Review Article

Xenon as Promising Treatment for Patients with PTSD: Case Report, Justification of Approach and Review of Literature

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Abstract

Posttraumatic Stress Disorder (PTSD) is a debilitating disease with very few available treatment options where novel effective interventions constitute a significant unmet need. This case report describes successful treatment of a patient with panic disorder/PTSD stemming from the 2010 Moscow subway terrorist attacks through the combination of script-driven trauma memory reactivation and inhalation of a xenon-based gas mixture. Xenon is a competitive inhibitor of NMDA receptors known to play a role in memory reconsolidation, a learning and memory process where memories temporarily enter a labile state after reactivation and may be modified. Literature describing, current pharmacological and exposure-based treatments are reviewed and provide the basis for use of this novel treatment strategy to target and modify emotional memories.

ABBREVIATIONS

PTSD: Posttraumatic Stress Disorder; Panic Disorder, PD; Xe: Xenon; NMDA: N-Methyl-D-Aspartate; DSM: Diagnostic and Statistic Manual of Mental Disorder; PCL-5, PTSD Checklist for DSM-5; SSRI; Selective Serotonin Reuptake Inhibitor; DCS: D-Cycloserine

INTRODUCTION

Posttraumatic Stress Disorder is a debilitating psychiatric condition associated with tremendous emotional and financial costs to the health care system. It is estimated that approximately 7% of Americans will suffer from PTSD at one point in their lives, with significantly higher proportions in war veterans suffering from PTSD (approximately 12% to 30%; Department of Veterans Affairs, National Center for PTSD). Diagnosis of PTSD is based on exposure by the individual to a traumatic event and the manifestation of symptoms categorized into four different clusters. The first, termed "re-experiencing", involves the emotional and perceptual reliving of a traumatic event either spontaneously or in response to triggers that remind one of the event. The second symptom cluster, termed "avoidance", involves avoidance of places and activities that are reminders of the event. The third cluster involves hypervigilance about one's surroundings, sleep disturbance, anxiety, and lack of ability to maintain anger control, sometimes leading to physical violence. In the DSM-5, a 4th cluster of symptoms, termed 'negative alterations in cognitions and mood', has been added. It incorporates several symptoms previously included in the DSM-4 avoidance and numbing cluster, and adds persistent distorted blame of self or others, persistent negative emotional state as new symptoms, the tendency to social isolation, and reduced ability to experience positive emotions in relationships with others based on empirical data on the phenomenology of the condition published since DSM-4 [1]. Together, symptoms must be present for over 1 month and create distress and functional impairment (e.g. social, occupational) for the diagnosis of PTSD.

In a United States government study conducted 10 years ago it was estimated that PTSD in veterans of the Iraq and Afghanistan wars cost the American Health Care System 2.8 billion dollars annually [2]. Patients with PTSD are reported to have a severely depressed quality of life [3], including deterioration of marital and family relationships [4], inability to maintain employment [5], exaggerated proclivity towards substance abuse, general medical illnesses such as increased risk of heart failure [6], suicidal tendencies and completed suicides [7], and early death [8]. In addition, patients with PTSD are reported to have an increased incidence of clinical depression as comorbidity [9].

Currently the main treatment interventions for PTSD include psychotropic medications and/or psychotherapy. Antidepressants are commonly prescribed [10]. The selective serotonin reuptake inhibitor (SSRI) antidepressants, sertraline and paroxetine, are the only US Food and Drug Administration (FDA) approved medications for the condition. Although positive effects were reported in the pivotal studies supporting the approval of sertraline, it is important to mention that these effects did not represent a major clinical improvement for PTSD sufferers [10-13]. In fact, two clinical studies evaluating SSRIs in combat-related PTSD demonstrated no significant benefit [14,15]; this finding, in part, is associated with recent recommendations against using SSRIs in treatment of PTSD [16]. The selective serotonin and norepinephrine reuptake inhibitor venlafaxine, and the sympatholytic alpha blocker prazosin have demonstrated some efficacy in open-label trials [17,18]. Prazosin, however, was recently shown to be ineffective in achieving various efficacy endpoints of PTSD in a large randomized, placebo-controlled trial in veterans with chronic PTSD [19].

