

Drug-Induced Rhinitis

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Opinion statement

One type of non-allergic, non-infectious rhinitis (NIR), representing the heterogeneous group is drug-induced rhinitis (DIR), which can be arranged into four and more subtypes related to pharmaceutical treatment (local inflammatory type, neurogenic type, idiopathic type, and rhinitis medicamentosa, a distinct phenotype caused by excessive use of intranasal decongestant sprays). DIR management implicates pharmacological and a non-pharmacological components only after the proposal to terminate and withdraw the causative medication; these components include factors inducing the disease and patients' education. A patient's individual sub-phenotype should be considered for management classification. Nowadays, intranasal glucocorticosteroids are considered to be the most reliable means available for DIR treatment. Intranasal antihistamines antagonizing H₁ receptors are used for treating nasal congestion, but their effect is much weaker than that of intranasal corticosteroids. In particular occasions, oral decongestants can be applied, and oral corticosteroids are last-resort treatment for symptoms resistant to all other therapeutic intervention, but their use is limited to the short term. Notwithstanding that there are no obvious data proving the benefit, nasal irrigation with isotonic or hypertonic saline is the auxiliary treatment usually applied in almost all rhinitis phenotypes. Rarely applied treatments include nasal cromolyn, sedatives/hypnotics, diode laser inferior turbinate reduction, and surgical referral for submucosal resection of the inferior turbinate bones, which may be indicated only in cases of extensive medical treatment failure. In this review article, we present a literature review on prevalence, mechanisms, mediators, treatment options, safety, and efficacy issues of drugs and QoL of the patients with DIR.

Introduction

According to recent data, the prevalence of rhinitis is 30–35 % of chronic airway diseases in Europe, while allergic rhinitis (AR) is 20–25 % and non-allergic rhinitis (NAR) is 15–20 % [1]. Therefore,

approximately 50 % of patients with chronic rhinitis are non-allergic [2••].

One type of non-allergic, non-infectious rhinitis (NIR), representing the heterogeneous group is drug-

induced rhinitis (DIR), which includes the following sub-phenotypes other than DIR: gustatory rhinitis, hormone-induced rhinitis, rhinitis of the elderly, atrophic rhinitis, and idiopathic rhinitis [3••, 4].

Of the different DIR sub-phenotypes, special importance is given to rhinitis medicamentosa (RM). Approximate incidence is 6-9 % in patients with nasal obstruction [5-7]. RM occurrence rate is proportional to gender; however, it is more frequent in young and middle-aged adults [8•, 9, 10]. Otorhinolaryngology clinics show an occurrence rate of about 1 to 7 % [9, 11, 12]. RM was revealed in approximately 9 % out of 500 consecutive patients with nasal congestion in an allergic clinic [8•, 9, 13]. As

reported by more than a hundred allergists, 6.7 % of the patient population had RM [7, 8•].

The other sub-phenotypes of DIR are aspirin-exacerbated respiratory disease (AERD), rhinitis induced by systemic alpha- and beta-adrenergic antagonists, rhinitis induced by phosphodiesterase (PDE) V inhibitors, rhinitis induced by other drugs (ACE inhibitors, calcium channel blockers, antipsychotics) [2••].

The literature review aims to discuss updated evidence-based data for better understanding of the pathophysiological basis and clinical aspects of different sub-phenotypes of DIR, contemporary possibilities of treatment options, as well as quality of life (QoL) of patients with DIR.

Mechanisms

There are at least four subtypes of DIR related to pharmaceutical treatment (local inflammatory type, neurogenic type, idiopathic type [3••, 14•], and RM, a distinct phenotype caused by excessive use of intranasal decongestant sprays) [3••, 8•, 14•].

The local inflammatory type is secondary to inflammation and it appears after drug delivery or intake [8•], caused mainly by use of aspirin and other NSAIDs [3••, 14•, 15]. It is exemplified by AERD [16], also called NSAIDs-exacerbated respiratory disease (NERD) [17]. Its pathogenesis is currently believed to involve inhibition of cyclooxygenase-1 (COX-1) and subsequent overproduction of cysteinyl leukotrienes (CysLTs) [14•].

