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Review Article

A Closer Look at the Evidence Supporting Appropriate Use of Nasal Oxymetazoline HCl Spray and the Risk of Rebound Congestion: A Systematic Review

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Abstract:

Purpose: Although intranasal decongestants provide rapid relief from nasal congestion—a major symptom in various upper respiratory disorders—their prolonged or excessive use may lead to rebound congestion (RC), a condition with poorly understood mechanisms. We reviewed published studies investigating the relationship between the use of oxymetazoline nasal sprays (as-directed versus prolonged) and the development of RC.

Methods: We conducted a literature search in PubMed, covering publications up until April 2024, to identify clinical trials investigating RC involving the use of oxymetazoline nasal spray. Two investigators screened articles and extracted data on study design, participant characteristics, interventions, and outcomes. We employed a narrative approach to integrate and summarize the findings on the duration of oxymetazoline treatment in managing nasal congestion with minimal RC.

Results: 17 studies were selected. In clinical trials assessing the as-directed use of oxymetazoline (up to 10 days), RC was not identified as a resulting complication. Conversely, some studies of oxymetazoline use beyond the recommended duration indicated an association with RC, though results varied. Some studies suggested that prolonged use symptoms could be mitigated with appropriate use of intranasal corticosteroids.

Conclusions: When used as directed, oxymetazoline nasal sprays provide an effective remedy for nasal congestion with minimal risk of RC. Healthcare practitioners can recommend short-term use of oxymetazoline for managing nasal congestion. Future research on the optimal duration and combination therapies is warranted to further minimize the risk of RC and enhance care for individuals with chronic nasal congestions.

Keywords: Oxymetazoline, rebound congestion, rhinitis, rhinitis medicamentosa, nasal decongestants, systematic review

Introduction:

Nasal congestion, a prominent symptom in upper respiratory disorders, including allergic rhinitis, common cold, and rhino sinusitis [1-3], is characterized by a sensation of nasal obstruction, hindering proper airflow. Nasal congestion imposes a significant quality-of-life and economic burden and is considered the most bothersome symptom of common cold or allergies [2, 4].

Several classes of remedies are available to relieve symptoms of nasal congestion, including saline nasal sprays, antihistamines (systemic and intranasal), intranasal corticosteroids (INCS), oral decongestants, and intranasal decongestants. Among these, intranasally-applied decongestants provide rapid-onset and potent relief of nasal blockage[5-7]. The active ingredient in over-the-counter (OTC) intranasal decongestants is typically a sympathomimetic amine (e.g., phenylephrine) or imidazoline derivative (e.g., oxymetazoline and xylometazoline)[6]. These agents work by activating α-adrenergic receptors, which induce vasoconstriction within the nasal mucosa [3, 6].

Although intranasal decongestants offer rapid, accessible relief from nasal congestion[5] their prolonged use (i.e., beyond the duration recommended in product labels[8]) or overuse may be associated with rebound congestion (RC). RC, or rhinitis medicamentosa, is a form of drug-induced rhinitis triggered by extended usage or sudden withdrawal following prolonged use of intranasal decongestants[3, 9-11]. It results in rebound swelling and inflammation of the mucosa[3, 11]. The diagnosis of RC relies primarily on the patient's history which describes prolonged usage of the agents[10]. Additionally, physicians may conduct sinonasal endoscopy to check for causes of nasal obstruction, primarily turbinate swelling in cases of RC, and other mechanical causes like nasal polyps, masses, or septal deviation [12].

Studies show that RC, though poorly understood and subject to debate, involves various mucosal abnormalities, including epithelial metaplasia/hyperplasia, loss of ciliated cells, thickening of the epithelial basement membrane, increase of mucus-secreting cells and submucosal glands, and submucosal perivascular edema[13]. However, there is at least one study that shows no mucosal abnormalities after the use of a topical decongestant for 6 weeks in a group of healthy subjects[14]. RC has been attributed to a perceived nasal stuffiness as the decongestant effects dissipate [15] and/or dependence on intranasal decongestants to relieve blockage from underlying conditions with a return of congestion related to these chronic conditions when the topical agents are stopped [13]. The exact underlying mechanism is unclear[3], but proposed hypotheses include ischemia due to prolonged and intense vasoconstriction from adrenergic receptor stimulation, vasoconstriction mechanism fatigue, and down-regulation of α-adrenergic receptors[3, 13]. Benzalkonium chloride (BAC), a common preservative in nasal decongestants [16], is also suspected to contribute to RC, although the evidence is conflicting [17-19].

