ANNUAL REVIEWS

Annual Review of Neuroscience

Anesthetics as Treatments for Depression: Clinical Insights and Underlying Mechanisms

Macauley Smith Breault,[1,2,*] Sirma Orguc,[2,3,*] Ohyoon Kwon,[1,2,4,*] Gloria H. Kang,[1,2,4] Bryan Tseng,[1,4] David R. Schreier,[1,2,5] and Emery N. Brown[1,2,3,4,6]

[1]Picower Institute for Learning and Memory, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA; email: enb@neurostat.mit.edu

[2]Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA

[3]Institute for Medical Engineering and Science, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA

[4]Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA

[5]Center for Neurotechnology and Neurorecovery, Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA

[6]Department of Anaesthesia, Harvard Medical School, Boston, Massachusetts, USA

Annu. Rev. Neurosci. 2025. 48:103–24

The *Annual Review of Neuroscience* is online at neuro.annualreviews.org

https://doi.org/10.1146/annurev-neuro-112723-062031

*These authors contributed equally to this article

Keywords

anesthetics, major depressive disorder, treatment-resistant depression, network dysfunction, GABA deficit hypothesis, BDNF signaling pathway

Abstract

Major depressive disorder and treatment-resistant depression are significant worldwide health problems that need new therapies. The success of the anesthetic ketamine as an antidepressant is well known. It is less widely known that several other anesthetic agents have also shown antidepressant effects. These include nitrous oxide, propofol, isoflurane, sevoflurane, dexmedetomidine, and xenon. We review clinical and basic science investigations that have studied the therapeutic value of these anesthetics for treating depression. We propose potential neurophysiological mechanisms underlying the antidepressant effects of anesthetics by combining our understanding of how anesthetics modulate brain dynamics to alter arousal states, current theories of depression pathophysiology, and findings from other depression treatment modalities.

Contents

1. INTRODUCTION

MDD: major depressive disorder

Mood disorder: a mental health condition characterized by significant mood disturbances

Anhedonia: a state of decreased interest in pleasurable activities

Treatment response: a ≥50% reduction in the total score of the Hamilton Depression Rating Scale

TRD: treatment-resistant depression

rTMS: repetitive transcranial magnetic stimulation

ECT: electroconvulsive therapy

DBS: deep brain stimulation

The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* defines major depressive disorder (MDD) as a mood disorder consisting of persistent anhedonia that causes social or occupational impairment. MDD requires five or more of the following symptoms over a minimum of two weeks: depressed mood, anhedonia, feelings of guilt, lack of energy, poor concentration, significant weight or appetite changes, psychomotor retardation or agitation, sleep disturbances, or suicidal thoughts. At least one of the symptoms is either depressed mood or anhedonia (Am. Psychiatr. Assoc. 2013). In the United States, an estimated 22 million adults and 5 million adolescents have had at least one major depressive episode in 2023 (SAMHSA 2023), and the economic burden of MDD, driven by healthcare and workplace costs, was $326.2 billion in 2020 (Greenberg et al. 2021). The COVID-19 pandemic increased the global prevalence of depression and anxiety by 25%, leading to a rise in both the number of affected individuals and associated costs (Santomauro et al. 2021).

First-line treatments for MDD are monoamine antidepressants such as serotonin reuptake inhibitors. The monoamine hypothesis of depression suggests that these drugs alleviate depression by replenishing depleted monoamine levels in the brain. However, over one-third of patients with MDD do not have an adequate treatment response to monoamine antidepressants (Rush et al. 2006). In fact, there is no consistent evidence supporting the monoamine hypothesis (Moncrieff et al. 2023). Patients who fail two trials of antidepressant monotherapies are diagnosed with treatment-resistant depression (TRD). Alternative therapies such as repetitive transcranial magnetic stimulation (rTMS), electroconvulsive therapy (ECT), and deep brain stimulation (DBS) are offered to these patients. The limited treatment efficacy and considerable side effects—particularly for ECT—have prompted searches for other therapies (Regenold et al. 2015, Vida et al. 2023).

Anesthetics have emerged as a promising therapeutic option for treating depression (see the sidebar titled Anesthesia 101). Both clinical observations and scientific evidence have demonstrated positive changes in mood following the administration of one of these agents (Lehmann & Bos 1947, Krystal et al. 1994, Brechmann et al. 2018). In fact, both inhalational and intravenous

ANESTHESIA 101

General anesthesia is a pharmacologically mediated state consisting of antinociception, unconsciousness, amnesia, and immobility with the maintenance of physiological stability (Brown et al. 2010, 2018). Anesthetics are intravenous or inhaled pharmacological agents used to create one or more of the behavioral states of general anesthesia. The anesthetics contribute to the state of general anesthesia by changing brain dynamics [neural spiking activity, local field potentials, and electroencephalogram (EEG) activity]. When brain dynamics are sufficiently altered, communication among brain regions is impaired and the patient loses consciousness. Anesthetic effects on the brain are clearly observed in the EEG. EEG patterns change with the anesthetic's mechanism of action, anesthetic's dose, patient's age, and patient's state of health.

anesthetics from different classes, and with different mechanisms for altering arousal, have shown some benefits in treating TRD.

In this review, we summarize the clinical and basic science literature on several anesthetics that have been used to treat MDD and TRD, including ketamine, nitrous oxide, propofol, isoflurane, sevoflurane, dexmedetomidine, and xenon. We first review current theories of the pathophysiology of depression beyond the monoamine hypothesis and then use these theories of depression as a neurophysiological framework for proposing the possible mechanisms that underlie the antidepressant effects of these seven anesthetics.

2. THEORIES ON THE PATHOPHYSIOLOGY OF DEPRESSION

The principal alternative theories to the monoamine hypothesis for the pathophysiology of depression are network dysfunction, impairment of the brain-derived neurotrophic factor (BDNF) signaling pathway, and the γ-aminobutyric acid (GABA) deficit hypothesis.

2.1. Network Dysfunction

The network dysfunction theory has been derived primarily from functional magnetic resonance imaging (fMRI) studies of depressed patients compared with typical, healthy controls. It suggests that depression arises from altered functional connectivity (typically measured during rest) within and between key brain regions, including the default-mode network (DMN), frontoparietal network (FPN), salience network (SN), and limbic system (Kaiser et al. 2015) (**Figure 1*a***). The DMN is responsible for introspection and self-referential thought (Raichle 2015). The network consists of brain regions distinct in depression literature, including the medial prefrontal cortex (mPFC) and subgenual anterior cingulate cortex (Gärtner et al. 2019). The FPN exerts cognitive flexibility through working memory and the dorsolateral prefrontal cortex (dlPFC) (Marek & Dosenbach 2018). The SN shifts attention between internal and external stimuli by mediating DMN and FPN communication (Sridharan et al. 2008). The limbic system contains interconnected subcortical structures such as the amygdala, hippocampus, and nucleus accumbens (NAc), which regulate memory, mood, and emotion (Bari et al. 2014). Hence, these networks collaborate to orchestrate behavioral adaptation and regulate emotion. In individuals with MDD and TRD, abnormal hypo- and/or hyperconnectivity between these networks has been observed (**Figure 1*b***), and treatments such as rTMS, ECT, and DBS have been shown to modulate these connectivity patterns (Abbott et al. 2013, Schiena et al. 2021, Cha et al. 2024). Similarly, anesthetics are believed to affect arousal states by directly altering the connectivity dynamics of these networks (Akeju et al. 2014a, Golkowski et al. 2019, Siegel et al. 2021, Stenroos et al. 2021, Palanca et al. 2023).

Functional connectivity: a measure of the correlated activity between different brain regions or networks

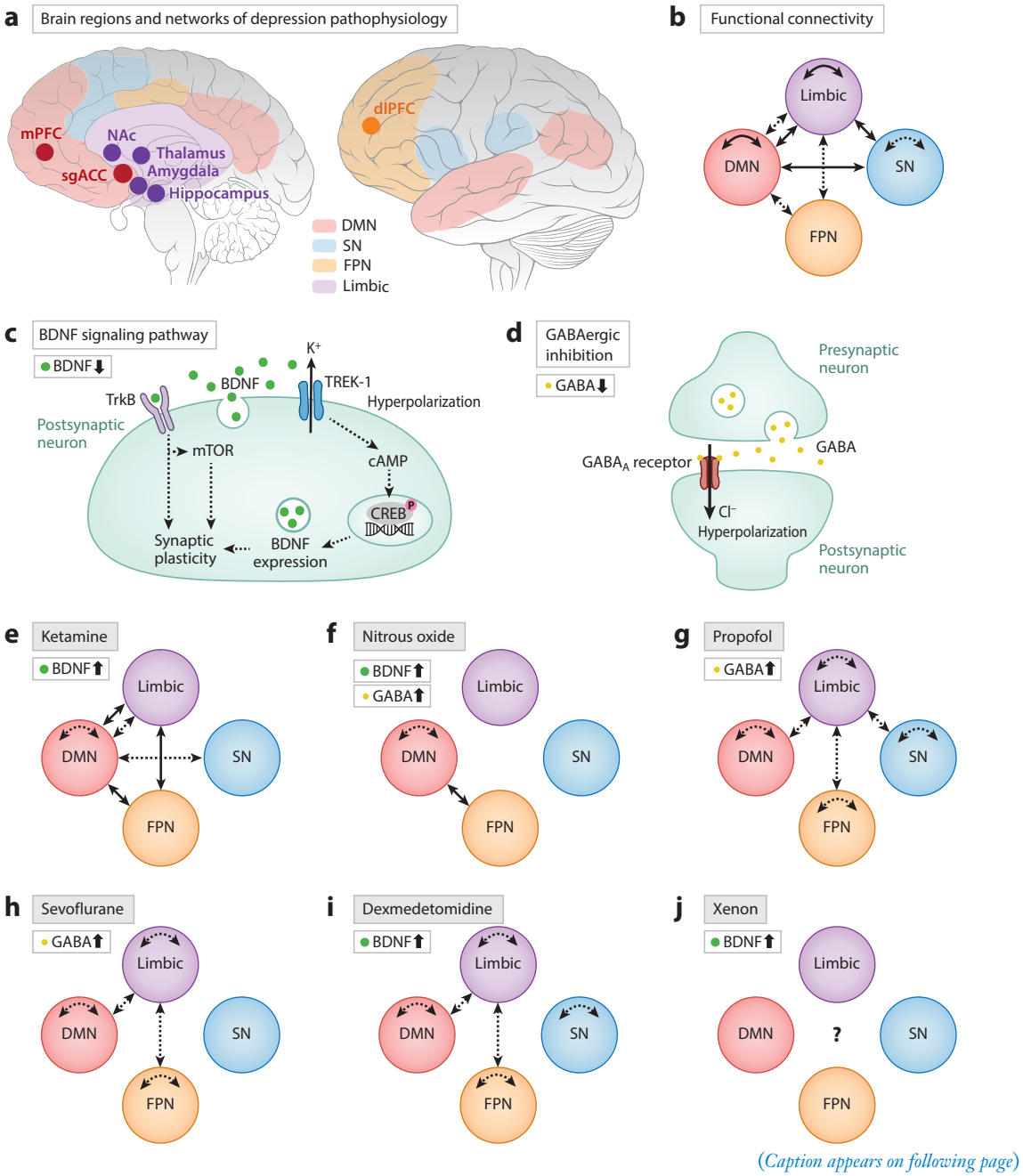
DMN: default mode network

FPN: frontoparietal network

SN: salience network

2.2. BDNF Signaling Pathway

BDNF is a growth factor crucial for regulating neuroplasticity (Duman et al. 2021). The BDNF signaling pathway is initiated when BDNF binds to the tyrosine kinase receptor (TrkB), which activates various downstream signaling pathways and enhances mammalian target of rapamycin (mTOR) signaling (**Figure 1*c***). This process is essential for neuronal survival, structural changes,



