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Xenon as an Alternative to Antidepressants in the Therapy of Post-Traumatic Stress Disorder

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Keywords

Antidepressive agents; neuroprotective agents; receptors, n-methyl-d-aspartate; stress disorders, post-traumatic; xenon

Abstract

Aim: To explore recent studies and synthesize current knowledge to use xenon gas as a potential treatment for post-traumatic stress disorder (PTSD). **Materials and Methods:** For this non-systematic narrative review, we searched PubMed, Scopus and Google Scholar for peer-reviewed studies on xenon's potential for PTSD. **Results:** Xenon's main mechanism of action appears to be N-methyl-D-aspartate receptor blockade. Through this mechanism, xenon exhibits neuroprotective, antidepressant, and anxiolytic effects, and it may also influence memory reconsolidation. In animal studies, xenon reduced the types of brain and behavior changes observed after trauma. Moreover, unlike some other drugs that targeting the same receptors (e.g., ketamine), xenon does not appear to cause serious side effects. **Conclusion:** Preliminary evidence suggests that xenon may be a safe and effective treatment for PTSD. Further studies are needed to confirm its efficacy and safety.

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Introduction

Post-traumatic stress disorder (PTSD) is a mental health condition that develops after a person experiences or witnesses a traumatic event [1]. Even though there are different ways to treat it, getting a handle on PTSD is still a real challenge for doctors and patients alike. Currently, selective serotonin reuptake inhibitors (SSRIs), such as sertraline and paroxetine, are the mainstain medications and the only drugs approved by the U.S. Food and Drug Administration for treatment of PTSD [2]. However, SSRIs, unfortunately, are not always effective. Studies show that only about 60 % of people with PTSD see any improvement with SSRIs, and just 20–30 % actually get full relief from their symptoms [3]. The mechanism of action of SSRIs is cumulative and delayed. And then there are the side effects – things like nausea, dizziness, sexual issues, and trouble sleeping – that can make it hard for people to stick with the treatment. Therefore, there's a real incentive to find new or additional treatments that work faster, hit harder, and come with fewer downsides. One option that's starting to get attention is xenon gas, which has shown some promise in early lab studies. Early results suggest xenon – a noble gas with calming, anesthetic, and brain-protecting effects – might be useful for PTSD. It works mainly by blocking N-methyl-D-aspartate (NMDA) receptors, which researchers think could be a key target for tackling PTSD

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symptoms. The aim of this review is to explore recent studies and synthesize current knowledge to use xenon gas as a potential treatment for PTSD.

For this non-systematic narrative review, we searched PubMed, Scopus and Google Scholar for peer-reviewed studies on xenon's potential for PTSD. The focus was on research exploring how xenon works pharmacologically, its mechanisms (like NMDA receptor antagonism) that might help with PTSD, and its use in models of trauma-related conditions.

Mechanism of action of xenon

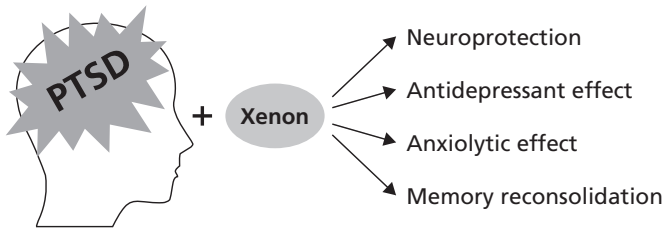
Xenon is a rare, colorless, tasteless, and odorless noble gas that exists as single atoms. Extracting it is complex and costly, requiring specialized equipment, which has limited its use in medicine [4]. However, researchers are working on ways to make xenon more accessible by improving extraction and storage techniques, developing systems to reuse it, optimizing dosing methods, and exploring new delivery forms, such as water-based solutions or tiny fat-based particles called liposomes.

Xenon's potential to help with PTSD comes from its unique way of interacting with the body. When inhaled, xenon dissolves into the fatty layer of cell membranes, temporarily disrupting how certain proteins on the cell surface (called receptors) connect with their usual partners. This effect isn't specific – xenon can influence a wide range of receptors, including serotonin receptors (5-HT3), potassium channels, calcium pumps in cells, and nicotinic acetylcholine receptors [5]. Its most significant impact, though, happens at normal atmospheric pressure, where it blocks the activity of glutamate, the brain's primary excitatory neurotransmitter [5].