Some commonly used pharmacologic strategies, including second-generation antipsychotic augmentation of unsuccessful antidepressant therapy, as well as divalproex and bupropion, have failed to separate from placebo in randomized clinical trials with combat veterans. Use of benzodiazepines, while widely used in clinical settings, has no supporting evidence and is described as ineffective and potentially harmful in the recent National Center for PTSD (NCPTSD) treatment guideline (VA/DoD Clinical Practice Guidelines for Management of Post-traumatic Stress, Version 3.0; 2017) and were further shown to decrease the efficacy of exposure therapy for combat-related PTSD [20]. According to the same guidelines the use of Exposure Therapy is one of the recommended treatments.

CASE PRESENTATION

The patient was a 32 year old female, a talented apparel designer, who was referred by a neurologist with a preliminary diagnosis of "Panic disorder [episodic paroxysmal anxiety] F41.0". Patient's complaints were summarized as episodes of shortness of breath, palpitations, a feeling of tension in the neck and head, dizziness, accompanied by fear of "losing consciousness" and fear of death. Patient also complained of insomnia.

History of illness

For the first time the above-described panic attacks occurred in the fall of 2010. While obtaining history from the patient it was uncovered that around 10.00 am on March 29, 2010, she witnessed the consequences of the terrorist attack that had just occurred in the Moscow subway. She recalled when an elderly woman entered the car she was riding in and reported two explosions at neighboring stations. At the next stop, people entered the car with signs of injuries "their clothes were covered in blood, they were agitated, some were crying, some were wondering about possible new explosions." Most of the passengers started calling mobile phones, everyone was discussing the incident, and often the words "nightmare, horror" were used in abundance. Patient remembered getting off and heading for the exit, surrounded by a crowd of worried passengers and feeling scared. She went to work on foot, which should have been a 5-mile trip but she

got to the office by 2 pm, without any recollection of how she got there. The patient's supervisor initially reprimanded her for being late; she had difficulty answering questions, was confused, pale and finally began to cry. The next day patient realized that she could no longer get to work not only by subway, but also by other means of public transportation. She was allowed to work from home, was married in the summer, but gradually, due to growing alarm and constant thoughts about the experienced event, her symptoms intensified and she had to quit her job in the early fall of 2010. Since the incident, the patient not only did not use the subway, but tried not to even pass by its entrances. Once passing by such an entrance, she experienced the specific smell of the subway and heard the noise of the passing train, all of which triggered memories of the 2010 incident that provoked a flashback that manifested as reliving of the event, seeing the face of the elderly woman who had informed the passengers of the explosions.

Eight years later, at the time of assessment, the patient still vividly remembered the face of the elderly woman who reported the terrorist attack, people with injuries, "blood-soaked clothes" and "an endless stream of people wanting to leave the subway." These memories were unprovoked, obsessive, forcing her to cease anything that she was doing at the time, often with sensation of impending doom and death. It took her on average at least 30 minutes to "calm down" and the residual somatic symptoms such as sweating and tachycardia often lasted for up to several hours. Within the last 12 months, 4 attacks were so severe that her husband had to call the ambulance and each time the ER staff repeatedly diagnosed these episodes as "panic attacks". At her husband's insistence she turned to a neurologist, was started on daily SSRI, and on benzodiazepine as needed for attacks. Prescribed therapy did not decrease the frequency of the attacks but reduced the severity of the somatic component. When the frequency and severity of the attacks would increase, the patient would start taking benzodiazepines more frequently.

The patient never returned to full time work, significantly decreased contacts with friends and relatives, began to help her husband with his work, essentially becoming his assistant; sometimes she performed freelance work from home, but more often it was the requests of friends and acquaintances, as she was afraid to bring new customers, because she felt that at any time her condition could worsen.

Clinical assessment

The patient was a well-developed female who looked her stated age. She was oriented to place, time, and self. Her height was 161, weight 52 kg, her blood pressure and heart rate were within normal limits. She was neatly dressed, held somewhat rigidly; her speech was literate, soft and slow, with normal prosody and modulations. The questions were answered in terms of the given. No alterations in thought process or stupefaction were noted.

During the interview, when asked to talk about the incident in the subway, the patient's mood changed drastically; her voice became quieter, it was obvious that she was fighting tears, blotchy red spots appeared on the skin of the neck and chest, she clasped her hands around her trunk as if trying to warm herself and described pronounced discomfort similar to the one

she experienced before the panic attacks. The line of questions was then changed and the focus of the conversation was turned to current affairs and her warm and supportive relationship with the husband; after 15 minutes she reported a reduction in unpleasant symptoms.