(*Caption appears on following page*)

Figure 1 (*Figure appears on preceding page*)

(*a*) The brain regions involved in depression are grouped into brain networks: the DMN, FPN, SN, and limbic system. (*b*) Dysfunctional hyperconnectivity (*solid lines*) or hypoconnectivity (*dashed lines*) within and between these networks may contribute to persistent depressive symptoms. (*c*) Changes in BDNF signaling may help normalize dysfunctional networks. Patients with MDD and TRD show reduced BDNF serum levels compared to healthy individuals. (*d*) In MDD and TRD patients, lower GABA levels at GABAergic synapses reduce inhibitory control, increasing neuronal excitability. (*e*) Ketamine may improve functional connectivity in dysfunctional networks by enhancing BDNF expression. (*f*) Nitrous oxide's GABAergic activation may provide short-term relief from depressive symptoms, while BDNF pathways may sustain altered connectivity. (*g*) Propofol alters connectivity at anesthetic doses and may help increase GABA levels. (*h*) Isoflurane and sevoflurane inhibit connectivity and enhance GABAergic inhibition at anesthetic doses. (*i*) Dexmedetomidine alters connectivity and BDNF concentration during sedation. (*j*) Xenon's impact on functional connectivity remains unexplored, but evidence suggests it enhances BDNF levels. See **Supplemental Figure 1** for spectrograms. Abbreviations: BDNF, brain-derived neurotrophic factor; CREB, cAMP response element–binding protein; dlPFC, dorsolateral prefrontal cortex; DMN, default mode network; FPN, frontoparietal network; GABA, γ-aminobutyric acid; MDD, major depressive disorder; mPFC, medial prefrontal cortex; mTOR, mammalian target of rapamycin; NAc, nucleus accumbens; sgACC, subgenual anterior cingulate cortex; SN, salience network; TRD, treatment-resistant depression; TREK-1, TWIK-related potassium channel 1; TrkB, tyrosine kinase receptor. Panel *a* adapted from Patrick J. Lynch/Wikimedia Commons (**https://commons.wikimedia.org/wiki/File:Brain_human_sagittal_section.svg**, **https://commons.wikimedia.org/wiki/File:Brain_human_lateral_view.svg**) (CC BY 2.5).

and plasticity (Castrén & Kojima 2017). Reduced expression of BDNF impairs these functions and can lead to hippocampal atrophy and diminished connectivity across cerebral cortical networks and the limbic system (Duman et al. 2021). Activation of the BDNF signaling pathway may help reverse network dysfunction in patients with MDD and TRD. BDNF serum levels, which are often depleted in depressed patients, have been shown to increase following treatments such as rTMS, ECT, and, as we discuss below, certain anesthetics (Lee & Kim 2010, Woelfer et al. 2020, Psomiades et al. 2022, Pan et al. 2023). A similar finding has been reported in animal models of depressive symptoms investigating DBS (Sun et al. 2022).

2.3. GABA Deficit Hypothesis

The GABA deficit hypothesis postulates that reduced GABA contributes to the pathophysiology of depression (Luscher et al. 2011) (**Figure 1*d***). This hypothesis is supported by evidence showing that patients with MDD and TRD have lower GABA concentrations in brain tissue (Rajkowska et al. 2007) and serum (Esel et al. 2008) than healthy individuals. Reduced GABA levels at GABAergic synapses can decrease inhibitory control, leading to increased neuronal excitability (Luscher et al. 2011). This dysregulation disrupts the balance between excitation and inhibition in the brain and likely contributes to anxiety and depressive symptoms. Consistent with this idea, rTMS and postictal suppression after ECT have been shown to increase GABA levels in depressed patients significantly (Esel et al. 2008, Dubin et al. 2016). Likewise, certain anesthetics are also known to affect GABA concentrations (Larsen et al. 1998, Jin et al. 2009, Liu et al. 2023). Finally, the roles GABAergic medications play in treating other mood-related psychiatric symptoms also support the GABA deficit hypothesis. For instance, benzodiazepines, positive allosteric modulators of $GABA_A$ receptors, are the first-line treatment for catatonia, a neuropsychiatric syndrome characterized by abnormal movements, unusual behaviors, and withdrawal, most often seen in mood disorders (Northoff et al. 1999). An fMRI study found reduced $GABA_A$ receptors in the dlPFC of catatonia patients (Northoff et al. 1999). Valproate, a first-line treatment for acute mania in bipolar disorder, a mood disorder characterized by unusual fluctuations in mood, increases brain GABA levels by inhibiting its breakdown and enhancing BDNF expression (Fukumoto et al. 2001, Rosenberg 2007). Long-term response to valproate for bipolar disorder is also associated with certain BDNF genotypes and dlPFC thickness (Rodríguez-Ramírez et al. 2024).

We incorporate these three theories of depression pathophysiology into our discussion of how these seven anesthetics could likely exert their antidepressant effects.

3. KETAMINE

HDRS: Hamilton Depression Rating Scale

EEG: electroencephalogram

The intravenous anesthetic ketamine is an *N*-methyl-D-aspartate (NMDA) receptor antagonist. At low doses (<0.75 mg/kg/h) (**Supplemental Table 1**), ketamine produces sedation, analgesia, hallucinations, and dissociation, whereas at high doses (1–2 mg/kg/h), it produces profound unconsciousness and antinociception (Domino & Warner 2010). Therefore, ketamine at high doses can serve as a single-drug general anesthetic (WHO 2023). First synthesized in the 1960s, its potential use as an antidepressant was not investigated until 2000 (Berman et al. 2000).

Krystal et al. (1994) first reported the potential antidepressant effects of ketamine in a clinical study designed to test its psychotomimetic effects. Berman et al. (2000), supervised by Krystal, conducted the first double-blind, placebo-controlled crossover trial of ketamine for treating MDD. Nine patients with MDD received a 0.5-mg/kg intravenous infusion of ketamine over 40 min as the treatment or a saline infusion as the placebo. The treatment and the placebo were administered a week apart. The Hamilton Depression Rating Scale (HDRS)-25 was used as the primary outcome measurement. It was assessed at baseline and up to 72 h after the infusion. The HDRS-25 scores decreased significantly 4 h after treatment, with four patients sustaining a treatment response for more than 72 h. Subsequently, Zarate et al. (2006) and others (Wilkinson et al. 2018) have substantiated the rapid antidepressant effects of single-dose intravenous ketamine. A meta-analysis concluded that a single infusion of ketamine reduced suicidal thoughts in patients within one day and that the effect lasted up to one week (Wilkinson et al. 2018). The ketamine doses used for antidepressant purposes are closer to those used for sedation than those used for general anesthesia (**Supplemental Table 1**).

3.1. Antidepressant Mechanism of Ketamine

We propose a framework to account for the antidepressant effects of ketamine on rapid (minutes to hours), short-term (hours to days), and long-term (days to weeks) timescales. The following mechanisms are summarized in **Figure 1*e***.

Within minutes of administering a subanesthetic dose of ketamine, the frontal electroencephalogram (EEG) in humans and nonhuman primates shows fast oscillations in the high beta and low gamma range (>20 Hz) (Akeju et al. 2016, Garwood et al. 2021) (**Supplemental Figure 1*a***). Biophysical modeling based on nonhuman primate local field potentials and human EEG recordings demonstrates that these continuous gamma oscillations are optimized at low doses, where they are not interrupted by intermittent slow-delta oscillations (<4 Hz) that occur at high doses (Adam et al. 2024). This model accounts for the complex interactions of ketamine as an open-channel blocker by representing NMDA channels as either blocked or unblocked, where unblocking leads to depolarization. Ketamine-mediated disinhibition of interneurons causes NMDA receptors to unblock, triggering bursts of spikes in single neurons at a gamma timescale (Adam et al. 2024). Of note, gamma oscillations are the frequency range in which the brain typically carries out communications (Fries 2009). They are associated with effective connectivity between different brain networks involved in the pathophysiology of depression and neuroplasticity signaling in the hippocampus. Therefore, they may serve as a crucial indicator of a successful antidepressant effect (Huang & Morozov 2011, Zheng et al. 2011). Tian et al. (2023) found that low doses in humans produce gamma oscillations in the PFC and hippocampus, two brain regions that are central to depression pathophysiology. Moreover, increased gamma oscillation power several hours after ketamine infusion correlates with improved treatment response in patients with MDD (Cornwell et al. 2012, Nugent et al. 2019). Ketamine's acute induction of gamma oscillations may create an environment that fosters a flexible cognitive state.

The short-term antidepressant effects of ketamine could primarily be attributed to its impact on the BDNF-mediated neurotrophic cascade. This cascade, which is activated through various mechanisms, leads to transcriptional changes that result in increased neurite outgrowth and synapse formation, as observed in in vitro and in vivo mouse studies (Jourdi et al. 2009, Moda-Sava et al. 2019). Ketamine-mediated NMDA receptor blockade initiates TrkB receptor signaling, which stimulates BDNF release and promotes rapid neuroplasticity (Autry et al. 2011) (**Figure 1*c***). Furthermore, the disinhibition of glutamatergic neurons at low doses leads to enhanced glutamate release. Rodent and human in vitro studies have shown activation of postsynaptic AMPA receptors and mTOR within the BDNF signaling pathway after ketamine administration (Li et al. 2010, Cavalleri et al. 2018). Previous preclinical studies have suggested that these mechanisms underlie the antidepressant effects of ketamine (Monteggia et al. 2004, Autry et al. 2011). Additional mouse and human studies suggest that ketamine's short-term antidepressant effect may also involve its metabolites (Zanos et al. 2016) and opioid receptor antagonism (Williams et al. 2018).

