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The nose has it: Opportunities and challenges for intranasal drug administration for neurologic conditions including seizure clusters

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ABSTRACT

Nasal administration of treatments for neurologic conditions, including rescue therapies to treat seizure clusters among people with epilepsy, represents a meaningful advance in patient care. Nasal anatomy and physiology underpin the multiple advantages of nasal administration but also present challenges that must be addressed in any successful nasal formulation. Nasal cavity anatomy is complex, with a modest surface area for absorption that limits the dose volume of an intranasal formulation. The mucociliary clearance mechanism and natural barriers of the nasal epithelia must be overcome for adequate absorption. An extensive vasculature and the presence of olfactory nerves in the nasal cavity enable both systemic and direct-to-brain delivery of drugs targeting the central nervous system. Two intranasal benzodiazepine rescue therapies have been approved by the US Food and Drug Administration for seizure-cluster treatment, in addition to the traditional rectal formulation. Nasal sprays are easy to use and offer the potential for quick and consistent bioavailability. This review aims to increase the clinician's understanding of nasal anatomy and physiology and of the formulation of intranasal rescue therapies and to facilitate patient education and incorporate intranasal rescue therapies for seizure clusters (also known as acute repetitive seizures) into their seizure action plans.
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Introduction

Nasal administration represents an advance in treatment for a growing number of neurologic conditions, including triptans and ergotamine for migraine, esketamine for depression, naloxone for opioid overdose, and, of particular interest to clinicians treating patients with epilepsy, the benzodiazepines diazepam and midazolam as rescue therapy for seizure clusters (also known as acute repetitive seizures) [1–8]. Epilepsy is a disabling condition with serious potential consequences. The US Centers for Disease Control and Prevention reports that 56% of adults taking antiseizure medications still experience seizures. Polytherapy is common in patients with drug-resistant epilepsy, while nondrug treatment options include surgery, neurostimulation, and diet [9]. Drug-resistant epilepsy may sometimes include treatment emergencies that may range on a continuum from multiple discrete events (seizure clusters) to continuous series without recovery between events and prolonged seizures (status epilepticus) [10]. Seizure clusters and their management are addressed in several recent reviews [11–13].

Rescue therapies for seizure clusters should be easy and safe to administer, with fast onset and reliable efficacy; administration should be socially acceptable to the patient and caregiver and can be administered during the seizure event [14]. Intravenous delivery of benzodiazepines is frequently used in the inpatient setting, particularly when venous access has already been established, however, it is not an option in outpatient settings. Rectal diazepam gel was approved by the U.S. Food and Drug Administration (FDA) in 1997 [15]. It is effective as an outpatient rescue therapy but has several drawbacks. It exhibits notable interpatient variability and may be difficult to administer during a seizure cluster, especially in adolescents and adults [16]. A 2002 survey of 91 adults with epilepsy reported that for seizure emergencies, they preferred early

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rectal benzodiazepine administration when compared with a visit to the emergency department, with some expressing embarrassment about the medication route [17]. More recently, other formulations of rescue therapy have been approved by the FDA, specifically intranasally delivered diazepam and midazolam; others are in development for prolonged seizures, including inhaled alprazolam [18]. Intranasal administration offers several advantages as a rescue therapy. Intranasal administration is noninvasive and easy to administer, with high patient acceptability [14]. It has potentially high and consistent bioavailability and rapid onset of action. It provides direct delivery into the circulation, circumventing first-pass metabolism in the liver, and it also offers the possibility of directly delivering the drug into the central nervous system (CNS), potentially facilitating more rapid seizure termination [14].

Other formulations, such as intravenous or oral formulations, are not designed for intranasal administration of CNS-targeted drugs and are thus likely suboptimal for addressing the challenges associated with nasal administration. These challenges are largely related to the anatomy and physiology of the nose. To be effective, nasal formulations must deliver adequate dosing in a limited dose volume (100–150 μL per nostril) [19]. Barriers to absorption include permeability across the nasal epithelia, which is poor for some molecules, and drug removal via mucociliary clearance and local cellular mechanisms [20]. There is the possibility that nasal irritation, congestion, or lesions may reduce absorption, and some patients and caregivers may have concerns about nasal administration. These concerns can typically be overcome with education, and patients who have used intranasal rescue therapy for seizure clusters generally have reported it to be easy to administer and preferable to rectal therapy [21–23].

This narrative review will address nasal anatomy and physiology within the context of intranasal drug delivery of rescue therapies for epilepsy. Elements of anatomy, neurovascular supply, physiology, and histology are discussed before turning to pathways of intranasal drug delivery to the CNS and challenges of intranasal drug formulations. Findings from studies of intranasal benzodiazepine rescue therapies highlight the importance of intranasal formulations for safety and effectiveness. The goal is to provide clinicians who prescribe rescue therapies with the context needed to understand and educate their patients on the benefits of intranasal formulations and the unique characteristics that make them key options in the care for patients with epilepsy who experience seizure clusters.

Anatomy and physiology

Nasal anatomy and development

The internal structures of the nose include a pair of large irregular cavities (Fig. 1) [24]. The roof is formed by the cribriform plate of the ethmoid at the base of the cranium, and each cavity extends down to the palate of the mouth. The septum, or inner wall, separates the 2 nasal cavities. The outer wall is convoluted into 3 (or 4) turbinates or conchae, each creating an associated canal, or meatus. The superior turbinate is located at the upper and posterior part of the cavity. It is the smallest, with the middle and inferior turbinates being increasingly larger in size. The total surface area of both nasal cavities in an adult is about 160 cm^2, and the total volume is about 15 mL [24]. The roles of the nasal cavity include heating and humidifying air for respiration, clearing particles and dust, and olfaction [25].

The nasal cavity contains 4 general regions: the vestibule, the respiratory region, the olfactory region, and the nasopharynx-associated lymphatic tissue (NALT) (Fig. 1). The vestibule rests behind the nostril openings and contains nasal hairs involved in filtering inhaled air. Its small surface area and squamous epithelial cell surface make it unsuited to extensive drug absorption [26]. Posterior to the vestibule is the nasal valve, a narrow, dynamic triangular slit leading to the respiratory and olfactory regions [27]. It is responsible for regulating the speed and direction of airflow during respiration. At the back of the cavity, the NALT, a part of the mucosal immune system, acts to prevent infection [28]. It is also important for intranasal vaccination via T-cell immunity, such as the seasonal flu vaccine [28,29].

