Exhalation Delivery System: Novel Device for Nasal Polyps Treatment

Rebecca Chu, PharmD

Nasal polyps are a concern for both adults and children. The treatment of nasal polyps typically is glucocorticoids, both topically and systemically administered. However, patients often experience refractory nasal polyps. A proposed reason for unsatisfactory treatment for the reoccurrence of nasal polyps is because of the drug delivery options through the nose that requires patients to coordinate actuation, head placement, and administration. In addition, many of these delivery systems have shown poor delivery efficiency due to medication depositing into the lungs. To combat these difficulties, Optinose has created an exhalation delivery system that could be used for both liquid and powered medications. Xhance[®] (fluticasone propionate), which uses this new delivery system, is currently approved for the treatment of nasal polyps in adults. It has shown promising results in adults and is currently undergoing evaluation in pediatric patients.

Keywords: nasal delivery, nasal polyps, inflammation, exhalation delivery system

Introduction

NASAL POLYPS ARE a relatively common disease affecting the nasal cavity and sinuses in adults. However, they are rarely described in the pediatric population.^{1,2} In children, the most common polyps are benign or malignant nasal masses. They are the result of an inflammatory process. Nasal polyps are associated with bacterial infections, cystic fibrosis, aspirin sensitivity, and chronic inflammatory diseases.^{1–4} Nasal obstruction, drainage, and reduction in the sense of smells are the most common presenting symptoms that substantially affect patient's quality of life. However, in severe cases patients may present with more dramatic symptoms, including epistaxis, dyspnea, dysphagia, and weight loss.^{4,5} Many studies of nasal polyps treatment include children with other underlying systemic disease, including cystic fibrosis.¹ A study by Al-Mazrou et al. demonstrated in pediatric patients that allergic polyps and inflammatory polyps are the result of abundant eosinophils and abundant neutrophils, respectively, in pediatric patients.⁵

The goals of medical management for nasal polyps are to reduce nasal polyps and rhinitis symptoms, re-establish nasal breathing and olfaction, and prevent the reoccurrence. Saline irrigations are recommended by most guidelines for patients with mild symptoms despite lack of randomized trials.⁶ Although antibiotics can be used for infectious etiologies, only glucocorticoids, including topically applied

and systemic steroids, have been proven effective for symptom management. For patients who have refractory nasal polyps, surgical management can also be performed.^{4,5} High rates of reoccurrence are unsatisfactory from the health care professional and patient perspective.⁷ Newer therapies, such as the monoclonal antibody dupilumab, have also been shown to be effective to reduce polyp size, but their use has been limited due to high costs, the risk of anaphylaxis, and the use of subcutaneous injections. These therapies are still currently being studied.⁶

Xhance[®] (fluticasone propionate), produced by Optinose, was approved by the Food and Drug Administration (FDA) in 2017 for the treatment of nasal polyps in adults. Unlike other nasal spray mechanisms that require patients to inhale medications through the nose, Xhance uses an exhalation delivery system that allows nasal delivery driven by the patient's exhaled breath.⁶ This also offers the potential to deliver a high-potency steroid to sites of chronic inflammation that may not be consistently accessible with standard delivery approaches.^{8,9} There have been published studies conducted in adults with Xhance that demonstrate promising evidence and superiority compared with standard delivery approaches; however, studies evaluating its use in pediatric patients are ongoing. This review will examine the novel mechanism of action, summarize the data from previously published trials, and identify the place in therapy for the breath-powered bidirectional delivery method.

Different Options for Drug Delivery Through the Nose

The most common delivery for nasal medications is the traditional nasal sprays. However, traditional nasal sprays are suboptimal for delivery of topically acting medications to some intranasal sites.¹⁰ When patients sniff and inhale, medication is drawn along the nasal cavity to the pharynx where medication can be deposited and swallowed.^{10,11} Other nasal delivery systems, such as nasal drops, high-volume lavage, or nasal nebulizers, are associated with significant challenges that may increase risk for side effects and poor dose control leading to polyp recurrence. Patients have difficulty with administration and head position placement.¹⁰⁻¹² The consequences of poor medication delivery leads to discomfort, lost work days, and cost burden.¹² Pediatric patients are also known to have difficulty with administration techniques of nasal medications. Patients also risk exposing their lungs and stomach to nasal medications when the medication runs back down the throat.¹⁰⁻¹²

Studies have suggested a need for additional research in nasal delivery devices and techniques.¹⁰⁻¹² A recent review of devices conducted by Laube concluded that well-controlled clinical studies are necessary to determine the efficacy of novel drug/device combinations.¹¹ Despite improvements to devices to overcome challenges related to nasal anatomy and physiology, even the most advanced nebulizer technologies have shown poor delivery efficiency with undesirable localized delivery away from the intended intranasal location.

