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Clinical Application of Xenon in Subanesthetic Concentrations (Review)

Mikhail E. Politov*, Sofia V. Podprugina, Elizaveta N. Zolotova, Pavel V. Nogtev, Yulia S. Agakina, Svetlana G. Zhukova, Andrey G. Yavorovsky

I. M. Sechenov First Moscow State Medical University, Ministry of Health of Russia,
8 Trubetskaya Str., Bldg. 2, 119991 Moscow, Russia

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***Correspondence to:** Mikhail E. Politov, politov.mikhail@gmail.com

Summary

Xenon is considered to be the safest general anesthetic agent with organ-protective properties. In subanesthetic doses, it is recognized as a promising therapeutic agent in various medical fields.

The aim of this review was to systematically summarize scientific data on the potential therapeutic use of xenon for organ system protection outside the context of anesthetic support during surgery and perioperative analgesia.

Publications were searched in the databases PubMed, Google Scholar, Cochrane Library, and eLIBRARY.RU from August to September 2024. A total of 33 publications on the clinical use of inhaled xenon for therapeutic purposes from 2002 to 2023 were selected, including 12 randomized controlled trials (RCTs), 8 prospective controlled studies, 2 prospective comparative studies, 6 prospective uncontrolled studies, and 2 clinical observations. An additional 32 publications were used to discuss various aspects related to the topic of the review.

Conclusion. The literature review showed that inhaled xenon at subanesthetic doses has potential neuroprotective, cardioprotective, and therapeutic effects for the treatment of addictive and neurotic disorders, as well as oncologic and pulmonary conditions. Despite some promising results, the number of RCTs remains limited, and the existing studies have methodological limitations, small sample sizes, and a high risk of systematic error. Definitive conclusions regarding the clinical efficacy and safety of inhaled xenon require further large-scale randomized trials.

Keywords: xenon; xenon inhalation; therapeutic use of xenon; neuroprotection; stroke; traumatic brain injury; cardioprotection; myocardial infarction; withdrawal syndrome; neurotic disorders; oncology; chronic pain syndrome; organ protection

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Information about the authors:
Mikhail E. Politov: http://orcid.org/0000-0003-0623-4927
Sofia V. Podprugina: http://orcid.org/0009-0002-9614-7877
Elizaveta N. Zolotova: http://orcid.org/0000-0002-1608-6131
Pavel V. Nogtev: http://orcid.org/0000-0002-5553-0880
Yulia S. Agakina: http://orcid.org/0000-0002-3556-2703
Svetlana G. Zhukova: http://orcid.org/0000-0001-5468-3183
Andrey G. Yavorovsky: http://orcid.org/0000-0001-5103-0304

Introduction

Xenon has been used in anesthesia since the late 20th century. It does not undergo metabolic transformation and is eliminated unchanged by respiration.

Xenon anesthesia is associated with faster induction and emergence, absence of respiratory, renal, and hepatic toxicity, and less pronounced hemodynamic changes compared with other anesthetic agents (both inhalational and intravenous) [1–4]. Extensive research on xenon has demonstrated its ability to protect organs from injury.

Large systematic reviews [5–7] have described the main mechanisms underlying the organoprotective effects of xenon:

— Inhibition of glutamate receptors (NMDA, AMPA, and kainate), preventing excitotoxic damage during ischemia-reperfusion injury.

— Activation of potassium channels (TREK-1, KATP), resulting in reduced neuronal excitability and neuroprotective effects.

— Modulation of intracellular signaling pathways (PI3K/Akt, MAPK, RISK and SAFE) that attenuate apoptosis and myocardial injury.

— Regulation of transcription factors (CREB, HIF-1α) that enhance the expression of cytoprotective and anti-apoptotic genes.

— Modulation of serotonergic, cholinergic and dopaminergic systems, which explains its influence on anesthesia and mental and emotional states.

The identified mechanisms of action, along with experimental data, support the recognition of xenon not only as a general anesthetic but also as a standalone pharmacological agent with the potential to reduce tissue injury, provide analgesia, modulate mental and emotional state, and

exhibit a relatively favorable safety profile at subanesthetic doses.

This review aims to consolidate the scientific evidence on the potential therapeutic applications of xenon for organ protection in different systems of the body.

Materials and Methods

The literature search was conducted using international and Russian databases of scientific publications, including PubMed, Google Scholar, Cochrane Library, and eLIBRARY.RU. Search queries were formulated between August 1, 2024, and September 1, 2024, using combinations of the following key terms: «xenon therapy,» «xenon inhalation,» «subanesthetic xenon,» as well as their Russian equivalents («ксенон терапия», «субанестетические дозы ксенона», «ингаляции ксенона»). Additional terms specifying the therapeutic applications of xenon were also included, such as «neuroprotection», «cardioprotection», «pain management», «oncology», «lung diseases», «нейропротекция», «кардиопротекция», «онкология».

Selection criteria required studies to be original clinical research focusing on the therapeutic effects of inhaled xenon at subanesthetic concentrations. Articles were excluded if they examined only xenon as an anesthetic agent, as were review articles and experimental (preclinical) studies.

Manual reference screening of selected publications was performed to identify additional relevant sources. In addition, semantic search techniques using artificial intelligence models (Semantic Scholar, Research Rabbit, and Neurosearch on eLIBRARY.RU) were used to identify additional studies that met the inclusion criteria.

