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REVIEW

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Bi-directional nasal drug delivery systems: A scoping review of nasal particle deposition patterns and clinical application

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Abstract

Objectives: To compare the deposition patterns within the nasal cavity between the bi-directional and unilateral nasal delivery systems. And to summarize the clinical application of the bi-directional nasal drug delivery devices.

Data source: PubMed, Cochrane Library, Embase, and Web of Science databases.

Methods: A scoping review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). We included studies exploring patterns and influencing factors of particle depositions within the nasal cavity among patients, healthy controls, and nose cast models using the bi-directional and unilateral nasal delivery system. The clinical application of the bi-directional delivery devices was also summarized.

Results: A total of 24 studies were included in this review. Bi-directional nasal delivery systems utilize forced exhalation to power the delivery of drugs to deeper areas of the nasal cavity and paranasal sinuses. Unilateral nasal delivery systems included traditional liquid spray pumps, the aerosol mask system, nebulization, and conventional nasal inhalation. Compared with unilateral delivery systems, the bi-directional nasal delivery system provided a more extensive and efficient nasal deposition in the nasal cavity, especially in the olfactory cleft, without lung deposition. Several parameters, including particle size, pulsatile flow, and nasal geometry, could significantly influence nasal deposition. The bi-directional nasal delivery system enables better delivery of steroids or sumatriptan to the sinonasal cavity's high and deep target sites. This bi-directional delivery device demonstrated an effective and well-tolerated treatment that produced high drug utilization, rapid absorption, and sustained symptom improvement among patients with chronic rhinosinusitis (CRS) or migraine.

Conclusion: The bi-directional nasal drug delivery systems demonstrated significantly higher drug deposition in superior and posterior regions of the nasal cavity than unilateral nasal delivery systems. Further studies should explore its potential role in delivering drugs to the olfactory cleft among patients with olfactory disorders and central nervous system diseases.

Level of evidence: N/A.

KEYWORDS
bi-directional delivery device, central nervous system, chronic rhinosinusitis, exhalation delivery system, nasal deposition, olfactory pathway, treatment

1 | INTRODUCTION

The sinonasal cavity has a large mucosal surface area and high vascularity, allowing rapid drug uptake into the systemic circulation.[1,2] In addition, the olfactory region is located at the top of the nasal cavity and covers less than 10% of the surface of the nasal passage.[3] The olfactory cleft provides a direct connection to the central nervous system (CNS) via neural pathways such as the olfactory and the trigeminal nerves, avoiding passage through the blood–brain barrier and consequently increasing the cerebral bioavailability of the drug.[4–7] As a non-invasive route of drug delivery to the sinonasal cavity and brain, intranasal drug delivery not only provides nose-to-brain transport but also circumvents gastrointestinal degradation and hepatic first-pass metabolism of the drug, which makes it an attractive option for many therapeutic agents for sinonasal diseases and brain disorders.[1,2]

Several devices have been developed to enhance intranasal drug delivery, including mechanical spray pumps, nasal pressurized metered dose inhalers (pMDI), and powder inhalers. The significant limitation of these devices is the large fraction of drug deposited in the nonciliated region of the nose anterior to the nasal valve and insufficient deposition in the upper or posterior nasal cavity.[3] Due to the complex structure of the sinonasal cavity, including the narrow anterior valve and many convoluted meatus, it is challenging to achieve efficient and convenient drug delivery within the sinonasal cavity.[8] Nasal inhalation from nebulizers has been utilized to improve delivery to the upper posterior nasal segments, with the major disadvantages of significant inhalation to the lungs and poor dose control.[9,10] Drops may achieve better deposition beyond the nasal valve, but cumbersome delivery procedures are required.[3] Developing novel nasal drug delivery methods is imperative to overcome these barriers.

Recently, a novel bi-directional delivery system has demonstrated significantly higher drug deposition in the superior and posterior regions of the nasal cavity than conventional nasal sprays.[11] The bi-directional device leverages a patient's exhaled breath to create a closed-palate, positive-pressure, and bi-directional flow, which has been shown to deposit drugs broadly in the nasal cavity, especially in the olfactory cleft, allowing for high local concentrations of medication within the nasal cavity.[12,13] Due to these advantages, it has attracted increasing attention in nasal disease and nose-to-brain drug administration. The bi-directional drug delivery system has been mainly applied to sinonasal disorders and migraine. Compared with sprays, the exhalation delivery system (EDS) with fluticasone has been developed to improve topical delivery and limit deposition in areas outside the nasal cavity, such as the oral cavity and pharynx.[14] Oral medications are generally preferred for patients with migraines, but it is not a route of administration conducive to rapid action.[15,16] The innovative EDS maximizes the amount of drug beyond the nasal valve and decreases the amount of drug that depends on absorption through the gastrointestinal tract.[17] This novel technique promotes most of the drug to enter the large posterior nasal cavity, which is covered by a richly vascularized mucosal surface that allows rapid drug absorption.

This scoping review compares the deposition patterns within the nasal cavity between the bi-directional and unilateral nasal delivery systems and then summarizes the clinical application and effect of the bi-directional nasal drug delivery devices. This work will provide essential information and guide further clinical research about bi-directional nasal delivery systems.

2 | METHODS

2.1 | Literature search strategy

The present study is a scoping review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Review (PRISMA-ScR) guidelines. A systematic search of PubMed, Cochrane Library, Embase, and Web of Science databases was conducted as guided by the PICOS (populations, interventions, comparisons, outcomes, and study design) approach: (1) population: (a) 3D printed nose cast, (b) healthy populations; (c) patients with CRS; (d) patients with migraine; (2) intervention: bi-directional nasal delivery system; (3) control: (a) unilateral nasal delivery system (b) placebo (c) subcutaneous/oral (4) outcome: nasal deposition patterns and therapeutic effect of nasal administration; (5) study design: human clinical trials and model experiments. Two authors independently reviewed the titles and abstracts of all related studies to screen out suitable articles in March 2023. The following terms were used for the literature search: nasal, intranasal, exhalation delivery system, bidirectional, bi-directional, breath, breath-powered, olfactory, deposition, disease, treatment, and therapy. The search strategy is illustrated in Figure 1.

