J Appl Biotechnol Rep. 2025 December;12(4):1784-1796

Journal of
Applied Biotechnology Reports

doi 10.30491/jabr.2025.549112.1921

Review Article

Intranasal Formulations for Organophosphorus Nerve Agent Poisoning: A Review of Recent Developments in Treatment and Prophylaxis

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Received September 24, 2025; **Accepted** October 13, 2025; **Online Published** December 30, 2025

Abstract

Organophosphorus (OP) nerve agents represent a grave global threat, encompassing both chemical warfare agents and highly toxic pesticides. The high morbidity and mortality associated with OP exposure, primarily due to the irreversible inhibition of acetylcholinesterase (AChE), underscore the critical need for rapid and effective medical countermeasures. Current standard-of-care, which relies on intramuscular or intravenous administration of anticholinergics (atropine) and cholinesterase reactivators (oximes), is limited by logistical challenges and, crucially, an inability to provide adequate protection to the central nervous system (CNS). This review examines the burgeoning field of intranasal (IN) formulations as a novel paradigm for OP antidote delivery. The IN route offers a direct nose-to-brain pathway that bypasses the restrictive blood-brain barrier (BBB), enabling CNS-targeted therapy. Preclinical research has demonstrated that IN obidoxime can completely prevent mortality and seizure-induced neuronal degeneration in animal models, an effect not observed with standard peripheral treatment. The clinical success of intranasal diazepam for seizure control provides a powerful precedent for this approach. Moreover, IN delivery holds promise for the rapid administration of prophylactic agents and next-generation bioscavengers. While the absence of human clinical trials for IN nerve agent antidotes remains a significant research gap, the well-documented advantages and efficacy of intranasal naloxone in a similar emergency setting provide a strong rationale for continued development. This report synthesizes recent findings, analyzes the comparative advantages of IN formulations, and identifies key research directions to translate these promising countermeasures into clinical practice.

Keywords: Organophosphorus Poisoning, Nerve Agent Antidotes, Prophylaxis, Intranasal Delivery, Nose-to-Brain Pathway, Blood-Brain Barrier

Citation: Baghersad MH. Intranasal Formulations for Organophosphorus Nerve Agent Poisoning: A Review of Recent Developments in Treatment and Prophylaxis. J Appl Biotechnol Rep. 2025;12(4):1784-1796. doi:10.30491/jabr.2025.549112.1921

Introduction

A Primer on Organophosphorus and Nerve Agents: A Global Public Health and Military Concern

Organophosphorus (OP) compounds are a diverse class of chemicals with widespread applications, ranging from agricultural pesticides to lethal chemical warfare agents.[1] While their cost-effectiveness has made them ubiquitous in agriculture, this has also led to a significant public health burden from occupational exposure, accidental poisonings, and intentional self-harm.[2] Beyond civilian use, OPs such as sarin (GB), soman (GD), tabun (GA), and VX are among the most toxic synthetic chemicals known, classified as nerve agents for their devastating effects on the nervous system (Figure 1).[1] The rapid onset of severe symptoms following exposure, often within seconds to minutes, coupled with their vigorous permeability through multiple routes (inhalation, ingestion, and dermal contact) necessitates a robust and immediate medical response.[2] The continued threat from these agents, evidenced by their use in conflict zones and potential for deployment in terrorist attacks, underscores a critical and persistent need for advanced medical countermeasures.[3,4]

Pathophysiology of Nerve Agent Poisoning: The Cholinergic Crisis and Beyond

The primary mechanism of action for nerve agents involves the irreversible inhibition of the enzyme acetylcholinesterase (AChE). In a normally functioning nervous system, AChE is responsible for hydrolyzing the neurotransmitter acetylcholine (ACh) in the synaptic cleft, thereby allowing nerve impulses to be transmitted and then promptly terminated. By forming a covalent bond with the active site of AChE, nerve agents prevent this crucial breakdown. The consequent accumulation of ACh leads to a state of continuous, uncontrolled stimulation, a phenomenon known as cholinergic crisis (Figure 1).[5]

The clinical presentation of this crisis is severe and multifaceted, affecting the muscarinic, nicotinic, and central nervous systems. Initial symptoms of low-dose exposure may

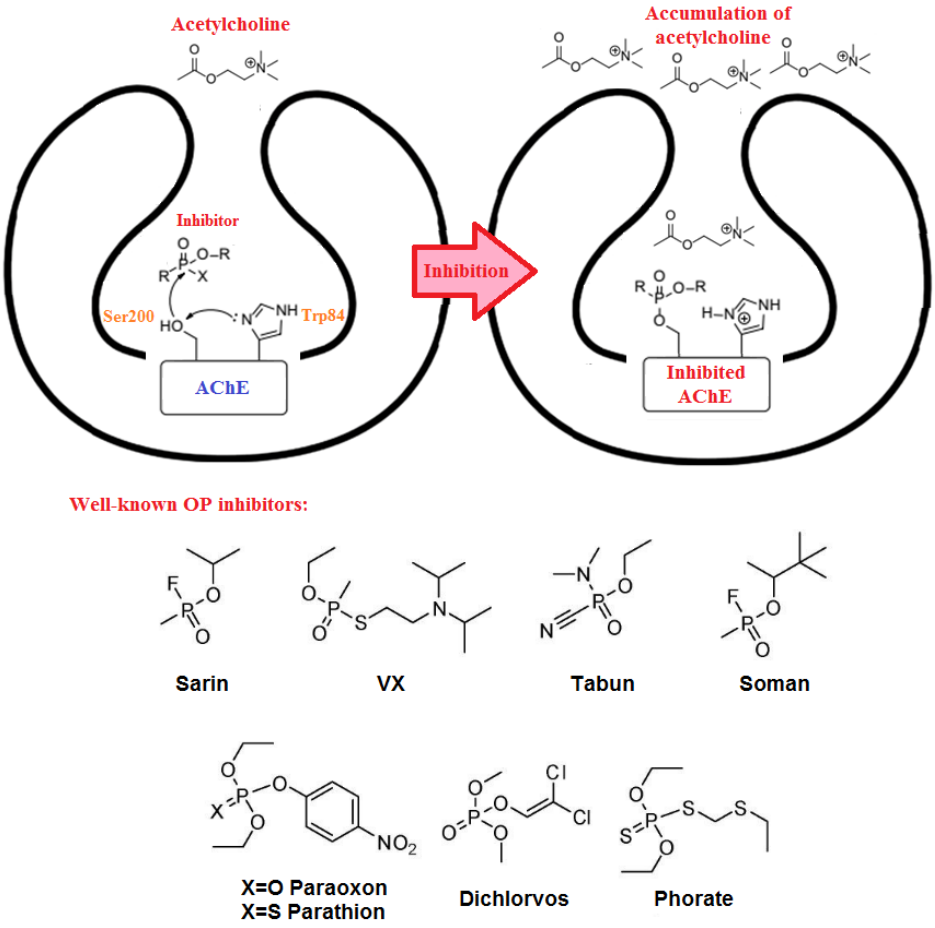

Figure 1. Inhibition of AChE and Accumulation of Acetylcholine and Well-known OP Inhibitors.