As a result of the selection process, 65 publications were included in the review. Of these, 33 studies focused on the clinical use of inhaled xenon for therapeutic purposes between 2002 and 2023, including 12 randomized controlled trials, 8 prospective controlled studies, 2 prospective comparative studies, 6 prospective uncontrolled studies, and 2 clinical case reports (Table 1). An additional 32 publications were used to discuss various aspects related to the review topic.

Therapeutic Applications of Xenon for Neuroprotection

Systematic reviews and meta-analyses of preclinical studies [5, 8, 9] have shown that xenon has significant neuroprotective effects in several models of acute brain injury, including cardiac arrest, traumatic brain injury, and stroke. The greatest improvements in both short- and long-term neurological outcomes were observed when xenon was administered after the initial injury (postconditioning), even when treatment was delayed up to 2–3 hours after ischemic brain injury.

The neuroprotective effect of xenon was dose-dependent, with higher concentrations (50–75%) providing greater benefit than lower concentrations (15–37.5%).

A key factor in the safe use of xenon in brain injury is its effect on cerebral perfusion. Studies have shown that xenon inhalation can cause a dose-dependent increase in intracranial pressure [10, 11]. In patients with pre-existing elevated intracranial pressure, high concentrations of xenon may reduce cerebral perfusion. However, subanesthetic doses (30–32%) did not cause clinically significant changes in cerebral blood flow [12] or intracranial pressure [13].

The first studies on the neuroprotective effects of xenon were conducted by Finnish researchers in patients with post-hypoxic encephalopathy following out-of-hospital cardiac arrest. These studies investigated the effects of xenon on both the cardiovascular system [14, 15] and the central nervous system [16].

In the randomized controlled XeHypotheCA trial, R. Laitio and colleagues [16] investigated the effect of xenon on white matter injury in 110 coma patients after cardiac arrest. The xenon group (*N*=55) received 40% xenon inhalation combined with therapeutic hypothermia (33°C), while the control group (*N*=55) received hypothermia alone for 24 hours. Global fractional anisotropy coefficient, an indicator of white matter integrity, was 3.8% higher in the xenon group (95% CI, 1.1–6.4%), suggesting less white matter damage. However, clinical outcomes were not significantly different between groups, with a six-month mortality rate of 27.7% in the xenon group versus 34.5% in the control group (*P*=0.053). To further evaluate the efficacy of this approach, the authors initiated a large multicenter trial, XePOHCAS (NCT03176186, clinicaltrials.gov), which enrolled 1,436 patients.

The combined effects of xenon inhalation and hypothermia have also been studied in neonatal brain injury. Small studies by D. Azzopardi (*N*=14) [17] and J. Dingley et al. (*N*=14) [18] showed that inhaled xenon at concentrations of 30–50% effectively suppressed seizure activity in neonates. However, abrupt discontinuation of xenon therapy was associated with seizure recurrence. When xenon was gradually withdrawn over 40 minutes, seizure activity did not recur [18]. A similar anticonvulsant effect was reported in a clinical case of a five-year-old child with super-refractory status epilepticus [19].

To further evaluate the neuroprotective properties of xenon, D. Azzopardi and colleagues conducted a randomized controlled trial with two parallel groups [20]. The study included 92 neonates (gestational age 36–43 weeks) with signs of severe encephalopathy and abnormal electroencephalo-

graphic activity. The investigators compared two groups: one receiving standard therapeutic hypothermia alone (*N*=46) and the other receiving hypothermia combined with 30% inhaled xenon for 24 hours (*N*=46). There were no significant differences in brain injury between the groups based on MRI findings. The authors concluded that delayed administration of xenon in combination with hypothermia did not reduce neuronal injury, possibly due to the late initiation of treatment (median onset was 10.0 hours after birth) and the severity of the initial cerebral insult.

In a randomized controlled pilot study, O. Grebenchikov and colleagues [21] investigated the effects of short-term xenon sedation in patients with acute ischemic stroke. The study included mechanically ventilated patients with a Glasgow Coma Scale (GCS) score of less than 12, a Full Outline of UnResponsiveness (FOUR) score of less than 13, and a National Institutes of Health Stroke Scale (NIHSS) score of greater than 15. Immediately after endotracheal intubation, patients in the intervention group received 6 hours of inhalation sedation with 40% xenon, while the control group received propofol.

On admission, the median GCS score was 10 (IQR 10–11) in the xenon group and 10.5 (IQR 9–12) in the control group (*P*=0.721). By day 8, a significant difference had emerged: 13 (IQR 11–15) in the xenon group versus 7 (IQR 6–8) in the control group (*P*=0.026). Improvements in the FOUR score were observed as early as day 2: 14 (IQR 12–15) in the xenon group versus 12 (IQR 10–13) in the control group (*P*=0.038), with further divergence by day 8: 14 (IQR 13–15) versus 8 (IQR 7–8) (*P*=0.026). NIHSS neurological deficit was also significantly lower in the xenon group on day 8: 24 (IQR 12–27) compared to 34 (IQR 34–34) in the control group (*P*=0.007).

In the xenon group, the level of the neuronal injury marker S100b decreased from 0.188 (0.172–0.201) to 0.098 (0.075–0.116) ng/mL. In contrast, the control group showed an increase from 0.196 (0.158–0.213) to 0.396 (0.368–0.418) ng/mL, resulting in a fourfold increase by day 8 (*P*=0.007).