Together, the respiratory and olfactory regions form the large, central portion of the nasal cavity and are most relevant for intranasal drug delivery. The respiratory region includes the lateral walls of the cavity, including the turbinates, and is the largest (approximately 130 cm^2) and most vascularized part of the nasal cavity, making it a prime site for systemic drug absorption after nasal administration [25,26,30]. The olfactory region comprises a small fraction ($\leq$10 %) of the total surface area of the nasal cavity, 2–12.5 cm^2 [24,25,31]. It is located in the uppermost part of the cavity, meaning it may be difficult to reach for nasally administered drugs [32]. The olfactory region contains olfactory sensory neurons (OSNs), and it represents the only site in the body where the CNS is in direct contact with the outer surface of the body, the nasal mucosal membrane in this case, and thus opens the possibility of direct-to-brain delivery of drugs [24,32].

Development of the nasal cavity during childhood

The nasal cavity changes dramatically during the first years of life. For example, the surface area of the turbinate region nearly doubles from age 3 ($\sim$55 cm^2) to age 5 ($\sim$107 cm^2), at which point it is approaching adult size ($\sim$113 cm^2) [33]. However, morphologic differences suggest that the area continues to develop after this age. Studies show heterogeneity in airway dimension and morphology in children, which impacts air flow dynamics and aerosol deposition [33]. Studies in adolescents show that the nasal passages reach adult proportions in the mid-teens, after undergoing a slight decrease in cross-sectional area sometime between the ages of 9 and 13 years [34]. The olfactory system is established before birth, with nasal chemoreception beginning during the last trimester of gestation. Vascular innervation in children follows the same general plan as adults, with nerves associated mainly with arteries but also veins in the nasal cavity [35,36].

Children and adults with respiratory conditions may also have changes in the upper respiratory system that could affect nasal delivery of rescue therapies, such as decreased nasal patency with asthma or laryngomalacia and chronic rhinitis in children with Down syndrome [37–39]. However, changes may not always lead to decreased absorption. For example, the presence of polyps in the nasal cavity has been associated with longer residence time of compounds, and the inflammation seen with chronic sinusitis or allergic rhinitis may render the nasal mucosa more permeable to drugs [40,41]. Clinical studies of several drugs, including zolmitriptan, hydromorphone, fentanyl, butorphanol, triamcinolone acetonide, testosterone, and buserelin, show that the presence of rhinitis does generally not seem to affect the absorption, bioavailability, clinical effect, and safety of drugs delivered intranasally [42].

Human vs animal models

Animal models, particularly the rat, but also the mouse, rabbit, dog, sheep, and monkey, are often used in studies of intranasal administration and CNS delivery of drugs, and care must be taken in extrapolating to humans because of anatomical and physiologic differences. For example, the nasal anatomy of dogs, which are

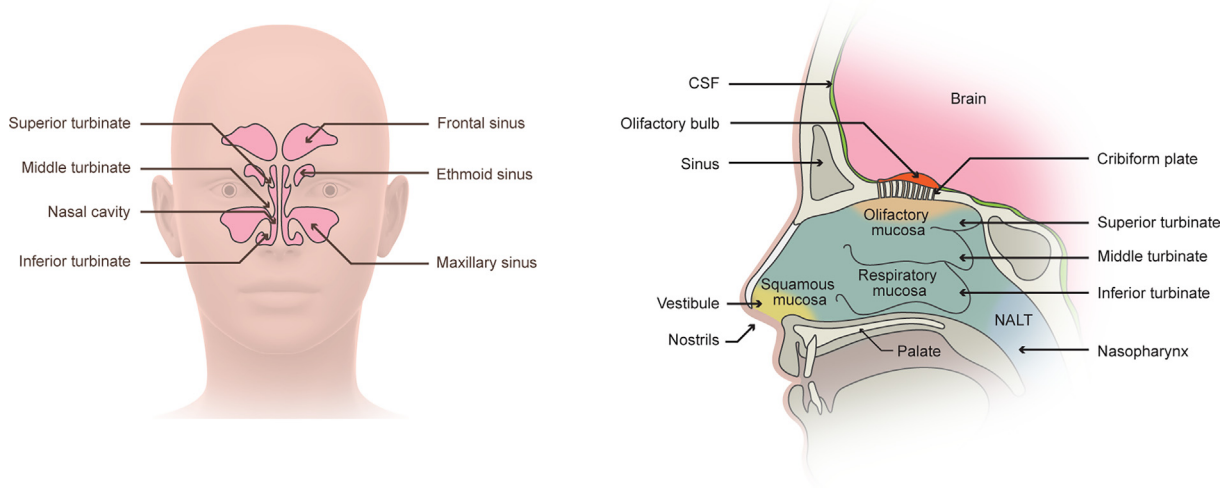


Fig. 1. Gross anatomy of the nasal cavity; frontal view (left) and sagittal view (right). Two irregularly shaped nasal cavities are bounded by the cribriform plate of the ethmoid at the top, the palate of the mouth on the bottom, the central septum, and outer walls with 3 turbinates and associated meatus. The nostrils open to the external environment and lead to the vestibule, lined with squamous mucosa. The central part of the cavity is divided into a large respiratory mucosa and a smaller olfactory mucosa above. The posterior of the cavity contains the nasopharynx-associated lymphoid tissue (NALT) and connects to the nasopharynx. The frontal sinuses, ethmoid sinuses, and maxillary sinuses drain into the middle and superior meatus through openings in the cavity wall. CSF, cerebrospinal fluid.

dependent on their sense of smell, is complex, with branched turbinates, compared with the single scroll in humans. And the olfactory region in rats makes up almost 50% of the nasal cavity, a 5-fold higher percentage than in humans [26].

Neurovascular supply

Blood is supplied to the nasal cavity from one branch of the sphenopalatine artery, as well as the ethmoidal branches of the ophthalmic artery (Fig. 2) [24]. Arterial blood flow in the nasal cavity is anteriorly against the flow of air. The venous network matches approximately the arterial structure. Blood in the ethmoidal veins flows into the ophthalmic plexus then proceeds to the cavernous sinus (cavernous plexi) [24].

The lower part of the septum contains a dense vascular bed with a rich blood supply, particularly at the transition from squamous to respiratory epithelium. The vascular bed extends over the middle and inferior turbinate and is composed of fenestrated vessels and capillaries that are thought to be a source of fluid for humidification of air during respiration. This fenestration may also play a role in facilitating drug absorption [24].

With respect to innervation of the nasal cavity, sensory nerves involved in olfaction are spread over the upper septum and outer wall and are connected through small openings in the cribriform plate to the olfactory bulb, an oval mass sitting on the ethmoid. These olfactory nerves comprise axons from OSN bodies in the olfactory epithelia [24]. Signals are transmitted from OSNs to mitral and tufted cells within the olfactory bulb. The latter cells act as efferent neurons and transmit signals to the olfactory cortex located on the ventral surface of the forebrain [31]. The olfactory pathway bypasses the thalamus, unlike other sensory neurons [24,31].