Ultimately, short-term synaptic changes induced by ketamine may lead to lasting relief by reversing functional connectivity in depression-related networks (**Figure 1*b***). In patients with MDD or TRD, ketamine treatments have been shown to produce sustained changes in connectivity that differ from baseline (**Figure 1*e***). Notable findings include increased connectivity between the FPN-limbic system (Vasavada et al. 2021), DMN-limbic system (Alexander et al. 2023), and FPN-DMN (Gärtner et al. 2019), as well as decreased connectivity between the DMN-limbic system (Abdallah et al. 2017) and DMN-SN (Chen et al. 2019). These alterations could disrupt the cycle of maladaptive thoughts, thereby enhancing patients' control over their emotional responses. For example, a 96-h subanesthetic ketamine infusion has been found to normalize pathological connectivity by decreasing DMN connectivity and increasing FPN-limbic connectivity (Siegel et al. 2021). This normalization could help alleviate depressive symptoms by reducing persistent introspective thinking and improving cognitive and emotional regulation.

3.2. The Current Status of Ketamine Therapy

As of 2024, the racemic mixture of ketamine has not been cleared by the United States Food and Drug Administration (FDA) to treat any psychiatric condition (Bloomfield et al. 2023). The rapid and effective antidepressant effects have popularized its off-label use through ketamine clinics, where patients receive ketamine infusions. There is no consensus among psychiatrists for an optimal treatment plan (**Supplemental Table 1**). Clinics typically require patients to remain for an observation period following ketamine administration to monitor any short-term side effects such as nausea, hypertension, tachycardia, perceptual disturbances, feelings of dissociation, respiratory depression, or prolonged sedation. Potential chronic side effects include liver and bladder damage (Kalsi et al. 2011).

S-ketamine (esketamine), the right-handed enantiomer of ketamine, was developed to mitigate these adverse effects. It is more potent than racemic ketamine and requires lower doses to produce similar antidepressant effects (Zeilhofer et al. 1992). In 2019, the FDA cleared intranasal esketamine to treat TRD in adults (FDA 2020). In 2020, they also cleared intranasal esketamine to treat acute suicidal ideation or behavior in adults.

4. NITROUS OXIDE

Nitrous oxide is an inhaled anesthetic. Since it is not potent enough to produce general anesthesia alone, it is used for sedation or as an anesthetic adjunct. It is commonly referred to as laughing gas due to the euphoric effects it can cause (Lehmann & Bos 1947). Because nitrous oxide and

ketamine share blocking of NMDA receptors as a principal mechanism, it was postulated that nitrous oxide could be an effective antidepressant (Nagele et al. 2015).

Remission: HDRS score of 7 or less

Nitrous oxide was first studied as a treatment for TRD by Nagele et al. (2015). In their double-blind, placebo-controlled crossover study, 20 patients with TRD inhaled either 50% nitrous oxide (treatment) or 50% nitrogen (placebo) with 50% oxygen for one hour each. Depressive symptoms were assessed using the HDRS-21 scale at baseline, 2 h post-session, and 24 h post-session. The patients in the treatment group had significantly improved HDRS-21 scores at both post-session time points, with 7 of 20 patients showing treatment response and 3 reaching full remission. Adverse effects, such as nausea and vomiting, were reported. After Zarate & Machado-Vieira (2015) critiqued their doses, time points, and blinding, a follow-up study by Nagele et al. (2021) found that a lower dose of 25% achieved similar therapeutic results with fewer side effects. Since then, several studies have repeated these findings (Guimarães et al. 2021, Liu et al. 2023, Ladha et al. 2024).

Nitrous oxide differs from its fellow NMDA antagonist, ketamine, in several ways. It is a non-competitive NMDA antagonist with distinct receptor effects, including different binding affinities and channel configurations (Nagashima et al. 2005). It has a far less complex set of interactions with the NMDA receptors relative to ketamine (Nagashima et al. 2005, Adam et al. 2024) and interacts with other receptors, including $GABA_A$ and opioid receptors (Zorumski et al. 2015). It also has unique EEG dynamics, which is illustrated in **Supplemental Figure 1*b***—transient slow-delta oscillations that shift to beta-gamma oscillations (Pavone et al. 2016). Therefore, its antidepressant mechanism is likely different from that of ketamine.

The mechanism by which nitrous oxide achieves its short-term antidepressant effects may overlap with its mild analgesic, anxiolytic, and euphoric effects. First, its mild analgesic effect has been attributed to its induction of endogenous opioid release from the periaqueductal gray, where it acts as a partial opioid agonist (Emmanouil & Quock 2007), producing results similar to those of less addictive opioids (Gillman 1986). Second, its anxiolytic effect, possibly due to $GABA_A$ receptor activation (similar to benzodiazepines) (Emmanouil & Quock 2007), may help with anxiety, which is a common comorbidity in MDD (Gorman 1996). Finally, its euphoric effect could be due to the activation of the mesolimbic reward pathway and dopamine release. The release of dopamine contributes to its common post-administration side effect of nausea and vomiting (Murakawa et al. 1994).

The long-term antidepressant effects of nitrous oxide may be the result of neuroplasticity. Like ketamine, nitrous oxide may achieve this through BDNF-mediated mechanisms but using slightly different pathways. In a rodent study, nitrous oxide exposure promoted synaptogenesis through BDNF signaling in the mPFC within the DMN (Liu et al. 2020). Low-dose nitrous oxide exposure appears to change synaptic function in the rodent hippocampus through mechanisms involving TrkB, mTOR, and nitric oxide synthase (Izumi et al. 2022). Activation of TrkB in the mPFC with transient slow waves (<1 Hz) was observed in the EEG during nitrous oxide inhalation in rodents (Kohtala et al. 2019). This finding suggests that slow waves may indicate synaptogenesis. Impairment in slow-wave activity is associated with MDD (Goldschmied & Gehrman 2019). In humans, slow waves have been postulated to originate from blocking the arousal projections from the brainstem to the thalamus and cortex (Pavone et al. 2016, Brown et al. 2018). Slow waves are also linked to homeostatic plasticity and synaptic regulation (Tononi & Cirelli 2003).

Connectivity research on nitrous oxide in humans has been conducted both during and shortly after exposure. During psychedelic levels of exposure (35% nitrous oxide in oxygen), DMN-FPN connectivity increases (Dai et al. 2023). Shortly after exposure (50% nitrous oxide), the connections between the visual and dorsal attention network and DMN-FPN increase in healthy volunteers (Palanca et al. 2023). One week after exposure, DMN connectivity decreases in adults

with MDD, but not in healthy controls or nonresponders (Desmidt et al. 2023). These findings are summarized in **Figure 1*f***. The altered brain connectivity seen during nitrous oxide exposure might reflect the possible therapeutic effects of beta-gamma oscillations. A study found that MDD patients had reduced beta and gamma connectivity in the left temporal region of the DMN compared to healthy controls (Wang et al. 2022). In addition, MDD patients showed weaker beta-gamma phase-amplitude coupling, which was linked to more severe cognitive disturbances such as negative thinking and excessive worry (Liu et al. 2022). This suggests that nitrous oxide may alter functional connectivity through increased beta-gamma oscillations.

Burst suppression: an EEG pattern characterized by alternating periods of high-amplitude electrical activity (bursts) and periods of significantly reduced, low-amplitude activity (suppressions)

Isoelectric period: an EEG pattern showing little to no electrical activity

5. PROPOFOL

Propofol is a GABAergic agonist used for the induction and maintenance of sedation and general anesthesia. It is administered intravenously as a bolus or as a continuous infusion. Patients frequently report euphoria after emergence from propofol-mediated sedation, a phenomenon not generally observed with other anesthetics (Brechmann et al. 2018). An in vivo rat study further supports this observation, linking the euphoria to increased dopamine release in the NAc (Pain et al. 2002). Additionally, Mickey et al. (2018) hypothesized that the burst suppression periods caused by high-dose propofol induce antidepressant effects like the prolonged isoelectric periods achieved during ECT. The same may be true for isoflurane, another GABAergic agonist (see below) (Langer et al. 1985). Consequently, propofol has become a promising candidate as a new possible antidepressant therapy.

In 2018, Mickey et al. (2018) investigated the feasibility, tolerability, and efficacy of high-dose propofol treatment for TRD. In their open-label clinical trial, 10 patients with TRD receiving propofol infusions (treatment group) were compared to 20 patients receiving ECT (ECT group). Patients in the treatment group received 10 treatments of propofol infusions over 4 weeks. Treatment sessions targeted burst suppression with a suppression ratio of 80–100%, which was maintained for 15 min. The EEG was tracked using the BIS monitor (BIS Vista monitoring system, Medtronic). Note that suppression ratios of this magnitude would require propofol doses significantly higher than usual (**Supplemental Table 1**). Despite this, patients met discharge criteria within 10 min after emergence. Patients reported only minor and temporary side effects, such as sore throat from intubation and discomfort at the injection site. Six out of 10 patients had a treatment response, as assessed from their HDRS-24 scores, by the fifth treatment. Five patients sustained this improvement for at least three months. No significant differences were found compared to the ECT group; both groups showed similar improvement by the tenth treatment, based on self-reported depression scores. This study suggests that propofol could be noninferior to ECT for TRD treatment without ECT's common cognitive side effects, such as retrograde and anterograde memory loss.

Tadler et al. (2023) have since conducted a randomized controlled trial using a lower propofol dose without burst suppression (**Supplemental Table 1**). Here, they achieved antidepressant effects similar to those who received higher doses but with fewer adverse effects, such as sore throat and decreased blood pressure. A separate study has since shown that postictal suppression after ECT neurophysiologically differs from propofol-mediated burst suppression (Kafashan et al. 2022). Another study using a single propofol infusion on two elderly patients yielded mixed results (Rios et al. 2023), underscoring the importance of proper study design.

Propofol induces unconsciousness or sedation by altering brain dynamics through GABA-mediated inhibition in the cortex, thalamus, and brainstem (Brown et al. 2010, Ching et al. 2010). This is evident in electrophysiological data from rodent, nonhuman primate, and human studies (Purdon et al. 2013, Shanechi et al. 2013, Bastos et al. 2021). In humans, it is tightly associated

with dose-dependent EEG signatures that range from beta oscillations to slow-delta and alpha oscillations to burst suppression at high doses (Purdon et al. 2015). These signatures, shown in **Supplemental Figure 1*c***, have been replicated in modeling studies (Adam et al. 2023). While the exact mechanism behind propofol's antidepressant effect is unknown, we propose four possibilities centered around its ability to alter brain dynamics when used as an anesthetic.

