Efficacy and safety of mometasone furoate nasal spray in allergic rhinitis, acute rhinosinusitis and nasal polyposis

Seasonal and perennial allergic rhinitis, acute rhinosinusitis and nasal polyposis are common inflammatory conditions of the airway that markedly impair patient health and quality of life. Treatment guidelines for each of these conditions recommend intranasal corticosteroids, which help to alleviate symptoms by reducing inflammation. One of the most extensively studied intranasal corticosteroids for these conditions is mometasone furoate nasal spray (MFNS). In more than 20 clinical trials, MFNS has been shown to reduce both objective and subjective signs of inflammation and promotes rapid resolution of nasal, sinus and ocular symptoms in adults, adolescents and children. MFNS is well-tolerated and local adverse events are generally mild and self-limiting, usually resolving without discontinuation of therapy. The low systemic bioavailability (<0.1%) and high first-pass metabolism of MFNS also reduce its risk for systemic adverse events.

KEYWORDS: allergic rhinitis ■ congestion ■ intranasal corticosteroids ■ mometasone furoate ■ nasal allergies ■ nasal polyposis ■ rhinosinusitis

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Seasonal and perennial allergic rhinitis, acute rhinosinusitis and nasal polyposis are inflammatory conditions of the nose and/or sinuses that produce bothersome symptoms and markedly affect patients' quality of life [1–3]. These diseases frequently coexist, suggesting that each may be a manifestation of an inflammatory process within the continuous airway [3–5]. Clinical treatment guidelines for each of these conditions conclude that research evidence supports treatment with an intranasal corticosteroid [5–9].

One of the most extensively investigated intranasal corticosteroids for inflammatory diseases of the nose and sinuses is mometasone furoate nasal spray (MFNS). Mometasone furoate is a potent 17-heterocyclic corticosteroid formulated in an aqueous suspension for intranasal use with a metered-dose, manual pump nasal spray (Figure 1) [10]. *In vitro* testing has shown that mometasone furoate has a high binding affinity for the glucocorticoid receptor and is a potent stimulator of glucocorticoid receptor-mediated gene expression [11]. Owing to its anti-inflammatory properties, MFNS has been proven to be effective for the prophylaxis and treatment of seasonal allergic rhinitis [12–16], the treatment of perennial allergic rhinitis [17–19], as an adjunct to antibiotics in the treatment of acute bacterial rhinosinusitis [20,21] or as monotherapy in uncomplicated cases of acute rhinosinusitis [22,23], and the treatment of nasal polyposis [24–27].

The purpose of this review is to summarize the efficacy and safety of MFNS for seasonal and perennial allergic rhinitis, acute rhinosinusitis and nasal polyposis.

Allergic rhinitis

Allergic rhinitis affects approximately 13% of the American population and 17–29% of the European population, with the prevalence varying widely in different regions [5,28,29,201]. It is the most prevalent chronic allergic disease among children [202], affecting approximately 40% by the age of 6 years [30]. Allergic rhinitis is generally classified as either seasonal or perennial [5,8,9], and, as per the Allergic Rhinitis and its Impact on Asthma guidelines, it is now further subdivided into intermittent or persistent disease [5,9]. Seasonal allergic rhinitis is an IgE-mediated response to outdoor seasonal allergens such as molds or pollen [5,10]. Perennial allergic rhinitis comprises a number of conditions that result from either continuous or intermittent exposure to allergens, most commonly indoor allergens such as dust mites, molds, insects (cockroaches) and animal dander [5,9]. Both seasonal and perennial allergic rhinitis are characterized by extensive infiltration of the nasal mucosa by inflammatory cells, such as eosinophils and basophils, as well as the release of inflammatory mediators such as histamine, prostaglandins and leukotrienes from mast cells [31].

Patients with allergic rhinitis typically report nasal itching, sneezing, rhinorrhea, postnasal drainage and nasal congestion [2]. Ocular symptoms which may also be present include itching, burning, tearing and redness of the sclera and

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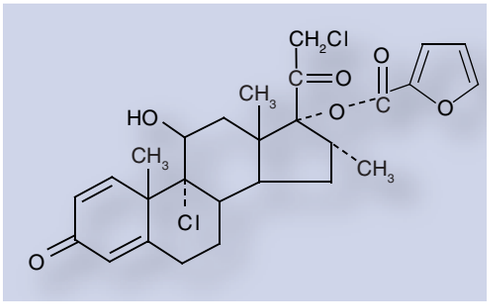

Figure 1. Mometasone furoate.

ocular mucosa [9,12]. Although allergic rhinitis is often considered a minor condition [32,33], it can substantially impair the ability of patients to function at work [34], in social situations [7–37,201,202] or at school [38,39]. These patients also have a lower quality of life and a greater degree of depression than those without allergic rhinitis [37–40]. The losses in workplace productivity attributed to the disease in the USA, where most of the available data have been collected, are estimated to be between US$2.4 and US$4.6 billion annually [41]; in addition, direct and indirect expenditures associated with the treatment of allergic rhinitis in the USA are approximately US$1.5 billion and US$2 billion, respectively, per year [40]. Costs of treating allergic rhinitis are also reported to be high in other countries [42].

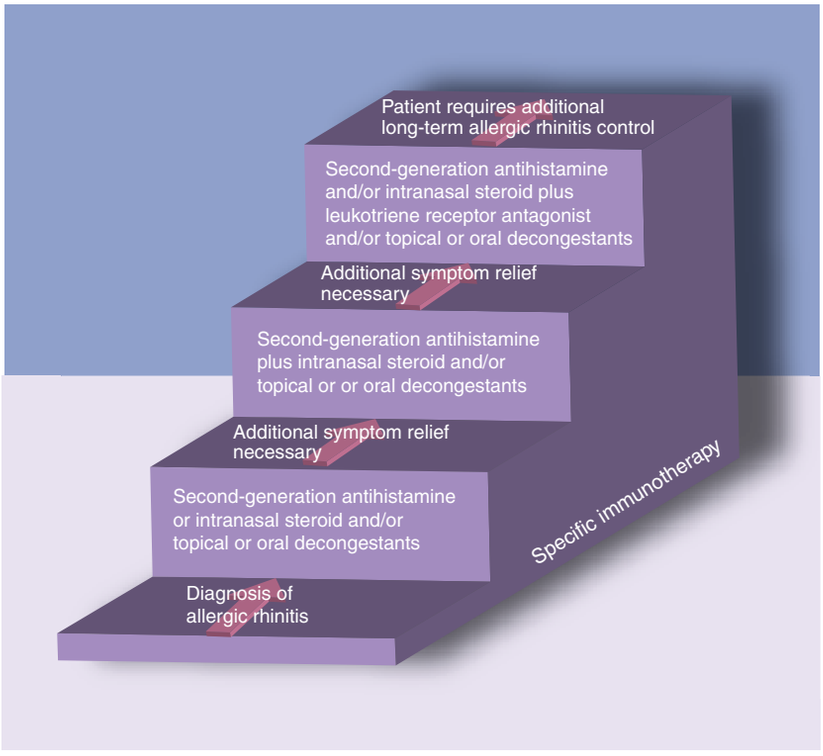

Figure 2. Stepwise approach to treatment for allergic rhinitis.
Adapted with permission from [33].