Glutamate is a key player in the central nervous system, exciting neurons through two types of receptors: ionotropic (which open ion channels) and metabotropic (which trigger slower chemical changes). Ionotropic glutamate receptors come in three main types, named after the chemicals that activate them: NMDA, AMPA, and kainate receptors [6]. These receptors are especially concentrated in brain regions like the hippocampus, cortex, amygdala, and striatum, which are critical for memory, learning, emotions, and sensory processing. Recent studies show that glutamate's role extends beyond the brain, acting almost like a signaling molecule throughout the body. For example, NMDA, AMPA, and kainate receptors have been found in the pancreas, where they regulate insulin and glucagon release, in the adrenal glands, where they trigger stress hormones, and in the peripheral nervous system, where they influence pain sensation [7,8].

Xenon's strength lies in its ability to suppress all three types of ionotropic glutamate receptors, which reduces how excitable neurons are and alters synaptic plasticity – the brain's ability to strengthen or weaken connections between neurons, which is crucial for forming and updating memories [9]. Beyond the brain, xenon's effect on glutamate signaling also impacts the body's broader regulatory systems, promoting processes that build up energy and support tissue repair. This makes xenon a promising tool not only for easing acute PTSD symptoms but also for potentially preventing its long-term effects. In this review, we'll explore xenon's key effects, summarized in a diagram (see Fig. 1).

Figure 1. Schematic representation of possible effects of xenon in post-traumatic stress disorder (PTSD)

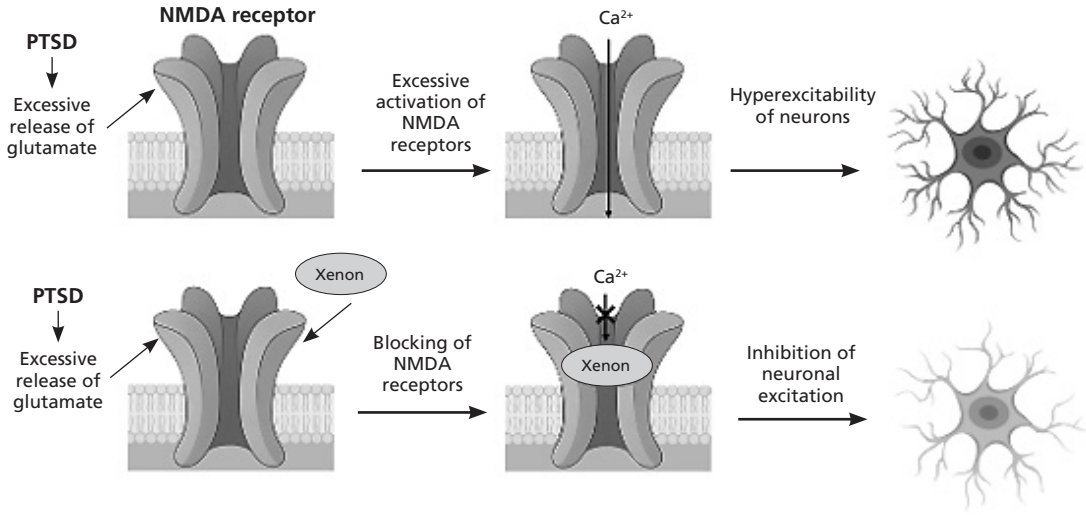


Effects on the central nervous system

Xenon, an inert gas functioning as an NMDA receptor antagonist, demonstrates significant neuroprotective properties in both in vitro and in vivo models [10]. By inhibiting NMDA receptor overactivation, xenon prevents excitotoxic cascades that lead to acute neuronal injury or cell death (see Fig. 2). In vitro studies have shown that xenon protects neuronal cell cultures from damage induced by NMDA, glutamate, or oxygen-glucose deprivation [11]. In vivo, xenon mitigates neuronal damage in rat models following subcutaneous administration of NMDA, as well as in models of hypoxia and ischemic stroke [12].

Unlike other NMDA receptor antagonists, such as ketamine, nitrous oxide, and dizocilpine, which are associated with behavioral disturbances and neurotoxicity at high doses or with prolonged use xenon exhibits a favorable safety profile [13]. Notably, xenon lacks these neurotoxic effects and can attenuate damage caused by other NMDA receptor antagonists [3]. In murine models of traumatic brain injury, xenon treatment significantly reduces secondary brain damage, improves short-term vestibular function, and prevents late-onset memory deficits [14]. Prolonged xenon administration over several