First, GABA deficits are associated with depression pathophysiology (Luscher et al. 2011). In patients with MDD, there are fewer GABAergic neurons in PFC (Rajkowska et al. 2007) and lower serum GABA levels than in healthy individuals (Esel et al. 2008). The interaction between propofol and $GABA_A$ receptors may help restore GABA levels by increasing the spontaneous release of GABA (Jin et al. 2009). Modeling studies suggest these changes may result in the characteristic EEG signatures observed during propofol use (Hindriks & van Putten 2012). This enhancement of GABA—which counters overexcitation in the brain—may contribute to propofol's rapid and short-term antidepressant effect.

Second, dysfunctional reward pathways are also implicated in the pathophysiology of depression, often leading to symptoms such as anhedonia (Hu et al. 2023). Both subanesthetic and anesthetic doses of propofol have been linked to increased dopamine levels in the NAc (Pain et al. 2002). A rodent model of chronic stress and anhedonia demonstrated that propofol reversed anhedonia by binding to dopamine transporters, thereby increasing dopamine accumulation in the NAc (Zhu et al. 2023). We propose that propofol likely activates this reward pathway to induce euphoria, leading to a rapid antidepressant effect.

Third, propofol also appears to influence the BDNF expression, which is likely crucial for sustaining its antidepressant effects given BDNF's role in neuroplasticity. In *in vitro* and *in vivo* rodent studies, propofol either promotes or inhibits BDNF in the hippocampus after neuronal injury, depending on the dose and the type of injury (Chen et al. 2012, Tu et al. 2019). In rodent tissue, elevated levels of BDNF are present in the hippocampus, a key brain region in the limbic system, and the PFC, a key brain region in DMN and FPN, up to three days after propofol exposure (Rafiq et al. 2018). Increased BDNF may enhance neuroplasticity in these regions, which could be critical in treating depression. Enhanced neuroplasticity could occur by improving functional connectivity.

Fourth, propofol-mediated unconsciousness is characterized by coherent alpha oscillations (Purdon et al. 2013). As shown in **Figure 1*g***, it is also associated with reduced connectivity within and between DMN, FPN, DN, and the limbic system, which are key brain networks in network dysfunction (Weiner et al. 2023). Asymmetry in EEG alpha oscillations between the left and right hemispheres is suggested to be a stable neurophysiological marker of MDD (Gollan et al. 2014). Coherent alpha oscillations induced by propofol may help normalize this pathological alpha EEG asymmetry in MDD patients. This normalization could alter their functional connectivity. Lastly, since propofol is commonly administered as part of the ECT sedation, it cannot be excluded that altered connectivity observed after ECT may be aided by propofol (Wei et al. 2021).

6. ISOFLURANE AND SEVOFLURANE

Isoflurane and sevoflurane are inhaled ether anesthetics used with oxygen to induce and maintain general anesthesia. **Supplemental Table 1** contains the doses typically used by anesthesiologists for isoflurane and sevoflurane maintenance of unconsciousness.

In 1985, Langer et al. (1985) were the first to explore the use of anesthetics to treat depression. They used isoflurane, postulating that the isoelectric periods of burst suppression observed on the EEG during profound levels of isoflurane-mediated unconsciousness resembled the postictal suppression after seizures induced by ECT. The group conducted an open-label study of isoflurane as a TRD treatment in which patients received one to six treatments, starting at 4%

[3.33 minimum alveolar concentration (MAC)] and decreasing to 2.4% (2 MAC) to maintain a suppression ratio of 80% for 15 min. Unlike ECT, isoflurane caused no significant cognitive side effects while still improving psychometric variables at follow-up visits. However, shortly after this study, only a minimal improvement was found when isoflurane was used for treating elderly patients with MDD (Greenberg et al. 1987).

Minimum alveolar concentration (MAC): the alveolar concentration of an inhaled anesthetic at which 50% of patients would fail to move in response to a painful stimulus

A subsequent clinical trial found isoflurane to have antidepressant effects similar to ECT but with fewer neurocognitive side effects (Weeks et al. 2013). Another randomized control trial comparing propofol induction followed by sevoflurane-mediated maintenance to only propofol-mediated induction in TRD patients showed no significant improvement (García-Toro et al. 2001). This result was partly due to inadequate dosing and the unappreciated fact that propofol is also a potential TRD therapy with modes of action similar to isoflurane (Tadler & Mickey 2018). These mixed results contributed to the discontinuation of research on inhaled ether anesthetics for TRD.

The exact mechanism behind the antidepressant effects of isoflurane and sevoflurane is still unclear. Initially, Langer et al. (1985) suggested using isoflurane-mediated burst suppression to mimic the postictal state of ECT. However, we now know their mechanisms of action are not equivalent (Kafashan et al. 2022). On one hand, the GABAergic deficit hypothesis says that the postictal suppression after ECT is due to the endogenous release of GABA (Moulier et al. 2022). On the other hand, isoflurane drives inhibition by modulating GABA receptors to increase presynaptic GABA release and inhibiting its reuptake (Larsen et al. 1998, Liachenko et al. 1999). Like propofol, isoflurane inhibits brainstem, thalamic, and cortical networks through metabolic effects on mitochondria (Kishikawa et al. 2018, Jiang et al. 2022).

The inhibitory effects of isoflurane and sevoflurane are apparent in frontal EEG oscillations. At sub-MACs, both isoflurane and sevoflurane show strong slow-delta and alpha oscillations (**Supplemental Figure 1*d***), similar to propofol, suggesting enhanced GABAergic inhibition (Akeju et al. 2014b). At 1 MAC and above, theta oscillations (4–7 Hz) appear, unlike with propofol, suggesting a possible non-GABAergic mechanism as well (Purdon et al. 2015).

Evidence suggests that lower power of theta oscillations is associated with more severe depressive symptoms. For instance, in a magnetoencephalography study, subjects with MDD had lower frontal theta power than controls (Jiang et al. 2016). Another study found that higher frontal theta power in the DMN was linked to milder depressive symptoms (Saletu et al. 2010). The level of theta power is related to treatment response as well; frontal EEG theta power increases following rTMS treatment (Noda et al. 2013) and is associated with favorable outcomes following ECT (Heikman et al. 2001). How isoflurane and sevoflurane produce theta oscillations, in addition to the slow-delta and alpha oscillations, may relate to their potential antidepressant effects.

Theta activity can also be linked to functional connectivity, as resting-state frontal theta power negatively correlates with the DMN (Scheeringa et al. 2008). Sevoflurane-mediated unconsciousness in humans has shown reduced connectivity within and between the DMN, FPN, and limbic system (Ranft et al. 2016) (**Figure 1*b***). Rodent models suggest that these effects can last for at least a month (Stenroos et al. 2021). The antidepressant effects of isoflurane and sevoflurane may arise from changes in brain dynamics, specifically through modifications of functional connectivity. This could be manifested by alterations in slow-delta and alpha oscillations at levels below 1 MAC and theta oscillations at levels above 1 MAC.

7. DEXMEDETOMIDINE

Dexmedetomidine is an α_2-adrenergic receptor agonist that acts on both the brain and spinal cord (Brown et al. 2018). It is known to mimic certain EEG features of nonrapid eye movement

(NREM) sleep, specifically sleep spindles (12–16 Hz) and slow-delta oscillations, as shown in **Figure 1*i*** (Akeju et al. 2018). While dexmedetomidine is predominantly used for intravenous sedation in intensive care units and as an anesthetic adjunct in operating rooms, its sublingual form is used to manage agitation in adults with schizophrenia or bipolar disorder under the supervision of healthcare professionals (FDA 2022). In addition to its role in reducing delirium, dexmedetomidine has well-documented antinociceptive and anxiolytic effects across various administration routes (oral, intranasal, inhalational, intrathecal, and intramuscular; see **Supplemental Table 1**) (Naaz & Ozair 2014).

In a pilot study conducted by Liu et al. (2024), 76 patients with TRD were randomized to receive either 10 sessions of intravenous dexmedetomidine or ECT administered under propofol. The study found that both dexmedetomidine and ECT significantly reduced depression scores (HDRS-24). However, the dexmedetomidine group showed a greater reduction during the initial sessions. It did not affect cognitive scores, while ECT temporarily decreased cognition. The ECT group experienced adverse effects such as tachycardia, memory gaps, and insomnia during and after treatment. The dexmedetomidine group reported only a few cases of temporary injection site discomfort and mild nausea. However, due to propofol's own antidepressant effects (as noted earlier), its use during ECT introduced a confounding factor in this study. Additionally, other studies have highlighted the preventive benefits of dexmedetomidine for postpartum depression (Yu et al. 2019, Zhou et al. 2024).

The exact mechanisms by which dexmedetomidine produces antidepressant effects are not fully understood. However, they may involve several factors, including promoting slow-wave-like sleep, (Goldstein et al. 2022), reducing inflammation (Kopschina Feltes et al. 2017), and alleviating pain (Bair et al. 2003), all of which are related to depression. Dexmedetomidine acts on the locus coeruleus adrenergic projections in the brainstem, enhancing EEG slow-wave and spindle activity, similar to NREM sleep (Akeju et al. 2018). Additionally, it reduces inflammatory factors (Li et al. 2015) and promotes neuronal survival by increasing BDNF concentrations (Dehbozorgi et al. 2024). These actions may also be related to dexmedetomidine's analgesic effects (Xu et al. 2022). During dexmedetomidine-mediated sedation, reduced connectivity has been observed within the DMN, FPN, and limbic system, as summarized in **Figure 1*i*** (Akeju et al. 2014a, Guldenmund et al. 2017). This altered connectivity, associated with EEG slow-delta and spindle oscillations (**Supplemental Figure 1*e***), may contribute to its antidepressant effects (Akeju et al. 2016). However, the effects of dexmedetomidine on functional connectivity after exposure have yet to be explored.

8. XENON

Xenon, a noble gas anesthetic, offers superior hemodynamic stability and faster onset and emergence than other anesthetics (Law et al. 2016). However, its high cost and need for specialized equipment for administration have limited its use (Neice & Zornow 2016).

To date, there have been no published clinical trials examining the use of xenon for treating depression in humans. However, clinical observations and animal models suggest it has an anxiolytic effect (Dobrovolsky et al. 2017, Shao et al. 2020). Significant antidepressant and anxiolytic-like effects from xenon gas and xenon-rich saline have been demonstrated in a mouse model (Shao et al. 2020). This study also found that xenon pretreatment blocked lipopolysaccharide-induced depressive behavior. In humans, xenon has also been explored as a treatment for panic disorders (Dobrovolsky et al. 2017). As of 2024, xenon is being investigated as a potential therapeutic agent for TRD and bipolar depression in a clinical trial (NCT03748446).