Given patient's history of a traumatic event and persuasive clinical findings the diagnoses of Post-Traumatic Stress Disorder (PTSD) was strongly suspected. The PTSD Checklist for DSM-5 (PCL-5) questionnaire was then administered, which supported the diagnosis of PTSD. Psychiatric comorbidity was assessed with MINI questionnaire and was negative. As a desensitizing therapy, the method of fear memory reconsolidation blockade through script-driven memory reactivation and subsequent inhalation of subanesthetic doses of xenon that had been successfully used in our clinic was proposed.

After informed consent was obtained and after receiving relevant instructions, the patient hand-wrote down her recollection of the traumatic event, which was 1.5 pages long.

Xenon administration: Therapy was started on 11.07.2018, with a total of eight sessions held, each including patient reading the script record of the event followed immediately by inhalation of xenon-oxygen (Xe/O2) mixture. At the beginning of each visit PCL-5 was administered.

Administration of xenon was performed through inhalation of xenon–oxygen mixtures that were escalated from 15%/85% to 25%/75%. The selected dosing regime and the composition of the gas mixtures were based on the historical evidence of safety of subanesthetic use of xenon in imaging. Medical grade xenon ("medksenon"®, 99.9999%, manufacturer: AtomMed center, Moscow, Russia) and medical grade oxygen in separate containers were admixed. Mixing and administration of gases in preset concentration and volume was accomplished with the use of the medical device MAGi-AMTS1, which enables the operator to adjust the concentration of xenon in the gas mixture, and which contains the electronic flow meter with a software module that allows for such adjustments. Administration of xenon–oxygen mixture to the patient was carried out via a face mask. Patient was asked to slowly inhale, holding breath for 5–10 s; exhale into the loop and after 35–40 s exhale outside the contour and breath in the new portion of gas mixture. Xenon inhalation lasted from 3 to 4 min, and the xenon consumption was capped at 3.0 L per procedure.

Patient's blood pressure, heart rate and oxygen saturation were measured before during and for 20 minutes following each session. Below is the Tables 1,2 that describes the treatments.

The patient tolerated xenon inhalations well with no intra- or post-procedural side effects, such as euphoria, lightheadedness, headache, nausea or vomiting.

Outcomes

On the fourth visit before the introduction of the script, the patient reported that she was able to recall the whole subway trip, the name of the subway station where she first heard about the explosion, the whole route with a transfer on her way to work on that day, and some details of the events that took place after she arrived at the office. Between the third and fourth treatment sessions, the patient reported a week-long period of increased irritability which the patient subsequently explained as increasing "emotional influx" of which she was "unaccustomed and somewhat scared". After the fourth and fifth sessions, the patient, without informing the physician, went into the vestibules of different subway stations and spent 15-20 minutes there. She described moderate discomfort without an influx of memories or the occurrence of a panic attack. According to a preliminary agreement with the physician, two weeks after the eighth session, together with her husband, she took a ride in a subway through several stations each way. The agreement included the possibility of carrying out another xenon inhalation after the trip. At the office visit that took place within 30 minutes of her subway ride, the patient appeared a little excited from the very fact of the trip but quickly calmed down and declined the procedure, believing

Table 1: Treatment sessions and corresponding physiological data.

	Inhaled Xenon/Oxygen (%)	Amount of Xenon used (L)	Duration of session (min)	Vital signs before script	Vital signs after script	Vital signs 20 min after Xe/O2
Session 1 (Day 1)	15%/85%	1.9	3	BP 105/73 HR 70	BP 129/80 HR 101	BP 100/78 HR 68
Session 2 (Day 4)	20%/80%	2.1	3.5	BP 108/76 HR 72	BP 131/80 HR 99	BP 101/72 HR 70
Session 3 (Day 7)	25%/75%	2.3	3.5	BP 110/74 HR 72	BP 128 /78 HR 94	BP 115/72 HR 68
Session 4 (Day 10)	25%/75%	2.3	3.5	BP 112/74 HR 74	BP 126/80 HR96	BP 106/76 HR 64
Session 5 (Day 14)	25%/75%	2.5	3.8	BP 110/74 HR 72	BP 128/78 HR 94	BP 105/72 HR 64
Session 6 (Day 20)	25%/75%	2.7	4	BP 106/74 HR 70	BP 120/74 HR 82	BP 105/72, HR 62
Session 7 (Day 27)	25%/75%	2.7	4	BP 106/74 HR 68	BP 116/74 HR80	BP 108/76 HR62
Session 8 (Day 33)	25%/75%	2.7	4	BP 110/74 HR 68	BP 116/72 HR 68	BP 102/68 HR 64