The neurogenic type is the result of the vascular effects of α - and β -adrenergic antagonists, which down-regulate the sympathetic tone (clonidine, guanethidine, doxazosin methyl dopa) [3••, 14•, 15]. Vasodilators, including phosphodiesterase-5 selective inhibitors such as sildenafil (Viagra®) [15, 18] and other medications such as adalafil and vardenafil can also be the triggers of acute rhinitis symptoms (“anniversary rhinitis”) [14•, 19•, 20].

RM is also known as rebound rhinitis. Excessive use of intranasal decongestants (α -adrenergic agonists) down-regulate α -adrenergic receptor function [2••]. Respiratory mucosa “adapts” (down-regulation of receptor expression) to the drug, resulting in minor [5, 21] and shorter [22] drug-induced effect (hyporeactivity). Nasal tissue hypoxia and negative neural feedback can be the result of long-term application of local α -adrenergic agonist vasoconstrictors [4, 23-25].

Chemical rhinitis can also be recognized as RM, although this can also mean non-pharmaceutical airborne irritants such as fumes and gases with air pollution and industrial exhausts. The nasal mucosa can become beefy-red and inflamed with areas of punctate bleeding and scant mucus [23]. Structural changes in RM include damage and loss of cilia, metaplasia [24], epithelial oedema [26], tears in the basal membrane [24], and openings in subepithelial endothelium [5, 24], together with vasodilatation [6]. Moreover, hyperplasia of goblet cells [27], [26] and infiltration of inflammatory cells [8•] were demonstrated probably as

equivalent of reparative changes with increased expression of epithelial growth factor [8•]. Septal perforation may be considered to be the complication [25]. In cases of improper treatment, this disease may result in secondary atrophic rhinitis up to frank clinical picture of ozaena [5, 10].

A new mechanism for trapping adrenergic decongestant drugs into cellular endomembrane compartments has been demonstrated. Phenylephrine and xylometazoline caused the V-ATPase-dependent sequestration that contributed to a component of the tissue reservoir of both cationic drugs, thus influencing the toxicity and pharmacology of individual agents. Such cytopathology was observed at a fraction of the usual topical concentrations [28, 29].

Cocaine

Patients with symptoms of chronic nasal irritation such as frequent nose bleeds, crusting, and scabbing may be suspected to be users of cocaine [30].

Mediators

The mediators involved in DIR are among the most potent cause of vasodilation, increased microvascular permeability, exudation of macromolecules, and oedema.

AERD is characterized by overproduction of leukotrienes and dysregulation of enzymes and receptors responsible for the production and function of protective lipid mediators [2••]. Some drugs, such as aspirin and non-steroidal anti-inflammatory drugs (NSAIDs), may cause acute inflammatory response in the nose, for instance. Aspirin-induced asthma (AIA) is a syndrome caused by NSAIDs use, and the most typical features for this condition is the triad of chronic rhinosinusitis with nasal polyps (CRSwNP), asthma, and aspirin or other NSAIDs sensitivity [14•]. Induction of inflammatory response by aspirin and other NSAIDs may be explained with various pathogenic mechanisms.

Nevertheless, it is acknowledged that the principle mechanisms consider the inhibition of cyclooxygenase-1 (COX-1). Arachidonic acid metabolism includes COX enzymes along with the enzyme lipoxygenase. Arachidonic acid is shifted to the lipoxygenase pathway through inhibition of COX-1, resulting in a decrease in available prostaglandin E₂ (PGE₂). The decrease in PGE₂ results in an increase in cysteinyl-leukotriene production by the lipoxygenase pathway involving the enzyme 5-lipoxygenase (5-LO) [14•].

Leukotrienes (LT) C₄, D₄, and E₄ are all products of this pathway and are collectively known as CysLTs; however, LTC₄ is thought to be the most significant CysLT responsible for the pathogenesis of AIA [14•, 31], LTC₄ synthase is the enzyme responsible for the production of LTC₄, and an allele of the LTC₄ synthase gene (allele C) has been identified in individuals with aspirin sensitivity. Allele C expression is more likely to occur in individuals with AIA [14•, 32].