The trigeminal nerve, the largest cranial nerve, is mainly a sensory nerve that has 2 branches that innervate the respiratory and olfactory epithelia near the anterior part of the septum and the anterior part of the outer wall of the nostril. It enters the brainstem at the pons level. Posterior sections of the nasal cavity are served by branches of the palatine and maxillary nerves [24,43].

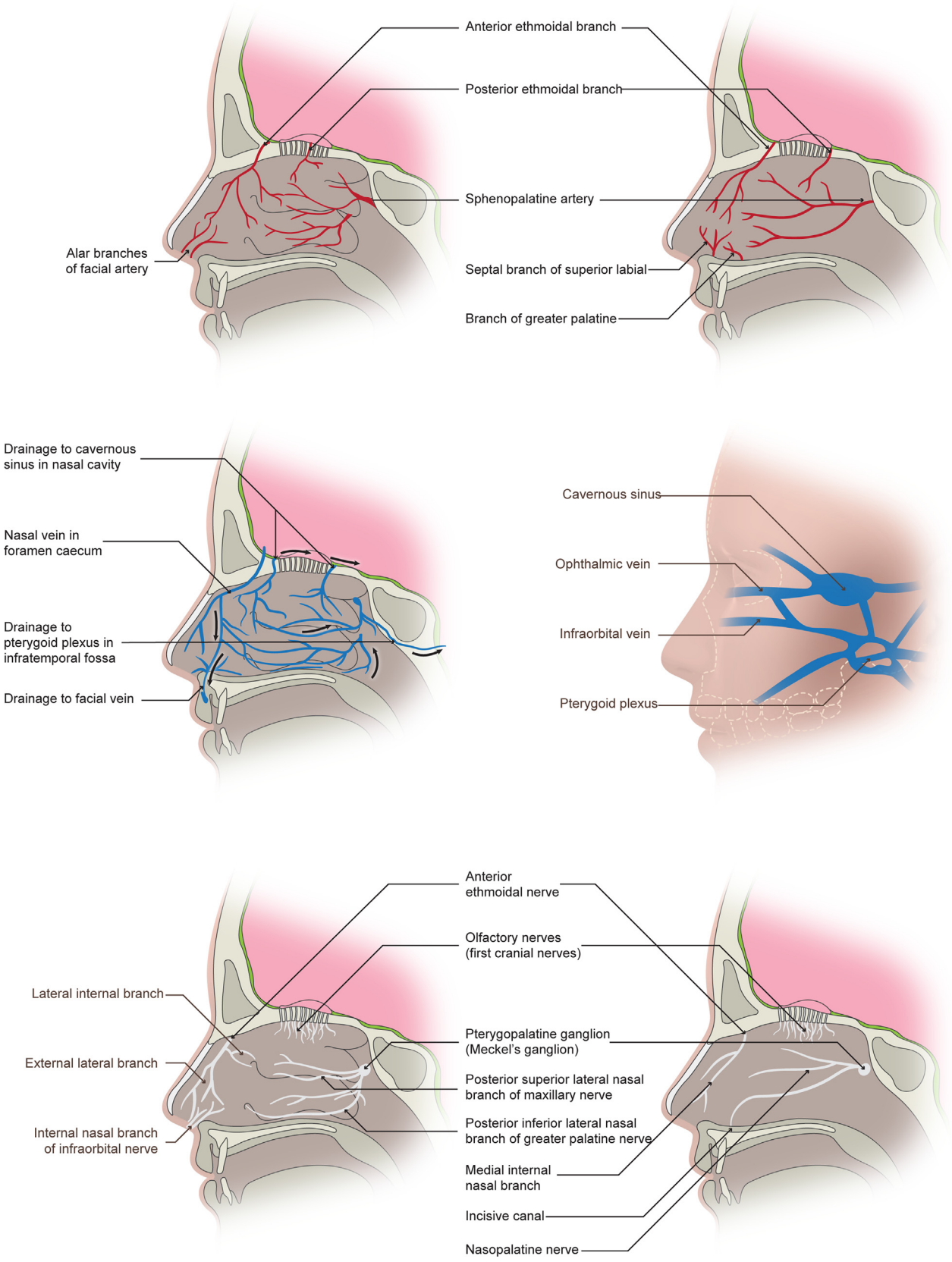
Cilia, mucus, and mucosal clearance

The composition of mucus and its constant removal from the nasal cavity represents challenges to drug delivery that can be addressed through formulation strategies to extend contact time with the nasal mucosa, thereby potentially improving absorption. The mucus overlaying the epithelium in the nasal cavity insulates the epithelium, provides humidification to inhaled air, maintains hydration, and protects from irritants, toxins, and pathogens through a removal system that uses motile cilia on epithelial cells to constantly sweep mucus and trapped particles out of the cavity [44]. Motile cilia are found on over 80% of cells in the respiratory mucosa [28]. Mucus is composed primarily of water and mucin proteins, which have both hydrophobic and hydrophilic regions and thus can capture particles of varying hydrophobicity by forming low-affinity bonds [28]. The mucus layer covering the nasal epithelium is biphasic, with an outer gel layer of higher viscosity and adhesive properties [25]. The inner periciliary, or serous fluid, layer allows for the beating of the cilia and the unidirectional movement of the gel layer posteriorly toward the nasopharynx for removal [44]. In adults, cilia beat at a rate of approximately 1000strokes per minute [40]. It is estimated that the respiratory mucus layer is renewed every 10 to 20 min [44]. Rates have been reported to be higher in children and adolescents [45,46]. Clearance time can be affected by disease. For example, nasal congestion can lengthen clearance time [40].

Nasal histology and drug delivery

Histology of nasal structures

The respiratory region is lined with a ciliated pseudostratified epithelium (Fig. 3) composed of 4 cell types: ciliated and nonciliated columnar cells, goblet cells, and basal cells [25]. The epithelium is covered by the mucus layer (described above). The lamina propria lies beneath the epithelium and contains a dense network of capillaries and blood vessels that drain directly into the systemic circulation [24]. Serous glands in the lamina propria and goblet cells in the epithelium keep the tissue moist and pro-


Anterior ethmoidal branch
Posterior ethmoidal branch
Sphenopalatine artery
Alar branches of facial artery
Septal branch of superior labial
Branch of greater palatine
Drainage to cavernous sinus in nasal cavity
Nasal vein in foramen caecum
Drainage to pterygoid plexus in infratemporal fossa
Drainage to facial vein
Cavernous sinus
Ophthalmic vein
Infraorbital vein
Pterygoid plexus
Anterior ethmoidal nerve
Olfactory nerves (first cranial nerves)
Lateral internal branch
External lateral branch
Internal nasal branch of infraorbital nerve
Pterygopalatine ganglion (Meckel's ganglion)
Posterior superior lateral nasal branch of maxillary nerve
Posterior inferior lateral nasal branch of greater palatine nerve
Medial internal nasal branch
Incisive canal
Nasopalatine nerve

duce mucus. The olfactory epithelium is also a ciliated pseudostratified epithelium that covers the superior turbinate and the uppermost part of the septum in each cavity [25]. The olfactory epithelium is marked by the presence of OSNs and Bowman's glands, involved in mucus production. The basement membrane beneath the epithelium contains blood and lymph vessels, olfactory axon bundles, and other nerve fibers, including the trigeminal nerve. OSNs are bipolar cells with dendrites on their apical surface that extend into the mucous membrane [24]. On the basal surface, the neurons form unmyelinated axon bundles that pass through the foramina in the cribriform plate to join the olfactory bulb [25]. The axon bundles are surrounded by olfactory ensheathing cells and olfactory nerve fibroblasts [25].