Treatment of allergic rhinitis

Since intranasal corticosteroids are considered to be the most effective medications available for the treatment of allergic rhinitis, as stated in the guidelines, they are recommended as first-line therapy, especially in patients with moderate-to-severe, persistent symptoms and impaired quality of life; nasal congestion and/or blockage; or continuing symptoms despite treatment with histamine H1-receptor antagonists (FIGURE 2) [9,33,202].

Mometasone furoate nasal spray is one of the most intensively studied intranasal corticosteroids for allergic rhinitis. More than 20 clinical trials involving more than 6000 adults, adolescents and children have assessed its efficacy and safety [12–15,17,43–50]. Ten of these were randomized, double-blind, placebo-controlled trials evaluating the use of MFNS to treat the nasal symptoms of seasonal and perennial allergic rhinitis (TABLE 1) [12–19,51,52].

Seasonal allergic rhinitis

To evaluate the clinical efficacy and optimum therapeutic dose of MFNS, Bronsky *et al.* conducted a multicenter, double-blind, dose-ranging study involving 480 adults (≥18 years) with moderate seasonal allergic rhinitis [13]. Subjects were randomly assigned to treatment with one of four daily doses of MFNS (50, 100, 200 or 800 µg) or placebo for 28 days. Treatment efficacy was determined using a seven-point scale to assess severity of nasal (discharge, rhinorrhea, stuffiness/congestion, sneezing or itching) and non-nasal (eye itching, tearing, and redness and itching of ears or palate) symptoms. Within 3 days of treatment, subjects in the 50, 200 and 800 µg daily MFNS groups reported a significant ($p < 0.05$) reduction of symptoms. By day 7, all four doses were found to be significantly more effective than placebo ($p \leq 0.05$). Since the two lower doses provided less consistent relief, the investigators concluded that 200 µg daily was the appropriate MFNS dose for alleviating the symptoms of seasonal allergic rhinitis.

A series of additional trials extended these findings across a broad range of subjects. In the double-blind, randomized, placebo-controlled trial of 121 adolescents (≥12 years) and adults carried out by Meltzer *et al.*, MFNS 200 µg daily was associated with a significant reduction in mean total morning nasal symptom scores (congestion, rhinorrhea, itching and sneezing) compared with placebo ($p = 0.02$) after 1 week [16]. At week 2, significant improvement was noted in the active treatment group ($p = 0.029$). In

Table 1. Summary of clinical studies of mometasone furoate nasal spray for the treatment of nasal symptoms associated with SAR and PAR.

Author/year	Subjects (n)	Age (years)	Treatment (duration)	Effect on symptoms	Ref.
SAR studies					
Hebert *et al.* (1996)	501	≥18	MFNS 100 µg q.d. MFNS 200 µg q.d. BDP 200 µg b.i.d. Placebo 4 weeks	MFNS (both doses) and BDP more effective than placebo ($p \leq 0.01$)	[15]
Graft *et al.* (1996)	349	≥12	MFNS 200 µg q.d. BDP 168 µg b.i.d. Placebo 8 weeks	MFNS and BDP initiated 4 weeks before ragweed season decreased minimal symptom days versus placebo ($p < 0.01$)	[14]
Bronsky *et al.* (1997)	480	18–65	MFNS 50 µg q.d. MFNS 100 µg q.d. MFNS 200 µg q.d. MFNS 800 µg q.d. Placebo 28 days	MFNS 200 µg q.d. and 800 µg q.d. consistently more effective than placebo ($p < 0.05$)	[13]
Meltzer *et al.* (1998)	121	≥12	MFNS 200 µg q.d. placebo 2 weeks	MFNS improved total nasal symptom score versus placebo ($p = 0.024$)	[16]
Meltzer *et al.* (1999)	679	6–11	MFNS 25 µg q.d. MFNS 100 µg q.d. MFNS 200 µg q.d. BDP 84 µg b.i.d. Placebo 4 weeks	MFNS 100 µg q.d. ($p = 0.03$) and 200 µg q.d. ($p = 0.04$) and BDP 84 µg q.d. ($p < 0.01$) more effective than placebo	[51]
Berkowitz *et al.* (1999)	239	12–60	MFNS 200 µg q.d. Placebo 1 day	MFNS improved total nasal symptom score in 7 h versus placebo ($p < 0.01$)	[12]
Gawchick *et al.* (2003)	245	≥12	MFNS 200 µg q.d. Placebo 14 days	MFNS improved total nasal symptom score versus placebo ($p \leq 0.017$)	[52]
PAR studies					
Drouin *et al.* (1996)	427	≥12	MFNS 200 µg q.d. BDP 200 µg b.i.d. Placebo 12 weeks	MFNS and BDP improved total nasal symptom score versus placebo ($p \leq 0.01$)	[17]
Mandl *et al.* (1997)	474	≥12	MFNS 200 µg q.d. FP 200 µg q.d. Placebo 12 weeks	MFNS and FP improved total nasal symptom score versus placebo ($p < 0.01$)	[18]
Bende *et al.* (2002)	438	≥18	MFNS 200 µg q.d. BDP 128 µg q.d. BDP 256 µg q.d. Placebo 4 weeks	MFNS and BDP improved total nasal symptom score versus placebo ($p < 0.002$)	[19]

BDP: Beclomethasone dipropionate nasal spray; b.i.d.: Twice daily; FP: Fluticasone propionate nasal spray; MFNS: Mometasone furoate nasal spray; PAR: Perennial allergic rhinitis; q.d.: Daily; SAR: Seasonal allergic rhinitis.

addition, MFNS was associated with a significant improvement in nasal cytology, including a reduction in the numbers of eosinophils, basophils and neutrophils.