include rhinorrhea (runny nose), chest tightness, miosis (pinpoint pupils), and excessive salivation. As the dose increases, more severe effects manifest, including difficulty breathing, involuntary urination and defecation, myoclonic jerks, and seizures. The ultimate cause of death is typically respiratory failure, which can result from a combination of excessive bronchial secretions, bronchoconstriction, and paralysis of the diaphragm. Survivors are not spared from long-term consequences, as chronic neurological damage and psychiatric effects are common, underscoring the agent's impact on the CNS.[6] The standard medical counter-measures, as detailed in Table 1, target different aspects of this complex pathophysiology.

Table 1. Mechanisms of Action of Key Antidotes

Antidote Class	Example Drugs	Mechanism of Action	Effects Countered
Anticholinergic	Atropine	Competitively blocks muscarinic receptors, antagonizing the effects of excess acetylcholine.	Muscarinic effects (e.g., increased secretions, bronchoconstriction, and bradycardia).
Cholinesterase Reactivator	Pralidoxime (2-PAM), Obidoxime (OBD)	Nucleophilically reactivates phosphorylated AChE, restoring enzyme function.	Reverses both muscarinic and nicotinic effects by hydrolyzing excess ACh.
Anticonvulsant	Diazepam, Midazolam	Potentiates the action of the inhibitory neurotransmitter γ-amino butyric acid (GABA).	Central nervous system effects (seizures).

Limitations of Current Countermeasures: The Need for Rapid, Central Nervous System-Targeted Interventions

The current paradigm for nerve agent poisoning treatment, which has been in place for decades, primarily relies on auto-injectors that deliver a combination of atropine and pralidoxime intramuscularly (IM). While effective in a controlled setting, this approach has several critical limitations. First, in a mass-casualty or high-stress scenario, the use of auto-injectors can be logistically challenging and may be impractical for self-administration or by laypersons. The need for rapid and repeated administration of atropine every 5 to 10 minutes underscores the urgency of treatment and the limitations of a device-dependent delivery system.[7]

A more profound limitation is the inadequate protection afforded to the central nervous system. The oximes, which are essential for reactivating the inhibited AChE, are

hydrophilic molecules that do not readily cross the blood-brain barrier (BBB) when administered peripherally. This leaves the brain unprotected from the excitotoxic damage caused by prolonged seizures, which can lead to irreversible CNS neuropathologies and chronic neurological deficits. Therefore, while current countermeasures may improve survival by addressing peripheral symptoms, they fall short of preventing the long-term morbidity that defines a survivor's outcome. This therapeutic gap points to a clear and urgent need for new formulations that can rapidly and effectively target the CNS.[8]

The Intranasal Route: A Promising Platform for Emergency Therapeutics

Anatomy and Transport Mechanisms: The Direct Nose-to-Brain Pathway

The intranasal route has emerged as a particularly promising platform for emergency therapeutics due to the unique anatomical and physiological properties of the nasal cavity. Unlike other non-invasive routes, the nose offers a direct connection to the brain via the olfactory and trigeminal nerve pathways. This "nose-to-brain" pathway allows drugs to be transported directly to the CNS, bypassing the formidable BBB, avoiding hepatic first-pass metabolism, and minimizing systemic drug exposure. Drug delivery via this pathway is not a single process but a combination of mechanisms (Figure 2).

Therapeutics can enter the CNS through neuronal transport via the olfactory and trigeminal nerves, through the lymphatic system and cerebrospinal fluid (CSF), and, to a lesser extent, through vascular transport across the BBB. The efficacy of this direct pathway is quantified by metrics like Drug Targeting Efficiency (DTE %) and Direct Transport Percentage (DTP %), which compare drug concentrations in the brain to the systemic circulation following intranasal versus intravenous administration. High DTE and DTP values indicate substantial and direct delivery to the CNS, highlighting the potential for a new generation of brain-protective agents.[9,10]

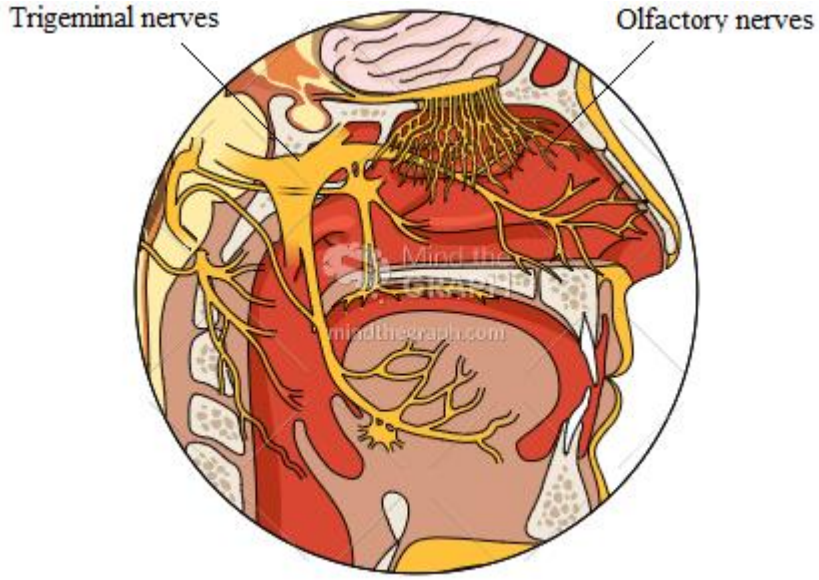

Figure 2. Illustration of the Direct Nose-to-Brain Drug Delivery Pathway via Olfactory and Trigeminal Nerves, Bypassing the Blood-Brain Barrier for Rapid CNS Access. Created using Mind the Graph (www.mindthegraph.com) under a Creative Commons license. The watermark is retained in accordance with platform requirements for free users.