As reported in recent studies, prostaglandin E₂ (PGE₂) deficiency induces an AERD phenotype in PGE₂ synthase-1 knock-out mice and also

PGE₂ resistance in granulocytes of AERD patients. In AERD, an increase of platelet-adherent leukocytes is observed, thus amplifying production of CysLTs via transcellular arachidonate metabolism. INF γ released from sinus tissue eosinophils of AERD patients promotes eosinophil maturation, increases leukotriene-associated gene expression, and releases CysLTs. Serum periostin level was considered to be a reliable biomarker to predict the AERD phenotype [33].

Resistant blood vessels (small arterioles, arteries, and arteriovenous anastomoses) drain into venous sinusoids, and the nasal mucosa is rich in such blood vessels. The sinusoids are innervated with sympathetic fibers; release of endogenous norepinephrine promotes α_1 and α_2 adrenoreceptors, which results in reduced blood flow, increased venous return into capacitance vessels, and, as a result, decreased nasal congestion. Parasympathetic nervous fibers release acetylcholine, which increases nasal secretions and vasoactive intestinal peptide (VIP), which causes vasodilation. Upon stimulation, abundant sensory C-fibers release neurokinin A, calcitonin gene-related peptide, and substance P, through which various receptors down-regulate sympathetic vasoconstriction, leading to congestion [28].

Upon stimulation of mast cells, eosinophils, and basophils, a complex milieu of local inflammatory mediators is released. These cells promote nasal congestion through the release of histamine, kinins, prostaglandins, and arachidonic acid metabolites can also be activated by such mediators and can promote goblet cells to increase production of mucin, which, in turn, promotes congestion [28].

Systemic α - and β -adrenergic antagonists.

These down-regulate nasal sympathetic tone [2••] and are known as neurogenic type α - and β -adrenergic antagonists. They include clonidine, guanethidine, and methyldopa, which are examples of drugs promoting rhinitis through a neurogenic mechanism. These medications are sympatholytic and cause down-regulation of sympathetic tone. Airways are innervated with sympathetic, parasympathetic, and sensory fibres [34] and are concentrated in nasal blood vessels, mucosa, and to a lesser extent secretory glands. Disruption of sympathetic and parasympathetic tone in the nasal mucosa may result in symptoms of congestion and rhinorrhea; however, the decreased sympathetic tone influencing the nasal blood vessels is predominantly responsible for the nasal congestion that follows the administration of sympatholytics [35]. Adrenergic sympathetic neuron fibers contain neuropeptide-Y (NPY). NPY is also involved independently in the modulation of postganglionic cholinergic responses by acting directly on NPY-2 receptors in the nasal mucosa [36]. Decreased sympathetic tone caused by sympatholytic drugs results in the down-regulation of the sympathetic nervous system in the nose and blunting of the effects of norepinephrine and NPY primarily causing nasal congestion and rhinorrhea [37].

Phosphodiesterase-5 (PDE V) inhibitors.

They increase local concentrations of nitric oxide causing vascular dilatation [2••]. There have been two case reports in the literature describing epistaxis after their use. Nasal stuffiness occurs during sexual activities

(honeymoon rhinitis), and the administration of this group of medications aggravates this phenomenon [38, 39].

The idiopathic type can be caused by several different drug classes: calcium channel blockers, β -blockers, angiotensin-converting enzyme inhibitors, exogenous oestrogens, oral contraceptives, antipsychotics, gabapentin.

Most common medications associated with drug-induced rhinitis

In order to diagnose DIR correctly, it is necessary to take into account careful medical history taking with questions regarding the last topical and complete current medication and physical examination.

Although DIR may occur in conjunction with AR and NAR, it is important to recognize medications that may contribute to this disease.

(a) Nasal decongestants

Two classes of nasal decongestants are described: sympathomimetics and imidazolines. Sympathomimetic drugs: amphetamine, benzedrine, caffeine, ephedrine, mescaline, phenylephrine, phenylpropranolamine, pseudoephedrine [6, 8, 40]. Imidazoline drugs: clonidine, naphazoline, oxymetazoline, xylometazoline [41]. They cause vasoconstriction primarily through α_2 -adrenoreceptors, but may also decrease endogenous norepinephrine [28].