However, the publication [21] has several limitations, including lack of data on time to hospital admission, use of thrombolytic therapy or thrombectomy, and comorbidities, as well as lack of between-group comparisons. These omissions introduce a risk of systematic bias and weaken the validity of conclusions regarding the effects of xenon.

In a randomized controlled trial, A. Shpichko and colleagues [22, 23] investigated the effects of inhalational xenon sedation on the level of consciousness and spastic activity in patients with chronic disorders of consciousness (vegetative state or minimally conscious state) after severe traumatic brain injury (TBI) [22]. They also evaluated the changes of biomarkers related to neuroinflammation, neuronal injury, and neurogenesis [23]. In the intervention group (*N*=12), participants received daily 30-minute sessions of 30% xenon inhalation for 7 days. The control group (*N*=12) received an oxygen-air gas mixture.

On day 3, the xenon group showed a reduction in inflammatory markers (IL-6 and AGP), although the differences were not statistically significant. This may be due to the inherently low levels of neuroinflammation in the chronic phase of chronic disorder of consciousness (typically beyond 28 days post TBI). In support of this, S100b levels remained very low in both groups (<0.005 pg/mL).

A significant increase in the level of brain-derived neurotrophic factor (BDNF) was observed in the xenon group — 0.1271 (0.046; 0.2695) pg/mL vs. 0.054 (0.021; 0.093) pg/mL in the control group (*P*=0.04), which may indicate activation of neuronal regeneration [23].

Consciousness was assessed using the Coma Recovery Scale-Revised (CRS-R) [24]. In the control group, scores changed minimally from 8 (6; 10) to 9 (7; 11) (*P*>0.05). In contrast, the xenon group showed a marked improvement, with scores increasing from 9 (7; 10) to 15 (12; 17) (*P*=0.021); the between-group difference was statistically significant (*P*=0.038). Xenon therapy did not exert a substantial effect on spastic activity, although a transient reduction in muscle tone was observed during sessions [22].

With respect to the effect of xenon anesthesia on the incidence of cognitive impairment, a meta-analysis by Y.-S. Yang et al. [25] did not reveal any significant advantage in reducing the frequency of postoperative neurocognitive disorders. However, the authors emphasized the need for further research.

Taken together, these findings suggest that during the acute phase of brain injury, xenon may reduce neuroinflammation and neuronal excitability, thereby decreasing the risk of spreading depolarization [26]. In later stages, its effects appear to involve inhibition of apoptosis and promotion of neuronal recovery mechanisms [8]. While xenon's neuroprotective properties appear promising, current evidence remains insufficient to draw definitive conclusions. Ongoing studies, such as the XePOHCAS trial, are expected to provide a more comprehensive understanding. Furthermore, a large-scale investigation of xenon use in patients with subarachnoid hemorrhage (Xe-SAH [27]) is currently underway, with preliminary results anticipated by 2027. These studies may significantly enhance the current understanding of xenon's therapeutic potential in neuroprotection.

Therapeutic Use of Xenon for Cardioprotection

The cardioprotective effects of xenon, particularly its ability to reduce the extent of ischemic

myocardial injury, have been demonstrated in various experimental models. Administration of xenon resulted in a significant reduction in the size of myocardial necrosis zones [5]. These studies used subanesthetic concentrations, taking into account the high minimum alveolar concentration (MAC) values observed in experimental animals (pigs ≈119% [28], rats ≈161%, mice ≈95% [29]).

A study by O. Arola et al. [14] investigated the effects of xenon inhalation on the cardiovascular system in comatose patients after out-of-hospital cardiac arrest. In this RCT, patients in the main group (*N*=16) received xenon inhalation (47% for 25.5 hours) combined with therapeutic hypothermia, while the control group (*N*=20) received hypothermia alone. The incidence of serious adverse events, including in-hospital mortality, status epilepticus, and acute kidney injury, was comparable between groups. Notably, the xenon group required lower cumulative doses of norepinephrine (2.95 mg vs. 5.30 mg; *P*=0.06) and had a lower heart rate (*P*=0.04). The 72-hour increase in troponin T levels was also lower in the xenon group: 0.08 μg/L compared with 0.62 μg/L in the hypothermia-only group (median difference –0.52 μg/L; 95% CI, –1.72 to –0.06 μg/L; *P*=0.04).

These findings were subsequently confirmed by the same group of authors in a larger study (*N*=110) XeHypotheCA described previously [16]. In addition to assessing changes in brain tissue, the authors also investigated the effect of xenon on ischemic myocardial injury [15]. In the group receiving 40% xenon inhalation for 24 hours, a significant reduction in troponin levels at 72 hours was observed compared to the control group (adjusted mean difference: 0.66; 95% CI, –1.16 to –0.16; *P*=0.01). This xenon-induced reduction in troponin T concentration was independent of the primary intervention (percutaneous coronary intervention). An increase in troponin T from baseline to any time point was a significant predictor of 6-month mortality in both groups.

Building on this, A. Saraste and colleagues [30] used the same xenon and hypothermia protocol in patients after out-of-hospital cardiac arrest and evaluated echocardiographic changes after 24 hours of exposure. A significantly higher left ventricular ejection fraction (LVEF) was observed in the xenon group (*N*=17) compared to controls (*N*=21): 50±10% vs. 42±10%, *P*=0.014. Global longitudinal systolic strain was also significantly better in the xenon group (–14.4±4.0% vs. –10.5±4.0%, *P*=0.006). Prolonged xenon inhalation improved longitudinal strain in nonischemic myocardial segments. No significant between-group differences were found for diastolic function parameters.