Meltzer *et al.* also confirmed that, when given in appropriate dosages, MFNS can alleviate the symptoms of seasonal allergic rhinitis in children as young as 6 years old [51]. This multicenter, double-blind, placebo-controlled, dose-ranging study enrolled 679 children between 6 and 11 years of age who received MFNS in doses of 25, 100 or 200 µg daily or beclomethasone dipropionate (BDP) nasal spray 84 µg twice-daily for up to 4 weeks. According to physician

evaluation of total nasal symptom scores at day 8, all three dosages of MFNS and the twice-daily dosage of BDP nasal spray afforded significantly greater relief than placebo ($p \leq 0.02$). At 4 weeks, both the 100 µg ($p = 0.03$) and 200 µg ($p = 0.04$) daily doses of MFNS were significantly more effective than the 25 µg daily dose. However, MFNS 200 µg daily provided no significant advantage over the 100 µg daily dose, leading the investigators to conclude that MFNS 100 µg daily is the most appropriate therapeutic regimen for children with seasonal allergic rhinitis [51].

The efficacy of MFNS in the prophylaxis of seasonal allergic rhinitis was established by Graft's study of 349 subjects, 12 years or older with a moderate-to-severe allergy to ragweed pollen [14]. Four weeks before the predicted start of ragweed season, subjects were randomly assigned to receive MFNS 200 µg daily, BDP nasal spray 168 µg twice-daily, or placebo for 8 weeks. Subjects receiving MFNS reported a significantly higher proportion of minimal symptom days compared with placebo ($p < 0.01$). The MFNS group had a median duration of 27 days before experiencing a non-minimal symptom day (defined as a day when the total nasal symptom score was ≥3 on a 12-point scale), compared with a median duration of 10.5 days in the placebo group [14].

Two additional retrospective analyses of data pooled from four randomized, double-blind studies comparing MFNS 200 µg daily (n = 494) with placebo (n = 497) confirmed the efficacy of MFNS in reducing the ocular symptoms of redness, tearing and itching commonly associated with seasonal allergic rhinitis [53,54]. During a 2-week study period, MFNS significantly reduced total ocular and individual symptom scores compared with placebo ($p < 0.05$) [53]. Subjects with moderate-to-severe symptoms experienced a significantly greater reduction in total ocular symptoms than those taking placebo ($p < 0.05$).

The mechanism of action of intranasal corticosteroids in relieving ocular allergy symptoms is not well understood. It has recently been shown that a nasal–ocular reflex follows nasal challenge with antigen and probably contributes to the ocular symptoms associated with allergic rhinitis. In addition to reducing inflammation, intranasal corticosteroids may reduce ocular allergy symptoms by attenuating this reflex mechanism [55].

Perennial allergic rhinitis

Three multicenter, randomized, double-blind, placebo-controlled trials confirmed that MFNS significantly alleviates the symptoms of perennial allergic rhinitis [17–19]. In the first study, Drouin followed 427 subjects of 12 years or older with a documented allergy to at least one perennial allergen for 12 weeks [17]. At 15 days, those receiving MFNS 200 µg daily and BDP nasal spray 200 µg twice-daily experienced significantly ($p < 0.01$) greater improvement in total nasal symptoms (congestion, rhinorrhea, sneezing and itching) than the placebo group, which persisted throughout the study period [17].

Two additional studies concluded that MFNS 200 µg daily significantly reduces the nasal symptoms of perennial allergic rhinitis (congestion, rhinorrhea, sneezing and itching), increases the number of symptom-free days, and improves nasal patency as measured by peak nasal inspiratory flow [18,19]. Mandl *et al.* found significant and equivalent efficacy with MFNS 200 µg once-daily and fluticasone propionate nasal spray (FPNS) 200 µg once-daily ($p < 0.01$ for both) in reducing the total nasal symptom score in both the morning and evening [18]. In the study by Bende *et al.*, significant improvement in nasal symptoms occurred within 4 h of the first MFNS 200 µg dose ($p = 0.014$) [19]. At 10 days, peak nasal inspiratory flow improved significantly in the MFNS group compared with the placebo group ($p < 0.01$), although BDP nasal spray 256 µg daily had a greater improvement than MFNS in this study compared with placebo.

Sensory perceptions of intranasal corticosteroids & compliance in allergic rhinitis

Despite the discomfort and impairment associated with allergic rhinitis, only 20% of patients are compliant with treatment [56]. One factor contributing to the high rate of noncompliance may be sensory perception [57,58], since patients prefer agents that do not have any taste or scent [58]. In a multicenter, randomized, double-blind, crossover study, 100 subjects with allergic rhinitis were randomized to an alcohol- and scent-free formulation of MFNS, 200 µg daily, followed by 200 µg daily of FPNS 30 min later, or vice versa [56]. Significantly more subjects preferred MFNS to FPNS ($p < 0.05$), and fewer subjects reported scent or odor (immediately and 2 min after drug administration; $p < 0.001$), taste (immediately after drug administration; $p = 0.002$), and aftertaste (2 min after drug administration; $p = 0.007$) with MFNS than with FPNS. In addition, 47% reported that they would be more likely to comply with a MFNS regimen than with a FPNS regimen ($p = 0.03$) [56].

Acute rhinosinusitis

Rhinosinusitis is an inflammatory process that involves the mucosa of the nose and one or more sinuses [3,8]. It is classified as acute (symptom duration <4 weeks), subacute (symptom duration 4–8 weeks), chronic (symptom duration >8 weeks), or recurrent (≥3 episodes of acute sinusitis per year) [3,8,59,60]. The European position paper on rhinosinusitis and nasal polyps also classifies acute rhinosinusitis as mild, moderate or severe, based on the total severity visual analogue scale score [3].

The etiology of rhinosinusitis may be viral, bacterial or allergic [4,8]. Acute rhinosinusitis is usually caused by a viral infection that, in some cases, may be complicated by a secondary bacterial infection [4,8,61,62]. Symptoms of acute rhinosinusitis resolve without the use of antibiotics in most patients [59,63]. One study reports that only 38% of adults presenting with symptoms of acute rhinosinusitis may actually have bacterial rhinosinusitis [63]. Perennial allergic rhinitis may also be a predisposing factor to acute rhinosinusitis, since allergic rhinitis contributes to rhinosinusitis in up to 30% of patients with acute maxillary rhinosinusitis and up to 80% of patients with chronic rhinosinusitis [4]. American and European guidelines for the diagnosis and treatment of acute rhinosinusitis provide algorithms to improve treatment outcomes (**Figures 3 & 4**) [3,8,9,62,64].