Figure 2. Schematic illustration the mechanism of xenon's action in post-traumatic stress disorder (PTSD). PTSD is associated with neuronal hyperexcitability due to dysregulation of glutamatergic system. Xenon blocks N-methyl-D-aspartate (NMDA) receptors, preventing calcium ions from entering neurons and thus inhibiting neuronal excitation.



months has been shown to reduce white matter loss in the corpus callosum and neuronal loss in the hippocampus and dentate gyrus [14]. Furthermore, xenon modulates microglial activity, a critical component of the neuroinflammatory response associated PTSD, thereby mitigating neurodegeneration in mouse models of amyloidosis and tauopathy [15]. Microglia, the brain's primary immune cells, contribute to the dysregulation of fear memory and neural circuits involved in fear processing [16,17]. Additionally, xenon provides neuroprotection when administered post-injury, preventing the progression of secondary brain damage for up to 48 hours in mouse models of brain trauma [18].

Preliminary clinical evidence supports xenon's neuroprotective potential. A randomized clinical trial involving comatose survivors of cardiac arrest demonstrated that xenon inhalation, combined with targeted temperature management, significantly preserved brain gray matter [19].

Antidepressant and anxiolytic properties

Xenon exhibits promising antidepressant and anxiolytic effects, likely mediated through its modulation of the glutamatergic system via NMDA receptor antagonism, a key mechanism in the pathophysiology of depression [20]. Additionally, xenon influences other molecular targets, including TREK-1 potassium channels, ATP-sensitive potassium channels, hypoxia-inducible factor 1-alpha, and microRNA-21, all of which are associated with antidepressant effects [20].

Preclinical studies provide robust evidence of xenon's psychopharmacological potential. In rat models, intravenous administration of xenon-containing liposomes significantly reduced immobility time in the forced swim test, indicating antidepressant-like effects [21]. In mouse models of lipopolysaccharide-induced depression, xenon therapy elicited rapid antidepressant and anxiolytic effects [22]. These findings highlight xenon's potential as a fast-acting therapeutic agent for PTSD, addressing neurochemical and behavioral dysregulation.

Impact on memory reconsolidation

One of the defining characteristics of PTSD is the presence of intrusive and distressing memories of traumatic events [23]. Consequently, PTSD therapy places significant emphasis on addressing these traumatic memories. One promising approach is memory reconsolidation therapy, which aims to weaken the emotional impact of such memories through both behavioral and pharmacological interventions [24]. Xenon has emerged as a potential pharmacological agent for this purpose. This hypothesis is based on xenon's ability to inhibit NMDA receptors, critical for memory reconsolidation [25]. Specifically, xenon has been shown to reduce NMDA-mediated synaptic currents and neuronal plasticity in key brain regions involved in fear processing, including the basolateral amygdala and the CA1 region of the hippocampus [26,27]. Furthermore, NMDA receptor blockers that target glycine-binding sites – such as xenon – demonstrate a low potential for addiction and do not induce psychosis, unlike some other NMDA antagonists [28].

These properties make xenon a particularly promising candidate for PTSD treatment, offering a novel pharmacological approach to reducing the emotional burden of traumatic memories.

Experimentally, this hypothesis has been tested in mouse models, demonstrating that xenon significantly and persistently inhibits memory reconsolidation in a reactivation and time-dependent manner [22,29]. According to the authors, the observed effect of xenon presents an opportunity for its translational application as a research tool to study reconsolidation and other memory processes, as well as for developing therapeutic approaches for individuals with PTSD and, potentially, other conditions associated with reconsolidation, such as addiction disorders [29]. A summary of key studies investigating the effects of xenon in PTSD models is presented in Table1.

Treatment parameters and methodological details

Xenon is currently classified as an inhalational general anesthetic. It's typically mixed with oxygen in ratios like 60:40, 70:30, or 80:20. Within two minutes of inhalation, you might feel tingling in your limbs and a reduced sense of pain. By the third minute, you could notice some psychomotor restlessness. By the fourth minute, partial amnesia and pain relief kick in, and by the fifth minute, you're likely under anesthesia deep enough for the first stage of surgical anesthesia, as described by Guedel's classification [30]. Recovery is impressively quick – most people regain full consciousness and awareness of their surroundings

Table 1. Summary of key studies investigating the effects of xenon in PTSD models