Transmucosal drug transport

Following drug deposition, absorption is critical for successful drug delivery. In general, drugs can follow either extracellular or intracellular routes to gain access to the circulatory system or the nervous system (Fig. 3).

In the respiratory region, the main challenge to drug absorption is to cross the epithelium. Extracellular transport across the columnar cells of the epithelium can occur via paracellular diffusion [47]. Tight junctions (zonula occludens) are hydrophilic and generally impermeable to many drugs. In its natural state, the epithelium allows passage of molecules up to 1000 Da, with decreasing absorption with increasing molecular weight [41,48]. Molecules passing through the epithelium enter the lamina propria where they can then enter the vasculature and systemic circulation [30]. Intracellular transport via transcytosis is another possible mechanism to reach the lamina propria [47]. Several intranasal drug formulation strategies aim to increase permeability of the epithelium by disrupting the cellular barrier or loosening tight junctions, as discussed below.

In the olfactory region, intracellular transport in olfactory neurons begins with internalization of the compound into the neuron and then transportation within the neuron toward the CNS, where it is released [49]. Olfactory neurons have been shown to use both endocytosis and pinocytosis to transport a range of molecules using receptor-mediated and nonreceptor-mediated mechanisms. Extracellular pathways in the olfactory epithelium use paracellular mechanisms to allow molecules to cross the epithelium into the lamina propria, similar to mechanisms in the respiratory mucosa [49].

Pathways to the CNS

After absorption through the nasal epithelium, multiple pathways are possible for delivery of neurotherapeutic drugs to the brain (Fig. 4). Drugs absorbed into the bloodstream and systemic circulation require transport across the blood–brain barrier. Olfactory and trigeminal nerve pathways offer the potential for direct nose-to-brain drug delivery. It is likely that individual drugs use the pathways to varying degrees depending on different factors, such as the molecular nature of the drug, the composition of the formulation, and the delivery system.

Vascular pathway

The rich vascularization of the respiratory region, and the olfactory region to a lesser extent, allows drugs to be absorbed into the systemic circulation [30]. The vascular endothelia in these regions are both continuous and fenestrated, allowing both large and small molecules to enter the general circulation. Generally, lipophilic and low-molecular-weight drugs can pass through the blood–brain barrier, and thus CNS drug formulations must overcome the challenge of hydrophobic tight junctions and a lipophilic blood–brain barrier. There is also evidence from animal models that drug transfer, including diazepam, from venous to carotid blood supply (and thereby on to brain) can occur via local countercurrent mechanisms [50,51]. Finally, there is the possibility of entry into the brain through the lymphatic system as the lymphatic system has connections with perineural spaces and the cerebrospinal fluid (CSF) [25,52]. Nasal administration may avoid first-pass metabolism. Because passage through the systemic circulation raises the possibility of systemic toxicities, intranasal formulations may show better tolerability compared to other routes of delivery, such as oral or intravenous [31].

Research in rats and rabbits suggest that diazepam delivered intranasally reaches the brain by passing through the blood–brain barrier after entering the systemic circulation, as suggested by similar diazepam concentration–time profiles in plasma, CSF, and brain tissue [53]. The study authors also concluded that direct-to-brain delivery of diazepam did not occur in either animal model, based on a lack of higher drug targeting efficiency in brain tissues.

Olfactory and trigeminal pathways

The olfactory pathway involves OSNs as a direct route to the brain and CNS. Drugs may enter the brain directly via intraneuronal transport or the CSF via paraneuronal transport, before then being transferred into neuronal cells. Studies have reported intracellular translocation times along the olfactory nerves of 1.5–6 h or even longer, up to 24 h in some early mouse studies [28,49,54]. Thus, it is not likely to be a primary mechanism for delivery to the brain and CNS [28]. For paraneuronal transport, compounds must first pass through the olfactory mucosa via transcellular or paracellular mechanisms. From there, drugs may move via diffusion extracellularly through the perineural channels that exist between the olfactory neuron–ensheathing cells and the surrounding olfactory neural fibroblasts. These channels run the length of the olfactory neuron from olfactory epithelium to olfactory bulb and create a continuous connection between the fluid in the lamina propria of the olfactory epithelium and the CSF in the subarachnoid space [49]. Transport along this path is faster than

Fig. 2. Neurovascular supply to the nasal cavity; arterial supply (upper), venous system (middle), and innervation (lower). The nasal cavity receives blood from multiple sources. One branch of the sphenopalatine artery enters behind the superior meatus. The ethmoidal branches of the ophthalmic artery, a second source, enter through openings in the cribriform plate and supply blood to the anterior part of the inner and outer wall of the nose and the ethmoidal and frontal sinuses.Veins in the nasal cavity begin in the venous plexus on the inferior turbinate and meatus and the back of the septum. Blood flows into the ophthalmic plexus, then proceeds to the cavernous sinus (cavernous plexi). The veins from the upper nasal cavity feed into veins in the skull's interior through the foramen coecum and collect into the superior longitudinal sinus. These sinuses are venous channels that change blood volume in response to stimuli. The nasal cavity is innervated by the trigeminal nerve, the fifth cranial nerve, and longest one of the head and face *(not shown)*. The first division of this nerve, the ophthalmic nerve, innervates the nasal cavity, frontal sinuses, integument of the nose, eyeball, and lachrymal gland. A branch of the ophthalmic nerve enters the nasal cavity through the anterior ethmoidal foramen and an opening on the anterior aspect of the cribriform plate. Two of 4 branches entering the pterygopalatine ganglion (Meckel's ganglion) supply the nose. The posterior sections of the turbinates are served by the nasopalatine nerve, a branch of the maxillary nerve, and the anterior parts are served by anterior ethmoidal nerve, a branch of the ophthalmic nerve. These nerves course with adjacent arteries. Twenty olfactory nerves enter the nasal cavity through openings in the cribriform plate. Within the cavity, each nerve divides and spreads over the lateral walls of the superior turbinate and upper third of the septum. They are connected to the olfactory bulb and convey signals from the olfactory neurons in the olfactory mucosa to the olfactory bulb.

