Nasal sprays: commonly used medications that are often misunderstood

Abstract

Sinonasal inflammatory disease is very common and all clinicians who care for these patients should understand the topical treatment options available. This article reviews the utility and application of steroidal, saline, decongestant, antihistamine and anticholinergic preparations for the treatment of sinonasal disease, with a particular focus on evidence-based guidelines for use in both specialist and non-specialist healthcare settings.

Key words: Allergic rhinitis; Antihistamines; Intranasal corticosteroids; Nasal decongestants; Nasal saline irrigation; Non-allergic rhinitis; Rhinosinusitis

Submitted: 8 June 2023; accepted following double-blind peer review: 26 June 2023

Stephen P Williams[1]

Andrew C Swift[1]

Author details can be found at the end of this article

Correspondence to:
Stephen P Williams;
spwilliams@doctors.org.uk

Introduction

Inflammatory sinonasal disease, encompassing allergic rhinitis, non-allergic rhinitis and rhinosinusitis, is extremely common. Current estimates suggest that chronic rhinitis affects at least 40% of the general population (of which roughly two-thirds report the more common non-allergic rhinitis) (Avdeeva et al, 2022). The prevalence of chronic rhinosinusitis is harder to define, as diagnostic criteria require both symptomatology and confirmatory investigation findings (Fokkens et al, 2020). In population-based surveys, 5–27% of individuals report consistent symptoms (Hastan et al, 2011), and more than 60% of these have corroborative findings on examination (Tomassen et al, 2011). In addition, viral acute rhinosinusitis (often referred to as the 'common cold') is extremely frequent, presenting between two and five episodes per person per year (Turner, 1997). Given these figures, it is important that all clinicians involved in the management of these patients, both in the specialist and non-specialist setting, are familiar with treatment options, in particular the topical medications that are most commonly available in spray form.

A detailed discussion of the pathophysiology of each of the sinonasal conditions is beyond the scope of this article, although the interested non-specialist reader is directed to existing guidelines (all of which include detailed management algorithms for those working in a non-specialist or primary care setting) (https://www.euforea.eu/news/euforea-treatment-algorithm-allergic-rhinitis; Brożek et al, 2010; Fokkens et al, 2020). This article will refer to the European Positional Paper on Rhinosinusitis and Nasal Polyps (Fokkens et al, 2020) for the management of rhinosinusitis and both the ARIA (Allergic Rhinitis and its Impact on Asthma) (Brożek et al, 2010) and EUFOREA (European Forum for Research and Education in Allergy and Airway Diseases) (https://www.euforea.eu/news/euforea-treatment-algorithm-allergic-rhinitis) documents for the management of allergic rhinitis.

Chronic inflammatory sinonasal disease has a multifactorial aetiology and requires individualised therapy based on symptom control. This article outlines the nasal sprays currently available for the management of sinonasal disease with a focus on corticosteroid, saline, decongestant, antihistamine and anticholinergic preparations, and demonstrates best practice technique when using nasal sprays.

Steroidal nasal sprays

Glucocorticoid steroids are widely used to manage sinonasal disease, both for their anti-inflammatory and their immunosuppressive activity. As primary chronic rhinosinusitis and allergic rhinitis are chronic inflammatory disorders, glucocorticoid treatment principally aims to decrease mucosal inflammation in the sinonasal cavity.

How to cite this article:
Williams SP, Swift AC. Nasal sprays: commonly used medications that are often misunderstood. Br J Hosp Med. 2023. https://doi.org/10.12968/hmed.2023.0212

Table 1. Topical intranasal corticosteroids sprays (dosage listed for adults as per British National Formulary (https://bnf.nice.org.uk/) guidance

Nasal sprays		Dose
First generation intranasal corticosteroids	Beclometasone dipropionate	50 mcg/dose; 1–2 sprays each side, once or twice daily
	Budesonide	64 mcg/dose; 1–2 sprays each side, once daily
	Triamcinolone acetonide	55 mcg/dose; 1–2 sprays each side, once daily
Second generation intranasal corticosteroids	Fluticasone furoate	27.5 mcg/dose; 1–2 sprays each side, once daily
	Fluticasone propionate	50 mcg/dose; 1–2 sprays each side, once or twice daily
	Mometasone furoate	50 mcg/dose; 1–2 sprays each side, once or twice daily

Adapted from Williams and Swift (2023)

Systemic corticosteroids are extremely effective at reducing the burden of symptoms (Head et al, 2016), but they are generally limited to short courses because of their extensive side-effect profile with more sustained use, including weight gain, osteoporosis, mood changes, peptic ulcer disease, hyperglycaemia and hypertension. The benefits of even relatively short periods of systemic steroid use may be even more unclear in patients with comorbid conditions, such as those who have had previous steroid-induced psychosis or those with diabetes mellitus.