Perhaps due to a limited understanding of RC and its mechanisms, reports suggest concerns among healthcare providers and patients linked to perceptions that any intranasal decongestant use causes RC and leads to dependence, sometimes inaccurately described as "addiction"[12, 20]. However, such symptoms may primarily arise from the overuse of these decongestants beyond their intended frequency and duration. This article focuses specifically on the link between RC and the as-directed versus prolonged use of oxymetazoline nasal sprays. Oxymetazoline, a fast-acting nasal decongestant with effects lasting 8–12 hours, has a favorable safety profile with minimal side effects, except RC, when used indiscriminately [6, 21, 22]. It has demonstrated effectiveness in rapidly increasing nasal cross-sectional area, decreasing nasal resistance, and improving patient-reported nasal symptom scores[23]. The recommended usage for oxymetazoline hydrochloride (HCl) is 2–3 sprays in each nostril twice-daily for a maximum of three days in the US[8, 24] and up to seven days in Asia and Europe[25-28]. In this article, we examine the evidence supporting the as-directed use of

oxymetazoline HCl on product labels based on existing clinical data and guideline recommendations.

Methods:

We conducted a PubMed search for clinical studies investigating RC involving the use of oxymetazoline HCl. The search terms used were ("rhinitis medicamentosa" OR "rebound congestion") AND "oxymetazoline" (filter: Clinical Trials; publication date: until April 2024). 14 articles were identified, and two [29, 30] were excluded for lack of relevance. Two investigators screened the reference lists of the 12 included articles, identifying four additional articles as English-language randomized controlled trials (RCT) investigating the impact of oxymetazoline on RC. Furthermore, based on author familiarity with the topic, one additional article was located, for a total of 17 articles (Figure 1).

Risk of bias analysis was conducted according to the Cochrane handbook, and the risk was assessed as low to some concern for most of the studies. This was mainly due to the age of the studies as some features including randomization and blinding were left implicit in a number of studies (Figure 2).