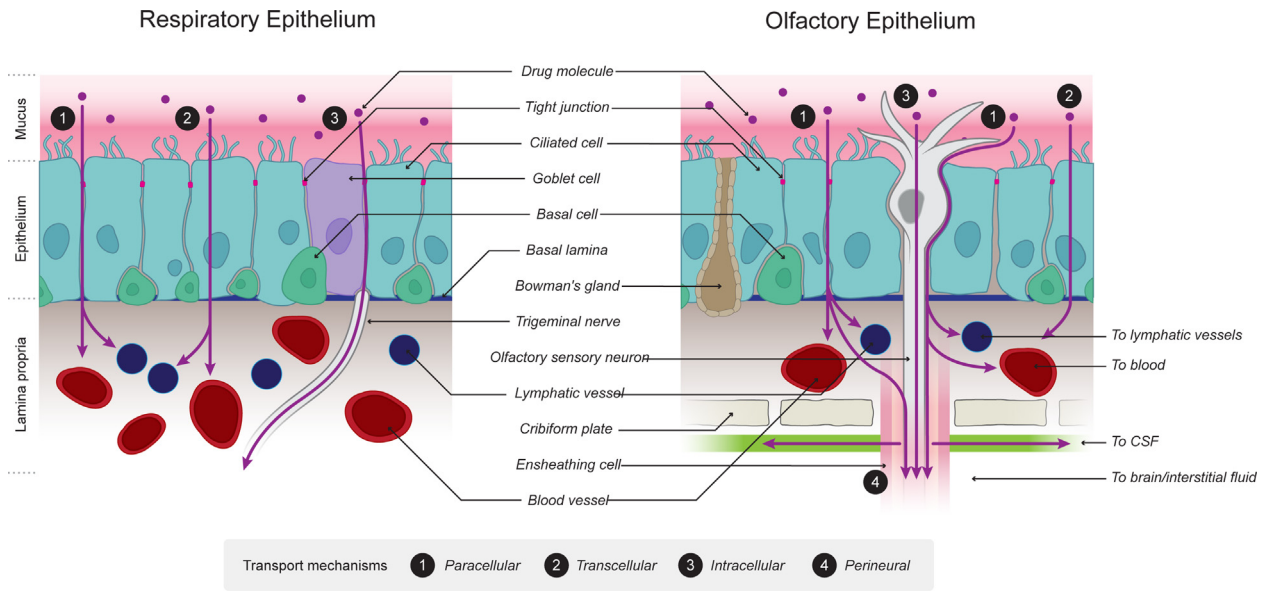


Fig. 3. Histology and drug transport across the epithelium of the nasal cavity; respiratory epithelium (left), olfactory epithelium (right). Drug transport across the epithelium can take different routes, labeled (1) to (4). Drug molecules may pass through the epithelium using paracellular (1) or transcellular (2) mechanisms (via tight junctions between cells) to enter the lamina propria underlying the epithelium and then be transported through blood or lymphatic vessels to the systemic circulation and on to the brain. Olfactory sensory neurons in the olfactory epithelium offer the potential for direct-to-brain delivery through intracellular (3) or perineural (4) routes. Perineural routes along the channels surrounding the olfactory neurons connect the fluid in the lamina propria of the olfactory epithelium and the cerebrospinal fluid (CSF) in the subarachnoid space. Intracellular transport is also possible through trigeminal nerve endings located in the respiratory epithelium.