2.2 | Inclusion and exclusion criteria

Studies were included exploring patterns and influencing factors of particle depositions in the nasal cavity using the bi-directional and unilateral nasal delivery system and the clinical application of the bi-directional nasal drug delivery devices. Exclusion criteria included non-English language, poor correlation, and non-experimental studies. Studies without a defined intervention were excluded. In addition, case reports, letters to the editor, abstracts, and book chapters were not included.

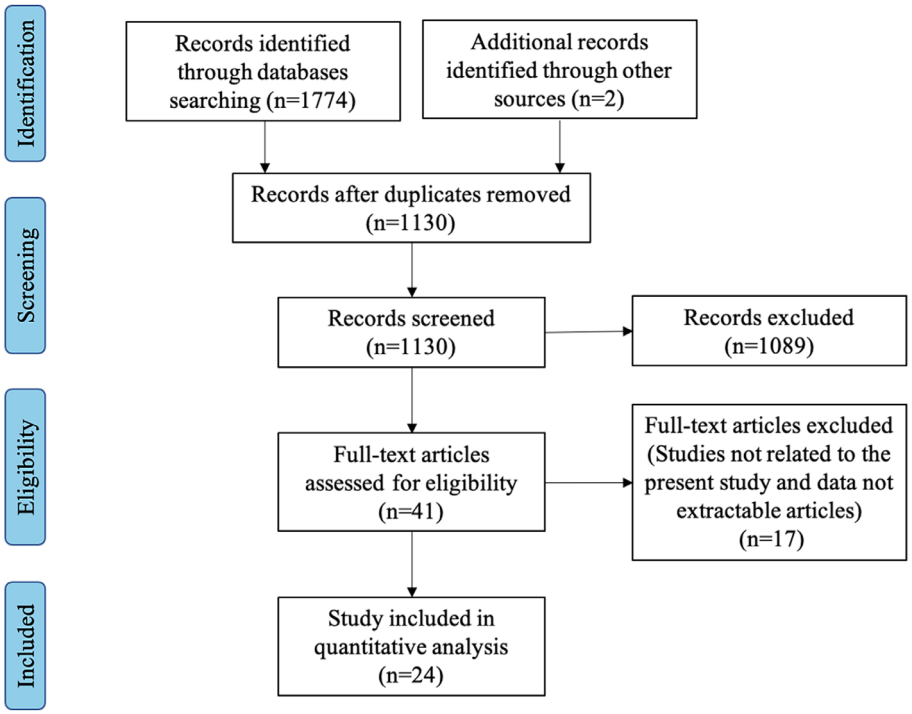

FIGURE 1 PRISMA diagram for the systemic literature search.

2.3 | Data extraction and analysis

Two reviewers each manually extracted important points from studies meeting inclusion criteria. Extracted data included delivery systems, study subjects, methods, results, and conclusions. Tables were developed after the extraction of articles. The quality of each article was evaluated using the categorization system provided by the Oxford Center for Evidence-Based Medicine Levels of Evidence.

3 | RESULTS

3.1 | Study characteristics

Our search identified 1776 studies by searching the corresponding keywords through the initial literature (Figure 1). After the removal of duplicates, 646 articles were excluded. Of the remaining studies, 24 studies were finally included in this systematic review. Ten articles were chosen for the deposition patterns between bi-directional and unilateral nasal delivery systems among healthy controls, and 3D-printed models of the sinonasal cavity. Eight articles were selected for the effect of bi-directional nasal drug delivery devices in CRS and six in migraine.

3.2 | Deposition patterns of particles in different nasal regions with the bi-directional delivery system

Ten studies compared the deposition patterns within the nasal cavity between bi-directional and unilateral nasal delivery systems (Table 1; Figure 2).[10,13,14,18–24] Seven studies were 3D printed nose cast model-based,[18–24] and the other three were selected from healthy populations as subjects.[10,13,14]

Two studies showed that the deposition following a bi-directional delivery system was significantly larger than the unilateral delivery system in the upper and posterior nasal regions.[13,14] One compared the percentage of particles deposited in the upper posterior region of the nose between the spray pump and bi-directional device (11% vs. 32%).[13] Another study showed initial 3-min deposition in the upper posterior region between the spray pump and bi-directional device was 18.3% versus 2.4%.[14]

For further studies, Dong J et al. found better olfactory delivery performance in the olfactory region by the breath-powered device compared to the aerosol mask case and both diffusive and that inertial particles could produce considerable olfactory depositions.[18] The bi-directional deposition was 2.2 times the normal technique in the nasal cavity and 3.3 times in the olfactory region.[22] In Clément Rigaut et al.'s study, the deposition in the olfactory region through a uni-directional device and a bi-directional device was 22.33% versus 7.11%,[19] which seemed contradictory to previous researches because Clément Rigaut et al. aimed the spray directly at the olfactory region instead of the center of the nasal valve as other studies.[19]

3.3 | Deposition variation under different conditions with the bi-directional delivery system

Dong et al. discovered that by breath-powered drug delivery approach, particles with diffusive 1 nm particles and inertial 10 μm caused peaking olfactory deposition. In contrast, particles ranging from 10 nm to 2 μm led to no significant olfactory deposition.[18]

TABLE 1 Comparison of the deposition patterns within the nasal cavity between bi-directional and unilateral nasal delivery system.