The main clinical characteristics of acute rhinosinusitis include nasal congestion, facial pain and/or pressure, rhinorrhea, postnasal drainage, headache and cough. The four signs and symptoms most predictive of acute bacterial rhinosinusitis include purulent nasal discharge, maxillary tooth or facial pain (especially unilateral), unilateral maxillary tenderness and worsening of symptoms after initial improvement [3,62,65]. Computed tomography is currently the preferred radiographic modality to confirm acute rhinosinusitis [8].

Annual crude prevalence rates of acute rhinosinusitis in the USA range from 14 to 16% of adults [203]. Definitive prevalence rates are lacking owing to inconsistencies in the definition of acute rhinosinusitis, and because not all patients with the disease seek professional care [61]. Still, the economic burden of this disease is high; total annual costs related to acute rhinosinusitis as either a primary or secondary diagnosis were estimated to be US$5.93 billion in one American study [66].

Treatment of acute rhinosinusitis

The rationale for the use of intranasal corticosteroids in acute rhinosinusitis resides in their anti-inflammatory properties. By reducing inflammation, intranasal corticosteroids foster drainage and increased aeration of the sinuses [3,5,6,8]. The use of intranasal corticosteroids as adjuncts to antibiotic therapy for acute bacterial rhinosinusitis is considered appropriate for patients who do not respond to initial treatment, have concomitant nasal polyposis, or are experiencing marked mucosal edema [3,8,64]. Treatment of acute bacterial rhinosinusitis with antibiotics and intranasal corticosteroids also hastens clearance of bacteria, decreases the frequency and severity of disease recurrence [6] and reduces the duration of infection [43,67,68].

Many recent studies support the benefits of intranasal corticosteroids as adjuncts to antimicrobial therapy in acute bacterial rhinosinusitis, and three randomized, multicenter, placebo-controlled studies have demonstrated that MFNS alleviates the course of acute bacterial rhinosinusitis (**Table 2**) [20–23]. In one study, Meltzer *et al.* compared a 21-day regimen of amoxicillin/clavulanate with or without MFNS in 407 subjects, 12 years or older with acute rhinosinusitis confirmed by CT scan of the paranasal sinuses [20]. The addition of MFNS to the antibiotic significantly ($p < 0.01$) reduced mean total symptom scores and individual symptom scores, including congestion and facial pain, during days 1–15 ($p \leq 0.01$), and headache ($p < 0.01$), congestion ($p < 0.01$) and purulent rhinorrhea ($p \leq 0.05$) during days 16–21.

In a similar study by Nayak *et al.* in 2002, 967 subjects 12 years or older with moderate-to-severe acute rhinosinusitis confirmed by CT scan received amoxicillin/clavulanate for 21 days with MFNS 200 µg twice-daily, MFNS 400 µg twice-daily, or placebo [21]. Addition of either the 200 µg ($p = 0.014$) or 400 µg ($p = 0.017$) regimen of MFNS produced a significantly greater improvement in the total symptom score than placebo. MFNS also reduced nasal stuffiness/congestion (200 µg, $p = 0.01$; 400 µg, $p = 0.025$), facial pain (200 µg, p = nonsignificant [NS]; 400 µg, $p = 0.008$), postnasal drip (200 µg, $p = 0.038$; 400 µg, p = NS), and rhinorrhea (200 µg, p = NS; 400 µg, $p = 0.045$).

Since intranasal corticosteroids are an effective adjunctive therapy for acute bacterial rhinosinusitis, they may have potential as monotherapy for acute uncomplicated rhinosinusitis [69]. A third study, by Meltzer *et al.* in 2005, investigated the use of MFNS as monotherapy in 981 subjects 12 years or older with acute uncomplicated rhinosinusitis lasting for 7 days or more but 28 days or less; those with acute bacterial