Abbreviations: BP: Blood Pressure; HR: Heart Rate

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Table 2: The results of PCL-5 administered on day one, at the completion of the study (day 33) and a month later (day 58).			
Day 1	**Day 33**	**Day 58**	**Reduction day 1-58 (%)**
71	25	14	80.3

that she coped with the task successfully. Patient was then seen a month later. She stated that she started drawing again with the feeling that she missed not only her favorite occupation, but also the former important part of her life before the traumatic event, that she now drew a lot, and with pleasure. She resumed reading fiction. She became interested in getting up to speed with her professional field. Her circle of activities had noticeably expanded, she started socializing with her husband, going out with friends, which she had not done for many years.

Exposure therapy: One effective treatment approach, Exposure Therapy, follows from the hypothesis that PTSD is a disorder of emotional learning [21]. Specifically, in Exposure Therapy the goal is to relive a traumatic event within a safe context in order to alter the emotional manifestations associated with the event. Since PTSD is the only psychiatric disorder that requires the occurrence of an external event as a prerequisite to diagnosis, this event provides the context for learning. It is known that across species, pairing a neutral stimulus with an aversive one leads to the learning of a conditioned fear response. In humans with PTSD, the matrix of sensory stimuli embedded in the traumatic memory serve as cues that evoke a conditioned fear response in the absence of the original trauma (the unconditioned aversive stimuli). This conditioned fear response manifests as avoidance of trauma-associated cues, including thoughts, feelings, or sensory (e.g., olfactory) reminders and the experience of emotional distress when faced with these reminders. A conditioned fear response can be initially adaptive, but it should extinguish when the conditioned cues are no longer accompanied by actual risk of danger. Individuals with PTSD have not learned that the stimuli associated with their trauma no longer signal danger. Thus, PTSD may manifest with a persisting conditioned fear response independent of the original trauma and difficulty learning that stimuli previously associated with a trauma should not lead to a fear response [22]. Through Exposure Therapy, the clinician attempts to correct the negative associations in PTSD and accelerate extinction of the emotional memory charged with negative consequences associated with PTSD.

Animal and human studies demonstrate that fear is extinguished experimentally by repeatedly presenting the conditioned stimulus in the absence of the aversive stimulus, a process that has been associated with amygdala depotentiation [23]. In humans, this model translates into repeatedly re-experiencing the traumatic memory in a safe environment (absence of the aversive stimuli) until the fear is extinguished. This process is hypothesized to be part of the mechanism of action in Exposure Therapy, the treatment with the strongest empirical evidence for PTSD [24]. According to the 2008 Institute of Medicine (IOM) Report, Exposure Therapy was the only intervention with sufficient evidence to "conclude efficacy" in the treatment of PTSD. Although Exposure Therapy has shown to be efficacious for treatment of PTSD, a recent randomized clinical study in 370 military personnel with PTSD showed relatively modest reductions in PTSD symptom severity [25].

Memory lability during reconsolidation: The mental re-experience of the traumatic event is critical to the maintenance of posttraumatic symptoms over time. Animal and clinical studies of memory consolidation have demonstrated that new memories are maintained in short-term memory until they are transferred at the cellular level into long-term storage [26]. This consolidation is necessary for the development of stable long-term memory of a traumatic event. When reactivated, the memory can again become labile, allowing for updating of new information before it is reconsolidated to long-term memory for more permanent storage [27]. This lability of memory during reconsolidation offers a very important window during which the long-term traumatic memories can be influenced. Thus, reconsolidation is an important mechanism for updating or modifying memories in which it may be possible to intervene. While exposure therapy alone has some success clinically [28], preclinical studies have shown the feasibility of degrading the persistence of a fear memory by interfering with the cellular mechanisms associated with memory reconsolidation [29]. Unfortunately, the chemical agents that have demonstrated efficacy in preclinical models are generally protein synthesis inhibitors (e.g. anisomycin,), which are not clinically feasible.