Xenon provides mild analgesia through noncompetitive inhibition of NMDA receptors in the central nervous system and dorsal horn of the spinal cord (Sanders et al. 2005). Although

classified as an NMDA antagonist, xenon also affects other channels such as hyperpolarization-activated cyclic nucleotide-gated channel-2 (HCN2) and TWIK-related potassium channel 1 (TREK-1) (McGuigan et al. 2023). In fact, its frontal EEG spectral characteristics, displayed in **Supplemental Figure 1*f***, resemble those of GABAergic anesthetics more than those of anesthetics that are NMDA antagonists (McGuigan et al. 2021).

Mechanistically, its antidepressant effect may be linked to the BDNF signaling pathway. Preclinical studies have shown that xenon enhances TREK-1 potassium channel activity and CREB phosphorylation, thereby increasing BDNF expression (Peng et al. 2013, McGuigan et al. 2023). Although behavioral evidence was not statistically significant, Dandekar et al. (2018) found increased BDNF and mTOR levels in the neural tissue of a rat model of depression following xenon treatment. Further research is needed to understand whether the potential neuroplastic effects of BDNF lead to any functional connectivity changes during or after xenon exposure (**Figure 1*j***).

9. SUMMARY AND FUTURE PERSPECTIVES

We began this review by defining MDD and TRD as well as summarizing current theories on the pathophysiology of depression to provide an analytic framework for our discussion. Motivated by our understanding of their mechanisms for mediating altered states of arousal, we reviewed the use of ketamine, nitrous oxide, propofol, isoflurane, sevoflurane, dexmedetomidine, and xenon as anesthetic therapies for MDD and TRD. We summarized basic science and clinical studies demonstrating their antidepressant efficacy and potentially more favorable side effect profiles compared to current treatments. Finally, we presented neurophysiological frameworks for understanding the antidepressant effects of anesthetics, grounded in three theories of depression's pathophysiology.

The network dysfunction theory has been supported by noninvasive imaging studies showing altered levels of hypoconnectivity or hyperconnectivity within and between networks involved in depression pathophysiology in depressed patients following rTMS and DBS (Abbott et al. 2013, Liston et al. 2014). For example, rTMS is thought to affect neural circuits involved in emotional regulation (Schiena et al. 2021), whereas DBS has been hypothesized to work through limbic-cortical dysregulation (Mayberg 1997, Rolls 2021). Similar to these therapies, anesthetics also alter brain connectivity in ways that may shift the brain from a maladaptive state to a healthy state. Except for xenon, all the anesthetics we reviewed appear to alter functional connectivity related to depression pathophysiology during and possibly after exposure, thereby potentially normalizing previously dysfunctional networks (**Figure 1*e–i***). Future research should continue to investigate the connectivity changes mediated by anesthetics, both during and after administration.

These effects on functional connectivity may be related to pathway changes in BDNF signaling that promote neuroplasticity. Research has shown that BDNF serum levels of patients with MDD increased after ECT, rTMS, and anesthetic administration, likely promoting synaptic plasticity that changes abnormal functional connectivity (Lee & Kim 2010, Woelfer et al. 2020, Psomiades et al. 2022, Pan et al. 2023) (**Figure 1*c***). We have shown that ketamine, nitrous oxide, dexmedetomidine, and xenon may promote synaptic plasticity and normalize pathological connections through BDNF signaling.

GABA is the primary inhibitory neurotransmitter in the brain, and GABAergic neurons are involved in mood regulation and reward learning (Sarawagi et al. 2021) as well as learning, memory, and neuroplasticity (Möhler 2007). Decreased GABA levels seen in some depressed patients suggest an imbalance of inhibitory and excitatory systems in the brain. Replenished GABA levels may restore these systems and help alleviate depression. The GABA deficit hypothesis has been supported by the significant increase in serum GABA levels after ECT in patients with depression (Esel et al. 2008) and PFC GABA levels after rTMS in patients with MDD (Dubin et al. 2016).

Similarly, we found evidence that nitrous oxide, propofol, sevoflurane, and isoflurane support this hypothesis by enhancing GABA levels. However, these theories do not exclude the possibility of other mechanisms being identified through further research.

The common factor among all the anesthetics is that they change brain dynamics. We propose that the therapeutic actions of anesthetics in treating MDD and TRD could be due to their capacity to disrupt and help rewire brain networks. More in-depth studies are required to understand how anesthetics alter brain dynamics to provide treatments for MDD and TRD. These investigations may also offer insights into the mechanisms of other therapies such as ECT, rTMS, and DBS for treating depression. Anesthetics may also offer significant therapeutic options for treating other psychiatric disorders such as obsessive compulsive disorder, schizophrenia, and bipolar disorder (Martinotti et al. 2021, FDA 2022). Realizing this potential will require collaboration among anesthesiologists, psychiatrists, neuroscientists, neurologists, and neurosurgeons. As the therapeutic use of anesthetics becomes more prevalent, these treatments must be administered by clinicians who are properly trained and licensed. With continued research and careful clinical application, anesthetics hold great promise for treating MDD, TRD, and potentially other neuropsychiatric disorders.

DISCLOSURE STATEMENT

M.S.B., S.O., O.K., G.H.K., B.T., and E.N.B. have filed a patent on the use of anesthetics to treat depression. E.N.B. holds patents on anesthetic state monitoring and control, has founding interests in PASCALL SYSTEMS, and receives royalties from Massachusetts General Hospital (MGH) for intellectual property licensed to Masimo. Conflicts are managed by MGH, Mass General Brigham, and MIT.

ACKNOWLEDGMENTS

This work was generously supported by the JPB Foundation (E.N.B.), the Picower Institute for Learning and Memory (M.S.B. and E.N.B.), the Schmidt Science Fellowship (S.O.), George J. Elbaum, Mimi Jensen, Diane B. Greene, Mendel Rosenblum, Bill Swanson, Louis and Cathy Paglia, annual donors to the MIT/MGH Brain Arousal State Innovation Center, the Swiss National Science Foundation P500PM_210834 (D.R.S.), and National Institutes of Health awards P01 GM118269 (E.N.B.) and R01 NS123120 (E.N.B.). We apologize to researchers whose work could not be cited due to space limitations. Thank you to everyone who contributed to this review, especially Steven McGuigan for his insights on xenon, and the MGH team for their valuable anesthesia data.

LITERATURE CITED

Abbott CC, Lemke NT, Gopal S, Thoma RJ, Bustillo J, et al. 2013. Electroconvulsive therapy response in major depressive disorder: a pilot functional network connectivity resting state fMRI investigation. *Front. Psychiatry* 4:10

Abdallah CG, Averill LA, Collins KA, Geha P, Schwartz J, et al. 2017. Ketamine treatment and global brain connectivity in major depression. *Neuropsychopharmacology* 42(6):1210–19

Adam E, Kowalski M, Akeju O, Miller EK, Brown EN, et al. 2024. Ketamine can produce oscillatory dynamics by engaging mechanisms dependent on the kinetics of NMDA receptors. *PNAS* 121(22):e2402732121

Adam E, Kwon O, Montejo KA, Brown EN. 2023. Modulatory dynamics mark the transition between anesthetic states of unconsciousness. *PNAS* 120(30):e2300058120

Akeju O, Hobbs LE, Gao L, Burns SM, Pavone KJ, et al. 2018. Dexmedetomidine promotes biomimetic non-rapid eye movement stage 3 sleep in humans: a pilot study. *Clin. Neurophysiol.* 129(1):69–78

Akeju O, Loggia ML, Catana C, Pavone KJ, Vazquez R, et al. 2014a. Disruption of thalamic functional connectivity is a neural correlate of dexmedetomidine-induced unconsciousness. *eLife* 3:e04499

Akeju O, Song AH, Hamilos AE, Pavone KJ, Flores FJ, et al. 2016. Electroencephalogram signatures of ketamine anesthesia-induced unconsciousness. *Clin. Neurophysiol.* 127(6):2414–22

Akeju O, Westover MB, Pavone KJ, Sampson AL, Hartnack KE, et al. 2014b. Effects of sevoflurane and propofol on frontal electroencephalogram power and coherence. *Anesthesiology* 121(5):990–98

Alexander L, Hawkins PC, Evans JW, Mehta MA, Zarate CA Jr. 2023. Preliminary evidence that ketamine alters anterior cingulate resting-state functional connectivity in depressed individuals. *Transl. Psychiatry* 13(1):371

Am. Psychiatr. Assoc. 2013. *Diagnostic and Statistical Manual of Mental Disorders*. Washington, DC: Am. Psychiatr. Assoc. 5th ed.

Autry AE, Adachi M, Nosyreva E, Na ES, Los MF, et al. 2011. NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. *Nature* 475(7354):91–95

Bair MJ, Robinson RL, Katon W, Kroenke K. 2003. Depression and pain comorbidity: a literature review. *Arch. Intern. Med.* 163(20):2433–45

Bari A, Niu T, Langevin JP, Fried I. 2014. Limbic neuromodulation: implications for addiction, posttraumatic stress disorder, and memory. *Neurosurg. Clin.* 25(1):137–45

Bastos AM, Donoghue JA, Brincat SL, Mahnke M, Yanar J, et al. 2021. Neural effects of propofol-induced unconsciousness and its reversal using thalamic stimulation. *eLife* 10:e60824

Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, et al. 2000. Antidepressant effects of ketamine in depressed patients. *Biol. Psychiatry* 47(4):351–54

First study to use ketamine to treat MDD.