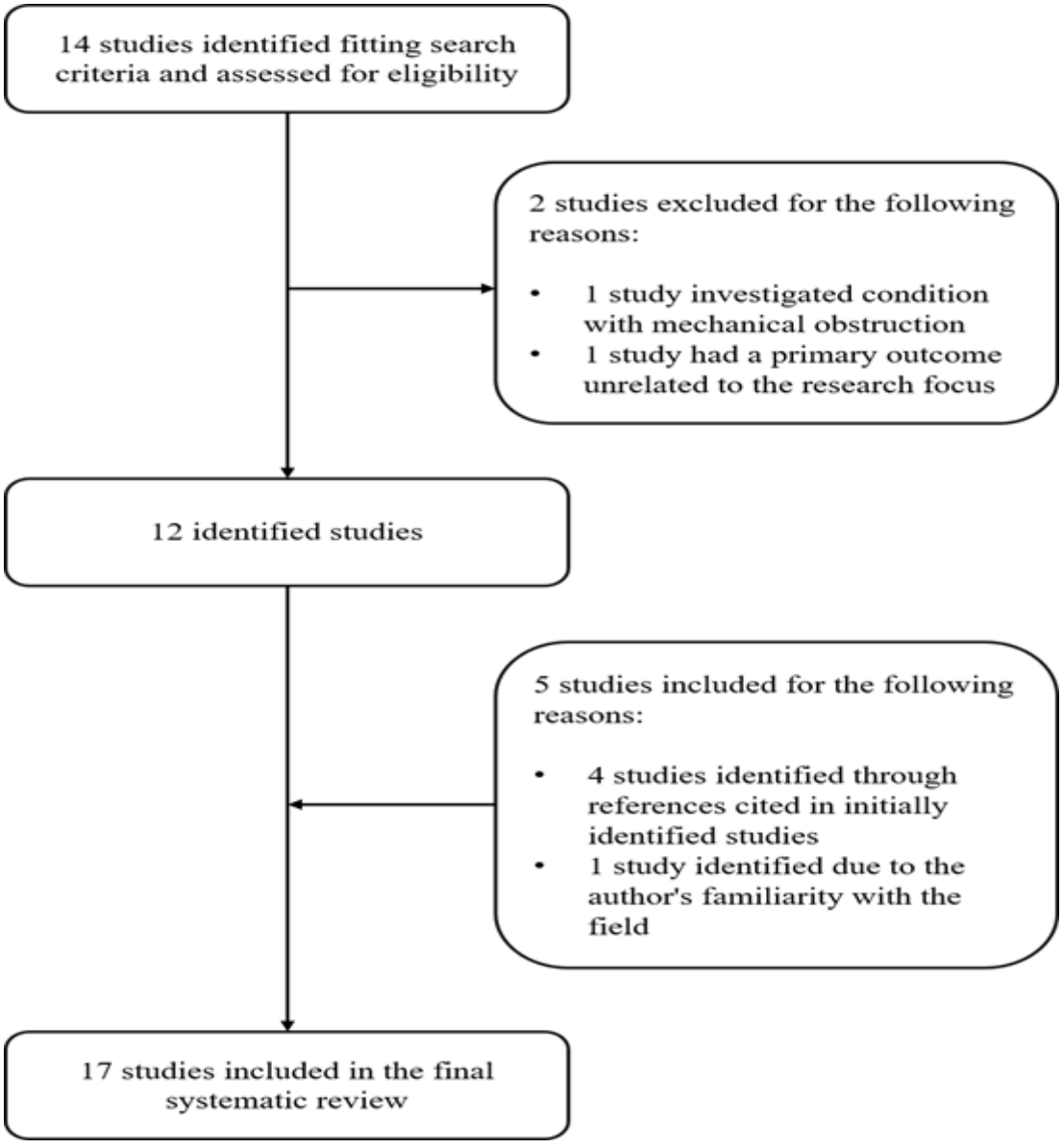

Figure 1. PRISMA* flowchart

* PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

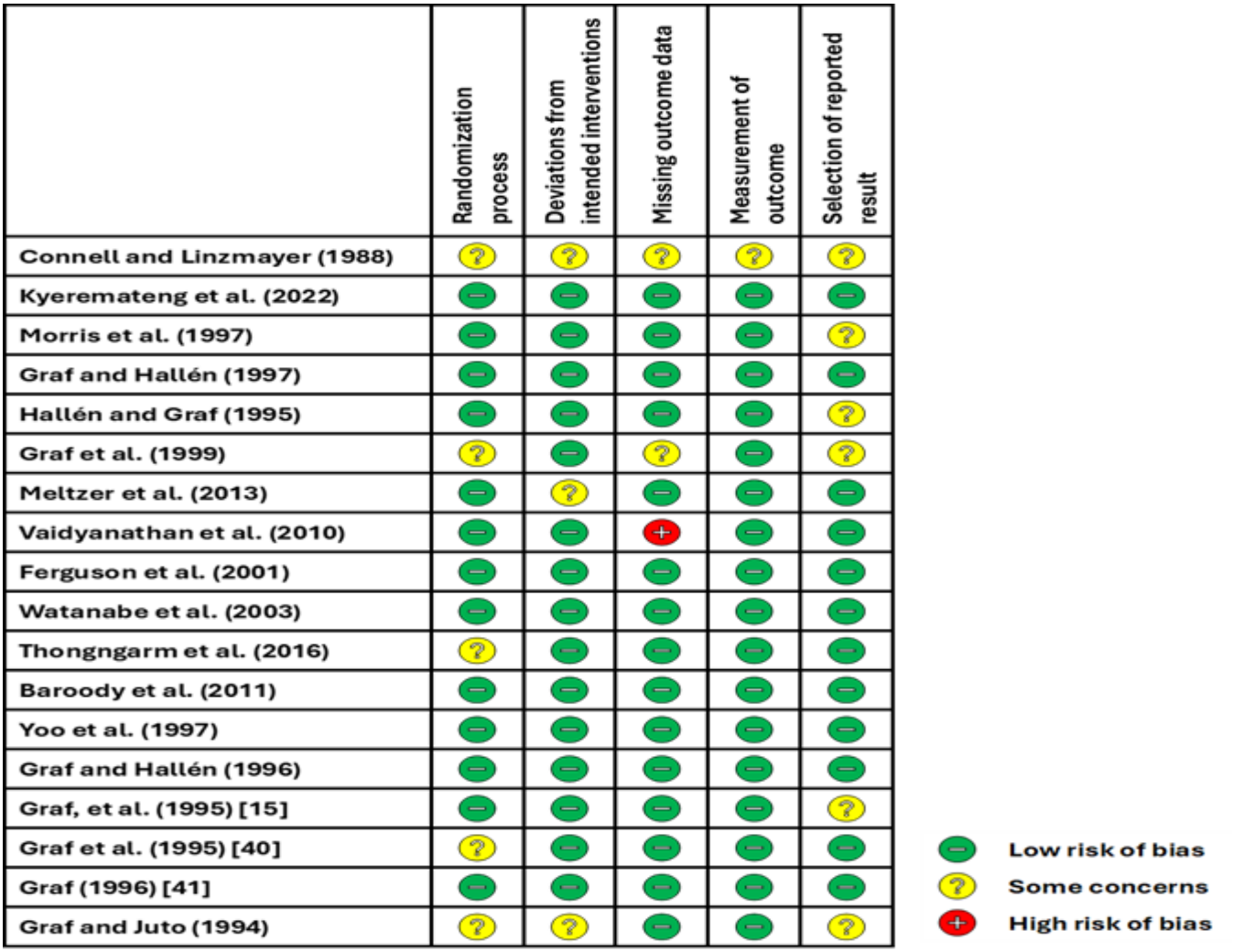

Figure 2. Risk of bias assessment

Results:

Short-term use for 10 days or less:

Studies investigating short-term use (≤10 days) of oxymetazoline HCl did not report an association with RC in subjects with or without pre-existing nasal mucosal inflammation (Table 1)[31-34]. Connell and Linzmayer investigated the short-term effects of oxymetazoline in a study with 40 hay fever patients randomized to receive either oxymetazoline or a placebo spray twice-daily for three days. Measurements of nasal airway resistance (NAR) at multiple time points on Days 1 and 3 showed no signs of RC in the oxymetazoline group post-treatment. Conversely, five placebo recipients experienced worsening congestion on Day 3[31]. To assess the safety of oxymetazoline and the effects of BAC in patients already experiencing nasal mucosal inflammation, Graf et al. conducted a double-blinded RCT. 35 patients with chronic, untreated vasomotor rhinitis were randomized to receive 0.1 mL of oxymetazoline HCl (0.5 mg/mL) with or without BAC twice to thrice-daily for ten days. This study, which utilized rhinostereometry and acoustic rhinometry for assessment within hours of treatment cessation, did not show any evidence of rebound nasal mucosal swelling, regardless of the presence of BAC. However, the group that used the BAC-containing spray was found to have a decrease in responsiveness to histamine after 10 days[32].