Augmentation of exposure therapy: One of the important aspects of Exposure Therapy is the mechanism by which during retrieval, the memory becomes sensitive to manipulation before reconsolidation. If manipulation is induced during the reconsolidation phase, but prior to the full extinction process, the memory may be lost, or its emotional significance may be altered. The experimental manipulation of memory reconsolidation was resurrected after a 30-year hiatus [30], by studies from Nader, LeDoux and colleagues, who described the disruption of Pavlovian fear memories by anisomycin administered after memory retrieval [31]. The principle of reconsolidation manipulation is based on the findings that 'new' memories are initially labile and sensitive to disruption before being consolidated into stable long-term memories. The process of memory reconsolidation appears to involve new protein synthesis, particularly in the areas of the brain known as the lateral and basal nuclei of the amygdala (LBA) that are believed to be a site of memory storage in fear learning. This has been previously demonstrated by experiments in which injections of the protein synthesis inhibitor anisomycin into the LBA shortly after training prevented consolidation of fear memories [32,33].

The experiments by Nader et al., showed that consolidated fear memories, when reactivated during retrieval, return to a labile state in which infusion of anisomycin shortly after memory reactivation produces amnesia on later tests, regardless of whether reactivation was performed 1 or 14 days after conditioning. However, in the absence of memory reactivation, treatment with anisomycin left memory intact. Consistent with a time-limited role for protein synthesis in consolidation, delay of the infusion until six hours after memory reactivation produced no amnesia. These data showed that consolidated fear memories,

when briefly reactivated, return to a labile state that requires *de novo* protein synthesis for reconsolidation [31]. This study demonstrated first, that consolidated memories could be "erased" after retrieval, and second, that mechanistically, this so-called "reconsolidation" process resembled the original consolidation in its requirement for protein synthesis.

Although the use of protein synthesis inhibitors is not clinically useful in humans for reconsolidation blockade, various pharmacotherapeutics are being developed for augmentation of the extinction learning process that may occur during Exposure Therapy. For instance, D-cycloserine (DCS; Seromycin) is a partial agonist at the NMDA receptor, a member of the glutamate receptor family, which has an essential role in mediating learning and memory. Both fear learning and extinction are blocked by antagonists at the glutamatergic NMDA receptor, whereas enhancement of NMDA function is thought to enhance both consolidation/reconsolidation and extinction.

The importance of the NMDA system in extinction is suggested by numerous studies [34-37]. In one experimental system, Zimmerman and Maren assessed the role of NMDA receptors in the central nucleus of the amygdala (CEA), which is known to be involved in the acquisition of conditioned fear, but it is not known whether it plays a role in fear extinction. Infusion of glutamate receptor antagonists into the basolateral complex of the amygdala (BLA) or CEA prior to the extinction of fear to an auditory conditioned stimulus (CS) in rats was performed. Infusion of the alpha-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptor antagonist, 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f]quinoxaline-2,3-dione (NBQX), into either the CEA or BLA impaired the expression of conditioned freezing to the auditory CS, but did not impair the formation of a long-term extinction memory to that CS. In contrast, infusion of the NMDA receptor antagonist, D,L-2-amino-5-phosphonopentanoic acid (APV), into the amygdala, spared the expression of fear to the CS during extinction training, but impaired the acquisition of a long-term extinction memory. Importantly, only APV infusions into the BLA impaired extinction memory. These results reveal that AMPA and NMDA receptors within the amygdala make dissociable contributions to the expression and extinction of conditioned fear, respectively [38].

The role of NMDA receptors is central in modulation of fear memories in conditions such as panic disorder (PD) and PTSD. In a recent article, NMDA receptor antagonists were identified as the most promising target for novel pharmacotherapies to treat PTSD [39]. The data were generated from a survey of 45 PTSD investigators from around the world that were asked to rank the top five potential new therapeutic targets for PTSD. Furini (2014) reviewed the history of fear extinction research and efforts to determine the mechanisms involved. He summarized that fear extinction is initiated and maintained by interactions between the hippocampus, basolateral amygdala, and ventromedial prefrontal cortex, which involves feedback regulation of the latter by the other two areas [40]. Fear extinction depends on NMDA receptor activation. It is positively modulated by D-serine acting on the glycine site of NMDA receptors.