Topical intranasal corticosteroids are well established as the cornerstone of treatment for both rhinitis and chronic rhinosinusitis and aim to minimise the side effects of long-term systemic use of steroids (Brożek et al, 2010; Fokkens et al, 2020). A wide range of different agents is available and is listed, alongside recommended doses, in Table 1. Although many patients with sinonasal disease use intranasal corticosteroid sprays on a long-term basis, a minimum of 3–6 months' treatment is recommended.

Epistaxis is the main side effect reported by patients and the risk appears to be increased with stronger preparations. More rarely, patients may describe a burning sensation following use and this is believed to be caused by sensitivity to benzalkonium chloride, which is used in many of these preparations. Raised intraocular pressure is also listed as a potential risk with intranasal corticosteroid use, but this has not been found with second generation sprays. Triamcinolone is not advised during pregnancy and breastfeeding, because of an association with respiratory tract abnormalities (Alhussien et al, 2018), although this is not commonly prescribed in the UK. This is not a risk with the other sprays listed in Table 1 and the newer second-generation intranasal sprays, particularly those containing fluticasone or mometasone furoate, have a low systemic bioavailability and so are also considered appropriate for use in children (with preparations of mometasone furoate licenced for children 3 years and older and fluticasone for those 4 years and older).

Currently, there is no evidence to convincingly propose one type of intranasal steroid as superior (Chong et al, 2016b). In those who fail to respond to treatment, it should first be clarified whether patients are using their spray on a consistent daily basis and are using the correct administration technique (see below).

Saline nasal sprays

Best treatment guidelines also recommend the use of topical saline irrigation for the evidence-based management of both rhinitis and rhinosinusitis, alongside treatment with intranasal corticosteroids (Brożek et al, 2010; Fokkens et al, 2020). It is understood that saline irrigation reduces the burden of both antigens and inflammatory mediators and improves ciliary beat frequency hence facilitating the clearance of nasal mucus. Nasal saline preparations are also relatively low cost, are widely available over the counter and are well tolerated by patients, particularly those with chronic rhinosinusitis (Rabago et al, 2006).

Nasal saline is available from many different manufacturers but can generally be divided into low volume preparations (usually nasal sprays), and large volume preparations (often described as rinses, irrigation, lavage or douche). In the UK, the most commonly available saline nasal spray is Sterimar (Sofibel SAS, Paris, France) and saline nasal irrigation is

NeilMed Sinus Rinse (NeilMed Pharmaceuticals, California, USA). However, there are many other commercial products and there is no evidence to recommend any single device or strategy at this point (Chong et al, 2016a).

Nasal saline products come in a range of different concentrations, with isotonic preparations (used most frequently) available alongside both hypertonic (proposed to have additional decongestant effects) and hypotonic preparations (as lower sodium concentrations have been shown to improve local immune function) (Low et al, 2014). Mixed results have been found in the literature, making it difficult to make strong recommendations, although isotonic preparations appear to be better tolerated than hypertonic solutions.

It is increasingly common to advise patients with recalcitrant and difficult to treat chronic rhinosinusitis to use high volume saline rinses (eg NeilMed Sinus Rinse), to administer intranasal corticosteroids by mixing the two agents together, and there is a growing body of evidence to support this combination strategy over separate use of saline irrigation and intranasal corticosteroids (Harvey et al, 2018). This mostly involves budesonide respules being emptied into the sinus rinse. Although these respules are higher in concentration than standard purpose-made intranasal corticosteroid preparations, they are obviously heavily diluted within the saline solution and there has been no detectable alteration in cortisol levels in patients using such therapy (Welch et al, 2010). Although these combined budesonide/saline rinses are well established internationally to treat chronic rhinosinusitis they are used more rarely in the UK, as this is unlicenced and comes at some expense. Their use is restricted to specialist centres and should not be commenced in the non-specialist setting.