Delivery devices	Subjects/cast	Methods	Outcome	Conclusion	Level of evidence
Bi-directional powder device vs. traditional liquid spray pump[14]	Seven healthy subjects	Dynamic gamma camera imaging after administration of either 99mTc-labeled lactose powder or liquid 99mTc-diethelyne triamine pentaacetic acid-aerosol.	Bi-directional powder device vs. spray 1. deposition in the upper posterior region: 18.3% ± 11.5 vs. 2.4% ± 1.8, $p < .02$; 2. Sum of upper and middle posterior regions: 53.5% ± 18.5 vs. 15.7% ± 13.8, $p < .02$; 3. Lower anterior and posterior regions: 17.4% ± 24.5 vs. 59.4% ± 18.2, $p < .04$; 4. No lung deposition was observed.	Compared with a spray pump, the bi-directional powder device provides significantly larger deposition in the upper and posterior nasal regions, whereas less was deposited in the lower regions.	3B
A novel breath actuated bi-directional device vs. conventional hand actuated spray pump[13]	Nine healthy adult volunteers	The deposition patterns achieved with the two devices were assessed by scintigraphy after administration of 99mTc-aerosols.	Bi-directional device vs. spray pump 1. Deposition in the upper posterior region: 32%vs. 11%; 2. Deposition in posterior segments beyond the nasal valve: 68% vs. 25%; 3. Deposition in the lower anterior region of the nose: 13% vs. 32%.	Compared with a spray pump, the breath actuated bi-directional device provides significantly larger deposition in the clinically important regions beyond the nasal valve and reduced anterior deposition.	3B
The breath-powered bi-directional system vs. the aerosol mask system[18]	Anatomical nasal model of a 60 years healthy male reconstructed from computed tomography images	The discrete phase particle tracking method was employed to capture the aerosol drug transport and deposition behaviors in the nasal cavity.	Bi-directional system vs. aerosol mask system: superior olfactory deposition: 1. For diffusive 1 nm particles: 2.2% vs. 1.2% for the right chamber and 0.8% for the left chamber; 2. For inertial 10 μm particles: 1.5% vs. 0.3% in the left chamber, and no olfactory deposition can be found in the right chamber.	Improved drug administration doses can be achieved in the targeted olfactory region through the breath-powered bi-directional aerosol delivery approach.	3B
A bi-directional device vs. a spray[19]	Nasal casts of two different geometries: the original one with the septum perforation and a "healthy" geometry.	A 3D-printed replica of a nasal cavity to reproduce in vitro the deposition of a solid powder.	Bi-directional device VS uni-directional device: 1. Depositing powder in the olfactory region:22.33% ± 4.86% vs. 7.11% ± 1.52%; 2. The choice of the nostril and the presence of a perforation in the septum significantly influence the olfactory deposition.	1. The Uni-directional device is more effective in targeting the olfactory zone than the bi-directional device. 2. Aiming the spray nozzle directly at the olfactory area is more effective than targeting the center of the nasal valve.	3B
Bi-directional airflow vs. nebulization[20]	3D-human nasal replica model geometries of three subjects	Human nasal cavities were reconstructed in silico, and deposition of microparticles under	1. Maximum olfactory deposition was observed with particles in the size range of 8–12 μm under	Tailoring particle size and a delivery protocol may provide a unique and pragmatic way to target drugs	3B

(Continues)

TABLE 1 (Continued)

Delivery devices	Subjects/cast	Methods	Outcome	Conclusion	Level of evidence
	generated from CT-scan images	nebulization and bi-directional airflow conditions was simulated.	nebulization and 14–18 μm under bi-directional airflow conditions. 2. Significant intra-subject variability in microparticle deposition was also observed in the bi-directional delivery cases. 3. Geometric differences between subjects were shown to significantly impact overall and regional particle deposition and introduced inter-subject variability.	to the olfactory region. Differences in nasal anatomy among humans can cause variability in particle deposition.	
Bi-directional delivery vs. unilateral delivery[21]	Three 3D printed casts with different levels of nasal passage dilations.	Sar-Gel visualizes the deposition distribution in the passage of the three nose models. N0, N1, and N2 were developed with different levels of nasal passage dilations. (The cross-sectional area of the nasal valve in N1 and N2 expanded by 30% and 50%, respectively, compared to the original model N0.)	1. Nasal dilation lowered the total dosage in the nose but increased the dosage to the olfactory region in both the unilateral and bi-directional deliveries. 2. The maximum bi-directional olfactory deposition fractions (3.48% in N2) was about four times the unilateral deposition fractions in N2 (0.79%) and eight times that in N0 (0.43%)	Nasal dilation in combination with bi-directional delivery is recommended over the conventional unilateral method for olfactory targeting.	3B
Bi-directional intranasal delivery technique vs. normal intranasal delivery technique[22]	Multi-sectional 3D printed nose cast model; a vibrating mesh nebulizer (Drive Voyager Pro) and a jet nebulizer (PARI Sinus)	In vitro tests and numerical simulations. Sar-Gel was used to visualize the deposition pattern inside the nose, and the delivered doses were measured using a high-precision scale. Numerical modeling was performed to understand the underlying mechanisms in both the normal and bi-directional deliveries.	1. The bi-directional technique performs better in the nasal cavity and olfactory region than the normal technique. 2. PARI Sinus performs better in delivering more doses to the vestibule-turbinate and olfactory regions with the normal delivery method, while the mesh nebulizer is better with the bi-directional technique. 3. Regarding the mesh nebulizer, there was a factor of 2.2 increase in the nasal cavity and 3.3 in the olfactory using the bi-directional technique. In contrast, the increase factor was 1.5 and 1.2 for the PARI Sinus nebulizer in the nasal cavity and olfactory region, respectively.	The bi-directional technique with a vibrating mesh nebulizer is recommended for both nasal systematic and olfactory drug deliveries.	3B

TABLE 1 (Continued)

Delivery devices	Subjects/cast	Methods	Outcome	Conclusion	Level of evidence
EDS vs. conventional nasal spray vs. high-volume irrigation[23]	Silicone casts of the nasal cavity and sinuses from a patient after Draf II and Draf III	Internal surfaces were coated with liquid-sensitive, color-changing gel. Color changes were evaluated following conventional nasal spray delivery (Nasonex®), EDS delivery (XHANCE™), and high-volume, low-flow (HVLF) delivery with head tilted either 45° or 90°.	Liquid deposition within the silicone casts: 1. Conventional intranasal corticosteroid spray: the anterior nasal segments, with similar deposition profiles in both Draf II and Draf III casts. 2. EDS delivery: throughout the nasal cavity and in both models' surgically opened ethmoid and maxillary spaces.	HVLF and EDS produced a deep intranasal/intrasinal deposition in the silicone cast compared with conventional nasal spray delivery; both deposited liquid inside the surgically opened sinuses. HVLF offers the benefit of lavage, whereas EDS may be more efficient and convenient.	3B
Bi-directional breathing technique vs. normal[24]	Anatomically-accurate nasal models of 2-, 5-, and 50-year-old subjects	Three models were tested to quantify the sub-regional deposition of an aqueous solution of a model drug, nebulized with PARI SinuStar™ and Sinus™ nebulizers	1. The use of a modified nasal adaptor resulted in a significantly higher percent recovery, 68.41 ± 13.56%, compared to the standard design, 10.35 ± 1.75%. 2. In the adult subject, paranasal delivery was equal to 19.34 ± 1.21% and 5.99 ± 0.95% using PARI Sinus™ nebulizer, with and without pulsating airflow, respectively.	Bi-directional breathing and pulsating airflow are beneficial for improved paranasal aerosol delivery in children, similar to previous findings for adults.	3B
The novel bi-directional nasal delivery vs. conventional nasal inhalation[10]	Sixteen healthy non-smoking adult volunteers	99mTc labeled nebulized particles with a mean particle size of 3.5 mm were administered with two devices; Scintigraphic images showing the deposition.	1. Lung deposition of bi-directional delivery vs. conventional nasal inhalation: 0.8 ± 2.0% vs. 22.3 ± 8.1%. 2. The fraction deposited in the lungs correlated significantly ($r^2 = 0.47$, $p < .004$) with the volume of the nasal passages.	The bi-directional nasal delivery concept minimizes the risks and problems related to lung deposition occurring during conventional nasal inhalation from a nebulizer and opens up a new range of opportunities for nasal delivery of drugs and vaccines.	3B