Pharmacological manipulation of extinction has been successfully performed in rodent models. For example,

Ledgerwood et al. (2003), established a system where rats received 5 light-shock pairings as conditioning. The following day, rats received 6 light-alone presentations in order to induce extinction. Twenty-four hours later, rats received 1 light-alone presentation (test). Subcutaneous DCS injection before or after extinction training significantly enhanced extinction, and the dose-response curve for this effect was linear. Increasing the delay of DCS administration after extinction training led to a linear decrease in the facilitatory effect. The effect of systemic administration was replicated by intra-basolateral amygdala infusion. These results suggested that DCS facilitates extinction of conditioned freezing by acting on consolidation processes partly mediated by the basolateral amygdala [41].

Xenon: Xenon is a noble gas that was first discovered in 1898 by British chemists Sir William Ramsay and Morris W. Trave as a result of repeated fractional distillation of the noble gas krypton. It is an extremely rare element in the atmosphere, comprising approximately 0.05 parts per million in air. Xenon is a competitive inhibitor of the NMDA receptor through blockade of the glycine co-agonist site (Figure), thus reducing glutamate neurotransmission and inhibiting neuronal excitation. Xenon also blocks excitotoxicity produced by excess glutamate (such as occurs after neuronal insult) and the deleterious effects of excessive influx of calcium ions, which results in neuroprotection [42]. In addition, xenon reduces excitatory neurotransmission through downregulation of 5-HT3 [43], nicotinic acetylcholine [44], and AMPA receptors [45] as well as potassium [46] and HCN channels [47]. It also facilitates inhibitory neurotransmission by upregulating glycine receptors [44] and activating TREK1 channels [48]. Xenon has been demonstrated to inhibit neuroinflammation in animal models of stroke and ischemia/reperfusion [49,50], has proven clinical safety and efficacy in reperfusion of neonatal ischemia [51], and has been demonstrated to inhibit NF-Kappa B, TNF-alpha and pro-inflammatory cytokines [52]. The medical use of the inert gas xenon for the induction of anesthesia was first reported in 1951 in the journal Science [52]. Subsequently, the unique properties of xenon which include: 1) rapid on/off kinetics; 2) lack of metabolites/excretion only through lungs; and 3) ability to inhibit glutamatergic signaling/excitotoxicity, led to numerous scientific investigations and publications of these preclinical and clinical data.

We recently conducted an open-label clinical trial to determine the safety and efficacy of subanesthetic concentrations of xenon gas in the treatment of patients with Panic Disorder (PD) [54]. Patients with PD alone (N=42) or PD with other comorbidities (N=39) received 6-7 treatment sessions where they inhaled increasing concentrations of xenon up to 30%. The study demonstrated that xenon is a potentially effective modality in acute treatment of PD, the anti-panic effect of xenon administration persisted for at least 6 months, and xenon was well tolerated.

Xenon inhalation therapy for blockade of trauma memory reconsolidation: In the described prior studies, DCS (acting as an NMDA receptor partial agonist) was used to explicitly enhance the extinction learning process. Of note, while a number of early extinction-augmentation clinical trials were positive with DCS [55,56], more recent studies and meta-analyses have been
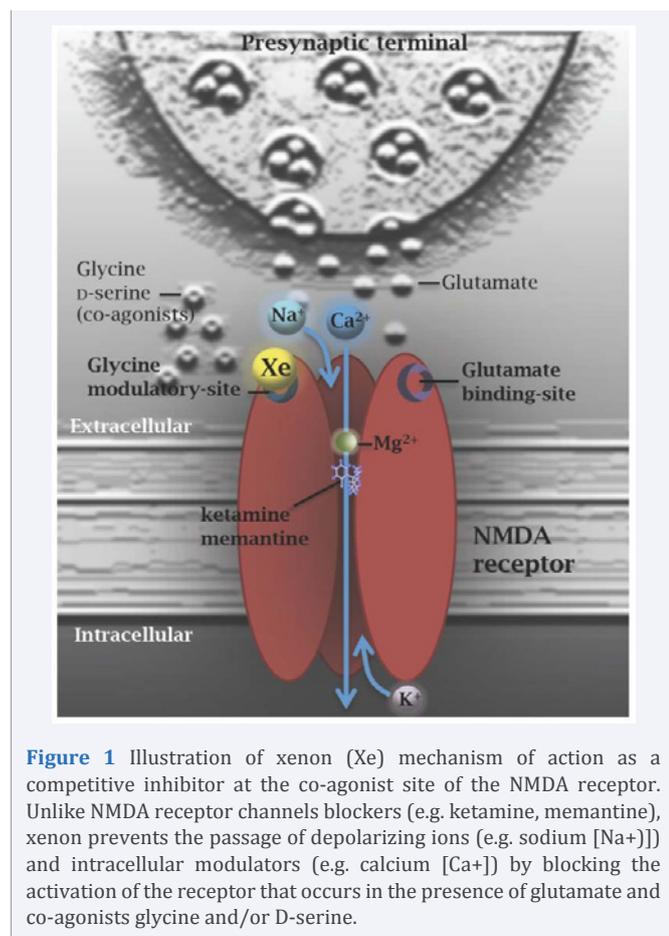
Figure 1 Illustration of xenon (Xe) mechanism of action as a competitive inhibitor at the co-agonist site of the NMDA receptor. Unlike NMDA receptor channels blockers (e.g. ketamine, memantine), xenon prevents the passage of depolarizing ions (e.g. sodium [Na+)]) and intracellular modulators (e.g. calcium [Ca+]) by blocking the activation of the receptor that occurs in the presence of glutamate and co-agonists glycine and/or D-serine.