Exhalation Delivery System

One technology that has been developed to avoid lung deposition is an exhalation delivery system with a breath-powered bidirectional delivery method, a novel concept that ensures the delivery of medication from the generation of a pressure gradient. This allows for a closed airway system, avoiding problems associated with suction and breathing instructions.^{13,14} The breath-powered bidirectional delivery method is an exhalation delivery system that can be used for both liquid and powdered medications. It consists of a mouthpiece and a sealing nose piece with a conical shape. The patient slides the sealing nose piece into 1 nostril until the nose piece forms a seal with the nostril opening. The medication is delivered into the nose by actuating the pump spray into 1 nostril while simultaneously blowing into the mouthpiece.¹³ Upon exhalation into the mouthpiece, the nasal cavity is isolated from the rest of the respiratory system due to positive pressure that expands the passages narrowed by inflammation. The pressure change that is transferred from the mouth to the device further expands the nasal passages and allows for an open flow path between the 2 nasal passages behind the nasal septum.¹⁴ Medication is then able to travel around to areas of obstruction.¹³⁻¹⁵

In a recent open-label crossover design in 7 healthy subjects, Djupesland and Skretting utilized a gamma camera image from the nasal cavity minutes after delivery to compare a traditional liquid spray, breath-powered bidirectional delivery method powder device, and breath-powered bidirectional delivery method liquid spray device.¹⁵ The breath-powered bidirectional delivery method device showed statistical significance in the initial deposition in the upper and middle regions of the nose when compared with a

spray pump (sum of upper and middle posterior regions: breath-powered bidirectional delivery method 53.5% versus traditional spray 15.7%, $P < 0.02$).¹⁵ The initial deposition after a traditional spray was greatest in the lower anterior regions, whereas for breath-powered bidirectional delivery method devices the deposition was the greatest in the upper posterior regions.¹⁵ These results suggest that superior deep nasal deposition can be achieved when using breath-powered bidirectional delivery method.

Xhance Trials in Adults 18 Years and Older

Xhance is fluticasone propionate using the breath-powered bidirectional delivery method. It is indicated for the treatment of nasal polyps in patients ≥ 18 years. The recommended dosage is 1 spray (93 mcg of fluticasone propionate per spray) in each nostril twice daily (total daily dose, 372 mcg) up to a max of 2 sprays in each nostril twice daily (total daily dose, 744 mcg).¹³

In the EXHANCE-12 trial, a 12-month multicenter single-arm study, 223 adult participants with chronic rhinitis symptoms with or without polyps received treatment with fluticasone propionate using the breath-powered bidirectional delivery method (Xhance) for 1 year. Approximately 96% of patients reported prior inhaled corticosteroid use and 29% of participants reported prior sinus surgery. Most participants reported symptom improvement, as indicated by patient-reported ratings of improvement on validated scales. When utilizing the 22-item Sino-Nasal Outcome Test (SNOT-22) that assessed efficacy, including symptoms, functioning, and quality of life, participants had a median score of 9 at 12 months. The SNOT-22 has been recommended for use from a recent systematic review.⁶ The score of 9 is comparable with the average score for healthy individuals. More than half of the participants also did not have observable polyps in at least 1 nostril at the 12-month follow-up. Notable limitations to this study included lack of a control group and blinding, and no requirement to confirm chronic rhinitis diagnosis by imaging.¹⁴

The NAVIGATE I and II were placebo-controlled double-blind trials of fluticasone propionate using the breath-powered bidirectional delivery method (Xhance) in 323 adult patients who demonstrated similar results compared with the EXHANCE-12 trial. The breath-powered bidirectional delivery method demonstrated efficacy with change in nasal congestion/obstruction at 4 weeks ($P = 0.07$) and summed bilateral polyp grade at 16 weeks ($P = 0.1$) compared with placebo. Although these results were not statically significant, $\sim 80\%$ of subjects reported improvement with 65% reporting “much” or “very much” improvement by week 16 compared with placebo. However, these 2 studies did not provide a direct comparison of fluticasone propionate using the breath-powered bidirectional delivery method with equivalent doses of other topical steroids delivered by traditional nasal sprays.^{16,17}

Additional information related to the breath-powered bidirectional delivery method can be found at <https://www.optinose.com/exhalation-delivery-systems/technical-overview>

Moving Forward with Use in Pediatric Patients

After the FDA approval of Xhance for adults, Optinose was additionally required to identify the role of this medication and

delivery system for pediatric patients with nasal polyps. Optinose is conducting a 16-week randomized double-blind placebo-controlled parallel-group study in children and adolescents of 6–17 years with bilateral nasal polyps associated with nasal congestion. This study is currently undergoing recruitment and will assess the safety, efficacy, pharmacokinetics, and pharmacodynamics of fluticasone propionate using the breath-powered bidirectional delivery method in improving nasal polyp grade and symptoms. Primary outcomes include change in nasal congestion/obstruction at the end of week 4 and mean change from baseline at week 16. The authors anticipated 120 pediatric participants will be enrolled and the study will be completed by December 2020.¹⁸