Abbreviations: DoE, designs of experiments; EDS, exhalation delivery system; HVLF, high-volume, low-flow; Opt-Powder, OptiNose powder device.

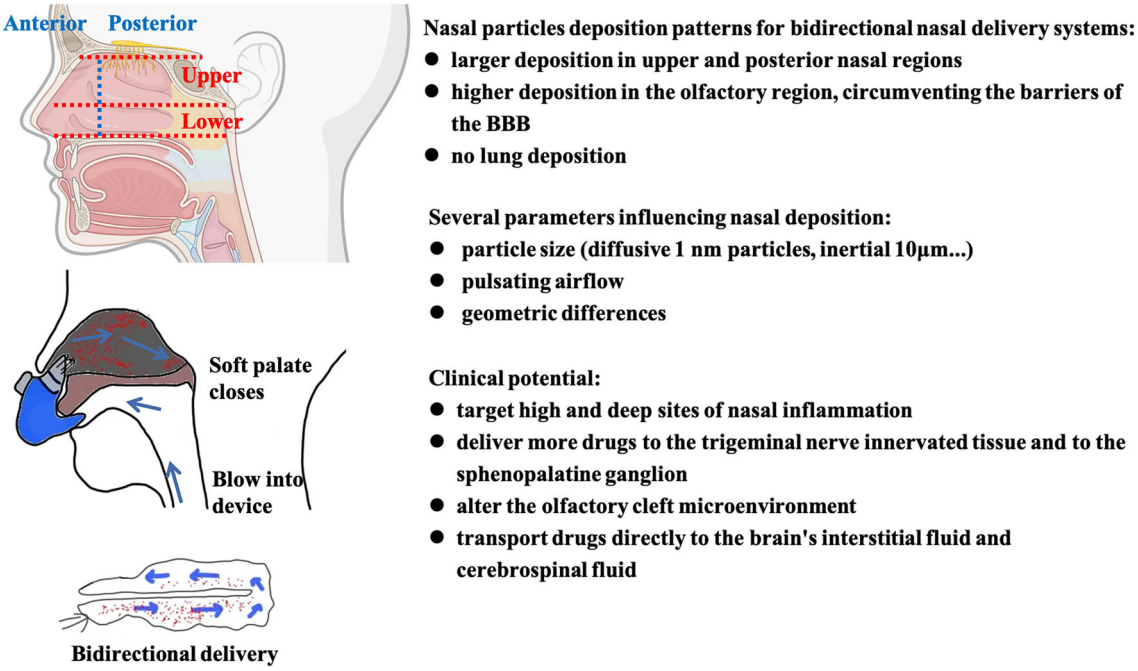

FIGURE 2 Summary of the bi-directional nasal drug delivery systems. BBB, blood–brain barrier.

A similar study showed that maximum olfactory deposition was observed with particles in the size range of 8–12 μm under nebulization and 14–18 μm under bi-directional airflow conditions.[19] They also found that geometric differences, such as a perforation in the septum between subjects, significantly impacted overall and regional particle deposition.[19,20]

A study developed different levels of nasal passage dilations to explore deposition distribution in the passage of the three nose models.[21] They found that nasal dilation lowered the total dosage in the nose but increased the dosage to the olfactory region in both the unilateral and bi-directional deliveries, and the maximum bi-directional olfactory deposition fractions (3.48% in N2) was about four times the unilateral deposition fractions in N2 (0.79%) and eight times that in N0 (0.43%).[21]

Compared to the normal technique, a study by Xi et al. showed that the mesh nebulizer delivered more doses to olfactory regions with the bi-directional technique.[22] Deposition of drugs in the nose and sinuses with an EDS vs. conventional nasal spray or high-volume irrigation (HVLF) was explored in Draf II/III post-surgical anatomy.[23] HVLF and EDS produced a deeper intranasal deposition in the silicone cast than in conventional nasal spray delivery. Moreover, bi-directional breathing and pulsating airflow improved paranasal aerosol delivery.[24] The bi-directional breathing technique resulted in a significantly higher percent recovery of 68.41%, compared to the standard design of 10.35%.

3.4 | Lung deposition with the bi-directional delivery system

Per Gisle Djupesland also found that lung deposition of bi-directional delivery was lower than unilateral delivery (0.8 ± 2.0% vs. 22.3 ± 8.1%).[10] In addition, no lung deposition was observed using a bi-directional nasal delivery system.[14]

3.5 | Bi-directional nasal drug delivery devices for treating inflammatory sinonasal disease

Eight studies (Table 2) aimed at exploring the effect of the bi-directional nasal drug delivery device in chronic rhinosinusitis.[25–32] Two of these studies were exploratory analyses of pooled data from two large, controlled trials (NAVIGATE I and II).[31,32] In these trials, the summed polyp score, the nasal Rhinosinusitis Outcome Measure-31 (RSOM-31) subscale, Endoscopy score for edema, Sino-Nasal Outcomes Test scores (SNOT-22) were involved to evaluate outcomes.