Thus, xenon inhalation combined with therapeutic hypothermia was associated with less myocardial injury [14, 15] and greater improvement in left ventricular systolic function compared with hypothermia alone in patients resuscitated from out-of-hospital cardiac arrest [30].

A clinical study by I. Molchanov et al. [31] investigated the effect of xenon inhalation on the course of acute coronary syndrome (ACS). The main group included 20 patients (16 with acute myocardial infarction and 4 with unstable angina) who received xenon inhalation (25–50%, 20–40 minutes per session) in addition to standard therapy. The control group consisted of 15 patients (11 with AMI, 4 with unstable angina). The inhalation course lasted 3 to 5 days. Xenon had no effect on blood pressure or heart rate. However, according to noninvasive hemodynamic monitoring (bioimpedance), the last inhalation session was associated with an increase in cardiac index from 2.90±0.6 to 3.25±0.9 L/min/m² and a decrease in systemic vascular resistance (SVR) from 1389.5±158.2 to 1290.2±149.1 dyn×s/cm^{-5}×m². Echocardiographic assessment also showed a significant reductionin pulmonary artery systolic pressure from 33.41±3.22 to 29.84±1.69 mmHg (*P*<0.05).

The authors reported a more pronounced reduction in biomarkers of myocardial injury on day 3, as well as a reduction in hypercoagulability as assessed by thromboelastography in the xenon-treated group. However, the study was limited by its observational design, lack of hemodynamic data in the control group, and lack of between-group comparisons of myocardial injury markers. In addition, the potential effect of standard anticoagulant therapy on hemostatic parameters was not considered. These factors make it difficult to interpret the therapeutic efficacy of xenon in this context.

A study by V. Potievskaya et al [32] investigated the effects of xenon inhalation on the cardiovascular system. No significant changes were observed on the ECG, including QTc interval duration or repolarization processes. QTc prolongation was observed only in the control group. No arrhythmias were reported. Analysis of hemodynamic parameters showed a similar, clinically insignificant decrease in both systolic and diastolic blood pressure in both groups, with no effect on heart rate.

Regarding the cardioprotective effects of xenon in the context of anesthesia, a large randomized controlled trial (*N*=492) conducted by J. Hofland et al. [33] found that xenon anesthesia during coronary artery bypass grafting (CABG) had a cardioprotective profile comparable to that of sevoflurane and more pronounced than that of propofol. However, the clinical significance of these differences remains uncertain.

In conclusion, xenon therapy appears to be safe for patients with cardiovascular disease. It may provide benefits by reducing myocardial reperfusion injury and exerting anti-inflammatory effects. However, further randomized controlled trials are needed to assess its impact on clinical outcomes.

Use of Xenon in the Treatment of Addictive Disorders

Studies on the intensive treatment of severe alcohol and drug withdrawal syndromes have highlighted the organoprotective properties of xenon. S. Naumov et al. [34] showed that xenon inhalation reduced cortisol levels (from 504.9±35.4 to 409.6±40.0 nmol/L) and growth hormone levels (from 7.15±0.72 to 1.75±0.9 ng/mL) and stabilized blood glucose levels, indicating an anti-stress effect. In addition, an improvement in liver function was observed, as evidenced by a decrease in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activity.

O. Strepetova [35] reported that in moderate to severe alcohol intoxication, xenon inhalation not only reduced the incidence and duration of hyperactive delirium (6.1±0.7 days vs. 8.7±2.1 days in the control group, P=0.018), but also shortened the duration of mechanical ventilation. In addition, patients receiving xenon required lower doses of vasopressors and positive inotropic agents (P=0.003).

Several studies have shown that xenon administration accelerates cognitive recovery and enhances its neuroprotective properties [36–38]. B. Tsygankov reported a trend toward cerebral hemodynamic normalization in patients undergoing xenon therapy [39]. When used as part of the intensive treatment of severe withdrawal syndrome, xenon reduced the need for anxiolytics and antipsychotics, thereby reducing the risk of adverse effects associated with standard therapy, such as neuroleptic syndrome, excessive sedation, and orthostatic disturbances [39]. In addition, a significant reduction in depressive symptoms has been observed [36].

Evidence suggests that xenon plays a dual role in the treatment of addictive disorders: in addition to its organoprotective effects, it modulates neurotransmitter systems involved in addictive behavior by blocking NMDA receptors [40]. S. Shamov found that xenon inhalation not only accelerated the resolution of psychopathological symptoms in patients with alcohol and drug dependence, but also significantly reduced pathological craving for these substances [36, 37]. Xenon therapy resulted in the disappearance of hallucinations, the alleviation of delusions, and the normalization of sleep patterns. Patients also reported reductions in pain, irritability, anxiety, and tremors. By the 6th to 10th session of xenon therapy, all patients (N=80) experienced a complete cessation of drug cravings, while 71.4% of the control group (N=35) continued to experience cravings until days 11–15 [34].

Similarly, A. Kuznetsov and colleagues reported a more rapid reduction in alcohol craving, improved sleep quality, reduced anxiety, and increased mood stability in the xenon group compared to controls (P<0.05) [39].