In a double-blinded RCT conducted with healthy volunteers, Morris et al. investigated the potential for RC over seven days of treatment. 20 participants received three sprays of 50µL (0.05% w/v) twice-daily oxymetazoline HCl for 7 consecutive days. Another 20 participants received oxymetazoline only in the morning on

days 1, 3, and 7, and vehicle the other times, and 10 participants received the vehicle spray twice-daily. Compared with vehicle treatment, there were no signs of congestion or tolerance to oxymetazoline as measured by changes in NAR 30 minutes post-dosing and by subjective measures[33]. While the study observed a statistically higher pre-dosing NAR at Day 3 compared with Day 1 in the oxymetazoline group, the trend was not consistently observed over the 7 days of treatment and was also seen in the vehicle group[33].

Furthermore, a recent study by Kyerematenge et al. examined the potential for RC after seven days of twice-daily oxymetazoline HCl use in 143 otherwise healthy adults with nasal congestion. The study examined four escalating doses of oxymetazoline, involving either 1 or 2 sprays per nostril, with dosages of 50 µL or 100 µL at concentrations of 0.025% or 0.05%. Utilizing a visual analog scale (VAS) to assess nasal congestion, there was no worsening of nasal congestion scores compared with baseline on the last treatment day (Day 7) and 12- and 24-hours post-treatment discontinuation (Day 8) across all dosing groups[34]. These results reinforce the safety of oxymetazoline HCl nasal spray when used for the short-term (≤10 days) treatment of nasal blockage.

While shorter-duration studies in healthy volunteers or individuals with no history of overusing nasal decongestants yielded favorable results, those in chronic users showed different outcomes (Table 1)[19, 35]. Graf and Hallén conducted a study on patients who had overused oxymetazoline or xylometazoline for up to six years. This study revealed that resuming oxymetazoline (0.5 mg/mL) with BAC (0.1 mg/ml) thrice-daily for 7 days, even after a year-long break, significantly increased mucosal swelling, morning and evening subjective nasal stuffiness, and histamine reactivity despite the short-term treatment[35]. In a double-blind follow-up study, 20 healthy volunteers who had been treated for four weeks with oxymetazoline nasal spray, either alone or in combination with BAC, received the same treatment for ten days after a three-month break. Pre- and post-treatment measurements of nasal mucosa congestion, reactivity, and symptom scores revealed that only those treated with the combination experienced significantly increased nasal stuffiness and mucosa swelling, suggesting long-term adverse effects of BAC when used with oxymetazoline[19]. These studies suggest that patients with a history of overusing topical decongestants should be cautious about restarting these medications, even for a short period, due to the risk of RC.

Longer duration of use at different dosing frequencies:

While the short-term use of oxymetazoline HCl does not appear to lead to RC, there is conflicting evidence regarding longer-term use beyond the recommended duration of 7 days (Table 1)[5, 15, 16, 36-43]. Graf and colleagues conducted a series of double-blind RCTs in healthy volunteers assessing RC with longer-term use of oxymetazoline HCl[15, 16, 41, 42]. These trials used rhinostereometry and VAS_{100} score to assess nasal mucosal swelling and stuffiness pre-treatment, post-treatment, and post-histamine provocation. After one month of 0.1 mL oxymetazoline HCl (0.5 mg/mL) treatment, increased nasal mucosal swelling and subjective nasal stuffiness were reported. These effects were observed regardless of the presence of BAC[15, 16, 42]. and whether oxymetazoline was administered once or thrice-daily[41, 42]. In a related study by Ferguson et al., 19 subjects with perennial allergic rhinitis and nasal congestion received oxymetazoline (0.05 mg/mL) twice-daily for three weeks following a one-week wash-out period. After two weeks of oxymetazoline, subjects were randomized to two additional weeks of budesonide aqueous nasal spray or placebo, with all treatments ceasing in the sixth week. This study reported that withdrawal of oxymetazoline after three weeks resulted in lower nasal volume and cross-sectional area at 24 hours post-withdrawal compared with baseline levels[37]. 9l-155/

no significant signs of nasal blockage or impaired response to further oxymetazoline treatment following four weeks of thrice-daily oxymetazoline (0.05 mg/mL) treatment in 30 healthy adult subjects[38]. In contrast, Watanabe et al., Thongngarm et al., and Yoo et al. reported improved nasal airflow and reduction in airway resistance[38-40].