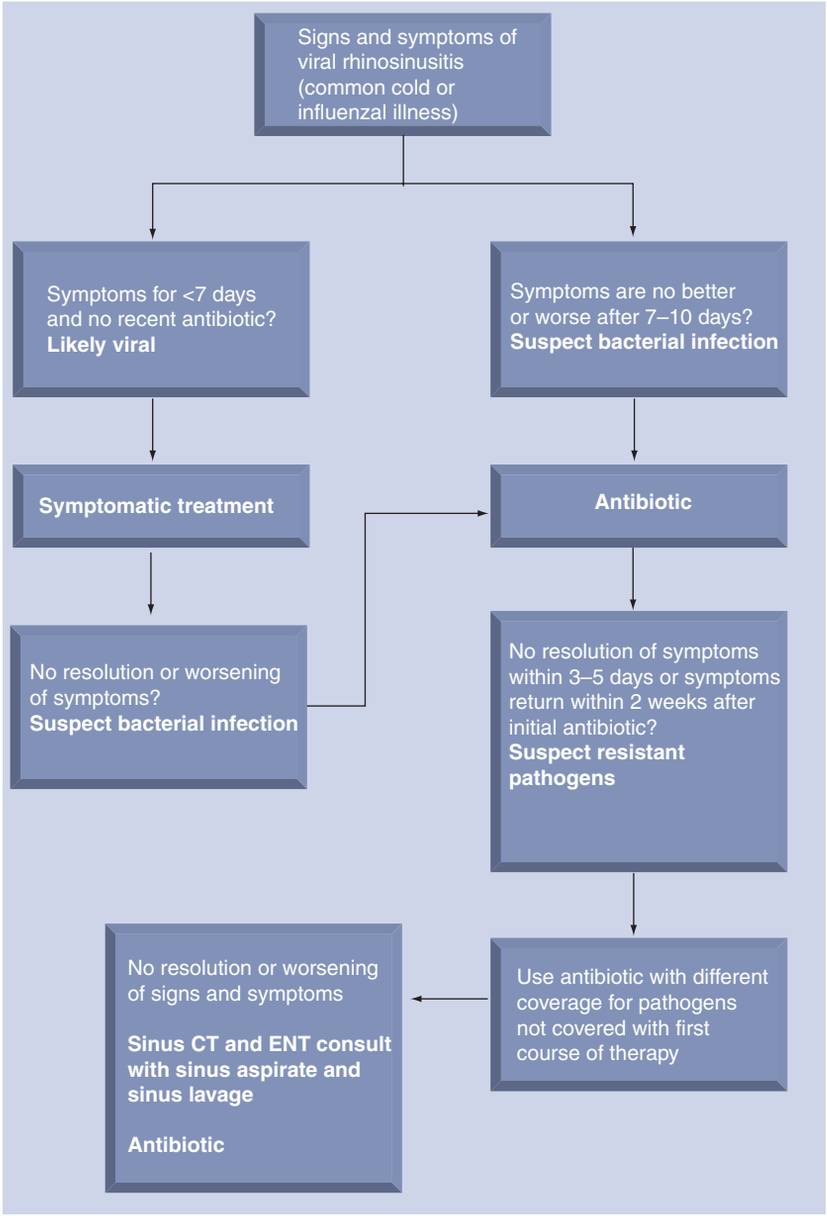

Figure 3. Algorithm for differentiating viral and bacterial acute rhinosinusitis.
CT: Computed tomography; ENT: Ear, nose and throat.
Adapted with permission from [62].

rhinosinusitis were excluded [23]. This study compared MFNS 200 µg once- or twice-daily for 15 days with amoxicillin alone or placebo alone. MFNS 200 µg twice-daily was superior to both placebo alone ($p < 0.001$) and amoxicillin monotherapy ($p = 0.002$) in improving symptom scores. In another study, MFNS monotherapy was also shown to provide a significantly greater improvement in patients' health-related quality of life [22].

Fokkens *et al.*, on behalf of the European Academy of Allergology and Clinical Immunology, recommends that adults with mild symptoms of acute rhinosinusitis lasting less than 5 days receive treatment, such as analgesics or decongestants, aimed at symptomatic relief, while patients with moderate symptoms persisting or increasing in severity after 5 days should receive intranasal corticosteroids [3]. In patients with severe acute rhinosinusitis, antibiotic therapy and intranasal corticosteroids are recommended (FIGURE 4) [3]. Current American treatment guidelines are similar [8]. Infection with resistant pathogens should be considered in severe cases if symptoms do not improve after 3–5 days of antibiotic treatment [8,62,69].

Nasal polyposis

Nasal polyposis is estimated to affect approximately 2.7–4% of the population [3,9,70]. Its prevalence increases to 7–15% in patients with asthma and to 36–96% in patients with aspirin sensitivity [3]. Symptoms include nasal obstruction, congestion, purulent nasal discharge and postnasal drip [71]. More than 75% of patients also have an impaired sense of smell [72]. These symptoms have a marked impact on quality of life, interfering with physical, social and normal daily activities. The symptoms can also cause sleep disorders and headaches, as well as impair patients' moods and their psychological well-being [73].

Nasal polyposis is characterized by an eosinophil-dominated inflammation of unknown cause and is often associated with asthma, aspirin sensitivity or cystic fibrosis [9,71]. One possible mechanism for the development of nasal polyposis involves bacterial colonization of the nasal cavity, causing the synthesis and release of enterotoxins that act as superantigens to stimulate the local immune system [74]. A hallmark of bilateral nasal polyposis, which is observed in approximately 90% of adults with the condition, is a mixed cellular infiltrate with predominant eosinophilia [75]. Increased levels of inflammatory mediators, such as interleukin-5 [76], eotaxin [77] and eosinophilic cationic protein [78] are also present.

Treatment of nasal polyposis

Treatment objectives for nasal polyposis include reducing or eliminating polyps, opening the nasal airway, improving or restoring sense of smell and preventing recurrence. Surgical removal of polyps, with or without medical therapy, for more severe cases and medical therapy for mild-to-moderate cases are the usual treatment regimens [79]. Although endoscopic surgery has been shown to be effective for reducing polyp size and temporarily improving nasal blockage [80–82], one randomized, controlled study in 2001 reported