Bloomfield A, Chan N, Fryml L, Horace R, Pyati S. 2023. Ketamine for chronic pain and mental health: regulations, legalities, and the growth of infusion clinics. *Curr. Pain Headache Rep.* 27(10):579–85

Brechmann T, Maier C, Kaisler M, Vollert J, Schmiegel W, et al. 2018. Propofol sedation during gastrointestinal endoscopy arouses euphoria in a large subset of patients. *United Eur. Gastroenterol. J.* 6(4):536–46

Brown EN, Lydic R, Schiff ND. 2010. General anesthesia, sleep, and coma. *N. Engl. J. Med.* 363(27):2638–50

Brown EN, Pavone KJ, Naranjo M. 2018. Multimodal general anesthesia: theory and practice. *Anesth. Analg.* 127(5):1246–58

Castrén E, Kojima M. 2017. Brain-derived neurotrophic factor in mood disorders and antidepressant treatments. *Neurobiol. Dis.* 97:119–26

Cavalleri L, Pich EM, Millan M, Chiamulera C, Kunath T, et al. 2018. Ketamine enhances structural plasticity in mouse mesencephalic and human iPSC-derived dopaminergic neurons via AMPAR-driven BDNF and mTOR signaling. *Mol. Psychiatry* 23(4):812–23

Cha J, Choi KS, Rajendra JK, McGrath CL, Riva-Posse P, et al. 2024. Whole brain network effects of subcallosal cingulate deep brain stimulation for treatment-resistant depression. *Mol. Psychiatry* 29(1):112–20

Chen G, Fu Q, Cao J, Mi W. 2012. Effect of propofol on brain-derived neurotrophic factor and tyrosine kinase receptor B in the hippocampus of aged rats with chronic cerebral ischemia. *Neural Regen. Res.* 7(21):1645–49

Chen MH, Lin WC, Tu PC, Li CT, Bai YM, et al. 2019. Antidepressant and antisuicidal effects of ketamine on the functional connectivity of prefrontal cortex-related circuits in treatment-resistant depression: a double-blind, placebo-controlled, randomized, longitudinal resting fMRI study. *J. Affect. Disord.* 259:15–20

Ching S, Cimenser A, Purdon PL, Brown EN, Kopell NJ. 2010. Thalamocortical model for a propofol-induced α-rhythm associated with loss of consciousness. *PNAS* 107(52):22665–70

Cornwell BR, Salvadore G, Furey M, Marquardt CA, Brutsche NE, et al. 2012. Synaptic potentiation is critical for rapid antidepressant response to ketamine in treatment-resistant major depression. *Biol. Psychiatry* 72(7):555–61

Dai R, Huang Z, Larkin TE, Tarnal V, Picton P, et al. 2023. Psychedelic concentrations of nitrous oxide reduce functional differentiation in frontoparietal and somatomotor cortical networks. *Commun. Biol.* 6(1):1284

Dandekar MP, Peng T, McPherson DD, Quevedo J, Soares JC, Huang SL. 2018. Intravenous infusion of xenon-containing liposomes generates rapid antidepressant-like effects. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 86:140–49

Dehbozorgi M, Fereidooni F, Bozorgmehr R, Bagherpour JZ, Shafiee A, et al. 2024. Dexmedetomidine administration as a possible cognitive enhancer through increasing the level of brain-derived neurotrophic factors in surgical patients: a systematic review and meta-analysis. *BMC Anesthesiol*. 24(1):256

Desmidt T, Dujardin PA, Andersson F, Brizard B, Remeniéras JP, et al. 2023. Changes in cerebral connectivity and brain tissue pulsations with the antidepressant response to an equimolar mixture of oxygen and nitrous oxide: an MRI and ultrasound study. *Mol. Psychiatry* 28(9):3900–8

Dobrovolsky A, Ichim TE, Ma D, Kesari S, Bogin V. 2017. Xenon in the treatment of panic disorder: an open label study. *J. Transl. Med.* 15:137

Domino EF, Warner DS. 2010. Taming the ketamine tiger. *J. Am. Soc. Anesthesiol.* 113(3):678–84

Dubin MJ, Mao X, Banerjee S, Goodman Z, Lapidus KA, et al. 2016. Elevated prefrontal cortex GABA in patients with major depressive disorder after TMS treatment measured with proton magnetic resonance spectroscopy. *J. Psychiatry Neurosci.* 41(3):E37–45

Duman RS, Deyama S, Fogaça MV. 2021. Role of BDNF in the pathophysiology and treatment of depression: Activity-dependent effects distinguish rapid-acting antidepressants. *Eur. J. Neurosci.* 53(1):126–39

Emmanouil DE, Quock RM. 2007. Advances in understanding the actions of nitrous oxide. *Anesthes. Prog.* 54(1):9–18

Esel E, Kose K, Hacimusalar Y, Ozsoy S, Kula M, et al. 2008. The effects of electroconvulsive therapy on GABAergic function in major depressive patients. *J. ECT* 24(3):224–28

FDA (US Food Drug Adm.). 2020. SPRAVATO® (esketamine) nasal spray, CIII. **https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/211243s004lbl.pdf**

FDA (US Food Drug Adm.). 2022. IGALMI™ (dexmedetomidine) sublingual film, for sublingual or buccal use. **https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021038s021lbl.pdf**

Fries P. 2009. Neuronal gamma-band synchronization as a fundamental process in cortical computation. *Annu. Rev. Neurosci.* 32:209–24

Fukumoto T, Morinobu S, Okamoto Y, Kagaya A, Yamawaki S. 2001. Chronic lithium treatment increases the expression of brain-derived neurotrophic factor in the rat brain. *Psychopharmacology* 158:100–6

García-Toro M, Segura C, González A, Perelló J, Valdivia J, et al. 2001. Inefficacy of burst-suppression anesthesia in medication-resistant major depression: a controlled trial. *J. ECT* 17(4):284–88

Gärtner M, Aust S, Bajbouj M, Fan Y, Wingenfeld K, et al. 2019. Functional connectivity between prefrontal cortex and subgenual cingulate predicts antidepressant effects of ketamine. *Eur. Neuropsychopharmacol.* 29(4):501–8

Garwood IC, Chakravarty S, Donoghue J, Mahnke M, Kahali P, et al. 2021. A hidden Markov model reliably characterizes ketamine-induced spectral dynamics in macaque local field potentials and human electroencephalograms. *PLOS Comput. Biol.* 17(8):e1009280

Gillman M. 1986. Nitrous oxide, an opioid addictive agent: review of the evidence. *Am. J. Med.* 81(1):97–102

Goldschmied JR, Gehrman P. 2019. An integrated model of slow-wave activity and neuroplasticity impairments in major depressive disorder. *Curr. Psychiatry Rep.* 21:30

Goldstein E, Palermo E, Costello S, Games M, Goldschmied J. 2022. The impact of slow-wave sleep disruption on response inhibition in individuals with depression. *SLEEP* 45(Suppl. 1):A288

Golkowski D, Larroque SK, Vanhaudenhuyse A, Plenevaux A, Boly M, et al. 2019. Changes in whole brain dynamics and connectivity patterns during sevoflurane-and propofol-induced unconsciousness identified by functional magnetic resonance imaging. *Anesthesiology* 130(6):898–911

Gollan JK, Hoxha D, Chihade D, Pflieger ME, Rosebrock L, Cacioppo J. 2014. Frontal alpha EEG asymmetry before and after behavioral activation treatment for depression. *Biol. Psychol.* 99:198–208

Gorman JM. 1996. Comorbid depression and anxiety spectrum disorders. *Depress. Anxiety* 4(4):160–68

Greenberg LB, Gage J, Vitkun S, Fink M. 1987. Isoflurane anesthesia therapy: a replacement for ECT in depressive disorders? *J. ECT* 3(4):269–77

Greenberg PE, Fournier AA, Sisitsky T, Simes M, Berman R, et al. 2021. The economic burden of adults with major depressive disorder in the United States (2010 and 2018). *Pharmacoeconomics* 39(6):653–65

Guimarães MC, Guimarães TM, Hallak JE, Abrão J, Machado-de Sousa JP. 2021. Nitrous oxide as an adjunctive therapy in major depressive disorder: a randomized controlled double-blind pilot trial. *Braz. J. Psychiatry* 43(5):484–93

Guldenmund P, Vanhaudenhuyse A, Sanders R, Sleigh J, Bruno MA, et al. 2017. Brain functional connectivity differentiates dexmedetomidine from propofol and natural sleep. *Br. J. Anaesth.* 119(4):674–84

Heikman P, Salmelin R, Mäkelä JP, Hari R, Katila H, Kuoppasalmi K. 2001. Relation between frontal 3–7 Hz MEG activity and the efficacy of ECT in major depression. *J. ECT* 17(2):136–40

Hindriks R, van Putten MJ. 2012. Meanfield modeling of propofol-induced changes in spontaneous EEG rhythms. *NeuroImage* 60(4):2323–34

Hu Y, Zhao C, Zhao H, Qiao J. 2023. Abnormal functional connectivity of the nucleus accumbens subregions mediates the association between anhedonia and major depressive disorder. *BMC Psychiatry* 23(1):282

Huang Y, Morozov A. 2011. Hippocampal deletion of BDNF gene attenuates gamma oscillations in area CA1 by up-regulating 5-HT3 receptor. *PLOS ONE* 6(1):e16480

Izumi Y, Hsu FF, Conway CR, Nagele P, Mennerick SJ, Zorumski CF. 2022. Nitrous oxide, a rapid antidepressant, has ketamine-like effects on excitatory transmission in the adult hippocampus. *Biol. Psychiatry* 92(12):964–72

Jiang H, Popov T, Jylänki P, Bi K, Yao Z, et al. 2016. Predictability of depression severity based on posterior alpha oscillations. *Clin. Neurophysiol.* 127(4):2108–14

Jiang J, Zhao Y, Liu J, Yang Y, Liang P, et al. 2022. Signatures of thalamocortical alpha oscillations and synchronization with increased anesthetic depths under isoflurane. *Front. Pharmacol.* 13:887981

Jin YH, Zhang Z, Mendelowitz D, Andresen MC. 2009. Presynaptic actions of propofol enhance inhibitory synaptic transmission in isolated solitary tract nucleus neurons. *Brain Res.* 1286:75–83

Jourdi H, Hsu YT, Zhou M, Qin Q, Bi X, Baudry M. 2009. Positive AMPA receptor modulation rapidly stimulates BDNF release and increases dendritic mRNA translation. *J. Neurosci.* 29(27):8688–97

Kafashan M, Hickman LB, Labonte AK, Huels ER, Maybrier H, et al. 2022. Quiescence during burst suppression and postictal generalized EEG suppression are distinct patterns of activity. *Clin. Neurophysiol.* 142:125–32

Kaiser RH, Andrews-Hanna JR, Wager TD, Pizzagalli DA. 2015. Large-scale network dysfunction in major depressive disorder: a meta-analysis of resting-state functional connectivity. *JAMA Psychiatry* 72(6):603–11

Kalsi SS, Wood DM, Dargan PI. 2011. The epidemiology and patterns of acute and chronic toxicity associated with recreational ketamine use. *Emerg. Health Threats J.* 4(1):7107

Kishikawa J-i, Inoue Y, Fujikawa M, Nishimura K, Nakanishi A, et al. 2018. General anesthetics cause mitochondrial dysfunction and reduction of intracellular ATP levels. *PLOS ONE* 13(1):e0190213

Kohtala S, Theilmann W, Rosenholm M, Penna L, Karabulut G, et al. 2019. Cortical excitability and activation of TrkB signaling during rebound slow oscillations are critical for rapid antidepressant responses. *Mol. Neurobiol.* 56:4163–74

Kopschina Feltes P, Doorduin J, Klein HC, Juárez-Orozco LE, Dierckx RA, et al. 2017. Anti-inflammatory treatment for major depressive disorder: implications for patients with an elevated immune profile and non-responders to standard antidepressant therapy. *J. Psychopharmacol.* 31(9):1149–65

Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, et al. 1994. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans: psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch. Gen. Psychiatry* 51(3):199–214

Ladha KS, Lee J, Mattina GF, Pazmino-Canizares J, Wijeysundera DN, et al. 2024. Sustained Mood Improvement with Laughing Gas Exposure (SMILE): study protocol for a randomized placebo-controlled pilot trial of nitrous oxide for treatment-resistant depression. *PLOS ONE* 19(1):e0297330

Langer G, Neumark J, Koinig G, Graf M, Schönbeck G. 1985. Rapid psychotherapeutic effects of anesthesia with isoflurane (ES narcotherapy) in treatment-refractory depressed patients. *Neuropsychobiology* 14(3):118–20

First study to use an anesthetic to treat TRD; in this case, they used isoflurane.