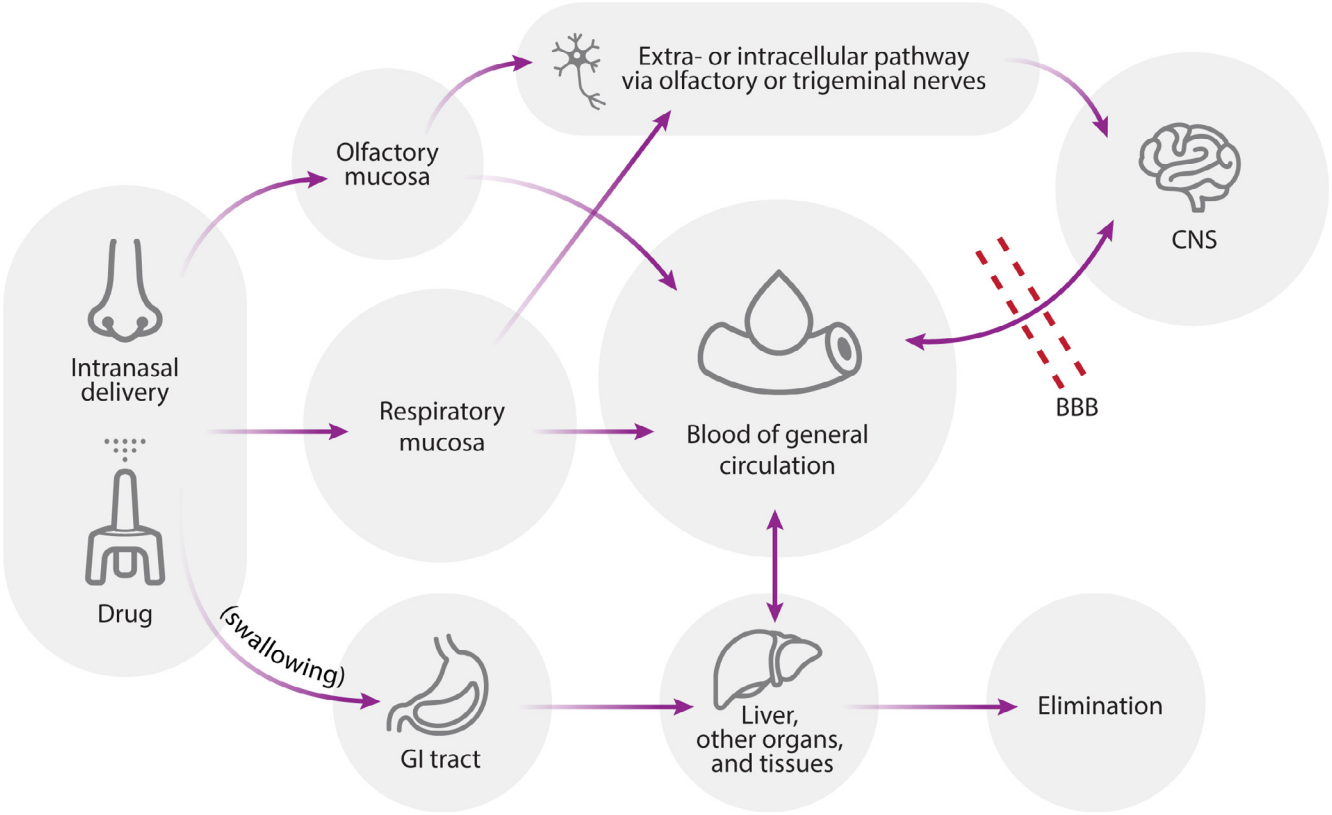


Fig. 4. Pathways to the central nervous system (CNS) following intranasal drug delivery. A drug absorbed through the respiratory mucosa enters the general circulation and then passes through the blood–brain barrier (BBB) to reach its site of action, the CNS. A drug in general circulation will also be distributed to organs and tissues and be eliminated. Absorption in the respiratory mucosa may also lead to intracellular transport along trigeminal nerves pathways and direct transport to the CNS, though this route is thought to be slow (17–56 h). Absorption in the olfactory mucosa can lead to direct-to-brain delivery through olfactory sensory neurons via intracellular or extracellular pathways, with evidence suggesting that delivery along extracellular pathways can take minutes. Finally, excess drug delivered to the nasal cavity may be swallowed and absorbed by the gastrointestinal (GI) tract, similar to an orally administered drug.

intraneuronal transport, with reported times ranging from 5 min to 2.3 h [47,55]. Evidence for intracellular or extracellular transport along the olfactory pathway has been obtained for compounds such as nerve growth factor, dihydroergotamine, morphine, carbamazepine, and albumin [55–59]. Transcellular pathways may be more relevant for lipophilic compounds, while hydrophilic compounds may follow passive diffusion along fluid-filled channels, with an inverse relationship to molecular weight of the compound [25]. Finally, arteries adjacent to the olfactory nerve bundles have been proposed to create a "perivascular pump" based on the high-pressure waves created by movement of blood through vessels after systole. This pump can move fluids within the perivascular space around arteries, moving solutes toward the brain in this region [49].

The trigeminal nerve, which innervates the respiratory epithelium, is less studied as a pathway of drug delivery to the brain [25]. Although trigeminal nerve endings are not directly exposed in the nasal cavity, it is assumed that drugs pass through the epithelium and then are transported extracellularly or intracellularly to the brain. Studies have implicated trigeminal nerves in the transport of insulin-like growth factor 1, lidocaine, and interferon-β-1b to the brain after intranasal administration [60–62]. Reported transport times are longer along the trigeminal nerve, 17–56 h, than the olfactory nerve [28].

Drug formulation considerations

Optimizing deposition in the nasal cavity

Because the volume of the nasal cavity is limited, the optimal administration volume is 100 μL (maximum 150 μL) per nostril in an adult [14,19]. Thus, high concentrations of drug may be needed to ensure adequate dosing in a limited volume. Nasal formulations of hydrophobic molecules may require specific approaches to ensure adequate absorption (discussed below). The targeting of drug deposition and subsequent absorption within the nasal cavity is affected by the geometry of the spray plume as influenced by drug formulation, device mechanics, and patient/-caregiver technique [63]. Droplet size also affects deposition, with droplets > 10 μm retained in the nasal cavity, while pulmonary deposition occurs with smaller droplets [64]. Narrower plume angles have been associated with better deposition in the respiratory and olfactory regions of the cavity, while wider angles result in more deposition on the nasal valve. Droplet velocity, formulation viscosity, and device type have less impact on deposition [63]. Minimizing off-target deposition is important so as to avoid loss of dose through leaking out of the nostrils, by swallowing into the gastrointestinal (GI) tract, or by inhaling or aspirating into the lungs. Excessive ingestion and absorption into the GI tract may impact bioavailability [14], while deposition in the lungs may lead to a range of adverse effects, from mild coughing to toxicity or infection [31].

Congestion in the nasal cavity is a potential consideration; however, rhinitis, including allergic, infectious, and vasomotor rhinitis, does not seem to have a clinical impact on nasal drug absorption, as seen in multiple studies [65–68]. Moreover, in a study of diazepam nasal spray to treat seizure clusters, rates of second dose administration within 24 h of the first were similar between patients with and without history or concomitant treatment of seasonal allergies or rhinitis [42]. Finally, there is the potential for local toxicity to the active compound or excipients, such as sol-

Table 1
Common categories of excipients for nasal formulations [30,32,76,99,100].

	Description	Potential Disadvantages	Examples
Permeation enhancers	Enhanced movement across the nasal mucosa, often by opening tight junctions or increasing the solubility of the drug	Possible local toxicity and irritation of nasal mucosa with some agents (eg, cosolvents isopropyl alcohol, PEG400, propylene glycol)	Cosolvents (alcohol, PEG400, propylene glycol) Ionic and some nonionic surfactants (PEG400, PEG3500, polysorbate 20, polysorbate 80, polyoxyl 400 stearate) Selected fatty acids (capric acid, DHA, EPA, oleic acid, oleyl alcohol, palmitic acid, palmitoleic acid, stearic acid) Chitosan Cyclodextrins Modified vitamin E (TPGS) pH modifiers (sodium hydroxide, sulfuric acid, hydrochloric acid) Polymers
Mucoadhesive agents	Slowed removal of drug by mucociliary clearance by increasing residence time via increased viscosity or slowed removal action	Reduced barrier function of mucosa	Chitosan Hyaluronan Gellan gum
Agents used in research studies			
Enzyme inhibitors	Inhibition of nasal cavity enzymes, prolonging drug stability and absorption	Reduced barrier function of nasal cavity	Fluvoxamine, α-aminoboronic acid derivatives
Lectin-mediated transport	Addition of agglutinin to target the nasal mucosa and increase brain uptake	Not specific to the nasal mucosa	Wheat germ agglutinin
P-glycoprotein inhibitors	Inhibit efflux of compounds from the brain, increasing concentrations in brain	Potential for reduced efflux of harmful compounds	Cyclosporin A, rifampin, pantoprazole, elacridar
Prodrugs	Chemical modification of drug to increase drug stability and absorption; drug activated by enzymatic modification after absorption (eg, esterases)	Enzymatic activation required	L-dopa butyl ester
Vasoconstrictors	Vasoconstriction of nasal blood vessels, leading to enhanced mucosal residence and decreased uptake in circulation	Increased blood pressure	Phenylephrine

DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; PEG, polyethylene glycol; TPGS, D-α-tocopheryl polyethylene glycol succinate.

vents, absorption enhancers, or mucoadhesives, which are discussed next.