Table 1. Clinical studies investigating the effects of Oxymetazoline HCl treatment duration on the potential for RC symptoms

Author, year Reference	Study design & population	Interventions	Treatment duration	Findings[a]
Connell and Linzmayer, 1988[31]	• Double-blind, placebo-controlled study. • 40 patients with symptomatic hay fever.	Two treatment groups: 1. 0.05% Oxymetazoline BID 2. Placebo BID BAC component not specified	3 days	No RC observed based on NAR measurements in oxymetazoline group. 5 out of 20 placebo subjects had worsened congestion after 3 days.
Kyerematenget al., 2022[34]	• Randomized, double-blind, placebo-controlled trial. • 143 subjects with nasal congestion.	Five treatment groups Twice daily of one of the following: 1. 0.025% Oxymetazoline HCl, one 50 µL spray per nostril 2. 0.025% Oxymetazoline HCl, one 100 µL spray per nostril 3. 0.05% Oxymetazoline HCl, two 50 µL sprays per nostril 4. 0.05% Oxymetazoline HCl, two 100 µL sprays per nostril 5. Saline BAC component not specified	7 days	No subjective RC based on visual analog scale (0-100) (VAS_{100}) score and verbal 7-item congestion score with any arms compared with baseline scores on day 7, at the end of treatment, and at 12- and 16 to 24-hours post discontinuation.
Morris et al., 1997[33]	• Randomized, double-blind trial. • 50 healthy subjects, 18–59 years old.	Three treatment groups 3 sprays per nostril of one of the following: 1. Oxymetazoline (0.05% m/v) twice-daily every day (n=20) 2. Oxymetazoline (0.05% m/v) only	7 days	No sign of RC based on mean change in NAR assessed by posterior rhinomanometry before and 30 minutes after dosing over 7 days in both oxymetazoline

		in the morning on days 1, 3, and 7 (n=20) 3. Vehicle solution* (n=10) *Vehicle contained BAC (0.04%)		groups. No difference in subjective measurement via VAS (50 items) was observed between the 3 groups. No sign of rhinitis based on clinical examination. Statistically increased pre-dose NAR was observed in both oxymetazoline groups on Day 3 but was not consistently observed throughout the study as the effect subsided with continued use in the latter part of the week, and some degree of increase was also observed in the group receiving the placebo (vehicle-only) spray.
Graf and Hallén, 1997[35]	• Prospective uncontrolled cohort study • 8 patients who had previously used oxy- and/or xylometazoline containing BAC for at least 4 months. • The study was conducted 13–19 months after stopping the previous nasal decongestant.	Oxymetazoline (0.5 mg/mL) containing BAC (0.1 mg/mL), 0.1 mL thrice daily.	7 days	Statistically significant mucosal swelling was found using rhinostereometry, and morning and evening nasal stuffiness was also found using the VAS100 score after 7 days of Rx. Mucosal swelling following histamine provocation was also observed on Day 7 compared with baseline. An increase in nasal stuffiness was reported from day 3.
Hallén and Graf, 1995[19]	• Parallel, double-blind trial • 20 healthy subjects • In a previous study, 10 treated with oxymetazoline nasal spray with	Two treatment groups Thrice-daily, one dose in each nostril of one of the following: 1. Oxymetazoline (0.5 mg/mL) with 0.1 mg/mL BAC, 0.1 mL 2. Oxymetazoline (0.5	10 days	Subjects treated with the combination of oxymetazoline and BAC showed increased nasal stuffiness and mucosa swelling after treatment. Those treated with

	BAC and 10 with oxymetazoline nasal spray alone. Both groups were treated thrice-daily for a duration of 4 weeks. • This study was conducted 3 months after stopping the previous treatment. • The subjects were allocated into the same treatment groups as in the previous study.	mg/mL)		oxymetazoline alone did not exhibit significant swelling or increased stuffiness.
Graf et al., 1999[32]	• Randomized, double-blind trial. • 35 subjects with vasomotor rhinitis.	Two treatment groups Twice or thrice-daily: 1. Oxymetazoline (0.5 mg/mL) with 0.1 mg/mL BAC, 0.1 mL 2. Oxymetazoline (0.5 mg/mL) without BAC, 0.1 mL	10 days	On Day 10, there was no sign of rebound swelling as assessed by nasal mucosal swelling through rhinostereometry and minimal cross-sectional area by acoustic rhinometry. The group that used the BAC-containing spray was found to have a decrease in responsiveness to histamine after 10 days.
Meltzer et al., 2013[44]	• Randomized, single-dummy, placebo-controlled trial • 705 subjects with minimum 2 year SAR history	Five treatment groups: 1. *MFNS (50 ug/spray) 2 sprays/nostril + OXY (0.05%) 3 sprays/nostril 2. *MFNS (50 ug/spray) 2 sprays/nostril + OXY (0.05%) 1 spray/nostril	15 days	Some tachyphylaxis during prolonged OXY twice daily monotherapy. Findings showed little to no rebound congestion when OXY was combined with MFNS.