mixed or negative [57]. One explanation for these more recent treatment failures is that if the memory was only briefly recalled during Exposure Therapy, the process of memory reconsolidation would prevail over memory extinction (which requires a more robust, longer duration and consistent reactivation). As a partial agonist, DCS would be predicted to enhance the reconsolidation (as meaningful extinction learning couldn't be achieved) instead of blocking it – resulting in an apparent treatment failure. This may be especially true in cases where DCS was administered before reactivation of the trauma memory. In contrast, if good extinction learning was achieved, DCS would be predicted to enhance extinction over reconsolidation. Hence, blocking memory reconsolidation with a short-acting NMDA antagonist, such as xenon – which can be given in a temporally-dependent manner, may be a more practical, robust and feasible way to modulate PTSD memories than to enhance extinction with NMDA partial agonists, such as DCS.

Xenon may have distinct advantages over other NMDA antagonists, such as ketamine, for future translation to the clinical setting. First, subsedative concentrations of xenon that would sufficiently block the NMDA receptor without producing full anesthesia could potentially be administered briefly in a safe and effective manner in the outpatient setting with minimal or no medical monitoring. Second, in contrast to existing NMDA receptor channel blockers like ketamine (see Figure 1), xenon has been shown to inhibit NMDA receptor activity through competitive inhibition of the co-agonist glycine at the glycine

site of the NMDA receptor [58] – an action that does not induce psychotomimetic effects. Given these unique characteristics, preliminary investigation into the safety and efficacy of administration of brief subsedative xenon concentrations as a pharmacologic intervention to treat PTSD is warranted.

While xenon has yet to be approved as an anesthetic agent in the United States, there is extensive clinical experience using subsedative concentrations of xenon as a contrast agent in xenon-enhanced computed tomography (Xe-CT). The safety of xenon diagnostic drug products has been evaluated in two large-scale studies. Latchaw conducted a large multicenter trial to assess safety in 1830 patients who underwent computed tomographic (CT) cerebral blood flow (CBF) examinations [59]. The dose included 32% Xe CT for a period of 4.3 minutes. In this analysis, the most common adverse event was respiratory irregularity (defined as a pause of >10 seconds) in 3.6% of patients. None of these events were prolonged or serious. Other less frequent events included headache (0.4%), seizures (0.2%), nausea and vomiting (0.2%), and change in neurologic status (0.1%).

Another more recent multicenter study, published by Carlson [60], was conducted in over 2000 patients with variety of neurological disorders, including stroke, occlusive vascular disease, traumatic brain injury, subarachnoid hemorrhage, aneurysms, tumors, and epilepsy. This large study was conducted under an FDA IND with data (including adverse events) presumably collected in accordance with Good Clinical Practice (GCP). Dosing was administered at a concentration of 28% Xe-CT and inhaled over a period of 4.3 minutes. Results from the study demonstrated a very low risk of adverse events and no risk of permanent morbidity or sequelae from xenon inhalation. Overall, respiratory adverse events were the most common with 5.9% of patients experiencing minimal respiratory suppression (10-19 seconds), 1.9% of patients experiencing prolonged respiratory suppression (>20 seconds), and 1.7% experiencing hyperventilation. Notably, none of these adverse events resulted in any consequence to any patient, and all events resolved spontaneously in response to normalized pCO2 or cessation of xenon administration. Other adverse events occurred in 2.6% of patients including impaired consciousness, tremors, hypertension, dyspnea, taste disturbance, and numbness. Importantly, for both of these large studies, the severity of underlying neurologic disorders in these patients may have contributed to the occurrence of adverse events.