Enhancing absorption

Cellular processes that can impact drug absorption include cell membrane permeability, drug efflux, and drug metabolism [20]. The physiologic process of mucociliary clearance can also affect absorption. Absorption can be enhanced through multiple mechanisms, including enhancing solubility of the drug, increasing permeability of the mucosa, and increasing residence time on the nasal mucosa. Enhanced absorption can be obtained by modifying the drug, adjusting the pH of the solution, adding excipients, or creating new drug delivery systems.

The addition of enhancers can increase the permeability of the epithelium up to 30-fold vs the natural state, allowing molecules up to 30 kDa to pass [69]. For many compounds, absorption is increased with lower pH, while the opposite is true for other compounds [70–73]. Excipients added to a formulation, such as permeation enhancers and mucoadhesive agents, may aid absorption (Table 1). Some absorption enhancers, however, can be associated with nasal irritation or cytotoxicity [74].

Benzodiazepines as a class have low solubility in aqueous solutions and enhancing techniques have been used in the development of the FDA-approved intranasal rescue therapies [20]. The approved intranasal formulation of midazolam contains the cosolvents polyethylene glycol (PEG) 400, PEG-6 methyl ether, propylene glycol, and ethanol [7,20,75,76]. Diazepam nasal spray contains a vitamin E–based formula to enhance the solubility of diazepam and dodecyl-beta-D-maltopyranoside, a nonionic alkylglycoside surfactant that is thought to enhance absorption by paracellular and transcellular routes (Fig. 5) [74]. It also contains benzyl and anhydrous alcohol [8].

Importantly, intranasal formulations have been specifically designed to optimize the bioavailability, effectiveness, and safety of intranasal delivery, while intravenous or oral formulations do not account for the specific parameters of intranasal delivery. In contrast, intravenous midazolam delivered using a spray tip or mucosal atomization device (MAD) to treat seizure clusters requires a large dose volume, which can result in significant loss of drug from the nasal cavity and variable dosing and absorption [77]. In addition, the low pH of the formulation may lead to irritation of nasopharyngeal tissues [78].

Using effective delivery devices

Integral to an intranasal formulation of a drug is the delivery device. Traditional nasal droppers require difficult maneuvers by the patient for correct administration and optimal deposition [79]. A MAD attached to a syringe has been used for intranasal delivery of several CNS-targeted drugs, including naloxone, ketamine, fentanyl, and the intravenous formulation of midazolam [78,80–82]. However, this method has disadvantages: it can be inconvenient and challenging as it requires multiple steps to assemble. The device may be assembled in a pharmacy, with a limited shelf-life after preparation, or be assembled during the stress of the seizure event, requiring additional time and training for the person administering the therapy. Finally, it may be difficult to administer a consistent, exact dose [76]. Both currently FDA-approved intranasal benzodiazepine rescue therapies are formulated as fixed-dose delivery systems [7,8]. These systems are designed for simple, intuitive use, which can be particularly important for rescue therapies delivered by nonmedical personnel in a stressful situation. They also deliver a premeasured drug volume, contributing to more consistent dosing. Although studies have indicated that spray administration angle can affect deposition,

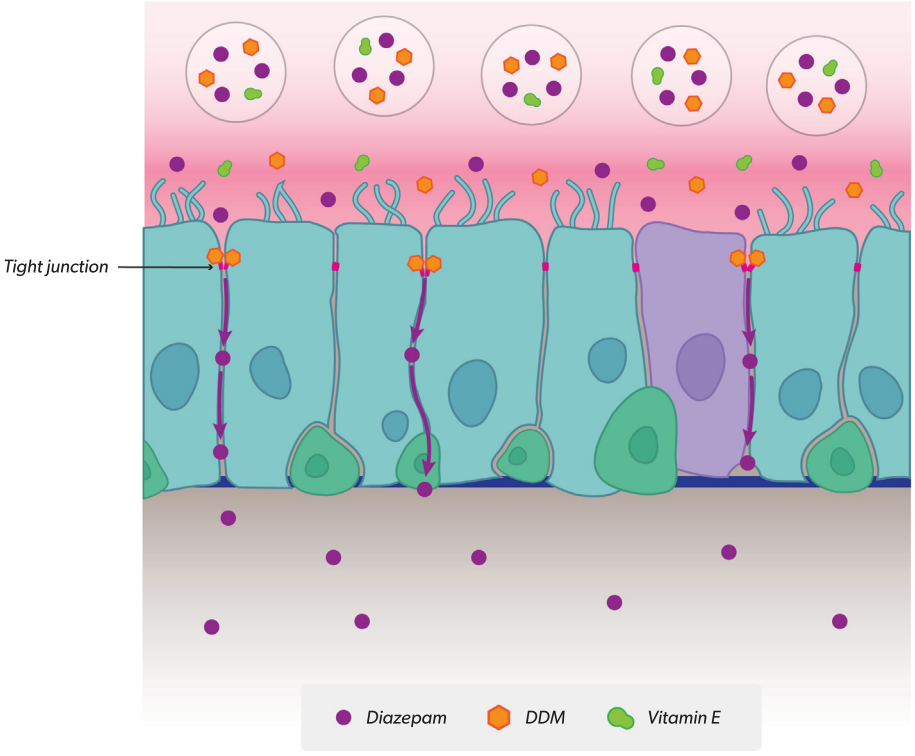


Fig. 5. Diagrammatic representation of mechanism of action of permeation enhancers used with diazepam nasal spray. Dodecyl-beta-D-maltopyranoside (DDM) is a nonionic alkylglycoside surfactant that alters electrical resistance values, mucosal viscosity, and membrane fluidity and can enhance absorption by temporarily loosening cell–cell junctions and increasing mucosal permeation. The related compound tetradecyl maltoside has been associated with vesicle-based transcellular transport. A vitamin E–based formula increases the solubility of diazepam.

Table 2
Pharmacokinetic and pharmacodynamic parameters of common rescue therapies to treat seizure clusters [7,8,75,96,101,102].