Decongestant sprays

Nasal mucosa is predominantly innervated by sympathetic fibres, which act via both alpha and beta adrenoreceptors; the former leading to vasoconstriction and the latter to vasodilatation. Topical decongestants produce vasoconstriction through action on alpha adrenoreceptors, by stimulating the endogenous release of noradrenaline. Decongestants can broadly be classified into two groups, sympathomimetic amines (eg phenylephrine and ephedrine) and imidazole derivatives (eg oxymetazoline and xylometazoline). Although sympathomimetic amines preferentially act on alpha-1 adrenoceptors and imidazole derivatives on alpha-2 adrenoreceptors, there is often a degree of action at both receptors.

Nasal decongestant sprays are widely available over the counter in the UK. They are recommended for short-term use for the symptomatic treatment of sudden onset nasal congestion and acute rhinosinusitis (Fokkens et al, 2020), and evidence supports a small but significant improvement in nasal congestion with treatment in these patients (Deckx et al, 2016). However, caution is needed regarding longer term use of decongestant therapy because of concerns over development of rhinitis medicamentosa. This is a form of drug-induced rhinitis typified by a rebound nasal congestion. Although its precise pathophysiology remains unclear, a number of mechanisms have been proposed including longer lasting beta-adrenoceptor action from sympathomimetic amine use and a reduction in sympathetic tone with prolonged use of imidazole derivatives, leading to parasympathetic dominance and vasodilation. Decreased sensitivity of alpha-adrenoceptors triggers a vicious cycle of ever-diminishing returns (Doshi, 2009).

Prevention rather than cure is the more prudent strategy and patients should be advised to use topical decongestants for a maximum of 7 days. Accordingly, nasal decongestants are not advised for the treatment of chronic rhinosinusitis (Fokkens et al, 2020). In the UK, xylometazoline hydrochloride is licenced for use in adults and children (above 12 years) and is recommended as one spray delivered to both sides, 1–3 times a day for a maximum of 7 days.

In rhinitis medicamentosa, removal of the topical decongestant is advised alongside use of a topical nasal corticosteroid to minimise the resultant rebound congestion (Doshi, 2009).

Anticholinergic sprays

The parasympathetic supply to the nasal cavity acts through muscarinic acetylcholine receptors to stimulate both vasomotor vasodilation and glandular secretion. Anticholinergic medications aim to inhibit this pathway and can be particularly useful in patients for whom

rhinorrhoea is the most troublesome symptom. A systematic review and meta-analysis found a significant improvement in both the severity and duration of rhinorrhoea in patients with allergic and non-allergic rhinitis with use of a topical anticholinergic spray (Pang et al, 2023). Concurrent use of anticholinergic sprays and corticosteroids can act synergistically to control rhinorrhoea (Dockhorn et al, 1999).

Non-allergic rhinitis is an umbrella term, covering a range of pathophysiology, which makes it challenging to predict the response of treatment. These patients often display cholinergic hyperactivity and, for those in whom rhinorrhoea is the predominant complaint, a trial of an anticholinergic spray should be considered (Liva et al, 2021). Patients with gustatory rhinitis respond particularly well in this regard (Papadopoulos and Guibas, 2016).

In the UK, an anticholinergic nasal spray can be considered as an adjunct for patients with rhinorrhoea (Fokkens et al, 2020). This is available on prescription only for adults and children above 12 years where the dose is two sprays delivered to both sides, 2–3 times a day (Rinaspray 21 mcg/dose, Sanofi SA, Paris, France). Potential side effects usually centre around problems with nasal dryness, and include epistaxis, nasal obstruction and discomfort.

Antihistamine sprays

Oral antihistamines are effective treatment for allergic rhinitis and, although less effective than intranasal corticosteroids (Brożek et al, 2010), are advised as first-line treatment in conjunction with intranasal corticosteroids by EUFOREA (https://www.euforea.eu/news/euforea-treatment-algorithm-allergic-rhinitis). Topical antihistamine sprays are also effective at managing allergic rhinitis symptoms but are inferior to intranasal corticosteroids, particularly for managing rhinorrhoea (Carr et al, 2012).

Patients with allergic rhinitis can struggle with the compliance required for polypharmacy and the rate of symptom control with multiple therapies remains disappointingly poor, with some studies reporting no significant benefit despite the addition of oral antihistamines to intranasal corticosteroids (Anolik and Mometasone Furoate Nasal Spray With Loratadine Study Group, 2008). A combination spray containing both azelastine hydrochloride and fluticasone propionate can be offered to patients with moderate-to-severe uncontrolled allergic rhinitis – this is more effective than intranasal corticosteroids and has a faster onset of action (Bousquet et al, 2015, 2018).