		3. MFNS (50 ug/spray) 2 sprays/nostril daily 4. OXY (0.05%) 2 sprays/ nostril twice daily 5. Placebo *MFNS = mometasone furoate nasal spray; OXY = oxymetazoline BAC component not specified		
Vaidyanathan et al., 2010[36]	• Randomized, double-blind trial. • 33 healthy subjects screened, only 19 healthy subjects received intranasal oxymetazoline.	Day 1–14: 2 sprays of oxymetazoline (0.05% m/v) in each nostril (200 µg per dose) thrice-daily. Day 15–17: 2 sprays of fluticasone furoate in each nostril (200 µg per dose) twice-daily + 2 sprays of oxymetazoline (0.05% m/v) in each nostril (200 µg per dose) thrice-daily * Days 1, 14, and 17, participants received a single dose of oral prazosin (1 mg), or placebo BAC component not specified	17 days	Prazosin (selective α1-antagonist) was used to estimate the differential effects of oxymetazoline (a mixed α1- and α2-agonist) and receptor tolerance on the α1- and α2- adrenoceptor-mediated components of tachyphylaxis Due to this, data suggest that the nasal congestive response is predominately mediated by α1-adrenoreceptors. After 14 days of oxymetazoline, significantly decreased peak nasal inspiratory flow and increased nasal mucosal blood flow compared with the start of treatment were observed. These changes were inhibited by fluticasone furoate.
Ferguson et al., 2001[37]	• Randomized, double-blind, placebo-controlled trial. • 19 subjects with perennial	Week 1: run-in (no treatment) Week 2–3: 2 sprays of oxymetazoline HCl (0.05%) twice-daily	3 weeks	Withdrawal of oxymetazoline in the placebo group led to an increased congestion score (based on a subjective

	allergic rhinitis with nasal congestion	Week 4: Oxymetazoline and either budesonide or placebo Week 5: Budesonide or placebo Week 6: no treatment BAC component not specified		10-point visual analog scale) lasting until Week 6. Withdrawal of oxymetazoline led to statistically lower nasal volume and mucosal cross-sectional area assessed by rhinomanometry compared with pre-treatment in both arms at 24 hours post-withdrawal. Subjective RC resolved in 48 hours in the budesonide aqueous nasal spray group but persisted for over 1 week in the placebo group.
Watanabe et al., 2003[38]	• Randomized, double-blind, placebo-controlled trial. • 30 healthy subjects 16-60 years old.	Two treatment groups: 1. 2 sprays of oxymetazoline (50 µg in 0.1 mL)* thrice daily 2. Placebo* *Contained BAC (0.1%)	4 weeks	Statistically increased nasal peak inspiratory flow and volume measurement (via acoustic rhinometry) and a decrease in airway resistance (via posterior active rhinomanometry) were observed in both oxymetazoline and placebo groups following oxymetazoline challenge before treatment at the end of treatment (week 4) and 2 weeks after the end of treatment (week 6). No statistically significant differences were observed in terms of changes in nasal measurements and subjective nasal congestion score from baseline between oxymetazoline and placebo groups at

				week 4 and week 6.
Thongngarm et al., 2016[39]	• Randomized, double-blind trial • 50 patients aged 18 or older with chronic rhinitis, who had previously used INCS and cetirizine but still experienced nasal congestion	Two treatment groups* Twice-daily, 2 sprays in each nostril of one of the following for 4 weeks: 1. Oxymetazoline (0.05%) 2. Placebo *All subjects received 2 sprays of INCS (budesonide, 100 µg/spray) in each nostril twice-daily and cetirizine (10 mg) daily for 6 weeks BAC component not specified	4 weeks	Oxymetazoline significantly reduced nasal congestion in subjects with chronic rhinitis compared with placebo, particularly on days 15–28 and 29–42. No RC was associated with the treatment.
Baroody et al., 2011[5]	• Randomized, double-blind, double-dummy trial. • 60 subjects with perennial allergic rhinitis 18–55 years old.	Four treatment groups: 1. Oxymetazoline (0.05%) 2 puffs in each nostril once-daily in the evening 2. Fluticasone furoate (110 µg per day) 3. Fluticasone furoate with oxymetazoline 4. Placebo BAC component not specified	4 weeks	No signs of RC based on nasal volume (via acoustic rhinometry), nasal peak inspiratory flow, or subjective congestion and total nasal symptom scores 2 weeks after cessation compared to the first day of treatment in subjects receiving oxymetazoline alone.
Yoo et al., 1997[40]	• Prospective uncontrolled cohort study. • 10 subjects, of which 4 had a history of allergic rhinitis, and 2 used topical nasal steroids.	Oxymetazoline 0.05% one spray once-daily at night. BAC component not specified	4 weeks	All subjects had higher nasal airflow and lower airway resistance assessed by anterior rhinomanometry at week 4 of treatment and 4 weeks after cessation. 8 subjects reported nasal congestion before daily administration, which resolved within 48 hours after cessation.