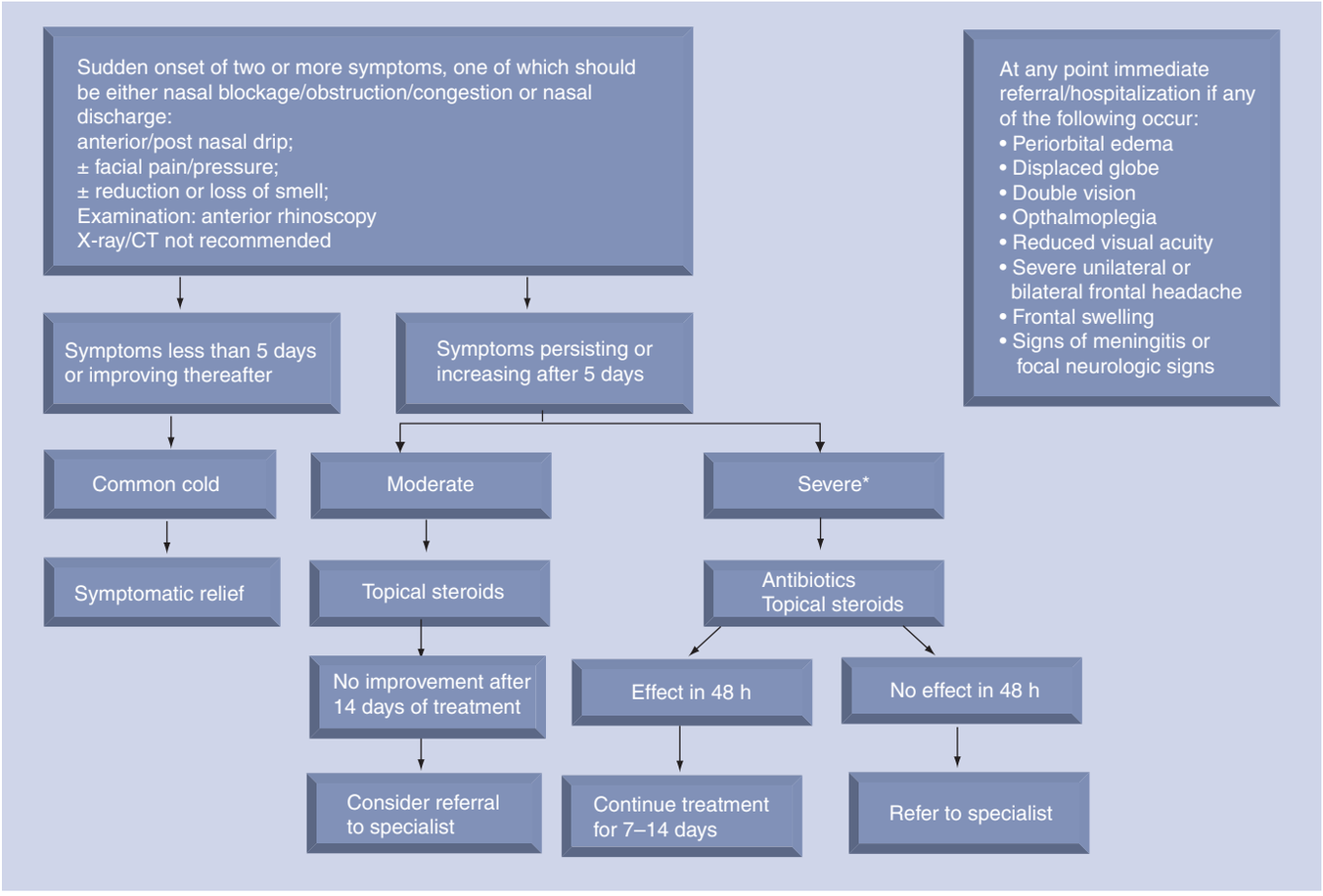

Figure 4. Treatment scheme for primary care for adults with acute rhinosinusitis.
*Fever of greater than 38°C and/or severe pain.
Adapted with permission from [3].

that medical treatment alone with oral or topical corticosteroids appeared to be sufficient to treat most of the symptoms of nasal polyposis [81]. Another study by Benitez and colleagues found that subjects with severe nasal polyposis had a significant improvement in their symptoms with a short course of oral corticosteroids followed by intranasal corticosteroids [83]. In addition, the postsurgical recurrence rate for nasal polyposis after 2 years is reported to be as high as 60% in some studies [84–86]. At this time, the benefits of surgery over medical therapy have not been established [81,82].

Treatment with intranasal corticosteroids reduces the eosinophil-associated inflammation of polyposis, thereby helping to control symptoms and reduce polyp size [9,24–25,81,87]. Fokkens *et al.* and the European Academy of Allergology and Clinical Immunology, as well as other authors, concluded that intranasal corticosteroids are generally effective for improving symptoms and decreasing polyp size, although little improvement in sense of smell was reported [3,88–90].

Mometasone furoate nasal spray is the first intranasal corticosteroid to be approved by the USA FDA for the medical treatment of nasal polyposis [24]. Results of the first large-scale clinical studies of MFNS for nasal polyposis were published in 2005 and 2006. Three 4-month, multicenter, randomized, placebo-controlled clinical trials enrolled 354, 310 and 298 patients, respectively [24–26], to evaluate the efficacy and safety of 200 µg daily and 200 µg twice-daily dosing of MFNS. The twice-daily regimen of MFNS was chosen to help overcome the possible obstruction of drug distribution by polyps. In all three studies, subjects receiving either dosage of MFNS experienced significantly greater improvement than those receiving placebo in the reduction of the size and extent of endoscopically verified bilateral nasal polyps, as well as in congestion/obstruction, loss of sense of smell, anterior rhinorrhea and postnasal drip (FIGURE 5) [24–26]. A statistically significant improvement with both doses of MFNS was observed within the first month of treatment and continued

Table 2. Summary of clinical studies of MFNS for the treatment of acute rhinosinusitis.

Author/year	Subjects (n)	Age (years)	Treatment (duration)	Effect on symptoms	Ref.
Meltzer *et al.* (2000)	407	≥12	ACP 875 mg b.i.d. + MFNS 400 µg b.i.d. or placebo 21 days	ACP + MFNS significantly better than ACP + placebo ($p \leq 0.01$)	[20]
Nayak *et al.* (2002)	967	≥12	ACP 875 mg b.i.d. + MFNS 200 µg b.i.d. or MFNS 400 µg b.i.d. or placebo 21 days	ACP + MFNS (both doses) significantly better than ACP + placebo ($p \leq 0.017$)	[21]
Meltzer *et al.* (2005)	981	≥12	Amoxicillin 500 mg t.i.d. 10 days or MFNS 200 µg q.d. 15 days or MFNS 200 µg b.i.d. 15 days or placebo	MFNS 200 µg b.i.d. significantly better than placebo ($p < 0.001$) or amoxicillin ($p = 0.002$); MFNS 200 µg q.d. significantly better than placebo ($p = 0.018$)	[23]

ACP: Amoxicillin/clavulanate potassium; b.i.d.: Twice daily; MFNS: Mometasone furoate nasal spray; q.d.: Daily; t.i.d.: Three-times daily.

up to the study end points at 4 months [24–26]. The twice-daily dosing regimen of MFNS was superior to the once-daily dosing formulation for improving the symptoms of congestion and obstruction ($p = 0.039$) [24–26].

In one study, the overall change in bilateral polyp grade score with MFNS represented a clinically significant reduction of approximately 30% relative to baseline [24]. Since reducing polyp size is thought to be a slow process, this degree of improvement in 4 months is noteworthy. Incremental improvements in polyp grade continued throughout the course of the study, suggesting that treatment with MFNS should be maintained to achieve a full response. Response to MFNS did not vary with the size of the polyps. In addition, 57% of patients receiving MFNS 200 µg twice-daily were considered to be improved based on its effect on polyp grade and congestion/obstruction score, compared with 43% of patients receiving MFNS 200 µg daily and 34% of patients receiving placebo [24].

The significant improvement in loss of sense of smell associated with MFNS contrasts with previous studies regarding endoscopic surgery or other intranasal corticosteroids, in which sense of smell did not improve [84,91–94]. Comparisons between medical and surgical treatment indicate that surgery has very little effect on hyposmia or anosmia [81], supporting the importance of medical therapy in treating this symptom [24].

For many patients, loss of sense of smell is one of the most disturbing symptoms of nasal polyposis [95], and its return is therefore an important therapeutic goal. However, change in sense of smell may be more subjective than other symptoms, which may account for the observed placebo effect in many studies [27]. Importantly, the improvement in sense of smell seen with MFNS therapy corresponds to the increased improvement in polyp grade scores over time [24,26,27].