Advantages and Challenges of Intranasal Drug Delivery: Speed, Convenience, and Physiological Barriers

The intranasal route offers numerous compelling advantages for emergency medical applications. Its non-invasive nature eliminates the risk of needle-stick injuries and the need for specialized training, making it a viable option for rapid self- or lay-administration in mass-casualty or out-of-hospital settings. This convenience, combined with the high vascularization of the nasal epithelium, can lead to a rapid onset of action comparable to or even faster than intramuscular injections.[11]

However, the nasal cavity's primary physiological function is to protect the lungs, not to serve as a drug delivery system. This protective role presents several significant challenges. The most prominent is mucociliary clearance, a process by which nasal secretions and cilia actively remove foreign particles and inhaled matter from the nasal lining, with the mucus layer being renewed every 15-20 minutes. This rapid clearance can significantly limit a drug's absorption time. Additionally, the limited nasal volume capacity and the potential for increased mucus production following OP exposure could further reduce the

efficacy of IN drug delivery. Furthermore, some formulations can cause irritation or even irreversible damage to the sensitive nasal mucosa.[1,12]

Overcoming Obstacles: The Role of Novel Formulations and Nanotechnology

To overcome the physiological challenges of intranasal delivery, a new generation of advanced drug formulations has been developed. Nanotechnology represents one strategy being investigated to overcome these challenges. Nanoparticles, such as liposomes, nanoemulsions, and solid lipid nano particles, offer several features that are well-suited for intranasal administration. They can encapsulate drugs, thereby increasing their solubility and protecting them from enzymatic and chemical degradation on the mucosal surface.[13,14]

The design of these carriers is crucial for their success. Lipid-based nanoparticles, for example, are highly biocom patible and can improve drug stability while also enhancing retention and absorption on the nasal mucosa due to their positive zeta potentials, which facilitate interaction with negatively charged mucin residues.[15] This focus on a sophisticated formulation is paramount. The ultimate efficacy of an intranasal therapeutic for nerve agent poisoning is not inherent to the route itself, but is highly dependent on the pharmaceutical engineering behind the drug delivery system, which must be designed to counteract the body's natural defenses and maximize nose-to-brain targeting.[16]

Intranasal Antidote Formulations

Anticholinergics

Anticholinergic agents such as atropine, glycopyrrolate, and scopolamine are cornerstone therapeutics in the management of organophosphorus (OP) nerve agent poisoning, where excessive acetylcholine at synapses leads to fatal cholinergic overstimulation. While traditional administration is intravenous (IV) or intramuscular (IM) (often via auto-injectors) these approaches can be limited in tactical, mass casualty, or field settings due to the need for trained personnel, risk of needle-stick injuries, delays in onset, and difficulties in self-administration.[17] The intranasal route offers unique advantages: it facilitates rapid systemic and central nervous system (CNS) absorption, bypasses the hepatic first-pass effect, may enable self- or lay administration, and, crucially, can provide direct nose-to-brain transport, thus bypassing the blood-brain barrier (BBB).[18] Direct CNS targeting is particularly important for mitigating the central effects of OP agents and for seizing windows of opportunity in which timely intervention prevents irreversible neurotoxicity and death. The rich vascularization and thin epithelium of the nasal mucosa, as well as the proximity to the olfactory and trigeminal neural pathways, provide a plausible mechanistic basis for rapid and enhanced CNS delivery.[18,19]

Intranasal Atropine

A key preclinical and clinical pharmacokinetic study involved a chitosan-based intranasal formulation of atropine sulphate. In healthy volunteers, intranasal atropine (6 mg with chitosan 0.5%) rapidly achieved therapeutic concentrations in serum within 5 minutes, with peak levels (49 ng/ml) reached with a time to peak concentration (T_{max}) of 30 minutes. This substantially outpaced oral and even IM routes, which peaked later and at lower concentrations. Notably, clinical atropinization was evident within 10–15 minutes following nasal dosing, confirming rapid pharma codynamic action. Importantly, the retention time of the chitosan formulation in the nasal cavity was prolonged (50% remained at 30 min), indicating slowed mucociliary clearance and extended absorption windows. Scintigraphic studies further supported significant nose-to-brain transport and systemic uptake without apparent local toxicity. All volunteers tolerated the formulation well, and side effects were mild and transient. Routine bloodwork remained normal pre/post dose.[17,20,21]

Glycopyrrolate and Other Anticholinergics

Glycopyrrolate, long used for muscarinic blockade in anesthesia, offers a favorable pharmacokinetic (PK) and safety profile relative to atropine, especially in patients at risk of cardiac arrhythmias or other cardiovascular comorbidities.[22] While intravenous glycopyrrolate has been shown to reduce secretions and maintain stable heart rate without significant dysrhythmias, studies suggest it could also be highly suitable for intranasal delivery given its rapid onset and intermediate duration (30-60 min). This is especially relevant where minimal CNS side effects are desired, as glycopyrrolate less readily crosses the BBB when delivered systemically; however, nose-to-brain formulations may alter this disposition, increasing CNS entry and potentially improving central efficacy for OP crises. The absence of major adverse events on intravenous use and rapid, predictable onset enhance its candidacy for intranasal formulations intended for emergency use. Scopolamine and derivatives (e.g., hyoscine) have also been explored in nasal gel and in-situ gelling systems, demonstrating enhanced mucosal adhesion, prolonged local retention, and effective CNS targeting in rodent models, paving the way for translational human studies.[9]

Mucoadhesive and Cubosome Systems

Recent innovation centers on cubosomes, nanostructured amphiphilic lipid carriers that self-assemble into bicontinuous cubic phases with interconnected aqueous channels and a continuous lipid matrix; when formulated as

stable, viscous intranasal gels they increase residence time on the olfactory epithelium, protect payloads from rapid mucociliary clearance, and provide sustained, diffusion-controlled release of hydrophilic, lipophilic, and amphiphilic anticholinergic drugs.[24] Cubosomal formulations carrying anticholinergics such as resveratrol have shown high brain bioavailability after intranasal administration, outperforming oral and IV analogs in rapidity of CNS effect, duration of brain exposure, and reduction of peripheral side effects. Surface engineering with mucoadhesive or receptor-targeting ligands, for example odorranalectin, further enhances epithelial binding, mucoadhesion, and receptor-mediated uptake across the olfactory mucosa, optimizing directional transport toward the CNS and reducing systemic exposure.[23]

