosenberg, Nitrous oxide and the inhalation anesthetics, Anesth. Prog. 55 (2008) 124–131, https://doi.org/10.2344/0003-3006-55.4.124.
[13] P. Onody, P. Gil, M. Hennequin, Safety of Inhalation of a 50% Nitrous Oxide/Oxygen Premix a Prospective Survey of 35 828 Administrations, 2006.
[14] P. Nagele, C.F. Zorumski, C. Conway, Exploring nitrous oxide as treatment of mood disorders: basic concepts, J. Clin. Psychopharmacol. 38 (2018) 144–148, https://doi.org/10.1097/JCP.0000000000000837.
[15] K.K. Patel, J.C. Mejia Munne, V.R.N. Gunness, D. Hersey, N. Alshafai, D. Sciubba, R. Nasser, D. Gimbel, J. Cheng, A. Nouri, Subacute combined degeneration of the spinal cord following nitrous oxide anesthesia: a systematic review of cases, Clin. Neurol. Neurosurg. 173 (2018) 163–168, https://doi.org/10.1016/j.clineuro.2018.08.016.
[16] P. Nagele, A. Duma, M. Kopec, M.A. Gebara, A. Parsoei, M. Walker, A. Janski, V. N. Panagopoulos, P. Cristancho, J.P. Miller, C.F. Zorumski, C.R. Conway, Nitrous oxide for treatment-resistant major depression: a proof-of-concept trial, Biol. Psychiatry 78 (2015) 10–18, https://doi.org/10.1016/j.biopsych.2014.11.016.
[17] P. Nagele, B.J. Palanca, B. Gott, F. Brown, L. Barnes, T. Nguyen, W. Xiong, N. C. Salloum, G.D. Espejo, C.N. Lessov-Schlaggar, N. Jain, W.W.L. Cheng, H. Komen, B. Yee, J.D. Bolzenius, A. Janski, R. Gibbons, C.F. Zorumski, C.R. Conway, A phase 2 trial of inhaled nitrous oxide for treatment-resistant major depression. http://stm.sciencemag.org/, 2021.
[18] M.C. Guimarães, T.M. Guimarães, J.E. Hallak, J. Abrão, J.P. Machado-de-Sousa, Nitrous oxide as an adjunctive therapy in major depressive disorder: a randomized controlled double-blind pilot trial, Braz. J. Psychiatry. 43 (2021) 484–493, https://doi.org/10.1590/1516-4446-2020-1543.
[19] P. Nagele, L.B. Metz, C.M. Crowder, Nitrous oxide (N2O) requires the N-methyl-D-aspartate receptor for its action in Caenorhabditis elegans, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 8791–8796, https://doi.org/10.1073/pnas.0402825101.
[20] Y. Sato, E. Kobayashi, T. Murayama, M. Mishina, N. Seo, Effect of N-methyl-D-aspartate receptor ε1 subunit gene disruption of the action of general anesthetic drugs in mice, Anesthesiology. 102 (2005) 557–561, https://doi.org/10.1097/00000542-200503000-00013.
[21] S. Mennerick, V. Jevtovic-Todorovic, S.M. Todorovic, W. Shen, J.W. Olney, C. F. Zorumski, Effect of nitrous oxide on excitatory and inhibitory synaptic transmission in hippocampal cultures, J. Neurosci. 18 (1998) 9716–9726, https://doi.org/10.1523/jneurosci.18-23-09716.1998.
[22] H. Jourdi, Y.T. Hsu, M. Zhou, G. Qin, X. Bi, M. Baudry, Positive AMPA receptor modulation rapidly stimulates BDNF release and increases dendritic mRNA translation, J. Neurosci. 29 (2009) 8688–8697, https://doi.org/10.1523/JNEUROSCI.6078-08.2009.
[23] M. Kyoung Seo, L.T. Hien, M.K. Park, A.J. Choi, D.H. Seog, S.H. Kim, S.W. Park, J. G. Lee, AMPA receptor-mTORC1 signaling activation is required for neuroplastic effects of LY341495 in rat hippocampal neurons, Sci. Rep. 10 (2020) 1–12, https://doi.org/10.1038/s41598-020-58017-3.
[24] P. Zanos, R. Moaddel, P.J. Morris, P. Georgiou, J. Fischell, G.I. Elmer, M. Alkondon, P. Yuan, H.J. Pribut, N.S. Singh, K.S.S. Dossou, Y. Fang, X.P. Huang, C.L. Mayo, I. W. Wainer, E.X. Albuquerque, S.M. Thompson, C.J. Thomas, C.A. Zarate, T. D. Gould, NMDAR inhibition-independent antidepressant actions of ketamine metabolites, Nature. 533 (2016) 481–486, https://doi.org/10.1038/nature17998.
[25] M. Li, L.R. Demenescu, L. Colic, C.D. Metzger, H.J. Heinze, J. Steiner, O. Speck, A. Fejtova, G. Salvadore, M. Walter, Temporal dynamics of antidepressant ketamine effects on glutamine cycling follow regional fingerprints of AMPA and NMDA receptor densities, Neuropsychopharmacology. 42 (2017) 1201–1209, https://doi.org/10.1038/npp.2016.184.

[26] T. Koyama, K. Fukuda, Involvement of the κ-opioid receptor in nitrous oxide-induced analgesia in mice, J. Anesth. 24 (2010) 297–299, https://doi.org/10.1007/s00540-010-0886-5.