Graf and Hallén, 1996[15]	• Randomized, double-blind, placebo-controlled trial. • 30 healthy subjects 14–52 years old.	Three treatment groups: Thrice-daily: 1. Oxymetazoline (0.5 mg/mL) 2. BAC (0.1 mg/mL) 3. Placebo	4 weeks	A statistically higher VAS_{100} score was observed on day 14 in the oxymetazoline group compared with the placebo. Histamine reactivity was also statistically higher in the oxymetazoline group compared with placebo when challenged with 1 mg/mL and 2 mg/mL but not 4mg/mL histamine. No significant difference in mucosal swelling measured by rhinostereometry before and after treatment was observed in the oxymetazoline group.
Graf et al., 1995[16]	• Randomized, double-blind trial. • 20 healthy subjects 22–41 years old.	Two treatment groups: Thrice-daily oxymetazoline (0.5 mg/mL), 0.1 mL, either: 1. with 0.1 mg/mL BAC 2. without 0.1 mg/mL BAC	30 days	Significantly increased nasal mucosal swelling measured by rhinostereometry, subjective morning and evening nasal stuffiness measured by VAS_{100}, and mucosal swelling following histamine provocation at day 30 of treatment in both groups. The magnitudes of changes were larger in subjects receiving oxymetazoline containing BAC.
Graf et al., 1995[41]	• Randomized, double-blind trial.	Oxymetazoline (0.5 mg/mL) 0.1 mL* either:	30 days	Statistically significant nasal mucosal swelling

	• 20 healthy subjects 19-41 years old	1. once-daily at night (placebo given in the morning and at noon) or 2. thrice-daily *Contained BAC (0.1 mg/mL)		measured by rhinostereometry, subjective morning and evening nasal stuffiness measured by VAS_{100} and mucosal swelling following histamine provocation were observed at day 30 of treatment with either once daily or thrice daily oxymetazoline. No significant difference was observed between subjects given once daily and thrice daily oxymetazoline.
Graf, 1996, Study 2[b][42]	• Randomized, double-blind trial. • 30 healthy subjects 19–41 years old.	Three treatment groups: 1. Oxymetazoline (0.5 mg/mL) with BAC (0.1 mg/mL) thrice-daily 2. Oxymetazoline (0.5 mg/mL) without BAC thrice-daily 3. Oxymetazoline (0.5 mg/mL) with BAC (0.1 mg/mL) once daily at night	30 days	Statistically higher nasal mucosal swelling following histamine provocation assessed by rhinostereometry and nasal stuffiness score were observed in all arms after 30 days of treatment.
Graf and Juto 1994[43]	• Prospective uncontrolled cohort study • 8 healthy subjects 21–36 years	One 0.1mL spray of oxymetazoline (0.5 mg/mL) thrice-daily BAC component not specified	30 days	Rebound mucosal congestion, assessed by rhinostereometry, was observed after 30 days of treatment, but not after 10 days. All subjects reported subjective nasal stuffiness on Day 30.

[a] Data were extracted on the following outcome measures: nasal congestion severity, nasal airway resistance (NAR), subjective ratings of rebound congestion (RC), signs of rhinitis, mucosal swelling, and nasal stuffiness.

[b] Graf's 1996 article reported three studies; however, only Study 2 met the inclusion criteria.

International guidelines on the duration of use for topical nasal decongestant:

We reviewed recommendations on RC within expert guidelines on allergic rhinitis, allergies, and the common cold from the British Society for Allergy & Clinical Immunology (BSACI), the Japanese Society of Allergology (JSA), the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS), the American Academy of Allergy, Asthma, and Immunology (AAAAI), and the American Academy of Family Physicians (AAFP). These guidelines acknowledge the risk of RC from prolonged use of intranasal decongestants but do not advise against their use within the intended short-term duration. US guidelines recommend using them for no longer than five days[45-47]. The AAFP 2007 guideline for common cold recommends topical intranasal decongestants for adults and adolescents for up to three days, based on available clinical evidence[45]. The AAO-HNS 2015 Clinical Practice Guideline for allergic rhinitis recommends adding oxymetazoline as a second medication to INCS for severe nasal congestion that precludes penetration of steroids into the nasal cavity[46]. Due to insufficient evidence on RC risk, the guideline recommends the combination treatment be used for three days or less to treat severe nasal congestion. Similarly, the AAAAI Joint Task Force Practice Parameters (2020) recommends short-term and intermittent use of intranasal decongestants for up to five days for severe mucosal edema that impairs the delivery of other agents[47]. Additionally, the US FDA specifies that OTC products containing oxymetazoline should include a warning against usage exceeding three days[24]. Collectively, these guidelines do not discourage short-term treatment with intranasal decongestants as indicated by product labeling and acknowledge these as viable treatment options for as-intended use.

Other international guidelines also support short-term use of intranasal decongestants, with some allowing longer periods of use than US guidelines. The BSACI 2017 guideline for the diagnosis and management of rhinitis suggests using intranasal decongestants for less than ten days in adults and three days in children[7]. Meanwhile, the Japanese Society of Allergology 2010 guideline for allergic rhinitis states that they can be used two to three times daily for one to two weeks for moderate to severe allergic rhinitis, alongside a second-generation antihistamine and INCS[48].