Two trials[25,26] used the OptiNose device containing fluticasone propionate (Opt-F) and conducted placebo-controlled studies. One of the studies investigated the therapeutical effect on patients with CRSwNP,[25] and the other study studied recalcitrant CRS.[26] Combined symptom score, nasal blockage, discomfort, rhinitis symptoms, and sense of smell were all significantly improved, and the Opt-FP was well tolerated.[25,26]

EXHANCE-3 and EXHANCE-12[27,28] were prospective, multicenter, single-arm studies including patients with CRSwNP and CRSsNP, which lasted 3 and 12 months, respectively. Most patients reported symptom improvement in two trials. SNOT-22 improved substantially in patients with and without CRSwNP. Improvement of polyp grade by ≥1 point and polyp elimination in at least 1 nostril was demonstrated in most patients with CRSwNP. EDS-FLU was generally well tolerated.[27,28] NAVIGATE I and II[29,30] were prospective, randomized, double-blind, controlled phase 3 trials with CRSwNP patients enrolled.

TABLE 2 Clinical application of the bi-directional nasal drug delivery devices among patients with chronic rhinosinusitis.

Groups	Subjects	Study design	Outcome	Conclusion	Level of evidence
Opt-FP vs. Placebo[25]	Mild-to-moderate bilateral nasal polyposis ($n = 109$)	A prospective, multicenter, randomized, double-blind, placebo-controlled, parallel group study	1. The proportion of subjects with improvement in summed polyp score ≥1 (Lildholdt's Scale) was significantly higher with Opt-FP compared with placebo at 4, 8 and 12 weeks (22% vs. 7%, $p = .011$, 43% vs. 7%, $p < .001$, 57% vs. 9%, $p < .001$). 2. The summed polyp score was reduced by 35% after 12 weeks ($p < .001$). 3. Combined symptom score, nasal blockage, discomfort, rhinitis symptoms, and sense of smell were all significantly improved.	Fluticasone propionate (400 μg b.i.d.) administered using OptiNose's breath actuated bi-directional delivery device was an effective and well-tolerated treatment for mild-to-moderate bilateral nasal polyposis.	1B
Opt-FP vs. Placebo[26]	Recalcitrant CRS ($n = 20$)	A prospective, single-center, randomized, double-blind, placebo-controlled, parallel group study	1. Endoscopy score for edema showed a highly significant and progressive improvement (12 weeks: Opt-FP, −4.0; placebo, −1.0, $p = .015$). 2. The nasal RSOM-31 subscale was significantly improved with Opt-FP treatment (4 weeks: $p = .009$, 8 weeks: $p = .016$, 12 weeks: NS). 3. Sense of smell, nasal discomfort, and combined score were all significantly improved ($p < .05$).	The OptiNose breath-actuated bi-directional delivery device administering fluticasone propionate (400 μg b.i.d.) is an effective and well-tolerated treatment for recalcitrant CRS.	1B
EXHANCE-3: EDS with fluticasone (EDS-FLU)[27]	CRSsNP ($n = 603$) and CRSwNP ($n = 102$)	Prospective, multicenter, 12-week, single-arm study of EDS-FLU 372 μg twice daily (b.i.d.) at 38 U.S. sites.	1. More than 90% reported improvement in treatment by PGIC. SNOT-22 scores improved substantially and similarly in patients with NP (−23.7) and without NP (−24.4). 2. Among patients with baseline Lund-Kennedy edema scores >0: 33.3% (CRSwNP) and 54.8% (CRSsNP) had complete resolution of edema. 3. In CRSwNP patients, 48% had polyp elimination in ≥1 nostril, 63% had ≥1-point improvement in polyp grade, mean bilateral polyp grade decreased from 2.9 to 1.6, and study-defined surgical eligibility decreased.	EDS-FLU 372 μg BID in treating CRS with or without polyps produced substantial improvement across a broad range of objective and subjective measures.	1B
EXHANCE-12: EDS-FLU[28]	CRSsNP ($n = 189$) and CRSwNP ($n = 34$)	A 12-month, multicenter, single-arm study evaluating the safety and efficacy of EDS-FLU 372 μg twice daily in CRS patients.	1. Most patients (87%) reported symptom improvement. Through 12 months, mean SNOT-22 scores improved by −21.5 and −21.1 for CRS with and without NP, respectively.	Over 1 year of treatment in CRS with and without NP, EDS-FLU 372 μg twice daily produced improvements across a broad range of objective and subjective measures. EDS-FLU may be a desirable new option for patients with this condition.	1B

(Continues)

TABLE 2 (Continued)

Groups	Subjects	Study design	Outcome	Conclusion	Level of evidence
			2. Among patients with NP, 54.2% had polyp elimination in at least 1 nostril, and 83.3% had ≥1-point improvement in polyp grade.		
NAVIGATE I: EDS-FLU vs. EDS-placebo[29]	CRSwNP ($n = 323$)	Randomized, double-blind, EDS-placebo-controlled, multicenter study	1. EDS-FLU vs. EDS-placebo at week 16: SNOT-22 improvement, −18.3 to −19.8 vs. −11.0 ($p \leq .005$). 2. ≥1 polyp grade improvement occurred in 56%, 66%, and 72% of patients receiving 93, 186, and 372 mg EDS-FLU, respectively. 3. EDS-FLU significantly improved all four cardinal symptoms of NP ($p < .05$), including congestion/obstruction, facial pain/pressure, rhinorrhea/post-nasal drip, and hyposmia/anosmia. 4. AEs were generally local in nature and similar to other intranasal steroids studied for similar durations in similar populations, with the most common being epistaxis.	In patients with CRSwNP who were symptomatic despite high rates of prior intranasal steroid use and/or surgery, EDS-FLU produced significant improvements compared to EDS-placebo in multiple subjective and objective outcomes.	1B
NAVIGATE II: EDS-FLU vs. EDS-placebo[30]	CRSwNP ($n = 323$)	Randomized, double-blind, EDS-placebo-controlled trial	1. EDS-FLU was superior on both coprimary end points ($p < .001$ vs. EDS-placebo, all doses). 2. Mean polyp grade improved continuously through week 24 ($p < 0.009$, all comparisons), with polyps eliminated on at least 1 side in approximately 25% of patients at week 24 vs. 8.7% with EDS-placebo ($p \leq .014$, all comparisons). 3. SNOT-22 at week 16: EDS-FLU vs. EDS-placebo, −21.05 to −21.43 vs. −11.70 ($p < .05$ all doses). 4. EDS-FLU significantly improved all 4 defining disease symptoms.	EDS-FLU produces clinically and statistically significant improvement in all four diagnostically defining disease symptoms, polyp grade, and quality of life in patients with chronic rhinosinusitis with NPs.	1B
CRSwNP patients with recurrent symptoms after sinus surgery versus patients without surgery[31]	CRSwNP patients with recurrent symptoms ($n = 482$)	Data were pooled from two large, controlled trials (NAVIGATE I and II) for exploratory analyses.	1. There was no statistically significant difference between the subgroups with or without prior sinus surgery with either dose of EDS-FLU: nasal congestion ($p = .499$ and $p = .714$, respectively), SNOT-22 total score ($p = .147$ and $p = .901$), patient global impression of change ($p = .976$ and $p = .918$), and polyp grade ($p = .982$ and $p = .460$).	EDS-FLU effectively reduces symptoms and improves the quality of life in both patients with recurrent symptoms after sinus surgery and patients who have never had surgery. The higher dose may provide greater benefit in patients with prior ESS than the lower dose.	1B