Effect	Model/population	Xenon treatment parameters	Outcomes	Study
Neuroprotection	Rats (female, Sprague-Dawley), brain injury model that involved the subcutaneous injection of N -methyl-dl-aspartate	20, 40, 60 and 75 % xenon inhalation	Exerted a concentration-dependent protective effect and reduced the injury	[12]
Neuroprotection	Mice (C57BL/6N young adult male)	75 % xenon inhalation	Reduced secondary injury, improved short-term vestibulomotor function, and prevented development of very late-onset traumatic brain injury-related memory deficits	[14]
Neuroprotection	Several mouse models of Alzheimer's disease (APP/PS1, 5xFAD, P301S)	-	Compaction of amyloid plaques, reduction in the number of dystrophic neurites, reduction brain atrophy and neuroinflammation	[15]
Neuroprotection	In vitro model (mouse organotypic hippocampal brain slices, subjected to a focal mechanical trauma)	50 % xenon inhalation at 24 hours, 48 hours and 72 hours after trauma	Neuroprotective against traumatic injury when applied after injury and prevents development of secondary injury up to 48 h after trauma	[18]
Neuroprotection	Patients (comatose survivors of out-of-hospital cardiac arres)	Target temperature management (33°C) in combination with inhaled xenon during the first 24 h after hospital admission	Preserved gray matter better than hypothermia alone	[19]
Antidepressant	Rats (Wistar, males)	Xenon-liposomes (15 μL/mg), tail vein injection	Increase in swimming time in the forced swimming test	[21]
Antidepressant, anxiolytic, memory reconsolidation	Mice (lipopolysaccharide-induced depression models)	Xenon gas inhalation and intraperitoneal injection xenon-rich saline	Improved results in behavioral tests, including the open-field test, novelty-suppressed feeding test, sucrose preference test, tail suspension test, and forced swimming test	[22]
Memory reconsolidation	Rats (Sprague-Dawley, Male)	25 % xenon inhalation (1 hour)	The assessment of fear-like behavior (freezing) in the contextual fear conditioning test showed positive results	[29]

within 2-3 minutes after the gas is stopped. A 30-40 % xenon-oxygen mix can provide pain relief, while a 65-70 % mix typically leads to unconsciousness [30].

So far, there aren't any official guidelines for using xenon therapeutically for other conditions, like specific dosages, how long to inhale it, how often, or who's eligible. That said, there are registered clinical trials exploring xenon therapy for psychiatric conditions, especially PTSD [31]. In Ukraine, interest in xenon therapy is growing, particularly among those dealing with the aftermath of military conflict. We can probably expect some clinical reports on this soon [31].

Compared to other treatments, like ketamine, which has been studied extensively for PTSD, xenon therapy has some unique benefits. Ketamine, given intravenously at low doses (usually 0.5 mg/kg over 40 minutes), can significantly reduce symptoms within 24 hours, with effects lasting up to two weeks after a single dose and even longer with repeated doses [32,33]. However, studies show ketamine increases c-Fos expression in areas like the posterior cingulate and retrosplenial cortices, indicating it ramps up neuronal activity [34]. When you compare how ketamine and xenon affect brain physiology and neurological monitoring, the differences are clear: ketamine has a stimulating effect on the nervous system, doesn't lower the bispectral index, and doesn't suppress mid-latency auditory evoked potentials. Xenon, on the other hand, has a calming effect, reduces the bispectral index depending on its concentration, and suppresses those auditory potentials [35]. This suggests xenon might have a more soothing and stabilizing impact on the brain.

Side effects and safety of use

When inhaled, xenon is efficiently absorbed into the body, crosses the blood-brain barrier, and rapidly diffuses into the central nervous system [36]. Due to its chemical inertness, xenon does not participate in metabolic reactions within the body and is therefore not subject to biotransformation. Consequently, it has been noted that xenon lacks embryotoxic, teratogenic, mutagenic, carcinogenic, or allergenic properties [37]. According to manufacturers' guidelines, the most commonly reported side effects of xenon inhalation hoarseness, metallic taste in the mouth, hypoxia. In very rare instances, allergic reactions might occur [30].

Additionally, a literature review was conducted on the clinical applications of xenon. Yang and asociates performed a systematic review and meta-analysis examining the effects of xenon anesthesia on postoperative neurocognitive disorders [38]. Their analysis demonstrated that xenon anesthesia had no significant impact on the incidence of postoperative neurocognitive disorders or cognitive performance in surgical patients. However, compared to other inhaled or intravenous anesthetics, xenon anesthesia significantly reduced the time to eye opening, extubation, response to verbal commands, and restoration of normal spatial orientation. It was also associated with higher scores on the Aldrete scale, indicating improved recovery profiles.