Larsen M, Haugstad T, Berg-Johnsen J, Langmoen I. 1998. Effect of isoflurane on release and uptake of γ-aminobutyric acid from rat cortical synaptosomes. *Br. J. Anaesth.* 80(5):634–38

Law LS-C, Lo EA-G, Gan TJ. 2016. Xenon anesthesia: a systematic review and meta-analysis of randomized controlled trials. *Anesth. Analg.* 122(3):678–97

Lee BH, Kim YK. 2010. The roles of BDNF in the pathophysiology of major depression and in antidepressant treatment. *Psychiatry Investig*. 7(4):231–35

Lehmann H, Bos C. 1947. The advantages of nitrous oxide inhalation in psychiatric treatment. *Am. J. Psychiatry* 104(3):164–70

Li B, Li Y, Tian S, Wang H, Wu H, et al. 2015. Anti-inflammatory effects of perioperative dexmedetomidine administered as an adjunct to general anesthesia: a meta-analysis. *Sci. Rep.* 5(1):12342

Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, et al. 2010. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science* 329(5994):959–64

Liachenko S, Tang P, Somogyi GT, Xu Y. 1999. Concentration-dependent isoflurane effects on depolarization-evoked glutamate and GABA outflows from mouse brain slices. *Br. J. Pharmacol.* 127(1):131–38

Liston C, Chen AC, Zebley BD, Drysdale AT, Gordon R, et al. 2014. Default mode network mechanisms of transcranial magnetic stimulation in depression. *Biol. Psychiatry* 76(7):517–26

Liu J, Zhao X, Wei X, Yan D, Ou W, et al. 2023. Empirical evidence for the neurocognitive effect of nitrous oxide as an adjunctive therapy in patients with treatment resistant depression: a randomized controlled study. *Psychiatry Res.* 326:115326

Liu W, Li Q, Ye B, Cao H, Shen F, et al. 2020. Repeated nitrous oxide exposure exerts antidepressant-like effects through neuronal nitric oxide synthase activation in the medial prefrontal cortex. *Front. Psychiatry* 11:837

Liu X, Liu S, Li M, Su F, Chen S, et al. 2022. Altered gamma oscillations and beta–gamma coupling in drug-naive first-episode major depressive disorder: association with sleep and cognitive disturbance. *J. Affect. Disord.* 316:99–108

First study to use dexmedetomidine to treat TRD.

Liu Y, Hu Q, Xu S, Li W, Liu J, et al. 2024. Antidepressant effects of dexmedetomidine compared with ECT in patients with treatment-resistant depression. *J. Affect. Disord.* 347:437–44

Luscher B, Shen Q, Sahir N. 2011. The GABAergic deficit hypothesis of major depressive disorder. *Mol. Psychiatry* 16(4):383–406

Marek S, Dosenbach NU. 2018. The frontoparietal network: function, electrophysiology, and importance of individual precision mapping. *Dialogues Clin. Neurosci.* 20(2):133–40

Martinotti G, Chiappini S, Pettorruso M, Mosca A, Miuli A, et al. 2021. Therapeutic potentials of ketamine and esketamine in obsessive–compulsive disorder (OCD), substance use disorders (SUD) and eating disorders (ED): a review of the current literature. *Brain Sci.* 11(7):856

Mayberg HS. 1997. Limbic-cortical dysregulation: a proposed model of depression. *J. Neuropsychiatry Clin. Neurosci.* 9(3):471–81

McGuigan S, Evered L, Silbert B, Scott DA, Cormack JR, et al. 2021. Comparison of the spectral features of the frontal electroencephalogram in patients receiving xenon and sevoflurane general anesthesia. *Anesth. Analg.* 133(5):1269–79

McGuigan S, Marie DJ, O'Bryan LJ, Flores FJ, Evered L, et al. 2023. The cellular mechanisms associated with the anesthetic and neuroprotective properties of xenon: a systematic review of the preclinical literature. *Front. Neurosci.* 17:1225191

First study to use propofol to treat TRD.

Mickey BJ, White AT, Arp AM, Leonardi K, Torres MM, et al. 2018. Propofol for treatment-resistant depression: a pilot study. *Int. J. Neuropsychopharmacol.* 21(12):1079–89

Moda-Sava R, Murdock M, Parekh P, Fetcho R, Huang B, et al. 2019. Sustained rescue of prefrontal circuit dysfunction by antidepressant-induced spine formation. *Science* 364(6436):eaat8078

Möhler H. 2007. Molecular regulation of cognitive functions and developmental plasticity: impact of $GABA_A$ receptors. *J. Neurochem.* 102(1):1–12

Moncrieff J, Cooper RE, Stockmann T, Amendola S, Hengartner MP, Horowitz MA. 2023. The serotonin theory of depression: a systematic umbrella review of the evidence. *Mol. Psychiatry* 28(8):3243–56

Monteggia LM, Barrot M, Powell CM, Berton O, Galanis V, et al. 2004. Essential role of brain-derived neurotrophic factor in adult hippocampal function. *PNAS* 101(29):10827–32

Moulier V, Guehl J, Evêque-Mourroux E, Quesada P, Rothärmel M. 2022. A retrospective study of postictal suppression during electroconvulsive therapy. *J. Clin. Med.* 11(5):1440

Murakawa M, Adachi T, Nakao Si, Seo N, Shingu K, Mori K. 1994. Activation of the cortical and medullary dopaminergic systems by nitrous oxide in rats: a possible neurochemical basis for psychotropic effects and postanesthetic nausea and vomiting. *Anesth. Analg.* 78(2):376–81

Naaz S, Ozair E. 2014. Dexmedetomidine in current anaesthesia practice—a review. *J. Clin. Diagn. Res.* 8(10):GE01–4

Nagashima K, Zorumski CF, Izumi Y. 2005. Nitrous oxide (laughing gas) facilitates excitability in rat hippocampal slices through γ-aminobutyric acid A receptor-mediated disinhibition. *J. Am. Soc. Anesthesiol.* 102(1):230–34

Nagele P, Duma A, Kopec M, Gebara MA, Parsoei A, et al. 2015. Nitrous oxide for treatment-resistant major depression: a proof-of-concept trial. *Biol. Psychiatry* 78(1):10–18

First study to use nitrous oxide to treat TRD.

Nagele P, Palanca BJ, Gott B, Brown F, Barnes L, et al. 2021. A phase 2 trial of inhaled nitrous oxide for treatment-resistant major depression. *Sci. Transl. Med.* 13(597):eabe1376

Neice A, Zornow M. 2016. Xenon anaesthesia for all, or only a select few? *Anaesthesia* 71(11):1267–72

Noda Y, Nakamura M, Saeki T, Inoue M, Iwanari H, Kasai K. 2013. Potentiation of quantitative electroencephalograms following prefrontal repetitive transcranial magnetic stimulation in patients with major depression. *Neurosci. Res.* 77(1–2):70–77

Northoff G, Koch A, Wenke J, Eckert J, Böker H, et al. 1999. Catatonia as a psychomotor syndrome: a rating scale and extrapyramidal motor symptoms. *Mov. Disord.* 14(3):404–16

Nugent AC, Ballard ED, Gould TD, Park LT, Moaddel R, et al. 2019. Ketamine has distinct electrophysiological and behavioral effects in depressed and healthy subjects. *Mol. Psychiatry* 24(7):1040–52

Pain L, Gobaille S, Schleef C, Aunis D, Oberling P. 2002. In vivo dopamine measurements in the nucleus accumbens after nonanesthetic and anesthetic doses of propofol in rats. *Anesth. Analg.* 95(4):915–19

Palanca BJA, Conway CR, Zeffiro T, Gott BM, Nguyen T, et al. 2023. Persistent brain connectivity changes in healthy volunteers following nitrous oxide inhalation. *Biol. Psychiatry Glob. Open Sci.* 3(4):698–704

Pan F, Mou T, Shao J, Chen H, Tao S, et al. 2023. Effects of neuronavigation-guided rTMS on serum BDNF, TrkB and VGF levels in depressive patients with suicidal ideation. *J. Affect. Disord.* 323:617–23

Pavone KJ, Akeju O, Sampson AL, Ling K, Purdon PL, Brown EN. 2016. Nitrous oxide-induced slow and delta oscillations. *Clin. Neurophysiol.* 127(1):556–64

Peng T, Britton GL, Kim H, Cattano D, Aronowski J, et al. 2013. Therapeutic time window and dose dependence of xenon delivered via echogenic liposomes for neuroprotection in stroke. *CNS Neurosci. Ther.* 19(10):773–84

Psomiades M, Mondino M, Galvão F, Mandairon N, Nourredine M, et al. 2022. Serum mature BDNF level is associated with remission following ECT in treatment-resistant depression. *Brain Sci.* 12(2):126

Purdon PL, Pierce ET, Mukamel EA, Prerau MJ, Walsh JL, et al. 2013. Electroencephalogram signatures of loss and recovery of consciousness from propofol. *PNAS* 110(12):E1142–51

Purdon PL, Sampson A, Pavone KJ, Brown EN. 2015. Clinical electroencephalography for anesthesiologists: Part I: background and basic signatures. *Anesthesiology* 123(4):937–60

Rafiq M, Mahmood Z, Ali S, Pain L. 2018. Effect of minor surgery under propofol anaesthesia on brain BDNF and cognition. *Pak. J. Neurol. Sci.* 13(1):6–9

Raichle ME. 2015. The brain's default mode network. *Annu. Rev. Neurosci.* 38:433–47

Rajkowska G, O'Dwyer G, Teleki Z, Stockmeier CA, Miguel-Hidalgo JJ. 2007. GABAergic neurons immunoreactive for calcium binding proteins are reduced in the prefrontal cortex in major depression. *Neuropsychopharmacology* 32(2):471–82