[27] M. Fujinaga, M. Maze, Neurobiology of nitrous oxide-induced antinociceptive effects, Mol. Neurobiol. 25 (2002) 167–190, https://doi.org/10.1385/MN:25:2:167.
[28] E. Falcon, C.A. Browne, R.M. Leon, V.C. Fleites, R. Sweeney, L.G. Kirby, I. Lucki, Antidepressant-like effects of buprenorphine are mediated by kappa opioid receptors, Neuropsychopharmacology. 41 (2016) 2344–2351, https://doi.org/10.1038/npp.2016.38.
[29] N.R. Williams, B.D. Heifets, C. Blasey, K. Sudheimer, J. Pannu, H. Pankow, J. Hawkins, J. Birnbaum, D.M. Lyons, C.I. Rodriguez, A.F. Schatzberg, Attenuation of antidepressant effects of ketamine by opioid receptor antagonism, Am. J. Psychiatr. 175 (2018) 1205–1215, https://doi.org/10.1176/appi.ajp.2018.18020138.
[30] D.L. Downie, A.C. Hall, W.R. Lieb, N.P. Franks, Effects of inhalational general anaesthetics on native glycine receptors in rat medullary neurones and recombinant glycine receptors in Xenopus oocytes, Br. J. Pharmacol. 118 (1996) 493–502, https://doi.org/10.1111/j.1476-5381.1996.tb15430.x.
[31] S. Daniels, R.J. Roberts, Post-synaptic inhibitory mechanisms of anaesthesia; glycine receptors, Toxicol. Lett. 100–101 (1998) 71–76, https://doi.org/10.1016/S0378-4274(98)00167-2.
[32] S.M. Todorovic, V. Jevtovic-Todorovic, S. Mennerick, E. Perez-Reyes, C. F. Zorumski, Cav3.2 Channel is a molecular substrate for inhibition of T-type calcium currents in rat sensory neurons by nitrous oxide, Mol. Pharmacol. 60 (2001) 603–610.
[33] E.D. Frank, J. Honet, M. Torjman, N. Janes, E. Rubin, M. Barber, T. Taraschi, Effects of chronic exposure to nitrous oxide on membrane fluidity in rats, Ann. N. Y. Acad. Sci. 625 (1991) 545–547, https://doi.org/10.1111/j.1749-6632.1991.tb33886.x.
[34] B.L. Foster, D.T.J. Liley, Effects of nitrous oxide sedation on resting electroencephalogram topography, Clin. Neurophysiol. 124 (2013) 417–423, https://doi.org/10.1016/j.clinph.2012.08.007.
[35] K.J. Pavone, O. Akeju, A.L. Sampson, K. Ling, P.L. Purdon, E.N. Brown, Nitrous oxide-induced slow and delta oscillations, Clin. Neurophysiol. 127 (2016) 556–564, https://doi.org/10.1016/j.clinph.2015.06.001.
[36] P. Paoletti, C. Bellone, Q. Zhou, NMDA receptor subunit diversity: impact on receptor properties, synaptic plasticity and disease, Nat. Rev. Neurosci. 14 (2013) 383–400, https://doi.org/10.1038/nrn3504.
[37] S.F. Traynelis, L.P. Wollmuth, C.J. McBain, F.S. Menniti, K.M. Vance, K.K. Ogden, K.B. Hansen, H. Yuan, S.J. Myers, R. Dingledine, Glutamate receptor ion channels: structure, regulation, and function, Pharmacol. Rev. 62 (2010) 405–496, https://doi.org/10.1124/pr.109.002451.
[38] J.E. Huettner, B.P. Bean, Block of N-Methyl-D-Aspartate-Activated Current by the Anticonvulsant MK-801: Selective Binding to Open Channels (Excitatory Amino Acid Receptors/Visual Cortex/Cell Culture/Single Channels), 1988.
[39] S.E. Kotermanski, J.T. Wood, J.W. Johnson, Memantine binding to a superficial site on NMDA receptors contributes to partial trapping, J. Physiol. 587 (2009) 4589–4604, https://doi.org/10.1113/jphysiol.2009.176297.
[40] R.K. Das, A. Tamman, V. Nikolova, T.P. Freeman, J.A. Bisby, A.I. Lazzarino, S. K. Kamboj, Nitrous oxide speeds the reduction of distressing intrusive memories in an experimental model of psychological trauma, Psychol. Med. 46 (2016) 1749–1759, https://doi.org/10.1017/S003329171600026X.
[41] M.K. Dimick, D. Omrin, B.J. MacIntosh, R.H.B. Mitchell, D. Riegert, A. Levitt, A. Schaffer, S. Belo, J. Iazzetta, G. Detzler, M. Choi, S. Choi, B.A. Orser, B. I. Goldstein, Nitrous oxide as a putative novel dual-mechanism treatment for bipolar depression: proof-of-concept study design and methodology, Contemp. Clin. Trials Commun. 19 (2020), https://doi.org/10.1016/j.conctc.2020.100600.
[42] A. Hochschild, M.F. Grunebaum, J.J. Mann, The rapid anti-suicidal ideation effect of ketamine: a systematic review, Prev. Med. 152 (2021), https://doi.org/10.1016/j.ypmed.2021.106524.