Penetration of cubosomes across the olfactory epithelium is multi-modal and formulation-dependent. Prolonged mucoadhesion increases local release and exposure time; certain excipients can transiently modulate tight junctions to enhance paracellular passage of small hydrophilic molecules; the fluid, fusogenic cubosome membrane and direct lipid–membrane interactions favor transcellular uptake via clathrin- and caveolae-mediated endocytosis and macropinocytosis followed by transcytosis into submucosal spaces. After epithelial transcytosis, released drug or nanoparticle-derived material may access perineural routes and be transported along olfactory sensory neuron axons through the cribriform plate to the olfactory bulb, providing a direct nose-to-brain route that bypasses systemic circulation; surface function alization (for example lectins such as odorranalectin or other receptor ligands) can bias uptake toward receptor-mediated transcytosis and improve CNS targeting.[24]

Compared with alternative intranasal nanocarriers, cubosomes present a distinctive combination of high internal surface area, broad payload compatibility, membrane fusion potential, mucoadhesive gel-forming behavior, and sustained release that frequently translates to improved brain bioavailability and prolonged CNS exposure. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) protect lipophilic drugs effectively and can produce rapid systemic or brain exposure when systemic absorption is acceptable, but their more rigid, crystalline structure may limit membrane fusion and neuronal uptake. Mucoadhesive polymeric systems such as chitosan nanoparticles yield powerful mucosal adhesion and can transiently open tight junctions to enhance paracellular transport—often producing short Tmax values (10-30 min) and rapid therapeutic brain concentrations—but typically offer less co-encapsulation flexibility and shorter-term release control than cubic-phase carriers.[25,26] Liposomes and niosomes remain useful for specific payloads but generally lack the thermodynamic stability, internal surface area, and prolonged-release profile characteristic of cubosomes. Consequently, cubosomes are especially advantageous when formulation goals prioritize sustained intranasal residence, multi-modal nose-to-brain transport, co-encapsulation versatility, and minimized peripheral side effects, whereas SLNs/NLCs or polymeric mucoadhesives may be preferred when rapid systemic access, payload crystallinity control, or maximal paracellular enhancement is required.[23,25,26]

Cholinesterase Reactivators

Mechanistic Background and Need for CNS-Targeted Reactivators

Cholinesterase reactivators (primarily oximes such as pralidoxime, obidoxime, HI-6) are essential for reversing phosphorylated acetylcholinesterase (AChE) and thus restoring synaptic function after OP poisoning (Figure 3). However, these quaternary ammonium salts are highly hydrophilic and generally unable to cross the BBB when given parenterally, limiting their efficacy against central (and often fatal) manifestations of OP toxicity, a major shortcoming in standard regimens.[27]

Intranasal Oximes

Intranasal administration can deliver oximes and emergent non-oxime reactivators directly to the CNS via nose-to-brain pathways, enabling effective central AChE reactivation and neuroprotection in preclinical OP poisoning models. Several recent studies highlight advances in formulation strategies:

The therapeutic efficacy of conventional oxime-based acetylcholinesterase (AChE) reactivators, such as pralidoxime (2-PAM), obidoxime, and HI-6, is severely limited by their poor penetration of the blood-brain barrier (BBB) due to their permanent quaternary ammonium structure and high hydrophilicity.[28-30] This presents a critical therapeutic gap in organophosphorus (OP) nerve agent poisoning, as failure to reactivate inhibited AChE in the central nervous system (CNS) permits the perpetuation of seizure activity and exacerbates excitotoxic brain damage, leading to long-term neurological deficits or death. This central excitotoxicity, driven by uncontrolled seizures, is a primary cause of long-term morbidity in survivors, underscoring the urgent need for CNS-effective reactivators.[6,8] The intranasal (IN) route has emerged as a promising alternative administration pathway to overcome this limitation, leveraging the nose-to-brain delivery mechanism to facilitate direct drug transport to the CNS while bypassing the BBB. This approach not only enhances brain bioavailability but also allows for rapid intervention, which is crucial during the narrow therapeutic window following nerve agent exposure.[8]

The rationale for intranasal delivery is rooted in the unique anatomy of the nasal cavity, which offers a direct conduit to the brain. This route facilitates rapid drug absorption into the cerebrospinal fluid and brain parenchyma, avoiding first-pass metabolism and potentially enhancing CNS bioavailability.[31,32] Pioneering work by Krishnan et al.

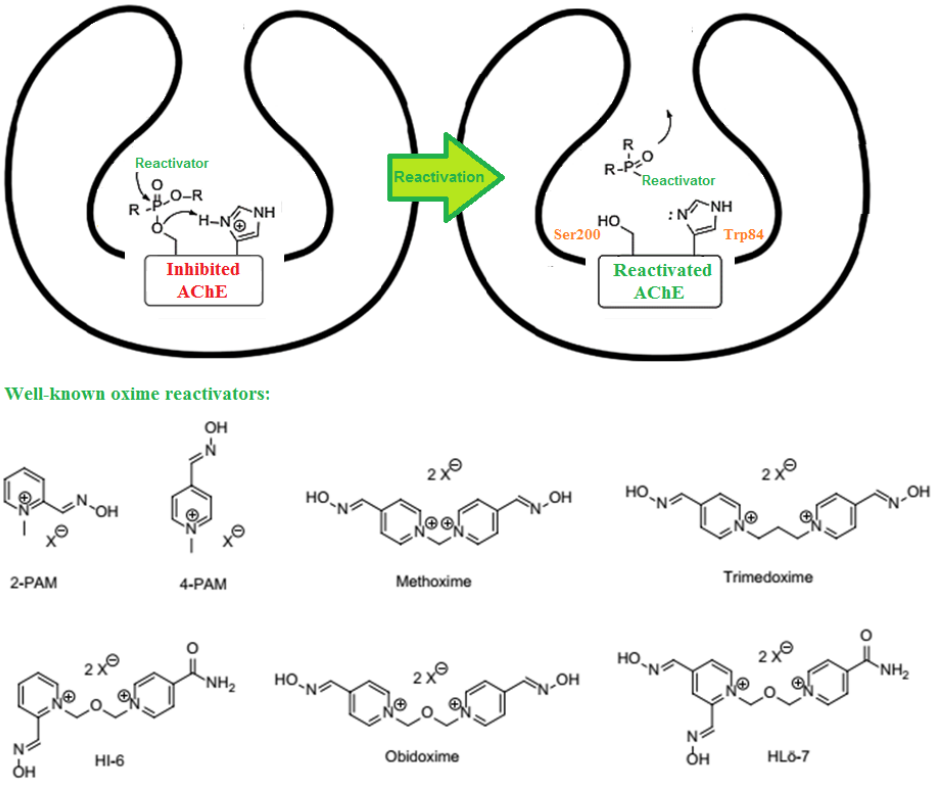

Figure 3. Reactivation of Inhibited-AChE and Well-known Oxime Reactivators.