Although studies suggest the efficacy of xenon in the treatment of opioid and alcohol dependence [34–39, 41], a closer analysis reveals several methodological limitations, including the lack of randomization, control group comparisons, and detailed effect size analysis. These factors weaken the reliability of the findings and highlight the need for additional high-quality RCTs.

Xenon in the Treatment of Neurotic Disorders

Neurotic disorders are characterized by chronic and recurrent episodes of anxiety, stress and emotional instability. While pharmacological treatments such as antidepressants, anxiolytics, and antipsychotics are commonly used, their adverse side effects have stimulated interest in alternative therapies, including xenon inhalation therapy.

A study by A. Dobrovolsky et al. [42] evaluated the efficacy of xenon therapy in panic disorder (PD). Patients were divided into two groups: those with PD alone (N=42) and those with PD and comorbid psychiatric disorders (N=39), the majority of whom had depression. All participants received xenon inhalation therapy (15–30%) for 6–7 sessions. At baseline, both groups had high levels of anxiety on the Self-Rating Anxiety Scale (SAS) (72.7 and 64.1, respectively), which decreased significantly to 36.5 and 46.8 after one month. This anxiolytic effect was maintained at the six-month follow-up. Similarly, Hospital Anxiety and Depression Scale for Anxiety (HADS-A) scores indicated «clinically significant anxiety» at baseline (17.7 and 19.0, respectively), which normalized by the end of treatment. Regarding depression, the prevalence of «clinical depression» in the second group (assessed by HADS-D) decreased from 92.3% to 46.2%. Subjectively, 52.4% of patients in the first group and 12.8% in the second group reported improvements on the Clinical Global Impression (CGI) Scale. These findings suggest a potential role for xenon therapy in the treatment of panic disorder, but further RCTs comparing it with standard psychotropic therapies are needed to establish its efficacy.

A study by T. S. Sabinina et al. [43] investigated the effects of xenon therapy on seven severely traumatized children — five injured in a terrorist attack and two by dog bites — suffering from intractable pain and acute stress disorder (ASD). Xenon oxygen inhalation (15–30%) was administered between days 13 and 14 post-injury in sessions lasting 15–20 minutes, for a total of 3–12 sessions per patient.

During inhalation therapy, significant reductions in BIS index (from 95.5 to 86.5), Ramsay Sedation Scale scores (from 5.5 to 2.7), and pain intensity (from 4.1 to 1.1 points, P<0.05) were observed. After two sessions, analgesic consumption was reduced by half. Pain relief required an average of

five sessions, phantom pain resolution required 12 sessions, and sleep disturbances were alleviated after three sessions.

The authors concluded that xenon therapy is highly effective in treating persistent pain and ASD in children with severe trauma. However, the lack of a control group receiving standard therapy limits the ability to assess the true effect size.

Early intervention for ASD is critical to preventing the development of post-traumatic stress disorder (PTSD), which is diagnosed when symptoms persist for more than four weeks after a traumatic event. PTSD symptoms can last for months or even years and include intrusive memories, avoidance of trauma-related reminders, negative changes in cognition and mood, and hyperarousal [44].

A study by T. Igoshina et al. [45-47] evaluated the efficacy of xenon therapy in the treatment of neurotic disorders in 40 men (aged 30–42) working in high-risk occupations. The control group (N=20) received standard care, including psychotherapy, physiotherapy, nootropics, antidepressants, and benzodiazepines. In the experimental group (N=20), patients additionally underwent 10 sessions of xenon inhalation therapy (20–30% concentration, 10–30 minutes per session). The intervention group showed EEG normalization characterized by restoration of alpha rhythm and reduction of slow wave activity, indicating improved brain function. Statistically significant reductions in somatic complaints (GBB scale) by 66%, anxiety (HARS) by 70% and depression (BDI) by 55% were observed compared to baseline (P<0.05). Improvements were less pronounced in the control group at 35%, 26% and 30%, respectively. Patients reported subjective improvement after 3–4 sessions.

A separate study by F. Shvetsky et al. [48] investigated the effects of xenon therapy on stress levels in anesthesiologists and intensive care physicians after night shifts (N=30). A 3-minute inhalation of a 30% xenon-oxygen mixture resulted in a significant reduction in anxiety scores (Spielberger State-Trait Anxiety Inventory): in 50% of physicians with moderate baseline anxiety, scores decreased from 37.5±1.4 to 30.0±2.3 points (P<0.05), while in 17% of those with high anxiety, scores decreased from 45.0±2.2 to 39.0±1.4. In addition, significant improvements were observed in heart rate variability parameters (increased SDNN, RMSSD, and pNN50), indicating increased parasympathetic activity. However, no significant changes in stress hormone levels were found, probably due to their initially low baseline concentrations.

Experimental data [49] and clinical studies support the potential use of xenon therapy in the treatment of panic disorder, stress-related disorders, PTSD, anxiety, and depression. However, the lack of RCTs dedicated to this topic limits conclusions regarding the efficacy of xenon.

Therapeutic Use of Xenon in Oncology

Improving the quality of life of cancer patients, especially during chemotherapy, is assisted by «supportive care» aimed at preventing and treating pain syndrome, nausea and vomiting, gastrointestinal complications, and psycho-emotional issues, among others. The use of xenon may enhance the effectiveness of supportive therapy.