In the UK, this combination treatment is prescribed as Dymista (azelastine hydrochloride/fluticasone propionate 137 mcg/50 mcg per dose; Viatris UK Healthcare Ltd) at one spray delivered each side twice a day and should be considered for adults (and children 12 years and older) with allergic rhinitis that is uncontrolled with first-line therapy (intranasal corticosteroid with/without oral antihistamine). There is no significant clinical benefit for patients with acute rhinosinusitis (De Sutter et al, 2015) and, while there is limited evidence of its efficacy as part of the long-term management of patients with chronic rhinosinusitis (Fokkens et al, 2020), it should be considered for those with coexistent or contributary nasal allergy.

It should be noted that this medication does, in contrast with the other sprays discussed in this article, have a poor taste profile and concerns over its comparatively higher cost have limited its prescription in some areas.

Technique

Most patients use nasal sprays poorly and nearly 90% omit essential steps when administering their medication (Rollema et al, 2019). Not only can this affect the distribution of the nasal spray within the nasal cavity but it also reduces the effect of the medication and therefore the likely compliance with ongoing treatment. An 11-step administration process has been suggested, as outlined in Table 2.

Clinicians prescribing topical intranasal medication should be clear on the best practice technique and stress the importance of this to patients. A head position tilted forwards is advised and the patient should be advised to aim the nozzle of their nasal

Table 2. Best practice technique for administration of nasal spray
1. Shake the spray
2. Remove dust cap
3. Blow nose
4. Hold nasal spray correctly (*Figure 1a*), consider use of contralateral hand
5. Place the tip of the nozzle in the nostril and close the other nostril
6. Tilt head slight forwards (*Figure 1b*)
7. Aim end of nozzle slightly laterally, away from septum (*Figure 1c*)
8. Squirt the spray during gentle nasal inspiration (avoid deep inspiration)
9. Exhale through the mouth
10. Clean the nozzle
11. Replace dust cap

Adapted from Rollema et al (2019)

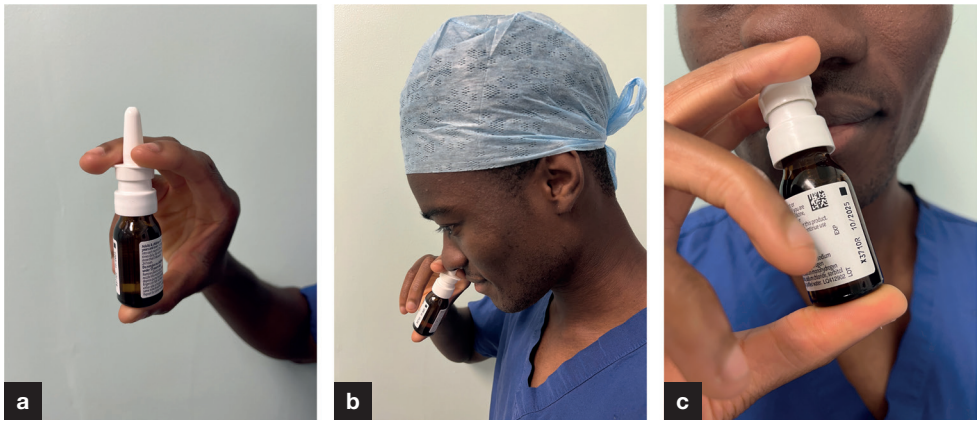

Figure 1. Administration of nasal spray. a. How to hold nasal spray. b. Appropriate head position. c. How to aim the spray.

spray slightly laterally, pointed away from the septum (Figure 1). It has been suggested that using the contralateral hand for each nostril (ie administering the nasal spray to the left side with the right hand and vice versa) can be an effective method to achieve this (Ganesh et al, 2017).

It should also be explained that gentle inspiration following delivery is the best strategy to allow appropriate dispersal of medication beyond the nasal valve, as the turbulent airflow associated with deep inspiration is likely to deposit unwanted medication in the pharynx (Tay et al, 2016).