demonstrated the profound efficacy of this approach in a severe rat model of paraoxon poisoning. The study revealed that intranasal administration of OBD, either 30 minutes pre- or 5 minutes post-exposure, in conjunction with standard intramuscular therapy (2-PAM and atropine), completely prevented mortality (0% vs. 41% in saline controls), substantially reduced seizure severity and duration, and abolished neuronal degeneration in key brain regions as assessed by Fluoro-Jade-B and silver staining. This robust neuroprotection was achieved despite only partial reactivation of brain AChE, suggesting that even modest enzyme recovery in critical "seizurogenic" regions like the amygdala may be sufficient to abort the cascade of excitotoxic injury.[33]

While the proof-of-concept for intranasal oximes is established, research has advanced to focus on optimizing delivery systems to further improve brain bioavailability and efficacy. Conventional aqueous oxime solutions, particularly of 2-PAM, can be limited by rapid mucociliary clearance and potential local irritation at high concentrations. To address these challenges, novel nanocarrier systems have been developed. Vasilieva et al. designed chitosan-decorated liposomes, or "chitosomes," for the intranasal delivery of 2-PAM. The mucoadhesive properties of chitosan enhance nasal residence time and promote paracellular transport by transiently opening tight junctions between epithelial cells. These chitosomes demonstrated a high encapsulation efficiency for 2-PAM (~60%), sustained release profiles, and significantly enhanced cellular uptake *in vitro* compared to free drug. Most importantly, in a rat model of paraoxon poisoning, intranasal administration of 2-PAM-loaded chitosomes resulted in up to 35% reactivation of brain AChE, a marked improvement over the negligible reactivation achieved with free intranasal 2-PAM. This underscores the potential of advanced formulations to maximize the therapeutic potential of intranasal oxime delivery.[32]

Beyond therapeutic reactivation, the concept of using oximes for proactive protection has also been explored. Mohan et al. developed an innovative "oxime-functionalized fabric" in which silyl-pralidoxime was covalently bound to cellulose. This fabric, designed as protective clothing and masks, catalytically hydrolyzes OP insecticides upon contact, preventing dermal and inhalation exposure before they can inhibit AChE. *In vivo* studies demonstrated that this fabric completely prevented AChE inhibition in blood and tissues, neuromuscular dysfunction, and mortality in rats repeatedly exposed to lethal doses of OPs, even after 50 wash cycles. Although this approach represents a prophylactic barrier rather than a CNS-targeted therapy, it highlights the versatile utility of oxime chemistry and complements direct neuroprotective strategies by preventing exposure at its source.[34]

In conclusion, intranasal delivery represents a transformative strategy for enhancing oxime-mediated CNS protection against OP poisoning. The evidence demonstrates that this route effectively bypasses the BBB, delivering oximes directly

to the brain to mitigate seizures, prevent neurodegeneration, and abolish mortality. Future directions should focus on the clinical translation of this approach, including the optimization of intranasal formulations (e.g., gels, nanoparticles), human factor studies for field-deployable delivery devices, and comprehensive toxicological assessments. The integration of intranasal oximes into existing treatment protocols, potentially alongside novel prophylactic tools like oxime-functionalized fabrics, holds immense promise for significantly reducing the global burden of mortality and long-term neurological morbidity associated with OP exposures.

Intranasal Nanocarriers for Reactivators

Cationic Liposomes

Cationic liposomes interact strongly with negatively charged mucin and epithelial membranes to promote membrane fusion or adsorptive endocytosis, enabling transcellular transport and sustained release compared with free solution; measurable brain AChE reactivation for 2-PAM in cationic liposomes demonstrates this mechanism *in vivo*.[35] A pivotal study formulated 2-PAM in cationic liposomes (L-α-phosphatidylcholine and dihexadecylmethylhydroxyethyl ammonium bromide, DHDHAB) for intranasal administration in rodents. Fluorescence microscopy confirmed significant brain uptake after nasal dosing, in contrast to negligible CNS entry with IV administration of free 2-PAM. Importantly, intranasal 2-PAM liposome delivery resulted in measurable reactivation of brain AChE (12% after paraoxon poisoning), a result rarely achieved via systemic administration. Liposomal encapsulation provided sustained release (~90% released over 3 hr versus near-instantaneous from solution), and formulations were stable, safe (hemolysis <10%), and non-cytotoxic at therapeutic concentrations.[36,37]

Solid Lipid Nanoparticles (SLNs)

Solid lipid nanoparticles (SLNs) stabilize lipophilic payloads within a solid or semi-solid lipid core, slowing release and extending systemic half-life; when deployed intranasally with mucoadhesive coatings, SLNs/NLCs can reach deep brain structures via integrated transcellular and lymphatic routes, though their more rigid matrix reduces fusogenicity and may limit neuronal uptake relative to cubosomes and fusogenic liposomes.[25,38] PEGylated SLNs coated with DSPE-PEG 2000 encapsulating 2-PAM (2-PAM-DSPE-PEG2000-SLNs) exhibited particle sizes of ~80 nm, negative zeta potential, and excellent *in vitro* stability. When administered intravenously in rodents, these SLNs extended 2-PAM plasma terminal half-life by over threefold and achieved brain AChE reactivation rates up to 36%—the highest yet reported for 2-PAM, although this study was not limited to nasal administration. A parallel development with chitosan-coated SLNs focused on intranasal delivery, leveraging the enhanced mucoadhesion and permeation conferred by chitosan. These SLNs delivered fluorescent tracers and model therapeutics into deep brain structures as confirmed by *in vivo* imaging studies.[37]

Comparative Efficacy, Pharmacokinetics, and Safety

Intranasal oximes (2-PAM, obidoxime) outperform IM injection for CNS parameters (reducing central inhibition, seizure burden, and mortality in animal models) but require formulation as carriers or high-concentration solutions for optimal effect. Radiolabelled studies demonstrate robust brain entry and quantifiable pharmacokinetics.