Moreover, because xenon gas rapidly dissolves in blood and freely crosses the blood-brain barrier, this subanesthetic concentration provides good brain penetration and establishes cerebral levels of xenon sufficient to be detected by Xe-CT [61]. In addition, several other small studies have examined the administration of subsedative doses of xenon (ranging from 10% to 47%), to patients or healthy volunteers and found it to be well tolerated and without any significant adverse physiological effects [62-66].

The hypothesis that xenon inhalation therapy could be used for blockade of trauma memory reconsolidation as a clinical strategy to treat disorders of emotional memory is supported by studies showing that 1) xenon inhibits NMDA receptors [58], which are known to play a role in memory reconsolidation

[67], 2) xenon reduces NMDA-mediated synaptic currents and neuronal plasticity in the basolateral amygdala and CA1 region of the amygdala [68] and the hippocampus [69]; brain areas involved in Pavlovian fear conditioning used to elucidate learning and memory processes, including reconsolidation [70,71], 3) NMDA receptor glycine site antagonists like xenon do not appear to have significant abuse potential and do not induce psychosis [72], which is consistent with clinical experience [62].

Along these lines, Meloni et al. (2014), examined whether xenon administered after fear memory reactivation could affect subsequent expression of fear-like behavior (freezing) in rats, hypothesizing that xenon would block fear memory reconsolidation [73]. Male Sprague-Dawley rats were trained for contextual and cued fear conditioning and the effects of inhaled xenon (25%, 1 hour) on fear memory reconsolidation were tested using conditioned freezing measured days or weeks after reactivation/xenon administration. Xenon administration immediately after fear memory reactivation significantly reduced conditioned freezing when tested 48 hours, 96 hours or 18 days after reactivation/xenon administration. Xenon did not affect freezing when treatment was delayed until 2 hours after reactivation or when administered in the absence of fear memory reactivation. Based on these data, Meloni et al., (2014) concluded that 1) xenon substantially and persistently inhibits trauma memory reconsolidation after reactivation in a time-dependent manner, 2) that it could be used as a new research tool to characterize reconsolidation and other memory processes, and 3) that it could be developed to treat people with PTSD and other disorders related to emotional memory. Similar amnestic-like effects were observed using ketamine given immediately after reactivation of a contextual fear memory - suggesting an NMDA receptor-dependent blockade of reconsolidation [74] - and support the development of translational studies examining the effects of ketamine-assisted psychotherapy for PTSD [75] along the same lines as that proposed for xenon.

CONCLUSIONS

Here we report on the remarkable improvement in a patient with PD/PTSD symptoms stemming from exposure to a traumatic event. We believe that by combining xenon inhalation with trauma memory reactivation through a script-driven recounting of the event, memory reconsolidation was effectively inhibited through this treatment. The overall effect was a reduction in the occurrence of panic attacks, a remission of avoidance of places and cues that triggered distress in the patient, and a regaining of quality of life through this course of trauma-focused pharmacotherapy. Given new evidence for the use of NMDA receptor antagonists as a promising treatment for PTSD, and emerging strategies that combine targeted medications with psychotherapy sessions, we believe these case report data firmly support further study of xenon-based treatments for this debilitating mental illness.

CONFLICT OF INTEREST

The authors report no financial or other relationship relevant to the subject of this article.

Dr. Dobrovolsky is the co-founder of Nobilis Therapeutics, Inc., a company that is developing treatments for psychiatric disorders using noble gas xenon.

Dr. Bogin is the co-founder and CEO of Nobilis Therapeutics, Inc., a company that is developing treatments for psychiatric disorders using noble gas xenon.

Dr. Meloni is a co-inventor on patent US9737562B2 owned by The McLean Hospital Corporation and licensed by Nobilis Therapeutics, Inc., covering the therapeutic use of xenon for PTSD and other anxiety disorders. He also has received licensing royalties from the above patent and grant funding from Nobilis Therapeutics, Inc., for preclinical research outside of the submitted work.

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