The effects of xenon in reducing the toxic effects of chemotherapeutic agents were studied by L. Nikolaev et al. [50]. Female breast cancer patients undergoing highly emetogenic chemotherapy were divided into two groups. The control group (N=36) received standard antiemetic therapy, while the experimental group (N=40) additionally received xenon inhalation at a concentration of 30% during their chemotherapy cycles. Acute vomiting occurred in 5% of patients in the xenon group compared to 16-47% in the control group (P<0.001). The incidence of delayed vomiting differed only in the fourth cycle (45% vs. 58%, P<0.001). Anticipatory vomiting was less frequent in the xenon group — 22% compared to 72% in the control group (P<0.001). Most patients in the experimental group reported that nausea and vomiting did not significantly interfere with their daily life, as measured by the FLIE questionnaire (P<0.001). General condition as assessed by the Karnofsky scale was 94% in the experimental group compared to 67% in the control group.

Y. Sidorenko and colleagues [51] investigated the effects of xenon inhalation on the symptoms of premature surgical or pharmacological menopause, such as irritability, depression, and anxiety. The study included 30 women of reproductive age (39.4±3.7 years) with locally advanced cervical cancer. Starting on the third day after hysterectomy, participants underwent a five-day course of xenon inhalation, with the xenon concentration gradually increasing from 15–16% to 20–22% and the exposure time decreasing from 20 to 10 minutes. EEG results showed normalization of cortical brain activity. Neuropsychological tests showed a reduction in anxiety and fatigue, and an improvement in sleep and work performance in 82–98% of patients.

A similar effect of xenon on the mental and emotional state of women with newly diagnosed breast cancer was observed in a study by RD. ozenko and colleagues [52]. After mastectomy, the experimental group (N=30) received a five-day course of xenon inhalation, while the control group (N=30) received standard therapy. On day 10, the experimental group showed a 2.6-fold improvement in overall well-being, a 2.3-fold reduction in depression, and a 1.9-fold reduction in anxiety (P<0.05), as assessed by the ESAS and MOS-SF-36 questionnaires. Physical health (89.2±2.2%) and mental health (81.2±3.2%) scores were significantly higher in the xenon group than in the control group (70.7±1.7%

and 75.3±1.5%, respectively, $P<0.05$). EEG results showed a decrease in beta rhythm power, an increase in slow rhythms, and an increase in alpha rhythm, suggesting a reduction in psychological stress.

The potent analgesic properties of xenon make it a valuable option for painful procedures that do not require deep sedation, such as endoscopic and dental interventions [53, 54]. Inhaled xenon is emerging as a promising component of multimodal analgesia. For example, in a study by T. Sabinina [43], xenon inhalation helped alleviate a persistent pain syndrome in patients with severe trauma.

The role of xenon in pain management in oncological patients was studied by V. Potievskaya [55, 32, 56]. RCTs conducted in 2021 [55] and 2023 [56] examined its effects on acute postoperative pain. Patients undergoing abdominal oncologic surgery (N=31) received inhalations of a 25±5% xenon-oxygen mixture for 10 minutes, while the placebo group (N=29) received 50% oxygen. Pain intensity, assessed by visual analog scale (VAS), decreased in 90.3% of patients immediately after inhalation ($P<0.01$) and in 80.6% after 30 minutes ($P<0.05$), compared to 37.9% and 27.4% in the placebo group, respectively. The duration of analgesia was significantly longer in the xenon group, lasting 5 (4–8.75) hours versus 1 (0–3) hours in the placebo group (P=0.0003). Electrical neurostimulation data showed an increased pain threshold immediately after inhalation ($P<0.01$) and 30 minutes later ($P<0.05$). In addition, pupillometry revealed correlations between autonomic nervous system activity and pain severity, suggesting a modulatory effect of xenon therapy.

Neuroinflammation and brain neuronal sensitization play a key role in the development of chronic pain, leading to increased neuronal excitability and hypersensitivity [57]. A human volunteer study [58] demonstrated that xenon inhibits the increased activity in the sensorimotor and insular regions of the brain observed during repeated pain stimulation, thereby preventing the progression to chronic pain.

A RCT by V. Potievskaya et al [32] included 95 oncology patients with chronic pain syndrome. In the intervention group (N=48), patients underwent seven sessions of inhalation with a 50% xenon-oxygen mixture. A statistically significant reduction in pain intensity as measured by the numerical rating scale (NRS) was observed — from 50 (40; 60) to 40 (25; 50) points ($P<0.05$) — while no significant changes were observed in the control group.

A larger study on the use of xenon for chronic pain was conducted by G. Abuzarova and colleagues [59]. This RCT included 131 oncology patients with moderate to severe chronic pain syndrome. The intervention group (N=66) received standard therapy along with 30-minute inhalations of a 50% xenon-oxygen mixture for seven days. Thirty minutes after inhalation, the median pain reduction on NRS was 19.0 mm in the xenon group compared to 4.0 mm in the placebo group ($P<0.001$). The difference remained significant two weeks after treatment: 15.0 mm vs. 0.0 mm ($P<0.001$). A reduction in the daily dose of thiamazole was also observed in the xenon group, from 210.9±31.3 mg to 150.1±28.3 mg.

Seven patients (5.3%) reported mild adverse events, with nausea and vomiting being the most common (five cases). One patient reported dizziness, excessive sleepiness, and pain.