With advanced carriers (liposomes, SLNs, cubosomes, NLCs) dosage can be reduced, and CNS levels optimized, while systemic exposure (and off-target toxicity) is minimized. Safety profiles are favorable in rodents and non-human primates, with little to no local or systemic toxicity at therapeutic doses. Nonetheless, species- and age-appropriate models, repeat-dose toxicology, and modeling for mucociliary clearance inhibition are priorities for future research.[23,25,36,37]

Intranasal Benzodiazepines for Seizure Control

The management of acute seizure emergencies, including seizure clusters and status epilepticus, has been significantly advanced by the development of intranasal benzodiazepine formulations, which offer a compelling alternative to traditional intravenous (IV), rectal, or buccal routes. Intranasal administration provides several distinct advantages, including rapid onset of action, ease of use by non-medical caregivers, avoidance of first-pass metabolism, and improved social acceptability compared to rectal delivery.[28,39] The nasal cavity's highly vascularized mucosa and direct connection to the central nervous system via the olfactory and trigeminal neural pathways facilitate efficient drug absorption and delivery, making it particularly suitable for emergency seizure control.[40,41] Two intranasal benzodiazepines are currently approved by the U.S. Food and Drug Administration (FDA) for seizure clusters: diazepam nasal spray (DNS) for patients aged ≥6 years and midazolam nasal spray (MNS) for patients aged ≥12 years.[28,39] Both formulations have demonstrated efficacy in terminating seizures rapidly, with DNS showing 97% bioavailability relative to IV administration and less interpatient variability compared to rectal diazepam.[28,42] MNS, formulated with organic solvents to enhance solubility, achieves absolute bioavailability of approximately 44% and has been shown in clinical trials to terminate seizures within 10 minutes in 54% of patients compared to 34% with placebo.[28,43]

The pharmacokinetic profiles of these intranasal formulations are critical to their effectiveness. DNS, which incorporates vitamin E for solubility and Intravail® (a permeation enhancer) for improved mucosal absorption, reaches peak plasma concentrations (T_{max}) in approximately 1.4-1.5 hours but demonstrates rapid seizure control due to

efficient CNS delivery. In contrast, MNS achieves a shorter T_{max} of 10-12 minutes, making it particularly advantageous for rapid intervention.[42] A meta-analysis of pediatric studies confirmed that intranasal midazolam significantly reduces the time between hospital arrival and seizure cessation compared to IV or rectal benzodiazepines, highlighting its utility in pre-hospital settings.[44] Beyond efficacy, the intranasal route is preferred by patients and caregivers due to its non-invasive nature and social acceptability, which encourages wider adoption and reduces the reluctance associated with rectal administration.[28,39]

Safety profiles for both DNS and MNS are generally consistent with known benzodiazepine effects, including somnolence, dizziness, and transient local irritation. Respiratory depression, though rare, has been reported but is typically not treatment-related.[39,43,45] Recent studies have expanded the evidence base for these therapies. For instance, a phase 1/2a study of DNS in pediatric patients aged 2-5 years demonstrated pharmacokinetics comparable to older children and adults, with a low rate of second-dose requirements (16.3% of seizure events) and no treatment-related serious adverse events.[45] Similarly, a systematic review of intranasal midazolam in adults found a 72.7% rate of successful seizure termination after the first dose, with adverse effects such as dizziness (23.5%) and sedation (12.7%) being relatively common but manageable.[43]

The development of intranasal benzodiazepines represents an important advancement in rescue therapy for epilepsy, as they can combine rapid efficacy with practical benefits for patients and caregivers. Future developments should focus on expanding age indications, optimizing formulations for higher bioavailability, and further exploring the potential of direct nose-to-brain delivery to maximize therapeutic outcomes.[40,41]

Critical Analysis and Translational Challenges of Preclinical Data

While the preclinical data summarized in this review are undeniably promising, demonstrating robust survival benefits and neuroprotection in animal models, a critical analysis is essential to contextualize these findings and identify the significant hurdles that must be overcome for clinical translation. The enthusiasm for the intranasal (IN) route must be tempered by a clear-eyed assessment of the limitations inherent in the current body of evidence.

First, the anatomical and physiological differences between rodent and human nasal cavities present a major challenge. The olfactory epithelium, which is the primary gateway for direct nose-to-brain transport, occupies a significantly larger relative surface area in rodents (~50%) compared to humans (~3-5%).[12,31] This fundamental difference raises questions about the scalability of the reported drug targeting efficiency (DTE %) and direct transport percentage (DTP %) from rodents to humans. The promising brain-to-plasma ratios observed in small animal studies may not be directly replicable in clinical settings, potentially requiring dose adjustments or more efficient formulation strategies.[9,13]

Second, standard preclinical models of OP poisoning, while valuable, often employ controlled laboratory conditions that may not reflect the chaos of a real-world mass exposure. Factors such as the co-exposure to other chemicals, varying routes of nerve agent entry (e.g., combined dermal and inhalation), and the profound physiological stress of a real attack are difficult to model. The stress response itself can alter nasal physiology, including blood flow and mucus composition, which could unpredictably impact the absorption and distribution of an IN antidote.[11,46] Furthermore, the common use of pure OP compounds like paraoxon in research may not fully represent the toxicokinetic profile of more persistent warfare agents like VX or soman.

A paramount, and perhaps the most formidable, challenge is the regulatory pathway. The ethical impossibility of conducting human efficacy trials for nerve agent poisoning means that approval will likely rely on the FDA Animal Rule or similar regulations in other jurisdictions. This pathway requires robust efficacy data in multiple animal species and a clear understanding of the pharma cokinetics and pharmacodynamics in humans.[47] As noted, the almost complete absence of human safety and pharmacokinetic data for IN antidotes like obidoxime is a critical research gap. Without Phase I studies establishing tolerability, bioavailability, and optimal dosing in healthy volunteers, progression to advanced development is stalled.[33,47]

Finally, the practicalities of formulating stable, field-deployable IN countermeasures are non-trivial. The long-term stability of complex nanocarriers like chitosomes or cubosomes under varying temperature conditions (e.g., in a soldier's kit or a first responder's bag) requires extensive investigation. The potential for local nasal toxicity with chronic or repeated use of permeation enhancers or novel excipients must be thoroughly evaluated.[12,16] Moreover, the cost and scalability of manufacturing Good Manufacturing Practice (GMP)-grade nanoparticle formulations for potential stockpiling must be considered alongside their efficacy.[48,49]

In conclusion, the compelling preclinical results for IN antidotes provide a strong rationale for continued investment. However, the path to clinical deployment is fraught with challenges related to species translation, model relevance, regulatory strategy, and pharmaceutical practicality. Addressing these limitations through rigorous, translational research programs is the essential next step to determine whether the promise of the nose-to-brain pathway can be fully realized

for victims of OP poisoning.