A recent analysis of the onset of symptomatic effect of MFNS 200 µg twice-daily revealed a rapid improvement in most symptoms of nasal polyposis from within 24 h after the first dose to within 5 days of initiating therapy [27]. Subjects receiving this dose of MFNS experienced statistically significant ($p < 0.05$) improvement compared with placebo at day 2 for anterior rhinorrhea, day 3 for nasal congestion, day 5 for postnasal drip and day 13 for sense of smell. Peak nasal inspiratory flow also improved significantly at day 2 ($p = 0.031$) [27]. The rapid onset of action of MFNS in nasal polyposis may be due to the high topical potency of the drug in inhibiting the synthesis and release of

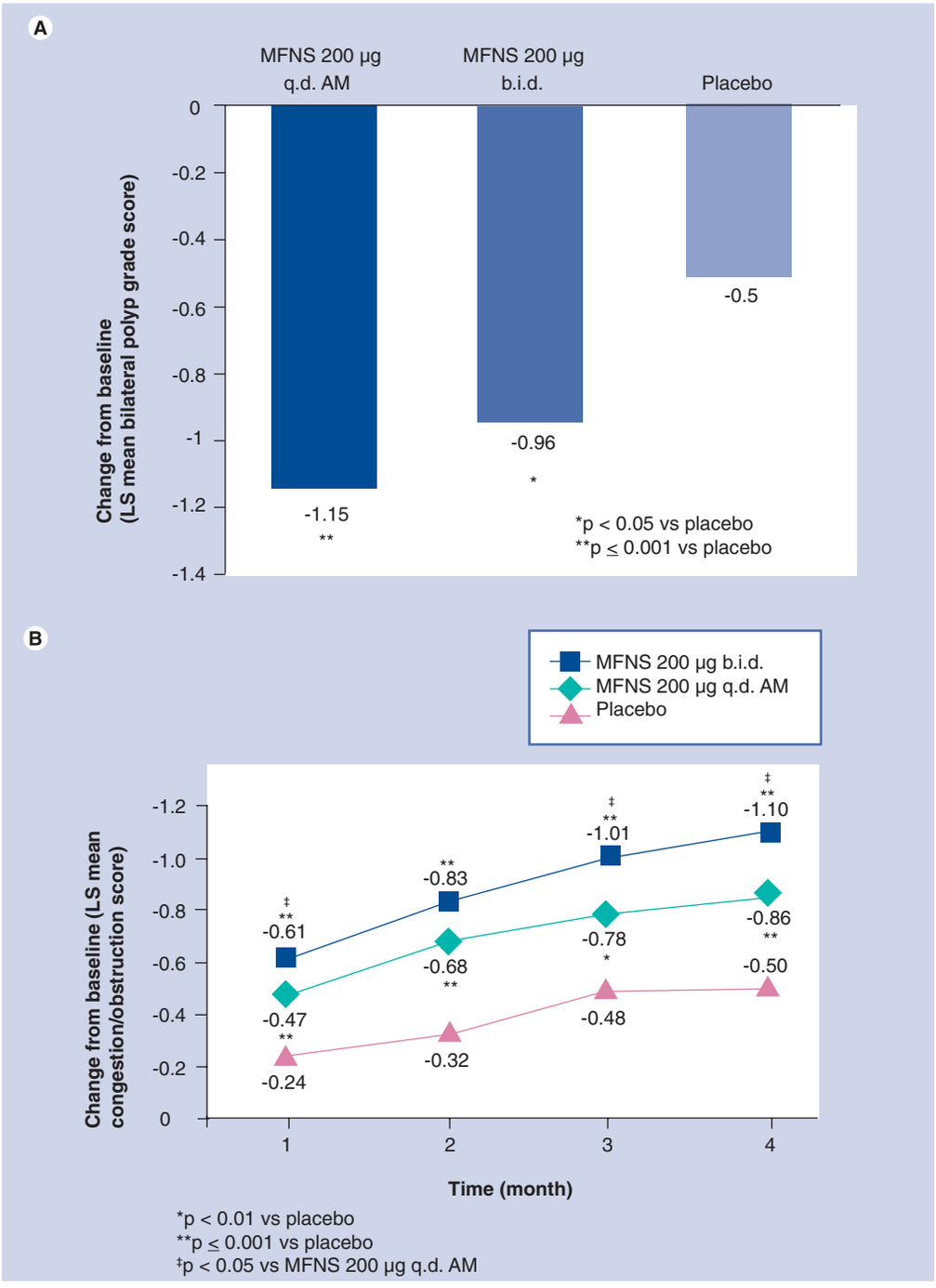

Figure 5. Change from baseline in bilateral polyp grade score (A) and congestion/obstruction score (B) following 4 weeks of treatment with MFNS.
b.i.d.: Twice daily; LS: Least squares; MFNS: Mometasone furoate nasal spray; q.d.: Once daily.
Adapted with permission from [24].

proinflammatory cytokines such as IL-1, IL-5, IL-6 and TNF [13,27,96]. Similar to the previous studies, the treatment effect of MFNS for all symptoms persisted for at least 4 months [24,26,27] and increased with the duration of therapy [27]. This improvement in symptom scores corresponds to the increased improvement in polyp grade scores over time.

A pronounced placebo effect occurred in this study, particularly for the end points of nasal congestion/obstruction and sense of smell, and increased over time [27]. Such an effect, observed in many studies of nasal polyposis [24,26,27], may be attributable to the inactive components of MFNS. Thus, the use of placebo groups remains important for future trials of nasal polyposis [26,27].

Table 3. Bioavailability of intranasal corticosteroids.

Intranasal corticosteroid	Bioavailability (%)
Flunisolide	49
Beclomethasone dipropionate	44
Budesonide	34
Fluticasone propionate	0.42
Mometasone furoate	0.46
Fluticasone furoate	0.50

Data taken from [100,102,103,105].

Mometasone furoate may thus offer patients with nasal polyposis a therapeutic option that can reduce or delay the need for surgery by effectively relieving the symptoms of this disease [24]. Once-daily dosing of MFNS appears to be as effective as twice-daily dosing across this population as a whole, except for nasal congestion and obstruction. Individual subject response should determine the optimal dosing regimen [24]. Further studies are necessary to determine the lasting effect of MFNS on the continued resolution of nasal symptoms associated with nasal polyposis, since maximal reduction in polyp size may take several months to achieve [24,27,89].