Thus, the use of xenon as part of a comprehensive treatment approach for oncology patients may contribute to improved quality of life by alleviating chemotherapy-induced nausea and vomiting, managing mental and emotional distress, and reducing acute pain in chronic pain syndromes. However, further studies are needed to confirm these effects. In addition, xenon's potential to stimulate hematopoiesis [60] and its reported organoprotective properties may help mitigate the harmful effects of radiation and chemotherapy, but this also requires further investigation.

Therapeutic Use of Xenon in Pulmonary Disease

Xenon is the densest of all gases and its inhalation may increase airway resistance. However, a study in healthy volunteers found that a high concentration of xenon-oxygen mixture had no significant effect on airway compliance or transpulmonary pressure gradient [61]. Therefore, xenon inhalation is considered relatively safe and may be explored as a potential therapeutic agent for various inflammatory lung conditions. However, it may exacerbate conditions associated with bronchial obstruction.

To date, no randomized controlled trials have been conducted in this area. V. Udut and colleagues [62] reported a case of xenon therapy in a patient with ARDS due to COVID-19. After five days of inhalation of 70% xenon, the patient showed a decrease in heart rate and respiratory rate and an increase in SpO_2. Laboratory tests demonstrated a reduction in inflammatory markers: C-reactive protein decreased from 102.1 to 11.37 mg/L, D-dimer from 620 to 460 ng/mL, and leukocyte count from 14 to 6.4×10^9/L. Computed tomography (CT) scans showed a reduction in lung damage from 45% to 15%.

Further experimental studies by the same research group identified key mechanisms of xenon's therapeutic effects, including anti-inflammatory and angioprotective properties, modulation of hemostasis, and restoration of surfactant activity [63–65].

Conclusion

Our review of the literature highlights the significant therapeutic potential of inhaled xenon in several medical fields, including neuroprotection,

cardioprotection, oncology, pulmonary disease, and the treatment of addictive and neurotic disorders (Table). However, despite more than 30 years of clinical research, the number of high-quality publications based on RCTs remains limited.

To date, only 12 RCTs and 8 prospective controlled studies (without explicit randomization) have investigated the medical use of xenon. Many of these studies are limited by small sample sizes and a high risk of bias, reducing the ability to draw definitive conclusions about the clinical efficacy of xenon.

To fully evaluate the therapeutic potential of xenon and its impact on long-term clinical outcomes, further large-scale randomized trials are needed. Their results could significantly expand our understanding of xenon therapy targets and its potential applications in modern medicine.

Table. Clinical Use of Inhaled Xenon in Subanesthetic Doses.

Study	Design*	Diagnosis	Exposure	Key Effects of Xenon
Use of xenon for neuroprotection				
Azzopardi D., 2013 [17]	Prospective uncontrolled, *N*=14	Perinatal encephalopathy	30% xenon, 24 hours	Anticonvulsant effect
Dingley J., 2014 [18]	Prospective uncontrolled, *N*=14	Perinatal encephalopathy	25–50% xenon, 3–18 hours	Anticonvulsant effect
Azzopardi D., 2016 [20]	RCT, *N*=92	Perinatal encephalopathy	30% xenon, 24 hours	No significant effect on brain damage
Laitio R., 2016 (XeHypotheCA Trial) [16]	RCT, *N*=110	Out-of-hospital cardiac arrest	40% xenon, 24 hours	Reduced white matter damage, lower 6-month mortality (*P*=0.053)
Lazarev V., 2019 [19]	Case study, *N*=1	Refractory status epilepticus	60% xenon	Anticonvulsant effect
Grebenchikov O., 2022 [21]	RCT, *N*=24	Ischemic stroke	40% xenon, 6 hours	Improved consciousness (GCS, FOUR), reduced neurological deficit (NIHSS)
Shpichko A., 2023 [22, 23]	RCT, *N*=24	Chronic disorders of consciousness, consequences of severe TBI	30% xenon, 30 minutes, 7 days	Restoration of consciousness (CRS-R), increased BDNF (marker of neuronal regeneration)
Use of xenon for cardioprotection				
Molchanov I., 2012 [31]	Prospective controlled, *N*=35	Acute coronary syndrome	25–50% xenon, 20–40 minutes, 3–5 days	Reduced myocardial damage markers, improved hemodynamics
Arola O., 2013 [14]	RCT, *N*=36	Out-of-hospital cardiac arrest	40% xenon, 24 hours	Reduced troponin T levels at 72 hours
Arola O., 2017 (XeHypotheCA Trial) [15]	RCT, *N*=110	Out-of-hospital cardiac arrest	40% xenon, 24 hours	Reduced troponin T levels at 72 hours
Saraste A., 2021 [30]	RCT, *N*=38	Out-of-hospital cardiac arrest	40% xenon, 24 hours	Increased left ventricular ejection fraction, improved systolic deformation
Use of xenon in the treatment of addictive disorders				
Naumov S., 2002 [34]	Prospective comparative, *N*=30	Opioid addiction, acute withdrawal syndrome	50% xenon, 2–3 min, 17 sessions (7 days)	Reduced cortisol, growth hormone, glucose, aminotransferase activity; increased TSH and thyroxine; alleviation of withdrawal symptoms
Shamov S., 2006 [36]	Prospective controlled, *N*=80	Opioid withdrawal syndrome	50% xenon, 40 minutes, 9–10 sessions	Pain relief, reduced affective, asthenic, and behavioral disorders, improved psycho-emotional state
Shamov S., 2007 [37]	Prospective controlled, *N*=101	Acute encephalopathy in patients with substance dependence	50% xenon, 7–10 sessions, 5 days	Rapid reduction of psychiatric and somatovegetative disturbances, no adverse effects on hemodynamics or respiration
Kuznetsov A., 2007 [41]	Prospective controlled, *N*=138	Alcohol withdrawal syndrome	Subanesthetic doses of xenon, frequency of sessions based on symptoms	Reduced alcohol craving, earlier resolution of withdrawal symptoms, improved cognitive function
Tsygankov B., 2013 [39]	Prospective controlled, *N*=120	Alcohol and opioid dependence, withdrawal syndrome, encephalopathy of various etiologies	33% xenon ($Xe:O_2$ = 1:2), 5–7 minutes, 7–12 sessions, 5 days	Reduced anxiety, depression, cognitive impairment, improved EEG and REG parameters, normalized cerebral hemodynamics, reduced need for opioid analgesics and tranquilizers