Prophylaxis and Next-Generation Countermeasures

Prophylaxis, or pretreatment, aims to increase survival chances by protecting the body against the lethal effects of nerve agents before exposure occurs. This is particularly vital for military personnel, first responders, or individuals at high risk of encountering these poisons, as the rapid onset of action—often within seconds to minutes—can outpace the time available for administering treatment after exposure. An ideal prophylactic strategy would provide broad-spectrum protection against various nerve agents with minimal side effects, a goal that continues to drive research in the field.[4]

Prophylactic Agents: Pyridostigmine as a Pretreatment Strategy and the Intranasal Opportunity

Beyond immediate treatment, intranasal delivery offers a compelling platform for prophylactic agents designed to protect individuals from a potential nerve agent exposure. Pyridostigmine bromide (PB) is a well-established prophylactic used as a pretreatment against soman. It works by reversibly inhibiting a portion of AChE, thereby "pre-protecting" it from irreversible inhibition by the more potent soman. While effective in animal models, PB is currently administered orally, a route limited by poor absorption and a delayed peak plasma level of 2 to 3 hours. This delay is problematic for situations requiring rapid readiness. An intranasal formulation could provide faster, more reliable systemic absorption, offering a significant advantage for military and first-responder personnel who may need to quickly prepare for a potential exposure.[50]

Enzyme-Based Bioscavengers: Catalytic Solutions for Neutralizing Agents Pre-Target

Enzyme-based bioscavengers fall into mechanistic classes with direct implications for dose, formulation, and translation. Stoichiometric bioscavengers such as human butyrylcholi nesterase (hBChE) act by high-affinity, one-to-one binding of OP molecules, sequestering toxins before they reach synaptic AChE; stoichiometric action requires gram-scale dosing for meaningful human protection and depends on circulating enzyme concentration, affinity, and half-life. Catalytic bioscavengers including engineered phosphotrieste rases and optimized hPON-1 variant hydrolyze multiple OP molecules per active site turnover, so catalytic efficiency (k_{cat}/K_m) and *in vivo* stability determine efficacy and permit sub-gram dosing if sufficiently robust. Hybrid nanoparticle -based constructs such as enzyme-armed nanocleaners combine membrane-anchored AChE decoys that concentrate OPs at the carrier surface with embedded catalytic enzymes that degrade sequestered toxins, producing rapid sequestration followed by catalytic destruction and substantially improving detoxification efficiency per administered enzyme mass.[51]

Intranasal delivery of bioscavengers primarily aims to raise systemic enzyme levels rapidly via vascular absorption in the respiratory region or via lymphatic uptake rather than to deliver intact large enzymes directly into brain parenchyma. Formulation must therefore protect enzyme activity during mucosal transit, overcome mucociliary clearance with mucoadhesive matrices or permeation enhancers, and preserve catalytic function through stabilizers, PEGylation, or encapsulation. Direct nose-to-brain transport of intact large enzymes is limited; strategies that prioritize rapid systemic uptake from the nasal mucosa are most practical for intranasal bioscavengers intended to provide circulating protection.[52]

Barriers to intranasal enzyme deployment include proteolytic degradation at the mucosa, mucociliary clearance, and potential immunogenicity with repeat dosing. Mitigation strategies include protective encapsulation, PEGylation, nanoparticle cloaking, use of lyophilized or dry-powder formats for thermal stability, and comprehensive immunogenicity assessment in repeat-dose toxicology programs. Translationally, stoichiometric and catalytic mechanisms imply different animal-to-human dose-scaling rules: stoichiometric systems scale with required molar binding capacity, while catalytic systems scale with *in vivo* catalytic efficiency and stability, making kcat/Km and serum half-life critical parameters for human dose prediction and regulatory considerations.[53]

Advanced Delivery Systems: Nanoparticles, Emulsions, and Microneedles in Development

The evolution of nerve agent countermeasures is increasingly dependent on the development of sophisticated drug delivery platforms capable of transporting complex therapeutics across physiological barriers. Among these, nanoparticle-based systems (including lipidic and polymeric carriers) have emerged as versatile tools for enhancing drug solubility, stability, and bioavailability, particularly for central nervous system (CNS) applications. These platforms are not limited to small molecules like atropine; they are being actively engineered to deliver enzymes, nucleic acids, and other biologics to the brain, overcoming the limitations of traditional systemic administration. A particularly promising route for CNS delivery is the intranasal pathway, which offers a non-invasive, rapid-access portal to the brain via the olfactory and trigeminal nerves. Polymeric nanomicelles, sized between 30-150 nm, have demonstrated high efficiency in nose-to-brain transport, with multiple studies confirming their ability to bypass the blood–brain barrier and achieve therapeutic concentrations in brain tissue. This approach has shown translational potential for treating neurodegenerative diseases and could be adapted for enzyme-based bioscavengers targeting nerve agents.[48]

Complementing this, nanoemulsions and microemulsions

have gained traction as intranasal delivery vehicles due to their ability to solubilize hydrophobic drugs and facilitate mucosal absorption. A recent bibliometric analysis spanning 2004-2024 highlights the surge in research on intranasal emulsions, particularly for CNS-active compounds such as curcumin, diazepam, and insulin. Thematic clusters around "brain targeting" and "intranasal administration" underscore the strategic importance of this route for bypassing systemic barriers.[54]

While microneedle technology has traditionally focused on intradermal delivery, its core principle (using minimally invasive protrusions to breach biological barriers) offers a conceptual parallel to intranasal strategies. Emerging research suggests that microneedle-inspired structures or dissolvable films could be adapted for nasal mucosa, enabling painless, rapid absorption of large molecules without the need for injection. This convergence of nano technology, emulsification, and barrier-modulating devices is paving the way for next-generation countermeasures that are both effective and deployable in field conditions.[55]

Future Directions and Recommendations

Intranasal (IN) formulations represent a strategic shift in medical countermeasures against organophosphorus (OP) nerve agent poisoning, moving beyond incremental refinement toward a non-invasive, rapid-intervention paradigm deployable by both trained personnel and lay responders. The compelling advantages of this route over the standard of care for key antidote classes, supported by preclinical and clinical evidence, are summarized in Table 2.