In cellular models derived from human neural stem cells, prolonged exposure to the anesthetic propofol has been shown to induce neuronal apoptosis. Notably, subclinical, non-anesthetic concentrations of xenon, when combined with propofol, can mitigate or prevent these neurotoxic effects [39].

Another large multicenter study evaluating the safety profile of 28 % xenon for computed tomography showed that this gas can be used safely, with a very low risk of side effects and no risk of long-term sequelae [40]. The most common side effects were transient respiratory depression, shorter respiratory pauses, and hyperventilation, none of which resulted in permanent neurological changes or other sequelae. It is important to note that the authors of the study recorded a few isolated serious adverse events (bradycardia, increased blood pressure, seizures, severe hypertension, vomiting, respiratory failure), but believe that these are most likely related to the severe underlying disease of the patients who underwent the study. Analysis of other, smaller study showed that the use of subsedative doses of xenon for sedation is well tolerated, does not cause significant physiological changes and ensures rapid recovery [41].

Xenon has also been shown to be safe in patients with organ damage. In particular, xenon anesthesia in patients with impaired left ventricular function provides cardiovascular stability, although episodes of increased left ventricular afterload without subsequent reduction in ejection fraction have been observed [42]. However, even with these data, patients with organ damage require careful risk assessment and close monitoring during the procedure.

It is known that xenon anesthesia provides relatively more stable intraoperative blood pressure, lower heart rate, and faster emergence from anesthesia, but is associated with a higher incidence of postoperative nausea and vomiting [43].

The results of a large meta-analysis evaluating neurological or cognitive outcomes after clinical use of xenon have shown that, despite promising preclinical results, the evidence for positive clinical neurological and cognitive outcomes associated with xenon is rather modest [44]. In particular, the authors note that xenon is associated with improved short-term cognitive outcomes, but no benefits were observed for longer-term outcomes.

We aimed to highlight a lesser-known effect of xenon exposure on the human body, specifically its influence

on cytokine levels, which has received limited attention. Some studies suggest xenon can alter cytokine profiles. For example, in patients undergoing cardiac surgery, xenon anesthesia significantly increased intraoperative interleukin-6 levels while suppressing interleukin-10 and macrophage migration inhibitory factor compared to sevoflurane anesthesia [45]. This cytokine pattern points to a temporary boost in pro-inflammatory responses during surgical stress, though the long-term consequences are not yet clear. In mouse models, BV-2 microglia cells treated with 50 ng/ml lipopolysaccharide showed that xenon amplifies lipopolysaccharide-induced interleukin-1β expression through the activation of the ERK 1/2 signaling pathway, further supporting its pro-inflammatory potential [46]. However, in models of chronic inflammation and autoimmune conditions, xenon exhibits anti-inflammatory effects. In a mouse model of lupus nephritis, daily exposure to 70 % xenon for two hours over five weeks improved kidney function and tissue health, reduced renal expression of neutrophil chemoattractants, and decreased glomerular neutrophil infiltration. These outcomes were linked to reduced activation of the NF-ϰB/NLRP3 inflammasome pathway and lower levels of anti-double stranded DNA autoantibodies [47]. Together, these findings indicate that xenon functions as a context-dependent immunomodulator, either enhancing or suppressing inflammatory signaling based on the disease state, immune environment, and exposure conditions. Therefore, we believe that using xenon in patients with immune system imbalances, such as autoimmune disorders or acute inflammatory conditions, calls for caution, close monitoring, and further investigation.

Limitations

This review outlines potential mechanisms for xenon's therapeutic use in PTSD, but several limitations must be noted. First, most evidence comes from preclinical studies or research on other conditions, as no clinical trials have specifically explored xenon's use for PTSD. Second, the diversity in experimental models and study designs makes it challenging to draw firm conclusions. Third, while this review has examined xenon's potential effects on memory reconsolidation, neuroprotection, and immune pathways, these findings need confirmation through clinical research. Well-designed clinical trials are critical to establish xenon's long-term safety, effectiveness, and optimal treatment protocols for PTSD. Additionally, future studies should investigate whether xenon's effects vary by sex or ethnicity, as these factors may influence treatment outcomes.

Conclusions

Xenon has significant therapeutic potential for the treatment of PTSD, due to its antidepressant and anxiolytic effects, as well as its ability to influence memory reconsolidation. Data on the effects of xenon on the central nervous system indicate its neuroprotective properties and its ability to reduce secondary neuronal damage. Regarding the safety of use, xenon demonstrates good tolerability, but caution and monitoring are necessary, especially in patients with existing diseases or pathological conditions.

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Conflict of Interest

Non to declare.

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