Suggestions for the Treatment and Mitigation of Rebound Congestion:

There is currently a lack of good evidence to support a treatment algorithm for RC following prolonged intranasal decongestant use, as deduced by a systematic review of the literature[9]. However, several options have been proposed, including treatment discontinuation, nasal saline, and, for more severe cases, using INCS, short-course systemic steroids and/or surgical interventions[3, 9, 11, 12]. Ferguson et al. showed that in patients with perennial allergic rhinitis, adding intranasal budesonide after the second week of oxymetazoline therapy resulted in faster resolution of rebound nasal congestion compared to placebo (48 hours with budesonide vs one week with placebo)[37]. Vaidyanathan et al. reported that RC after a 14-day treatment with oxymetazoline was reversed by intranasal fluticasone treatment in healthy adults[36]. In a nasal reactivity study, 20 patients with RC were randomized to placebo or intranasal fluticasone and underwent a nasal histamine challenge. Compared with placebo, treatment with fluticasone resulted in increased histamine sensitivity, suggesting that the mechanism of nasal congestion in RC is related to mucosal edema, which is alleviated by INCS[49]. However, there is still a paucity of clinical evidence to establish a uniform treatment algorithm.

The AAAAI Practice Parameters state that the risk of RC can be mitigated by co-administration with INCS[47]. A combination therapy of INCS and intranasal decongestants is recommended for up to four weeks to treat persistent nasal congestion that is unresponsive to INCS[47]. The BSACI guideline further supports the use of INCS together with intranasal decongestant, but only for short-term use[7]. Thongngarm et al. showed that using oxymetazoline (two sprays per nostril, twice-daily) with budesonide and cetirizine significantly reduced nasal congestion and improved quality-of-life compared with placebo, without evidence of RC[39]. Baroody et al. found that fluticasone furoate combined with oxymetazoline is more effective than either alone, also without RC[5]. Similarly, Meltzer et al. showed that combining mometasone furoate with oxymetazoline relieves seasonal allergic rhinitis[44].

Discussion:

In the majority of published prospective clinical studies that investigated short-term, as-directed use of oxymetazoline, RC was not reported as an associated outcome[31-34]. In the study by Graf and Juto (1994) as well, which investigated the long-term effects of oxymetazoline, no signs of RC were reported after daily treatment for 10 days, although some signs were reported after 30 days of daily treatment[43]. The study reported no other signs of RC assessed through other measures, and the authors concluded that seven days of oxymetazoline treatment was not associated with tolerance or RC.

Some clinical studies investigating oxymetazoline use beyond the recommended duration have reported an association between oxymetazoline use and the development of RC [15, 16, 36, 37, 41, 42]. However, these studies either had small sample sizes, lacked a placebo control arm, and/or involved healthy subjects without rhinitis. The use of healthy subjects instead of subjects with persistent nasal blockage also limits the extent to which these findings can be extrapolated to the primary users of oxymetazoline due to the potential differences in nasal mucosal structures caused by inflammation[13, 34]. Furthermore, in contrast to studies investigating short-term use of oxymetazoline, results of studies investigating the association between longer-term use of oxymetazoline and RC have been conflicting.

Conclusion:

In conclusion, this review supports that short-term use of intranasal decongestants (≤10 days) does not lead to RC. International guidelines also recommend them for short-term treatment of the common cold and allergic rhinitis while noting the paucity of high-quality evidence regarding the duration of use. Future studies are needed to optimize dosing frequency and use in combination with INCS to minimize RC risk and manage chronic nasal congestion. Given their effectiveness in quickly relieving nasal blockage and improving quality-of-life, relevant stakeholders, including general practitioners and pharmacists, should feel confident in prescribing intranasal decongestants such as oxymetazoline, which act rapidly and lasts up to 12 hours. However, it is important to educate patients on the importance of short-term use of these treatments as approved by various regulatory agencies and refer those with persistent symptoms to specialists for further evaluation.

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Maliha Malik, Leena Pasupuleti, and Charlene Ng have declared that they are either current employees or contractors of Bayer Consumer Health. Leena Pasupuleti was employed by Bayer

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Abbreviations

AAAAI	American Academy of Allergy, Asthma, and Immunology
AAFP	American Academy of Family Physicians
AAO-HNS	American Academy of Otolaryngology–Head and Neck Surgery
BAC	Benzalkonium chloride
BSACI FDA FF	British Society for Allergy & Clinical Immunology Food and Drug Administration Fluticasone Furoate
HCl	Hydrochloride
INCS	Intranasal corticosteroid
JTF JSA	Joint Task Force Japanese Society of Allergology
NAR	Nasal airway resistance
OTC	Over-the-counter
RC	Rebound congestion
RCT US	Randomized controlled trial United States
VAS	Visual analog scale

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