Ranft A, Golkowski D, Kiel T, Riedl V, Kohl P, et al. 2016. Neural correlates of sevoflurane-induced unconsciousness identified by simultaneous functional magnetic resonance imaging and electroencephalography. *Anesthesiology* 125(5):861–72

Regenold WT, Noorani RJ, Piez D, Patel P. 2015. Nonconvulsive electrotherapy for treatment resistant unipolar and bipolar major depressive disorder: a proof-of-concept trial. *Brain Stimul.* 8(5):855–61

Rios RL, Kafashan M, Hyche O, Lenard E, Lucey BP, et al. 2023. Targeting slow wave sleep deficiency in late-life depression: a case series with propofol. *Am. J. Geriatr. Psychiatry* 31(8):643–52

Rodríguez-Ramírez AM, Cedillo-Ríos V, Sanabrais-Jiménez MA, Becerra-Palars C, Hernández-Muñoz S, et al. 2024. Association of BDNF risk variant and dorsolateral cortical thickness with long-term treatment

response to valproate in type I bipolar disorder: an exploratory study. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 195(3):e32966

Rolls ET. 2021. Attractor cortical neurodynamics, schizophrenia, and depression. *Transl. Psychiatry* 11(1):215

Rosenberg G. 2007. The mechanisms of action of valproate in neuropsychiatric disorders: Can we see the forest for the trees? *Cell. Mol. Life Sci.* 64(16):2090–103

Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, et al. 2006. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am. J. Psychiatry* 163(11):1905–17

Saletu B, Anderer P, Saletu-Zyhlarz G. 2010. EEG topography and tomography (LORETA) in diagnosis and pharmacotherapy of depression. *Clin. EEG Neurosci.* 41(4):203–10

SAMHSA (Subst. Abuse Ment. Health Serv. Adm.). 2023. *2023 National survey on drug use and health (NSDUH) releases*. Rep., SAMSHA, Rockville, MD

Sanders RD, Ma D, Maze M. 2005. Xenon: elemental anaesthesia in clinical practice. *Br. Med. Bull.* 71(1):115–35

Santomauro DF, Mantilla Herrera AM, Shadid J, Zheng P, Ashbaugh C, et al. 2021. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. *Lancet* 398(10312):1700–12

Sarawagi A, Soni ND, Patel AB. 2021. Glutamate and GABA homeostasis and neurometabolism in major depressive disorder. *Front. Psychiatry* 12:637863

Scheeringa R, Bastiaansen MC, Petersson KM, Oostenveld R, Norris DG, Hagoort P. 2008. Frontal theta EEG activity correlates negatively with the default mode network in resting state. *Int. J. Psychophysiol.* 67(3):242–51

Schiena G, Franco G, Boscutti A, Delvecchio G, Maggioni E, Brambilla P. 2021. Connectivity changes in major depressive disorder after rTMS: a review of functional and structural connectivity data. *Epidemiol. Psychiatr. Sci.* 30:e59

Shanechi MM, Chemali JJ, Liberman M, Solt K, Brown EN. 2013. A brain-machine interface for control of medically-induced coma. *PLOS Comput. Biol.* 9(10):e1003284

Shao J, Meng L, Yang Z, Yu P, Song L, et al. 2020. Xenon produces rapid antidepressant- and anxiolytic-like effects in lipopolysaccharide-induced depression mice model. *NeuroReport* 31(5):387–93

Siegel JS, Palanca BJ, Ances BM, Kharasch ED, Schweiger JA, et al. 2021. Prolonged ketamine infusion modulates limbic connectivity and induces sustained remission of treatment-resistant depression. *Psychopharmacology* 238:1157–69

Sridharan D, Levitin DJ, Menon V. 2008. A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *PNAS* 105(34):12569–74

Stenroos P, Pirttimäki T, Paasonen J, Paasonen E, Salo RA, et al. 2021. Isoflurane affects brain functional connectivity in rats 1 month after exposure. *NeuroImage* 234:117987

Sun Z, Jia L, Shi D, He Y, Ren Y, et al. 2022. Deep brain stimulation improved depressive-like behaviors and hippocampal synapse deficits by activating the BDNF/mTOR signaling pathway. *Behav. Brain Res.* 419:113709

Tadler SC, Jones KG, Lybbert C, Huang JC, Jawish R, et al. 2023. Propofol for treatment resistant depression: a randomized controlled trial. medRxiv 2023.09.12.23294678. **https://doi.org/10.1101/2023.09.12.23294678**

Tadler SC, Mickey BJ. 2018. Emerging evidence for antidepressant actions of anesthetic agents. *Curr. Opin. Anesthesiol.* 31(4):439–45

Tian F, Lewis LD, Zhou DW, Balanza GA, Paulk AC, et al. 2023. Characterizing brain dynamics during ketamine-induced dissociation and subsequent interactions with propofol using human intracranial neurophysiology. *Nat. Commun.* 14(1):1748

Tononi G, Cirelli C. 2003. Sleep and synaptic homeostasis: a hypothesis. *Brain Res. Bull.* 62(2):143–50

Tu Y, Liang Y, Xiao Y, Lv J, Guan R, et al. 2019. Dexmedetomidine attenuates the neurotoxicity of propofol toward primary hippocampal neurons in vitro via Erk1/2/CREB/BDNF signaling pathways. *Drug Des. Dev. Ther.* 13:695–706

Vasavada MM, Loureiro J, Kubicki A, Sahib A, Wade B, et al. 2021. Effects of serial ketamine infusions on corticolimbic functional connectivity in major depression. *Biol. Psychiatry Cogn. Neurosci. Neuroimaging* 6(7):735–44

Vida RG, Sághy E, Bella R, Kovács S, Erdősi D, et al. 2023. Efficacy of repetitive transcranial magnetic stimulation (rTMS) adjunctive therapy for major depressive disorder (MDD) after two antidepressant treatment failures: meta-analysis of randomized sham-controlled trials. *BMC Psychiatry* 23(1):545

Wang J, Liu Q, Tian F, Zhou S, Parra MA, et al. 2022. Disrupted spatiotemporal complexity of resting-state electroencephalogram dynamics is associated with adaptive and maladaptive rumination in major depressive disorder. *Front. Neurosci.* 16:829755

Weeks HR III, Tadler SC, Smith KW, Iacob E, Saccoman M, et al. 2013. Antidepressant and neurocognitive effects of isoflurane anesthesia versus electroconvulsive therapy in refractory depression. *PLOS ONE* 8(7):e69809

Wei Q, Ji Y, Bai T, Zu M, Guo Y, et al. 2021. Enhanced cerebro-cerebellar functional connectivity reverses cognitive impairment following electroconvulsive therapy in major depressive disorder. *Brain Imaging Behav*. 15:798–806

Weiner VS, Zhou DW, Kahali P, Stephen EP, Peterfreund RA, et al. 2023. Propofol disrupts alpha dynamics in functionally distinct thalamocortical networks during loss of consciousness. *PNAS* 120(11):e2207831120

WHO (World Health Organ.). 2023. *The selection and use of essential medicines 2023. Executive Summary of the report of the 24th WHO Expert Committee on Selection and Use of Essential Medicines*. Exec. Summ. WHO, Geneva. **https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.01**

Wilkinson ST, Ballard ED, Bloch MH, Mathew SJ, Murrough JW, et al. 2018. The effect of a single dose of intravenous ketamine on suicidal ideation: a systematic review and individual participant data meta-analysis. *Am. J. Psychiatry* 175(2):150–58

Williams NR, Heifets BD, Blasey C, Sudheimer K, Pannu J, et al. 2018. Attenuation of antidepressant effects of ketamine by opioid receptor antagonism. *Am. J. Psychiatry* 175(12):1205–15

Woelfer M, Li M, Colic L, Liebe T, Di X, et al. 2020. Ketamine-induced changes in plasma brain-derived neurotrophic factor (BDNF) levels are associated with the resting-state functional connectivity of the prefrontal cortex. *World J. Biol. Psychiatry* 21(9):696–710

Xu S, Zhao X, Zhu Z, He M, Zheng X, Zhang X. 2022. A new potential antidepressant: Dexmedetomidine alleviates neuropathic pain-induced depression by increasing neurogenesis in the hippocampus. *Pharmacology* 107(5–6):317–29

Yu HY, Wang SY, Quan CX, Fang C, Luo SC, et al. 2019. Dexmedetomidine alleviates postpartum depressive symptoms following cesarean section in Chinese women: a randomized placebo-controlled study. *Pharmacotherapy* 39(10):994–1004

Zanos P, Moaddel R, Morris PJ, Georgiou P, Fischell J, et al. 2016. NMDAR inhibition-independent antidepressant actions of ketamine metabolites. *Nature* 533(7604):481–86

Zarate CA Jr., Machado-Vieira R. 2015. Potential pathways involved in the rapid antidepressant effects of nitrous oxide. *Biol. Psychiatry* 78(1):2

Zarate CA Jr., Singh JB, Carlson PJ, Brutsche NE, Ameli R, et al. 2006. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch. Gen. Psychiatry* 63(8):856–64

Largest study to use ketamine to treat TRD.

Zeilhofer HU, Swandulla D, Geisslinger G, Brune K. 1992. Differential effects of ketamine enantiomers on NMDA receptor currents in cultured neurons. *Eur. J. Pharmacol.* 213(1):155–58

Zheng K, An JJ, Yang F, Xu W, Xu ZQD, et al. 2011. TrkB signaling in parvalbumin-positive interneurons is critical for gamma-band network synchronization in hippocampus. *PNAS* 108(41):17201–6

Zhou Y, Bai Z, Zhang W, Xu S, Feng Y, et al. 2024. Effect of dexmedetomidine on postpartum depression in women with prenatal depression: a randomized clinical trial. *JAMA Netw. Open* 7(1):e2353252

Zhu XN, Li J, Qiu GL, Wang L, Lu C, et al. 2023. Propofol exerts anti-anhedonia effects via inhibiting the dopamine transporter. *Neuron* 111(10):1626–36

Zorumski CF, Nagele P, Mennerick S, Conway CR. 2015. Treatment-resistant major depression: rationale for NMDA receptors as targets and nitrous oxide as therapy. *Front. Psychiatry* 6:172

RELATED RESOURCES

Al-Mahrouqi T, Al Alawi M, Freire RC. 2023. Dexmedetomidine in the treatment of depression: An up-to-date narrative review. *Clin. Pract. Epidemiol. Ment. Health* 19:e174501792307240

Krystal JH, Kavalali ET, Monteggia LM. 2024. Ketamine and rapid antidepressant action: new treatments and novel synaptic signaling mechanisms. *Neuropsychopharmacology* 49(1):41–50

Sheth SA, Mayberg HS. 2023. Deep brain stimulation for obsessive-compulsive disorder and depression. *Annu. Rev. Neurosci.* 46:341–58