	Single Dose (maximum)	Route	Onset* (min)	t_{max} (range)	Bioavailability† (%)	$t_{1/2}$ (hr)
Diazepam (Valtoco®)	5–20 mg (20 mg)	IN	2–10	1.5 hr (0.8–4.0) ‡	97	~49
Diazepam (Valium®)	5–10 mg (30 mg)§	IV	1–3		100	
Diazepam (Diastat®)	0.2–0.5 mg/kg (20 mg)	PR	2–10	1.2 hr**	90	~46
Lorazepam (Ativan® injection)	4 mg††¶	IV	1.6		100	9–19
Lorazepam (Ativan® sublingual tablets)‡‡	0.05 mg/kg (4 mg)§§	SL	15–17	1 hr	>90	12–15
Midazolam (Nayzilam®)	5 mg (5 mg)	IN	3–10	17.3 min (7.8–28.2)	~44	2–6
Midazolam + atomizer	0.2 mg/kg (15 mg)	IV solution given IN	6–14		44–83	
Midazolam (Versed®)	0.3–0.35 mg/kg***	IV	1.5–2.5		100	2–6

IN, intranasal; IV, intravenous; PR, rectal; SL, sublingual; $t_{1/2}$, elimination half-life; t_{max}, time to peak plasma concentration.
† Relative to intravenous formulation.
‡ 10-mg dose.
§ Maximum dose according to US prescribing information to treat status epilepticus and severe recurrent convulsive seizures in adults.
* Onset of action is less well studied than other pharmacokinetic parameters listed and should be considered an approximation.
** 15-mg dose.
†† For the treatment of status epilepticus in adults.
‡‡ Not available in the US.
§§ To treat excessive anxiety prior to surgical procedures in adults.
*** Initial dose to induce general anesthesia in an average adult under the age of 55 years.

inhalation patterns during administration do not seem to have a significant influence [63]. Neither intranasal spray provides any recommendations on head position [7,83], and the device itself can be used in any position [84]. Patients and caregivers report that training on the use of the device is easy and could be part of a larger program to develop a seizure action plan for patients with epilepsy [85].

Studies of intranasal rescue therapies compared with other routes of administration

The pharmacokinetic profiles of approved and off-label seizure-cluster rescue therapies are listed in Table 2. The time to maximum plasma concentration varies between the 2 available intranasal therapies, but therapeutic levels are achieved quickly for both benzodiazepines (~70–200 ng/mL for diazepam [86,87] and > 30–100 ng/mL for midazolam [88]). Changes in electroencephalogram (EEG) spike-wave activity occur very soon after administration of diazepam to treat status epilepticus: within 5 min after intravenous administration and after 10 min with rectal administration [89]. Peak serum diazepam concentrations were achieved at 50 min for intravenous administration and 58 min for rectal administration [89]. Similar results to intravenous administration have been obtained with an intranasal formulation of midazolam, with cessation of status epilepticus on EEG occurring within a median time of about 5 min after intranasal administration in a hospital setting [90]. Using an increase in β-band power as an early surrogate marker, researchers found evidence of midazolam exerting its effect on the brain at as soon as 4:07 min, on average, after administration [90].

In clinical trials, intranasal administration of diazepam rescue therapy led to seizure termination within 10 min for the majority of patients and was comparable to the results with rectal diazepam [91,92]. In a safety study of adults and children with epilepsy using diazepam nasal spray, median overall duration from seizure onset to cessation was 6 min, with nearly two-thirds (63 %) of seizures ending within 10 min [91]. In adolescents and adults with epilepsy (age > 14 years) taking intranasal midazolam to treat seizure clusters, just over half (54 %) of seizures ended within 10 min with no recurrence within the next 6 h [93]. Moreover, studies suggest that intranasal administration leads to shorter total times to cessation compared with intravenous delivery, in part because of the time required to administer the treatments [94].

The duration of action of rescue therapy has been evaluated through assessment of the need for retreatment of seizure clusters within a certain period following initial dosing. For rectal diazepam gel, in an open-label clinical trial, 77 % of administrations prevented further seizures for the 12 h following the first dose [95,96]. With intranasal midazolam, 38.5 % of episodes in an outpatient cohort required a second dose between 10 min to 6 h after the initial dose [7,78], while a separate analysis of those data found that, among patients treated with a single dose within 10 min, 56.2 % of seizure-cluster episodes were treated with another dose or were followed by another seizure within 24 h [97]. Finally, in a long-term safety study of diazepam nasal spray, 12.6 % of treated seizure clusters were treated with a second dose within the full 24 h after the initial dose [92]. However, as there are no head-to-head studies for comparison of the above presented results, any comparison should be done with the understanding of the differences in their patient populations, including severity of epilepsy and historic duration of seizure clusters; availability of second doses; and study designs.

As a class, benzodiazepines carry a boxed warning on risks of concomitant use with opioids due to the possibility of profound respiratory depressive effects and the potential for abuse, misuse, and addiction. In clinical trials, the common adverse events associated with the intermittent use of benzodiazepine nasal sprays included somnolence, nasal discomfort, and headache. No signs of respiratory depression were observed during the long-term safety study of diazepam nasal spray [92]. During the test-dose phase of a phase 3 trial of intranasal midazolam (n = 292), 5 patients experienced an adverse event of acute central respiratory depression leading to or contributing to discontinuation [93]. Safety data for approved intranasal rescue therapies have not identified an impact on olfaction [78,92]. Intranasal corticosteroids, which have been used to treat allergic rhinitis and other conditions of the upper respiratory tract for decades, have shown a good safety profile with no evidence of atrophy or deleterious pathologic changes in the nasal mucosa after 6 months to 5 years of use [98].

Conclusion

The anatomy and physiology of the nasal cavity present unique opportunities and challenges to implementing intranasal treatments for neurologic conditions. Intranasal formulations are designed to meet the specific parameters of the nasal

anatomy and physiology in ways that oral, intravenous, or other formulations may not. Intranasal delivery offers an alternative route to rectal administration that is preferred by many patients for rapid delivery of rescue therapy to treat seizure clusters in people with epilepsy in outpatient settings, such as at home, school, or work. Rescue therapies are also an important part of a seizure action plan among appropriate patients. By overcoming specific challenges, the successful formulation of intranasal rescue therapies offers the opportunity of improved patient acceptance, better management, and potentially better patient outcomes.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr Chung is a consultant for Neurelis, Inc.; SK Life Science; Sunovion; and UCB and is a speaker for Eisai, Jazz Pharma, SK Life Science, Sunovion, and UCB. Dr Peters has served as a speaker and consultant for Greenwich Biosciences; Neurelis, Inc.; and Novartis. Dr Detyniecki is a consultant for Aquestive; Greenwich Biosciences; Neurelis, Inc.; and UCB. Dr Tatum receives a stipend from Elsevier as Editor-in-Chief of *Epilepsy & Behavior Reports* and is on the editorial board of the *Journal of Clinical Neurophysiology*. He has received grant funding from Esai, Martin Family Foundation, Mayo Clinic, and McElvey Fund and industry research support from Cerevel, Engage, Liva Nova, and Xenon. He serves as a consultant for Bioserenity; Medtronics; Neurelis, Inc.; and Zimmer-Biomet. He receives royalties from Demos, Springer, and Wiley publishers. He has patents/patents pending on intraoperative monitoring devices (#62527896; #62770362). Dr Rabinowicz is an employee of and has received stock options from Neurelis, Inc. Dr Carrazana is an employee of and has received stock and stock options from Neurelis, Inc.

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