Although not widely available in the UK, there is a growing body of evidence to support the use of alternative devices for administering intranasal medication, such as an exhalation delivery system with fluticasone. This system aims to improve topical corticosteroid delivery over conventional sprays, particularly in the setting of chronic rhinosinusitis. Rather than using a standard aerosol, the patient's own exhalation drives the medication into the nasal cavity and, as this is naturally performed with palatal closure, this should increase retention and deposition of medication throughout the nasal cavity. While these techniques are effective, there are no robust comparative studies to support their adoption over conventional topical therapy (Leopold et al, 2019).

As topical saline irrigation includes both low volume saline sprays and larger volume saline rinses, attention should also be paid to the technique used with such rinses, particularly in chronic rhinosinusitis. Computational flow dynamic studies demonstrate that high volume low pressure devices (such as the NeilMed saline sinus rinse) irrigates through

Key points

- Sinonasal inflammatory disease is very common and all clinicians involved in the care of these patients should be familiar with the topical treatments available.
- Steroidal nasal sprays form the cornerstone of management of rhinitis and chronic rhinosinusitis and patients must be informed of the best technique for using such devices.
- Saline solutions, decongestant, antihistamine and anticholinergic preparations are all available in spray form with different indications, usually dependent upon patient symptomatology.
- Future developments focus on both novel delivery devices for current treatment and new treatments largely based around the prevention of upper respiratory tract infections, including COVID-19.

progressive flooding of sinuses, rather than direct jet action, and that this is best achieved when leaning forwards over a basin (Craig et al, 2016). While the sphenoid sinus is best irrigated in a head back position, this is a rarer more specific indication (Craig et al, 2016).

Future of nasal sprays

The nasal sprays reviewed in this article are longstanding established therapy for sinonasal disease. Undoubtedly triggered by the effect of the COVID-19 pandemic, work has focused on using nasal sprays for other purposes and, while their utility has yet to be fully determined, it is hoped that the encouraging results so far could lead to their successful introduction in the near future.

A variety of agents have been evaluated for their ability to combat upper respiratory tract infections both in terms of pre-exposure prophylaxis and post-exposure treatment. Iota-carrageenan is a polysaccharide derived from a species of seaweed and exerts antiviral properties by creating a physical barrier preventing the binding of viruses, including rhinovirus and coronavirus species, (Eccles, 2020). However, while studies have demonstrated that the use of iota-carrageenan nasal sprays significantly reduces viral load, there are few data to support sustained clinical improvement in terms of symptoms (Bichiri et al, 2021).

Other groups have considered the use of nasal sprays in the post-exposure treatment phase, exploring the effect of a nitric oxide nasal spray. Results have been promising, demonstrating that patients with mild COVID-19 infection using nitric oxide nasal spray clear the virus significantly quicker, but it is unclear whether this translates to clinical improvements, in terms of both symptom burden and potential hospitalisation (Tandon et al, 2022).

Finally, there is hope that nasal sprays containing monoclonal antibodies could act as a vaccination method for patients against COVID-19. However, this treatment is early in its development phase and the challenges of administering such widescale treatment would be considerable (Hadjichrysanthou et al, 2022).

Conclusions

This article has considered sinonasal disease through the guise of a single medicinal route and, in doing so, has discussed a variety of pharmacological agents and specific conditions. As many patients self-manage their condition before seeking medical care, it is vital that clinicians have a thorough understanding of best practice for these agents to ensure that these, often chronic, conditions are treated appropriately in the long term.

Author details

[1]Liverpool Head and Neck Centre, Liverpool University Hospitals NHS Foundation Trust, Liverpool, UK

Conflicts of interest

AC Swift is a member of the editorial board of the *British Journal of Hospital Medicine*, but was not involved in the peer review of this article; SP Williams has no conflicts of interest to declare.

Acknowledgements

The authors would like to thank Dr Paul Koroma for acting as a model in Figure 1.