Table 2. Key Advantages of Intranasal Delivery for OP Countermeasures

Agent Category	Standard Route & Key Limitations	Intranasal Route & Advantages	Supporting Evidence / Key Findings	Ref.
Atropine	IM auto-injector: Needle-stick risk, sharps disposal, challenging for lay use.	Non-invasive spray: Eliminates needle risk, suitable for self/lay administration, rapid systemic absorption.	Therapeutic serum levels within 5 min; T_{max} ~30 min; rapid atropinization (10-15 min).	(1, 17, 21)
Oximes	Parenteral (IM/IV): Poor BBB penetration, limited CNS efficacy.	Direct nose-to-brain delivery: Bypasses the BBB, enables CNS-targeted AChE reactivation.	IN obidoxime prevents mortality & seizure-induced neurodegeneration in animal models; IN nanocarriers (e.g., chitosomes) achieve ~35% brain AChE reactivation.	(8, 32, 33, 56)
Benzodiazepines	Rectal gel or IM injection: Socially stigmatizing, administration delays, requires training.	Non-invasive spray: Socially acceptable, rapid absorption, enables self-administration.	Seizure termination within 10 min (midazolam nasal spray); high bioavailability relative to IV administration (diazepam nasal spray).	(28, 39, 42, 43, 57)
Prophylaxis (Pyridostigmine)	Oral tablets: Low (~7.6%) and variable bioavailability; significant first-pass metabolism.	Bypasses GI/hepatic metabolism: Potential for faster, more reliable, and uniform systemic absorption.	Intranasal route avoids first-pass effect, offering a pharmacokinetic profile superior to oral dosing for rapid pretreatment.	(50, 58)

Despite compelling preclinical evidence, a significant translational gap remains, as no human trials have yet evaluated the safety, tolerability, or pharmacokinetics of IN nerve agent antidotes.[47] This gap stems from ethical constraints but also a lack of Phase 1-style studies. Bridging this divide will require:

Expanded Preclinical Work: Studies in multiple animal species to refine dose-response relationships and identify predictors of human pharmacokinetics, accounting for anatomical differences in nasal physiology.[12,31]

Innovative Clinical Protocols: Early-phase studies using microdosing, adaptive designs, or physiological challenge models to characterize systemic absorption and establish human safety margins without toxic challenge.[47]

Concurrently, advances in formulation science are critical to overcome the nasal cavity's physiological defenses.[11,12] Priority research areas include:

Mucoadhesive Systems: Polymers (e.g., chitosan) and in situ gelling systems to prolong nasal residence time and combat mucociliary clearance.[20,32]

Permeation Enhancement: Safe, transient enhancers (e.g., cyclodextrins) to increase epithelial uptake without causing irreversible damage.[13]

Advanced Platforms: Dry-powder or spray-freeze-dried formulations to improve stability, reduce cold-chain needs, and enable compact, field-ready devices.[49]

A critical frontier is the development of multifunctional co-formulations. Combining an anticholinergic, an oxime reactivator, and an anticonvulsant in a single device could provide simultaneous symptom relief, AChE reactivation, and seizure control, drastically simplifying mass-casualty response. Early animal studies of IN obidoxime show complete prevention of OP-induced mortality and CNS damage, underscoring this potential.[33,47] This strategy could be enhanced by incorporating catalytic bioscavengers; for instance, enzyme-armed "nanocleaners" that catalytically degrade OPs in circulation could be co-delivered intranasally, reducing the burden on small-molecule antidotes.[51] The most promising candidates under investigation are summarized in Table 3.

In conclusion, the path to clinical deployment is multifaceted, requiring parallel progress in translational clinical research, advanced formulation engineering, and the pioneering of multi-agent delivery systems. By addressing

Table 3. Promising Intranasal Countermeasure Candidates and Formulations

Candidate	Mechanism/Type	Rationale	Development Status	Ref.
Intranasal Atropine	Anticholinergic	Rapid systemic absorption; non-invasive; eliminates needle-stick risk.	Phase 1 DPI study completed; animal models ongoing.	[16, 20]
Intranasal Obidoxime	Cholinesterase reactivator	Bypasses BBB via olfactory/trigeminal routes; prevents CNS AChE inhibition and neuropathology.	Preclinical efficacy in paraoxon model; safety tests.	[30]
Enzyme-based Bioscavengers	Catalytic enzymes (e.g., OP hydrolase)	Neutralizes OP molecules in bloodstream; high turnover reduces required dose.	Conceptual; early-stage animal studies.	[44, 45]
Polymeric/Lipid Nanoparticles	Drug carrier (e.g., chitosomes, SLNs)	Enhances stability/solubility; enables targeted nose-to-brain transport.	Extensive preclinical research.	[29, 33, 46]

these priorities through multidisciplinary collaboration, the promise of intranasal formulations (to provide a more effective, accessible, and brain-protective response to OP poisoning) can be realized, potentially dramatically reducing mortality and long-term neurological morbidity.

Conclusion

The intranasal route has the potential to be a major advance in medical countermeasures against organophosphorus nerve agent poisoning by directly targeting the CNS via the nose-to-brain pathway. Preclinical studies of intranasal atropine formulations have shown rapid systemic and central uptake with sustained mucosal retention, while intranasal obidoxime completely prevented mortality and seizure-induced neuronal degeneration in animal models, outcomes not achieved with conventional peripheral delivery. Complementing these findings, intranasal benzodiazepines such as diazepam and midazolam have demonstrated rapid seizure control and high bioavailability, underscoring the feasibility of nose-to-brain delivery in emergency settings.

Beyond acute therapy, intranasal prophylaxis and next-generation bioscavengers promise to shift the paradigm from reactive treatment to pre-exposure protection. An intranasal pyridostigmine formulation could deliver pretreatment faster and more reliably than oral dosing for personnel at risk, and enzyme-armed nanocleaners combining catalytic hydrolases with biomimetic carriers have shown superior detoxification *in vivo*-paving the way for needle-free, pre-target neutralization strategies. Nevertheless, the path to clinical translation requires bridging several critical gaps. No human trials to date have assessed the safety, tolerability, or pharmacokinetics of intranasal nerve agent antidotes, highlighting an urgent need for early-phase studies using microdosing or adaptive designs to de-risk translation. Concurrently, innovation in formulation science (such as mucoadhesive polymers, transient permeation enhancers, and dry-powder or spray-freeze-dried platforms) will be essential to overcome mucociliary clearance, enzymatic degradation, and field-stability challenges. The integration of optimized intranasal formulations for anticholinergics, oxime reactivators, benzodiazepines, and bioscavengers into a cohesive, needle-free countermeasure kit, could potentially lead to treatments that perform as well as, or offer advantages over, current parenteral therapies. Continued multidisciplinary collaboration among formulation scientists, pharmacologists, and regulatory bodies will be pivotal to translate these promising preclinical advances into deployable solutions that can dramatically reduce mortality and long-term neurological morbidity from nerve agent exposures.

Conflict of Interest Disclosures

The authors declare that they have no conflicts of interest.

Acknowledgment

I would like to thank the guidance and support from Research and Technology Comprehensive Laboratory (RTCL) of Baqiyatallah University of Medical Sciences.

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