Although rarely described in pediatric patients, nasal polyps are an inflammatory disease that causes nasal obstruction and drainage. Medications for the treatment of nasal polyps are typically nasal sprays and commonly prescribed for treatment. However, they have not been satisfactory for preventing reoccurrence due to poor dose control and adverse reactions associated with poor medication delivery. As seen with previous studies, the breath-powered bidirectional delivery method may be an alternative for patients and providers in need of another type of delivery systems aside from traditional nasal medications. The breath-powered bidirectional delivery method has demonstrated greater deposition into the nasal cavities and symptom improvement, when compared with placebo. The results of this forthcoming pediatric trial may demonstrate efficacy and safety of fluticasone propionate using the breath-powered bidirectional delivery method for children <18 years.

Author Disclosure Statement

No competing financial interests exist.

Funding Information

The author of this manuscript has nothing to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this manuscript.

References

1. Caimmi D, Matti E, Pelizzo G, et al. Nasal polyposis in children. *J Bio Regul Homeost Agents* 2012; 261 (1 Suppl): S77–S83.
2. Schramm VL Jr, Effron MZ. Nasal polyps in children. *Laryngoscope* 1980; 90:1488–1495.
3. Zheng H, Tang L, Song B, et al. Inflammatory patterns of antrochoanal polyps in the pediatric age group. *Allergy Asthma Clin Immunol* 2019; 15:39.
4. Newton JR, Ah-See KW. A review of nasal polyposis. *Ther Clin Risk Manag* 2008; 4:507–512.
5. Al-Mazrou KA, Bukhari M, Al-Fayez AI. Characteristics of antrochoanal polyps in the pediatric age group. *Ann Thorac Med* 2009; 4:133–136.
6. Hopkins C. Chronic rhinosinusitis with nasal polyps. *N Engl J Med* 2019; 381:55–63.
7. Brown GA. Nasal polyposis. *Postgrad Med J* 1969; 45:680–683.
8. Djupesland PG. Nasal drug delivery devices: characteristics and performance in a clinical perspective—a review. *Drug Deliv Transl Res* 2013; 3:42–62.
9. Geurkink N. Nasal anatomy, physiology, and function. *J Allergy Clin Immunol* 1983; 72:123–128.
10. Palmer JN, Jacobson KW, Messina JC, et al. EXHANCE-12: 1-year study of the exhalation delivery system with fluticasone (EDS-FLU) in chronic rhinosinusitis. *Int Forum Allergy Rhinol* 2018; 8:869–876.
11. Laube BL. Devices for aerosol delivery to treat sinusitis. *J Aerosol Med* 2007; 20(Suppl 1):S5–S17; discussion S17–S18.
12. Merkus P, Ebbens FA, Muller B, et al. The ‘best method’ of topical nasal drug delivery: comparison of seven techniques. *Rhinology* 2006; 44:102–107.
13. XHANCE® (fluticasone propionate) [package insert]. Yardley, PA: OptiNose US, Inc., 2019, p. 7.
14. Palmer JN, Jacobson KW, Messina JC, et al. EXHANCE-12: 1-year study of the exhalation delivery system with fluticasone (EDS-FLU) in chronic rhinosinusitis. *Int Forum Allergy Rhinol* 2018. [Epub ahead of print]; DOI: 10.1002/alr.22141
15. Djupesland PG, Skretting A. Nasal deposition and clearance in man: comparison of a bidirectional powder device and a traditional liquid spray pump. *J Aerosol Med Pulm* 2012. DOI:10.1089/jamp.2011.0924
16. Leopold DA, Elkayam D, Messina JC, et al. NAVIGATE II: randomized, double-blind trial of the exhalation delivery system with fluticasone (EDS-FLU) for nasal polyposis. *J Allergy Clin Immunol* 2018. DOI:10.1016/j.jaci.2018.06.010
17. Soteres DF, Messina JC, Carothers J, et al. NAVIGATE I: a randomized double-blind trial of a Fluticasone Propionate Exhalation Delivery System (FLU-EDS) for treatment of chronic rhinosinusitis with nasal polyps (CRSwNP). *J Allergy Clin Immunol* 2017; 139(2 Suppl):AB66.
18. ClinicalTrials.gov, Bethesda (MD): National Library of Medicine (US). Identifier NCT03747458, OPN-375 efficacy and safety in adolescents with bilateral nasal polyps; November 20, 2018. Available from: <https://clinicaltrials.gov/ct2/show/study/NCT03747458> (last accessed July 9, 2019).

Address correspondence to:
 Rebecca Chu, PharmD
 NYU Winthrop
 259 1st Street
 Mineola, NY 11501

E-mail: rebecca.chu915@gmail.com

Received for publication July 10, 2019; accepted after revision August 28, 2019.