References

Alhussien AH, Alhedaithy RA, Alsaleh S. Safety of intranasal corticosteroid sprays during pregnancy: an updated review. Eur Arch Otorhinolaryngol. 2018;275(2):325–333. https://doi.org/10.1007/s00405-017-4785-3

Anolik R; Mometasone Furoate Nasal Spray With Loratadine Study Group. Clinical benefits of combination treatment with mometasone furoate nasal spray and loratadine vs monotherapy with mometasone furoate in the treatment of seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2008;100(3):264–271. https://doi.org/10.1016/S1081-1206(10)60452-8

Avdeeva KS, Fokkens WJ, Segboer CL, Reitsma S. The prevalence of non-allergic rhinitis phenotypes in the general population: a cross-sectional study. Allergy. 2022;77(7):2163–2174. https://doi.org/10.1111/all.15223

Bichiri D, Rente AR, Jesus Â. Safety and efficacy of iota-carrageenan nasal spray in treatment and prevention of the common cold. Med Pharm Rep. 2021;94(1):28–34. https://doi.org/10.15386/mpr-1817

Bousquet J, Bachert C, Bernstein J et al. Advances in pharmacotherapy for the treatment of allergic rhinitis; MP29-02 (a novel formulation of azelastine hydrochloride and fluticasone propionate in an advanced delivery system) fills the gaps. Expert Opin Pharmacother. 2015;16(6):913–928. https://doi.org/10.1517/14656566.2015.1020789

Bousquet J, Meltzer EO, Couroux P et al. Onset of action of the fixed combination intranasal azelastine-fluticasone propionate in an allergen exposure chamber. J Allergy Clin Immunol Pract. 2018;6(5):1726–1732.e6. https://doi.org/10.1016/j.jaip.2018.01.031

Brożek JL, Bousquet J, Baena-Cagnani CE et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. J Allergy Clin Immunol. 2010;126(3):466–476. https://doi.org/10.1016/j.jaci.2010.06.047

Carr WW, Ratner P, Munzel U et al. Comparison of intranasal azelastine to intranasal fluticasone propionate for symptom control in moderate-to-severe seasonal allergic rhinitis. Allergy Asthma Proc. 2012;33(6):450–458. https://doi.org/10.2500/aap.2012.33.3626

Chong LY, Head K, Hopkins C et al. Saline irrigation for chronic rhinosinusitis. Cochrane Database Syst Rev. 2016a;2016(4):CD011995. https://doi.org/10.1002/14651858.CD011995.pub2

Chong LY, Head K, Hopkins C et al. Different types of intranasal steroids for chronic rhinosinusitis. Cochrane Database Syst Rev. 2016b:2016(4):CD011993. https://doi.org/10.1002/14651858.CD011993.pub2

Craig JR, Zhao K, Doan N et al. Cadaveric validation study of computational fluid dynamics model of sinus irrigations before and after sinus surgery. Int Forum Allergy Rhinol. 2016;6(4):423–428. https://doi.org/10.1002/alr.21677

De Sutter AI, Saraswat A, van Driel ML. Antihistamines for the common cold. Cochrane Database Syst Rev. 2015;2015(11):CD009345. https://doi.org/10.1002/14651858.CD009345.pub2

Deckx L, De Sutter AIM, Guo L, Mir NA, van Driel ML. Nasal decongestants in monotherapy for the common cold. Cochrane Database Syst Rev. 2016;2016(10):CD009612. https://doi.org/10.1002/14651858.CD009612.pub2

Dockhorn R, Aaronson D, Bronsky E et al. Ipratropium bromide nasal spray 0.03% and beclomethasone nasal spray alone and in combination for the treatment of rhinorrhea in perennial rhinitis. Ann Allergy Asthma Immunol. 1999;82(4):349–359. https://doi.org/10.1016/S1081-1206(10)63284-X

Doshi J. Rhinitis medicamentosa: what an otolaryngologist needs to know. Eur Arch Otorhinolaryngol. 2009;266(5):623–625. https://doi.org/10.1007/s00405-008-0896-1

Eccles R. Iota-carrageenan as an antiviral treatment for the common cold. Open Virol J. 2020;14(1):9–15. https://doi.org/10.2174/1874357902014010009

Fokkens WJ, Lund VJ, Hopkins C et al. European position paper on rhinosinusitis and nasal polyps 2020. Rhinology. 2020;Suppl. 29:1–464. https://doi.org/10.4193/Rhin20.600

Ganesh V, Banigo A, McMurran AEL, Shakeel M, Ram B. Does intranasal steroid spray technique affect side effects and compliance? Results of a patient survey. J Laryngol Otol. 2017;131(11):991–996. https://doi.org/10.1017/S0022215117002080

Hadjichrysanthou C, Beukenhorst AL, Koch CM et al. Exploring the role of antiviral nasal sprays in the control of emerging respiratory infections in the community. Infect Dis Ther. 2022;11(6):2287–2296. https://doi.org/10.1007/s40121-022-00710-z