(b) Benzalkonium chloride

Benzalkonium chloride (BKC) is a preservative frequently used in aqueous nasal, ophthalmic, and optic products that are available both by prescription and over the counter. It has been in use since 1935, and the American College of Toxicology concludes that it can be safely used as an antimicrobial agent at concentrations $\leq 0.1\%$ [28, 42]. BKC aids development of DIR [43, 44], aggravates its symptoms [6, 45], and may provoke RM if used alone [21]; only a few formulations are still available in Europe containing BKC [6]. During the past several years, conflicting reports have described damage to human nasal epithelia or exacerbation of RM associated with intranasal products that contain BKC. More recent review of the literature demonstrates that intranasal products with BKC seem to be safe and well tolerated for short-term and long-term use [42].

Intranasal cocaine use: Intranasal cocaine also causes nasal congestion.

M. Varghese and et al described and listed the medications associated with DIR by mechanism presented in Table 1 (See Table 1). Others were described in Table 2 after systemic drug application (See Table 2).

EBM for treatment recommendations

Efficacy and safety

Medical history of the patients and physical examination is very important in the management of DIR. DIR treatment varies with cause.

Table 1. Medications associated with DIR, modified by Varghese M et al [14•]

I. Mechanism – local inflammatory type
Aspirin
NSAIDs
II. Mechanism – neurogenic type
Centrally acting sympatholytics
Clonidine (a ₂ -agonist, anti-hypertensive (anti-HTN))
Guanfacine (a ₂ -agonist, anti-HTN)
Methyldopa (a ₂ -agonist, anti-HTN)
Moxonidine (imidazoline receptor agonist, anti-HTN)
Rescinnamine (ACE inhibitor, anti-HTN)
Reserpine (vesicular monoamine transport inhibitor anti-psychotic/HTN)
Rilmenidine (imidazoline receptor agonist, anti-HTN)
Ganglion blocking sympatholytics
Mecamylamine (a ₃ , b ₄ nicotinic receptor inhibitor, anti-HTN)
Trimethaphan (ganglion type receptor inhibitor, anti-HTN)
Peripherally acting sympatholytics
Prazosin (a ₁ -antagonist, anti-HTN)
Guanethidine (magnesium-ATPase inhibitor, anti-HTN)
Indoramin (a ₁ -antagonist, anti-HTN)
Doxazosin (a blocker, anti-HTN)
Phentolamine (a ₁ -antagonist, anti-HTN)
Vasodilators – Phosphodiesterase type-5 inhibitors
Sildenafil
Tadalafil
Vardenafil
III. Mechanism - Idiopathic (Unknown) Type
Antihypertensives:
Amiloride
Angiotensin-converting enzyme inhibitors
Oral b-Blockers
Calcium channel blockers
Intraocular or ophthalmic preparations of b-blockers [18]
Chlorothiazide
Hydralazine
Hydrochlorothiazide
Hormones
Exogenous estrogens
Oral contraceptives
Psychotropics
Chlordiazepoxide–amitriptyline
Chlorpromazine
Risperidone
Thioridazine
Miscellaneous
Gabapentin

The most common form of DIR is that caused by excessive use of over-the-counter decongestant nasal sprays as RM. Physical examination in patients with this disorder often reveals swollen, red nasal mucous membranes. Diagnosis

Table 2. Typical indication, drug group, and ingredients, which may trigger DIR (modified by Achim G. Beule[5])

After systemic application	
diuretics	Amyloride/Hydrochlorothiazide
high blood pressure drugs	ACE inhibitor
	beta blocker
	alpha-adrenergic blocker (doxazosin, phentolamine, prazosin)
	Imidazoline (clonidine)
	Guanethidine
	Hydralazine/Dihydralazine
	Methyldopa
	(Reserpine)
drugs for erectile dysfunction	Phosphodiesterase Inhibitor (sildenafil citrate, tadalafil, vardenafil)
hormones	Oestrogen
	Oral contraceptives
pain relievers	Acetylsalicylic acid
	Non-steroidal anti-inflammatory drugs (NSAIDs)
psychotropic drugs	Benzodiazepine (chlordiazepoxide)
	Tricyclic antidepressant (amitriptyline)
	Classical neuroleptics/Phenothiazin (chlorpromazine, thioridazine)
	Atypical antipsychotic/Risperidone
Others	Tropane Alkaloids (cocaine)
	Anticonvulsants (gabapentin)
	Cyclosporine
After topical application:	
Sympathomimetic drugs	Amphetamine (norephedrine, amphetamine)
	Alkaloids (ephedrine, pseudoephedrine, mescaline, caffeine)
	α 1-adrenergic receptor agonist (phenylephrine)
Imidazoline	Clonidine
	Naphazoline
	Oxymetazoline
	Xylometazoline
Other	Benzalkonium chloride