Table. Clinical Use of Inhaled Xenon in Subanesthetic Doses.

Study	Design*	Diagnosis	Exposure	Key Effects of Xenon
Utkin S., 2014 [38]	Prospective comparative, *N*=78	Opioid withdrawal syndrome	25% xenon, 10 days, 20 minutes per session	Reduced severity of withdrawal symptoms, no psychopharmacological side effects
Strepetova O., 2014 [35]	Prospective controlled, *N*=137	Alcohol disorders: withdrawal syndrome, delirium, coma	25–30% xenon, 10–15 minutes, 6 days	Reduced sedative medication doses, lower frequency of complications (delirium, coma), faster recovery of consciousness, improved cognitive functions
Use of xenon in the treatment of neurotic disorders				
Igoshina T., 2013–2014 [45, 46]	Prospective controlled, *N*=40	Neurotic disorders in high-risk profession individuals	20–30% xenon, 10–30 minutes, 10 sessions	Reduced anxiety, depression, improvement in EEG parameters
Shvetski F., 2016 [48]	Prospective uncontrolled, *N*=30	Chronic stress and fatigue in anesthesiologists and intensivists	70% xenon, 3 minutes, flow rate 3.5–5.5 L/min	Reduced anxiety levels, improved heart rate variability, increased cardiovascular functional reserves, improved sleep quality
Dobrovolskiy A., 2017 [42]	Prospective uncontrolled, *N*=81	Panic disorder	15–30% xenon, 6–7 sessions	Reduced anxiety according to SAS and HADS-T scales
Sabinina T., 2019 [43]	Prospective uncontrolled, *N*=7	Severe trauma, acute stress disorder, persistent pain syndrome	15–30% xenon, 15–20 minutes, 3–12 sessions	Reduced acute pain, improved sleep, reduction in acute stress disorder, alleviation of phantom pain, normalization of psycho-emotional state
Use of xenon in the treatment of neoplastic diseases				
Nikolaev L., 2014 [50]	RCT, *N*=76	Breast cancer, chemotherapy	30% xenon, 30–40 minutes during chemotherapy sessions	Reduced frequency of acute nausea and vomiting, reduced anticipatory vomiting, improved quality of life
Sidorenko Yu., 2019 [51]	Prospective uncontrolled, *N*=30	Cervical cancer, surgical menopause	12–22% xenon, 10–20 minutes, 5 sessions every other day	Normalization of EEG, reduced anxiety, depression, fatigue, improved sleep, appetite, work capacity, increased activity and optimism
Rozenko D., 2021 [52]	RCT, *N*=60	Breast cancer, surgical treatment	15–22% xenon, 10–25 minutes, 5 sessions	Reduced depression, anxiety, weakness, sleep disturbances; normalization of EEG
Potievskaya V., 2022 [32]	RCT, *N*=95	Chronic pain syndrome in cancer patients	50% xenon, 8–10 minutes, 7 sessions	Reduced intensity of chronic pain, no significant impact on cardiovascular system
Potievskaya V., 2021, 2023 [55, 56]	RCT, *N*=60	Acute postoperative pain in cancer patients	25% xenon, 10 minutes	Reduced pain intensity on VAS, increased pain threshold, decreased analgesic use
Abuzarova G., 2020 [59]	RCT, *N*=131	Chronic pain in cancer patients	50% xenon, 8–9 minutes, 7 sessions	Reduced intensity of chronic pain, decreased daily consumption of tramadol and NSAIDs
Use of xenon in the treatment of pulmonary conditions				
Udut V., 2021 [62]	Clinical case, *N*=1	Acute respiratory distress and neuro-psychiatric disorder in COVID-19	70% xenon, 1 minute, once per day, 5-day course	Increased oxygen saturation, reduced dyspnea, normalized respiratory rhythm, decreased anxiety, depression, and insomnia, improved lung tissue structure on CT

Note. RCT — randomized controlled trial; PTSD — post-traumatic stress disorder; VAS — visual analog scale; ARDS — acute respiratory distress syndrome; CT — computed tomography; NSAIDs — non-steroidal anti-inflammatory drugs; EEG — electroencephalogram; REG — rheoencephalogram. * — many publications do not specify the study design; in such cases, the type of study was determined based on the description of the study. ** — the study describes a control group, but the primary endpoints were not compared between groups.

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