Harvey RJ, Snidvongs K, Kalish LH, Oakley GM, Sacks R. Corticosteroid nasal irrigations are more effective than simple sprays in a randomized double-blinded placebo-controlled trial for chronic rhinosinusitis after sinus surgery. Int Forum Allergy Rhinol. 2018;8(4):461–470. https://doi.org/10.1002/alr.22093

Hastan D, Fokkens WJ, Bachert C et al. Chronic rhinosinusitis in Europe–an underestimated disease. A GA^{2}LEN study. Allergy. 2011;66(9):1216–1223. https://doi.org/10.1111/j.1398-9995.2011.02646.x

Head K, Chong LY, Hopkins C et al. Short-course oral steroids alone for chronic rhinosinusitis. Cochrane Database Syst Rev. 2016;2016(4):CD011991. https://doi.org/10.1002/14651858.CD011991.pub2

Leopold DA, Elkayam D, Messina JC et al. NAVIGATE II: randomized, double-blind trial of the exhalation delivery system with fluticasone for nasal polyposis. J Allergy Clin Immunol. 2019;143(1):126–134.e5. https://doi.org/10.1016/j.jaci.2018.06.010

Liva GA, Karatzanis AD, Prokopakis EP. Review of rhinitis: classification, types and pathophysiology. J Clin Med. 2021;10(14):3183. https://doi.org/10.3390/jcm10143183

Low TH, Woods CM, Ullah S, Carney AS. A double-blind randomized controlled trial of normal saline, lactated Ringer's, and hypertonic saline nasal irrigation solution after endoscopic sinus surgery. Am J Rhinol Allergy. 2014;28(3):225–231. https://doi.org/10.2500/ajra.2014.28.4031

Pang JC, Vasudev M, Du AT et al. Intranasal anticholinergics for treatment of chronic rhinitis: systematic review and meta-analysis. Laryngoscope. 2023;133(4):722–731. https://doi.org/10.1002/lary.30306

Papadopoulos NG, Guibas GV. Rhinitis subtypes, endotypes and definitions. Immunol Allergy Clin N Am. 2016;36(2):215–233. https://doi.org/10.1016/j.iac.2015.12.001

Rabago D, Barrett B, Marchand L, Maberry R, Mundt M. Qualitative aspects of nasal irrigation use by patients with chronic sinus disease in a multimethod study. Ann Fam Med. 2006;4(4):295–301. https://doi.org/10.1370/afm.552

Rollema C, van Roon EN, de Vries TW. Inadequate quality of administration of intranasal corticosteroid sprays. J Asthma Allergy. 2019;12:91–94. https://doi.org/10.2147/JAA.S189523

Tandon M, Wu W, Moore K et al. SARS-CoV-2 accelerated clearance using a novel nitric oxide nasal spray (NONS) treatment: a randomized trial. Lancet Reg Health Southeast Asia. 2022;3:100036. https://doi.org/10.1016/j.lansea.2022.100036

Tay SY, Chao SS, Mark KTT, Wang DY. Comparison of the distribution of intranasal steroid spray using different application techniques. Int Forum Allergy Rhinol. 2016;6(11):1204–1210. https://doi.org/10.1002/alr.21807

Tomassen PE, Newson RB, Hoffmans R et al. Reliability of EP3OS symptom criteria and nasal endoscopy in the assessment of chronic rhinosinusitis–a GA^{2}LEN study. Allergy. 2011;66(4):556–561. https://doi.org/10.1111/j.1398-9995.2010.02503.x

Turner RB. Epidemiology, pathogenesis and treatment of the common cold. Ann Allergy Asthma Immunol. 1997;78(6):531–540. https://doi.org/10.1016/S1081-1206(10)63213-9

Welch KC, Thaler ER, Doghramji LL, Palmer JN, Chiu AG. The effects of serum and urinary cortisol levels of topical intranasal irrigations with budesonide added to saline in patients with recurrent polyposis after endoscopic sinus surgery. Am J Rhinol Allergy. 2010;24(1):26–28. https://doi.org/10.2500/ajra.2010.24.3418

Williams SP, Swift AC. Rhinological dilemmas and questions from clinical practice. In: Swift AC, Carrie S, de Souza CE (eds). Contemporary Rhinology: Science and Practice. NY, USA: Springer:2023 (in press)