relies most heavily upon the history of use of a causative medication [46]. In some patients, even several days of regular use of decongestant sprays leads to rebound nasal congestion as the medication wears off, prompting patients to administer the medicine more frequently to obtain relief. This starts a vicious cycle of nasal congestion both caused and temporarily relieved by the medication with escalating use and eventual dependency [47].

The first step is to propose termination and withdrawal of the causative medication (if clinically feasible), otherwise it is suggested to initiate treatment empirically to alleviate symptoms. Evidence-based guidelines for DIR treatment

have recommended choosing the appropriate medications on the basis of the severity and frequency of the patient's symptoms.

DIR management includes a pharmacological component and a non-pharmacological component: avoidance of disease triggering factors, patient education. Management can be classified by the individual subphenotype of each patient.

In this section, we present the treatment options and recommendations that are supported by current evidence for assessing treatment of DIR phenotypes and to simplify monitoring.

Nowadays, there are some helpful drugs available for treatment of DIR. The medications have different indications and effectiveness in different subphenotypes.

Intranasal corticosteroids

Nowadays, intranasal corticosteroids (INCS) are considered to be the most effective medications available for the treatment of DIR. They are usually required to reduce symptoms while patients discontinue the culprit decongestant [6, 8, 48, 49].

INCS have been shown in case reports, animal models, and randomized controlled trials to be beneficial in the treatment of RM [14]. The effectiveness of INCS is based on their local activity since administration of an equivalent amount of medication orally produces no benefit.

However, not enough evidence is available to predict the treatment recommendations for DIR other than avoidance. While the recommended clinical practice to initiate use of INCS for symptomatic treatment is not conclusive, there is some evidence suggesting that INCS are appropriate for the management of RM, which is refractory to mere discontinuation of the offending nasal decongestant [3, 14, 19, 47, 50–53].

Treatment of RM begins with withdrawal of the causative medication. It is important to counsel patients that nasal congestion will probably worsen temporarily as the offending medication is stopped, and it is not interpreted as treatment failure. Intranasal fluticasone was shown in a small randomized trial of 19 patients to be effective in countering rebound nasal congestion in this setting [54].

High local concentrations are guaranteed through intranasal administration, while minimizing the risk of systemic adverse effects (grade A). There is no compelling evidence that any INCS is superior to others in terms of clinical effectiveness (grade B). The local and systemic safety profiles are excellent, particularly with the dosages recommended for chronic rhinitis (grade A) [55]. In cases where protracted use is necessary, most notably in children, the lowest effective dosage must be considered. The modern INCS are safe when given in recommended doses in adults and in children [56] and are potentially effective on an as-needed basis [19, 57, 58].

Depending on the mechanism of action, efficacy appears after 7–8 h of dosing, but maximum efficacy may require up to 1 week [59–61], or improvement may not be apparent for a few days and maximal effect may not be apparent until after 2 weeks [62, 63]. Long-term growth studies in children using fluticasone, mometasone, and budesonide have reassuring safety data,

unlike beclomethasone [56, 63–67]. Concomitant treatment with CYP3A inhibitors such as itraconazole or ritonavir may increase systemic bioavailability of INCS [63, 68, 69].

INCS adverse events: nasal irritation (dryness, burning, and stringing) and epistaxis, the latter occurring in 5 % to 10 % of patients [15]. BKC as used as a preservative in all topical corticosteroids, except budesonide (Rhinocort®, Astrazeneca International, London, UK) nasal spray and fluticasone nasules (Flixonase®, GSK), and may irritate the nose, but does not adversely affect mucociliary clearance [70]. Reduction of local adverse effects can probably be achieved by correct use (grade D); hypothalamic–pituitary axis suppression may occur when multiple sites are treated with topical corticosteroids in the same person (e.g. skin, nose, and chest). It is advisable to monitor growth in children [64]. Increased intra-ocular pressure has been described with INCS [71], and patients with a history of glaucoma should be monitored more closely [63].