TABLE 2 (Continued)

Groups	Subjects	Study design	Outcome	Conclusion	Level of evidence
			2. In previously operated patients, unlike surgery-naive patients, multiple outcomes (SNOT-22, RSDI, polyp grade) consistently showed numerically but not statistically greater responses to the higher dose.		
CRSwNP patients treated with a conventional nasal steroid at trial entry vs. the overall study population[32]	CRS who remains symptomatic on standard nasal steroid sprays ($n = 482$)	Data were pooled from two large, controlled trials (NAVIGATE I and II) for exploratory analyses.	1. For EDS-FLU 372 μg, "switchers" receiving EDS-FLU vs. the overall population: congestion (−0.73 vs. −0.62), rhinorrhea (−0.71 vs. −0.51), facial pain/pressure (−0.48 vs. −0.41), sense of smell at week 4 (−0.35 vs −0.30), SNOT-22 (at week 16 − 21.01 vs −20.52). 2. Results for EDS-FLU 186 μg were similar.	Patients who remain symptomatic with a standard glucocorticoid nasal spray have the potential to benefit across a range of clinical and patient-reported outcomes when treated with EDS-FLU.	1B

Abbreviations: AEs, adverse events; BID, twice daily; CRS, chronic rhinosinusitis; CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; EDS-FLU, exhalation delivery system with fluticasone; NP, nasal polyps; Opt-FP, OptiNose device containing fluticasone propionate; PGIC, patients' global impression of change; RSDI, rhinosinusitis disability index; RSOM-31, rhinosinusitis outcome measure-31; SF-36, the 36-item short form; SNOT-22, sino-nasal outcome test.

In these trials, improvements in SNOT-22 and polyp grade was substantial in all EDS-FLU groups and statistically superior to EDS-placebo. Besides, EDS-FLU significantly improved all four cardinal symptoms of nasal polyps.[29,30] Adverse events were generally local and similar to other intranasal steroids studied for similar periods in similar populations; the most common was epistaxis.[29]

Ow et al.[31] compared CRSwNP patients with recurrent symptoms after sinus surgery with patients who had not undergone surgery. According to their results, there was no statistically significant difference in multiple outcomes between the two groups no matter which dose of EDS-FLU. Compared with the overall study population, Senior et al.[32] found that CRSwNP patients who used standard nasal steroid sprays at entry and later received EDS-FLU were comparable with improvements across multiple outcome measures.

3.6 | Bi-directional nasal drug delivery devices achieve rapid headache relief

A total of six trials were included, and all the studies used the breath-actuated bi-directional powder delivery device to treat migraine[33–38] (Table 3).

Luthringer et al.[33] compared the novel breath-actuated bi-directional powder delivery device (10 and 20 mg sumatriptan) with subcutaneous sumatriptan (6 mg). Three studies[34–36] compared the AVP-825 intranasal delivery system with 100 mg oral sumatriptan. They all found that sumatriptan was rapidly absorbed after intranasal administration with the bi-directional powder delivery device and that most participants were pain-free with all treatments from 15 min to 8 h post-dose. Pain relief between 15 and 90 min after dosing was significantly greater in the sumatriptan powder group than oral sumatriptan 100 mg.[34–36] Regarding side effects, nasal discomfort, and abnormal taste were more common with AVP-825 than oral sumatriptan (16% vs. 1% and 26% vs. 4%, respectively), but approximately 90% were mild except for one disruption.[34]

Phases 2 and 3 trials were two double-blind, placebo-controlled, parallel-group studies with a low incidence of adverse events.[37,38] The efficacy results of this Phase 3 trial were similar to the Phase 2 study, demonstrating that AVP-825 provides not only early onset of efficacy for moderate or severe migraines but also sustained efficacy. Patients treated with AVP-825 showed a significantly higher rate of pain relief compared to placebo at any time point up to 2 h post-dose and at 24 and 48 h.[37,38]

4 | DISCUSSION

This is the first systematic review summarizing deposition differences in the nasal cavity between bi-directional and unilateral nasal delivery systems, as well as the clinical application and effect of the bi-directional nasal drug delivery devices. For conventional nasal spray delivery, its larger deposition in the lower anterior regions of the nasal cavity, lack of dose control, and significant lung deposition are serious

TABLE 3 Clinical application and effect of the bi-directional nasal drug delivery devices among patients with headache.