Intranasal antihistamines that antagonize H₁ receptors are effective for nasal congestion [3••, 72•] and have a rapid onset of action [3••, 73]. Some data demonstrate the combination of intranasal fluticasone and azelastine provides improvement in symptoms of nasal congestion in patients with AR, thus it may be reasonable to start combination therapy in patients with DIR in an attempt to control symptoms [74]. A recent meta-analysis has proven the new intranasal formulation of “fluticasone propionate + azelastine” is more effective in treating AR than corticosteroids alone and may be considered the drug of choice for AR (Carr W et al. *J Allergy Clin Immunol* 2012), Meltzer EO et al. *Int Arch Allergy Immunol* 2013[75, 76].

It was suggested that this approach may be particularly helpful in patients with hypertension, in whom use of oral decongestants may exacerbate hypertension [14•].

Adverse events: local irritation, taste disturbance with azelastine [63]. Further research will be needed.

Intranasal decongestants

In some patients, even several days of regular use of decongestant nasal sprays results in rebound nasal congestion and prompts patients to administer the medicine regularly to achieve relief. This starts a vicious cycle of nasal congestion both caused and temporarily relieved by the medication with escalating use and concluding with dependency.

Oral decongestants

Nasal obstruction is the predominant symptom, a short course of oral adrenergic agents (pseudoephedrine and/or phenylephrine) can be considered rescue medication [3••, 19•]. The effect lasts 30 min to 6 h or longer with slow-release preparations, do not cause a rebound effect on withdrawal, but are less effective than topical preparations for nasal obstruction [63, 77].

However, these pharmaceuticals are characterized by a less favorable safety profile [3••, 19•, 78–80], leading some to recommend that these agents

should not be used regularly [3••, 80], should be avoided in young children, and should be used with caution in adults of over 60 years of age and in any patient with cardiovascular conditions [19•].

Adverse events: Hypertension, interaction with antidepressants, insomnia, agitation, tachycardia [63].

Intranasal decongestants.

These include vasoconstrictor sympathomimetic (alpha-adrenergic agonist) agents (e.g., phenylephrine, oxymetazoline, xylometazoline). These agents can be used as rescue medication for any rhinitis phenotype with congestion as a predominant symptom [81]. They are not recommended for long-term therapy because, in a significant percentage of patients, tolerance and/or RM can appear as early as 3 days into treatment [3••, 78, 79, 82]. It is available as nasal drops or spray for adults and children over 3 months of age. Although there are reports of safe administration of up to 4 weeks [3••, 83, 84], especially in combination with INCS [3••, 41, 54], a maximum of 5–10 days of continuous use is recommended [3, 19•, 79].

Adverse events: Regular use can lead to RM with tachyphylaxis to the drug and marked chronic nasal obstruction [85]. Nasal irritation, may increase rhinorrhea [63] tachycardia, increased blood pressure, and insomnia [15].

Oral corticosteroids

This is a last resort treatment for symptoms refractory to all other appropriate therapeutic modalities, and its application is limited to the short term. A short burst of oral corticosteroids may help to wean patients off topical nasal decongestants when discontinuation causes refractory rebound symptoms [3••, 14•]. The short course of systemic corticosteroids for 5–7 days may be needed to wean patients off topical nasal decongestants [14•, 86]. A brief course of oral glucocorticoids (e.g., prednisone, 0.5–1 mg per kg for 5 days) has also been proposed for treatment of DIR during withdrawal in some case reports [46].

Nasal saline irrigations

Despite limited evidence of benefit, a commonly used auxiliary treatment for most rhinitis phenotypes is nasal irrigations with isotonic or hypertonic saline [3••, 87]. A Cochrane review concluded that saline irrigation was well tolerated, had minor side effects [15, 88]. Several recent studies found that hypertonic solutions were superior to the widely used isotonic solutions (grade B). Buffering the solution with sodium bicarbonate is useful to loosen the secretions (grade C) [55]. In the only prospective study, the use of nasal irrigation significantly improved 23 of 30 nasal symptoms [89]. It remains unclear whether hypertonic saline provides a better effect, as compared to normal saline [3••, 90, 91]. A variety of over-the-counter devices including bulb syringes and bottle sprayers are effective provided the system delivers an adequate volume of solution (>200 mL per side) into the nose. Patients can make their own solutions or buy commercially

prepared kits. Nasal lavage with warmed saline can be performed as-needed only, daily at baseline, or twice daily for increased symptoms. Intranasal saline sprays have also been found effective for symptoms relieving postnasal drip, sneezing, and nasal congestion [16, 92]. Saline sprays are somewhat less effective than larger volume nasal lavage, although they may be more convenient for some patients [93].

The use of topical saline is associated with minimal side effects, such as burning, irritation, and nausea, has low cost, and overall good patient acceptance [94, 95]. The preferred method of delivery is nasal spray, bottle pump, irrigation, or nebulizer; the volume and the dose frequency have not been established [19•].

Other treatments

Other drugs:

Nasal cromolyn and sedatives/hypnotics were presented in several review papers; however, they did not include prospective trials evidencing their application [7, 8•, 9, 96, 97]. Neither is there scientific information about other drugs such as intranasal anticholinergics, oral antihistamines, leukotriene receptor antagonists, or combined therapy.

Nasal surgery.

Surgical referral for submucosal resection of the inferior turbinate bones may be indicated only in cases of extensive medical treatment failure [63, 98]. Indication is the main determinant of the success of all the above mentioned surgical procedures.

Diode laser inferior turbinate reduction (ITR).

Caffier et al. assessed long-term outcomes of outpatient-based ITR for therapy-refractory RM, which was a highly effective, safe, and well-tolerated treatment option providing long-lasting recovery stopping addiction to nasal decongestants [99].

Review of the current literature demonstrates a limited amount of data that defines statistically significant safety concerns. Additional analysis and research are needed in the future.

Quality of life

Quality of life (QoL) is a standard outcome measure in clinical trials acknowledging the fact that the classical outcome variables may only partially characterize the disease of the patient [100•].

Both generic (measures physical, psychological, and social domains) and disease-specific (better discriminative and evaluative properties) questionnaires

are being used to evaluate the influence of rhinitis on QOL [19•, 100•]. Papadopoulos et al. suggested application of rhinitis control assessment. This approach is intended to be a practical guide in the clinical setting for all rhinitis patients regardless of phenotype or endotype and to supplement the several tools that are currently validated for assessment of rhinitis control [3••].

DIR is a clinical condition usually observed in individuals taking commonly prescribed medications. It is often impairs QoL and results in persistent symptoms [14•]. The poorly controlled symptoms as nasal congestion, secondary sleep apnea, and disordered sleep can lead to systemic symptoms of headache, fatigue, irritability, and can reduce QoL. The effects of DIR on daily performance, work and school activities, anxiety, and family dysfunction as reported by the patient are considered important characteristics of disease severity. QoL improvement may be achieved in cases of proper control of the disease.

The main goal of therapy is to understand the influence of DIR on the QOL of the patient. QOL overall improvement may be achieved through realistic outcome of therapy, understanding how to use appropriate methods of drug administration, medication benefits and possible side effects, concurrent diseases, and the effect that disease control [19•].

The importance of QoL issues of DIR should be studied in the future. To date, there are no cost-effectiveness studies in patients with DIR have been conducted. To estimate the burden of DIR, establishment of standardized QoL questioner, which might be helpful and will assist in comparing the cost effectiveness of various medical treatments of DIR. For control of DIR, QoL questionnaires should be developed and validated.

Conclusions

DIR has a significant impact on patients' QoL and socioeconomic burden. Unfortunately, the prevalence and other epidemiological and pathomechanisms of DIR and its sub-phenotypes are unclear.

Since in many cases DIR is underdiagnosed, increasing awareness for medical workers, patients, and the general population about DIR phenotypes may help the proper management and conduct effective preventive measures. More evidence-based research studies and creation of national and international clinical guidelines for the prevention and management of DIR are needed.

Compliance with ethical standards

Conflict of interest

Maia Rukhaze declares that she has no conflicts of interest. Maia Gotua declares that she has no conflicts of interest. Amiran Gamkrelidze declares that he has no conflicts of interest.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

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