Groups	Subjects	Study design	Outcome	Conclusion	Level of evidence
A novel breath-actuated bi-directional powder delivery device (10 mg and 20 mg sumatriptan) vs. subcutaneous sumatriptan (6 mg)[33]	Patients with migraine without aura of moderate or severe intensity for at least 1 year ($n = 12$)	An open-label, randomized, active treatment-controlled, three-way crossover study	1. Sumatriptan was rapidly absorbed after intranasal administration using the new device. 2. Most study participants were pain-free according to the headache severity score with all treatments from 15 min to 8 h post-dose. 3. Using the glyceryl trinitrate challenge, sumatriptan powder delivered intranasally at a dose of 20 mg by the new device had effects similar to those of subcutaneous sumatriptan on EEG and reported headache pain despite much lower systemic exposure. 4. All AEs were of mild or moderate severity, were generally transient in nature (resolved within 1 day), and recovered spontaneously.	Administration of sumatriptan intranasally at doses of 10 mg and 20 mg by the breath actuated bi-directional powder delivery device results in rapid absorption. Delivery to target sites beyond the nasal valve induced a similar EEG profile to subcutaneous sumatriptan 6 mg and prevented migraine attacks in patients following GTN challenge.	1B
AVP-825 vs. oral sumatriptan[34]	Episodic migraine ($n = 275$)	A randomized, multicenter, double-dummy, crossover, multi-attack, comparative efficacy study with two 12-week double-blind periods	1. The sum of pain intensity differences from dosing to 30 min (SPID-30): sumatriptan powder group vs. oral sumatriptan 100 mg, 10.80 vs. 7.41, $p < .001$. 2. Significantly greater rates of pain relief and pain freedom occurred with AVP-825 treatment compared with oral sumatriptan (between 15 and 90 min). 3. Nasal discomfort and abnormal taste were more common with AVP-825 than oral sumatriptan (16% vs. 1% and 26% vs. 4%, respectively), but ~90% were mild, leading to only one discontinuation.	AVP-825 is superior to 100 mg oral sumatriptan based on earlier onset of efficacy (patients want fast migraine relief), superior efficacy (patients want complete migraine relief), greater consistency (patients want consistent relief), and good overall tolerability, including lower triptan effects that are consistent with the lower systemic exposure	1B
AVP-825 vs. oral sumatriptan[35]	Episodic migraine with or without aura ($n = 185$)	A randomized, multicenter, double-dummy, crossover, multi-attack, comparative efficacy study with two 12-week double-blind periods	1. AVP-825 provided a greater reduction in migraine pain intensity than oral sumatriptan in the first 30 min post-dose, regardless of whether attacks were treated when the pain was mild (least squares mean SPID-30 = 3.90 vs. 0.24, $p = .0013$) or moderate/severe (least squares mean SPID-30 = 13.83 vs. 10.07, $p = .0002$). At every time point from 15 to 90 min post-dose, the proportion of attacks achieving total migraine freedom	Treatment with AVP-825 provides earlier onset and more consistent across-episode improvement of pain and migraine-associated symptoms compared with oral sumatriptan, highlighting the clinical advantages of this newly approved intranasal delivery system for low-dose sumatriptan powder.	1B

TABLE 3 (Continued)

Groups	Subjects	Study design	Outcome	Conclusion	Level of evidence
			was greater and statistically significant after treatment with AVP-825 compared to 100 mg oral sumatriptan. 2. AVP-825 treatment resulted in greater odds of achieving pain freedom (odds ratio, OR = 1.29, $p < .01$) and meaningful pain relief (OR = 1.32, $p < .0001$), which were also statistically significant compared with oral sumatriptan.		
AVP-825 breath-powered intranasal delivery system vs. 100 mg oral sumatriptan[36]	Episodic migraine ($n = 259$)	A comparative randomized clinical trial across multiple attacks from the COMPASS Study	1. Over the first 30 min and the first 45 min, a typical individual showed significantly faster reductions in migraine pain when treated with AVP-825 compared with oral sumatriptan. 2. Overall levels of pain and disability also favored AVP-825 over 2 h following treatment. 3. Model-based OR comparing AVP-825 to oral sumatriptan ranged from 0.38 to 0.76 for pain and 0.37 to 0.65 for disability, with OR <1 indicating reduced pain/disability in the AVP-825 condition.	Compared with 100 mg oral sumatriptan, treatment with AVP-825 was associated with faster reductions in migraine pain intensity and migraine-related disability starting at 10 min post-dose and continuing through the first 30 min for migraine pain intensity and the first 45 min for migraine-related disability.	1B
Phase 2 AVP-825 vs. placebo delivery system[37]	Migraine ($n = 117$)	A multicenter, randomized, double-blind, parallel group, placebo-controlled study	1. A greater proportion of subjects who received sumatriptan were pain-free at 120 min compared with those who received a placebo (10 mg/20 mg sumatriptan vs. placebo = 54%/57% vs. 25%, $p < 0.05$). 2. Significant benefits were also observed for pain relief at 120 min (84%/80% vs. 44%, $p < 0.001/0.01$) and as early as 60 min (73%/74% vs. 38%, $p < .01$) and for 48 h sustained pain-free ($p < .05$). 3. Treatment-related AEs were rare, with a metallic taste being the most commonly reported (10%/13%).	Sumatriptan at doses of 10 or 20 mg administered using the new bi-directional powder delivery device was effective, safe, and well tolerated in treating a single migraine attack.	1B
Phase 3 AVP-825 vs. placebo delivery system[38]	Migraine ($n = 230$)	A double-blind, placebo-controlled, parallel-group study	1. AVP-825 vs. placebo device: patients reported headache relief at 30 min post-dose, 42% vs. 27%; at 2 h post-dose, 68% vs. 45%; at 24 h, 44% vs. 24%; at 48 h, 34% vs. 20%.	Targeted delivery of a low dose of sumatriptan powder via AVP-825 provided fast relief of moderate or severe migraine headaches in adults that reached statistical significance over placebo by 30 min. The treatment was	1B

(Continues)

TABLE 3 (Continued)

Groups	Subjects	Study design	Outcome	Conclusion	Level of evidence
			2. AVP-825 vs. placebo device: pain-free at 2 h, 34% vs. 17%; meaningful pain relief within 2 h of treatment, 70% vs. 45%; rescue medication required, 37% vs 52%; total migraine freedom (patients with no headache, nausea, phonophobia, photophobia, or vomiting) at 1 h, 19% vs. 9%. 3. There were no serious AEs or systemic AEs in more than one patient.	well tolerated, with a low incidence of systemic AEs	

Abbreviations: AEs, adverse events; EEG, electroencephalogram; GTN, glyceryl trinitrate; OR, odds ratio; SPID-3, the sum of pain intensity differences from dosing to 30 min.

drawbacks when used for intranasal administration.[10,11] Nevertheless, efficient drug delivery to superior and posterior intranasal target sites beyond the nasal valve, including the olfactory region, can be achieved by bi-directional nasal drug delivery devices.[13,14,18,21]

The deposition pattern after the bi-directional device showed marked differences compared with the traditional spray pump, indicating that the bi-directional airflow alters the geometry of the plume and carries particles past the nasal valve into critical areas of the upper and posterior nasal sections.[13] Furthermore, the geometry of the nozzle and the airflow reduce the unwanted deposition of particles in the anterior nasal segment.[13] Another study by Clément Rigaut et al.[19] showed that the higher particle ejection velocity of the nasal spray and the direct spray to the olfactory region rather than the center of the nasal valve might account for the high particle deposition within the olfactory region. Except for ejection velocity and action sites, the deposition of particles in the nasal cavity is also influenced by many parameters, including particle size, airflow rate, and nasal geometry. Nasal dilation, nasal structures, the mesh nebulizer, and pulsating airflow also contribute to the increased deposition in the olfactory regions.[19–22]

The bi-directional nasal delivery system utilizes a posterior connection between the nasal passages, and the soft palate automatically closes when exhaling through the mouth.[10] A bi-directional airflow within the nasal cavity characterizes the bi-directional nasal delivery. Therefore, compared to the unilateral nasal delivery system, little or no lung deposition was observed by bi-directional nasal delivery.[10,14] Considering the toxicologic profile in nasal formulations, pulmonary problems induced by drugs are intensively described, ranging from mild effects such as coughing or breathing problems during sleep to severe effects such as pulmonary toxicity, infections, pneumonia and acidosis.[39] Bi-directional nasal delivery is greatly helpful to decrease the risks related to lung deposition during conventional nasal inhalation and open up a new range of opportunities for nasal delivery of drugs or vaccines.

Clinically, conventional nasal sprays often do not efficiently deliver topical medications to disease sites beyond the nasal valve area, especially failing to reach the middle meatus/the ostiomeatal complex (OMC) and olfactory cleft among patients with CRS.[3,11] Therefore, conventional nasal sprays cannot efficiently access polyps as they often regress from the OMC or olfactory cleft, where polyps will continue to obstruct sinus drainage and ventilation. By contrast, a breath-actuated bi-directional delivery device demonstrated an effective and well-tolerated treatment, enabling better delivery of steroids to high and deep target sites of inflammation.[3] Further clinical studies are warranted to compare the efficacy of bi-directional nasal drug delivery devices with nasal steroid sprays. It should be pointed out that patients with CRSwNP during the acute exacerbation differed from those during the chronic phase of CRSwNP. For patients with acute exacerbation of CRSwNP, it may be necessary to combine bi-directional nasal drug delivery devices with other pharmacotherapies, including saline, antibiotics, and biologics.[40] It has also been reported that fluticasone propionate is effective and safe when administered to children via the breath-powered bi-directional delivery method.[41]

Rapid relief from headaches is very important for patients. Therefore, in recent years, efforts toward seeking alternative formulations and effective delivery routes have been increasing.[42,43] Migraine pathophysiology involves inherited alteration of brain excitability, recurrent activation, sensitization of the trigeminovascular pathway, etc.[44] Asghar et al. described the reversal of unilateral intracranial dilatation of the medial meningeal artery by sumatriptan, along with the amelioration of same-sided headaches.[45] The deep nasal cavity deposition associated with Breath Powered delivery allows for broader delivery of the drugs to the trigeminal nerve innervated tissue and to the sphenopalatine ganglion, which may prove to be beneficial in the treatment of a range of headache disorders.[15] AVP-825 is a non-oral delivery system containing 22 mg of sumatriptan and utilizes the patient's breath to deliver medication beyond the nasal valve to the upper posterior nasal cavity with richly vascular mucosa, which is conducive to rapid drug absorption into the systemic circulation.[46] In the above clinical trial data, AVP-825 produces earlier improvement in migraine pain, disability, and associated symptoms, and sustained efficacy and favorable tolerability with few triptan-related adverse effects.[34–38]

AVP-825 has the potential to be used at all phases of a migraine attack and is also likely to be more effective in advanced migraines accompanied by nausea or other gastrointestinal problems since the absorption of intranasal administration does not depend on the gastrointestinal tract.[47] This bi-directional nasal delivery system will be particularly useful as an effective treatment option for patients whose migraine treatment with oral medications is unsatisfactory or for those whose oral medications are poorly absorbed during migraine treatment.

The bi-directional device has not been tested and applied to other diseases except CRS and migraine patients. But this device has great potential. The blood–brain barrier plays a vital role in protecting the delicate milieu of the brain. Still, it also prevents 98% of small molecules and more large molecules from arriving at their intended targets.[48] The intranasal route has emerged as a promising administration site for CNS therapeutics. The bi-directional nasal delivery system provided a larger deposition in the upper and posterior nasal regions and yielded higher depositions in the olfactory region. It has been discovered that drugs can be transported directly to the brain's interstitial fluid and cerebrospinal fluid when administered intranasally.[49] Through intranasal administration, it is possible to bypass the barriers of the blood–brain barrier by taking advantage of the olfactory epithelium where the CNS is in direct contact with the olfactory cleft environment.[50] Therefore, administering the drug from the nose to the brain along the olfactory and trigeminal nerve pathways offers an alternative route for treating CNS disorders.

Even though numerous studies of bi-directional devices focus on treating topical nasal diseases or migraines, the effect of a bi-directional nasal drug delivery system on olfactory dysfunction remains unknown. Olfactory training has been proven effective for patients with olfactory dysfunction with varied etiologies such as sinonasal disease, viral infection, and head trauma.[51] Due to the targeted drug delivery to the olfactory region, a bi-directional nasal drug delivery system has the potential to alter the olfactory cleft microenvironment and may improve the effect of olfactory training. Therefore, in the future, more studies are warranted to seek the clinical effect of olfactory training equipped with bi-directional nasal drug delivery devices.

5 | CONCLUSION

The bi-directional nasal delivery system provided a more extensive and efficient nasal deposition in the nasal cavity without lung deposition. The breath-actuated bi-directional delivery device enables better delivery of steroids to high and deep target sites of inflammation among patients with CRS and produces rapid relief in migraine pain and associated symptoms. More work is needed to explore the role of the bi-directional nasal delivery system. In the future, it may be applied to many other fields, such as CNS diseases and olfactory disorders, because of the potential to alter the olfactory cleft microenvironment and possibly treat olfactory disorders and CNS diseases.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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