Safety of MFNS

Local adverse events

In clinical studies involving both adults and children, the incidence of adverse events is generally similar in patients receiving MFNS in doses ranging from 50 to 800 µg daily, and is comparable to those receiving placebo. Local adverse events in patients from all age groups are mild in intensity and self-limiting, and resolve without discontinuation of therapy [12–19,51,52,97]. The most common local adverse events include epistaxis (ranging from blood-tinged mucus to bleeding) and headache [12–15,17–19,51,52,98]. A multicenter, open-label, 12-month study of changes in nasal histopathology reported that MFNS did not lead to changes in epithelial thickness or focal metaplasia, suggesting that long-term treatment is not associated with nasal atrophy [99].

Systemic safety

The possible routes of systemic exposure with intranasal corticosteroids include absorption of the locally deposited dose through the nasal mucosa or absorption of a potentially swallowed dose through the gastrointestinal tract [100]. Some clinicians are reluctant to prescribe intranasal corticosteroids, particularly for pediatric patients, owing to concerns regarding possible systemic effects, including impairment of the normal response to stress, growth retardation due to suppressed cortisol levels, formation of cataracts and osteoporosis [101,102]. However, use of intranasal corticosteroids has not been associated with serious side effects.

One indication of an agent's potential for systemic adverse events is its bioavailability, which depends partly on its absorption across the highly vascular nasal mucosa [103]. The degree of systemic absorption depends on its lipophilicity. Thus, intranasal corticosteroids with lower systemic bioavailability, such as MFNS, fluticasone furoate and fluticasone propionate, are highly lipophilic, whereas those with higher bioavailability, such as flunisolide, beclomethasone dipropionate and budesonide, are less lipophilic [103,104]. Systemic bioavailability is also partly determined by the degree of first-pass hepatic metabolism, which is generally favorable with intranasal corticosteroids [101]. When used at recommended doses, MFNS has a systemic concentration of less than 0.5%, which is equal to or lower than that reported for other intranasal corticosteroids (**Table 3**) [100,102–105].

Studies of the systemic safety of MFNS reveal no effect on hypothalamic–pituitary–adrenal (HPA)-axis function in adults, as assessed by the measurement of cortisol levels. In a placebo-controlled, randomized, parallel-group study of 24 adult volunteers, eight received MFNS, administered at single doses of 1, 2 and 4 mg; none experienced clinical symptoms of HPA-axis suppression [48]. Effects on the plasma cortical concentration curve, urinary free cortisol, and 8 am plasma cortisol were similar to placebo at all doses of MFNS. These findings reveal that even when given in doses up to 20-times the projected clinical dose, MFNS does not affect cortisol secretion. In another study involving 27 adults with perennial allergic rhinitis, randomized to MFNS 200 µg daily or triamcinolone acetonide 220 µg daily for 3 weeks, there were no differences between the two drugs in values obtained at baseline and at 3 weeks in systemic bioactivity markers, including plasma and urine cortisol levels [106]. In a third study of MFNS in nasal polyposis, no significant differences in 24-h urinary free cortisol were found over the treatment period among the MFNS 200 µg twice-daily, MFNS 200 µg daily or placebo groups [24].

Suppressed cortisol levels impair the normal response to stress and can retard growth rate in children [107]. However, studies of MFNS in children have not demonstrated that it produces any relevant absorption. In a randomized, evaluator-masked, placebo-controlled study of 96 children

aged 3–12 years with allergic rhinitis, MFNS doses of up to 200 µg daily for as many as 14 days were well-tolerated and did not result in clinically relevant exposure [48]. In addition, no significant differences were observed between mean plasma cortisol and 24-h urinary free cortisol concentrations between children receiving MFNS or placebo. Other studies with MFNS in children as young as 3 years did not report any signs of suppression of HPA-axis function [51,107]. For example, a 52-week study of 98 children aged between 3 and 9 years with perennial allergic rhinitis who were randomized to MFNS 100 µg daily or placebo found that children in the MFNS group had no suppression of growth compared with those in the placebo group [108].

Conclusion

Extensive clinical evidence has confirmed that MFNS is a highly effective treatment for common inflammatory disorders of the upper respiratory tract. Multiple clinical studies have consistently revealed that MFNS rapidly alleviates the symptoms of seasonal allergic rhinitis, perennial allergic rhinitis and nasal polyposis. MFNS is also important in the treatment of acute rhinosinusitis, as monotherapy in uncomplicated cases, or as an adjunct to antibiotics in documented cases of acute bacterial rhinosinusitis.

The safety profile of MFNS is well-established. Local adverse events tend to be mild-to-moderate and resolve without discontinuation of treatment. No systemic adverse events have been reported in adults or children. In summary, extensive clinical testing has demonstrated that MFNS is a safe and effective therapeutic option for the prophylaxis and treatment of seasonal allergic rhinitis and the treatment of perennial allergic rhinitis, acute rhinosinusitis and nasal polyposis.

Future perspective

Current clinical investigations with MFNS are providing substantial evidence regarding its efficacy in reducing the ocular symptoms of allergic rhinitis. Numerous clinical studies have found that MFNS is not associated with ocular-related adverse events, such as the development of glaucoma or subcapsular cataracts. They also indicate that MFNS could be a primary treatment for both the nasal and ocular symptoms of allergic rhinitis, possibly eliminating the need for patients to use separate medications for the two symptoms. In addition, MFNS has demonstrated an improved quality of life in patients with allergic rhinitis by increasing their quality of sleep and workplace productivity.

Mometasone furoate nasal spray has been recommended as an adjunct to antibiotics for

Executive summary

- Mometasone furoate is a potent 17-heterocyclic corticosteroid formulated in an aqueous suspension for intranasal application with a metered-dose, manual pump nasal spray.
- Mometasone furoate nasal spray (MFNS) is safe and effective for the treatment and prophylaxis of seasonal allergic rhinitis and the treatment of perennial allergic rhinitis, nasal polyposis, and as an adjunct to antibiotics for acute bacterial rhinosinusitis, as well as monotherapy for acute uncomplicated rhinosinusitis.

Allergic rhinitis

- When administered to patients with seasonal or perennial allergic rhinitis, MFNS reduces nasal congestion, rhinorrhea, nasal itching, sneezing and postnasal drainage, as well as the ocular symptoms of itching, redness and tearing.

Acute rhinosinusitis

- The rationale for using intranasal corticosteroids in acute rhinosinusitis resides in their anti-inflammatory properties.
- The administration of MFNS together with an antibiotic significantly reduces the symptoms of acute bacterial rhinosinusitis, including purulent rhinorrhea, nasal congestion, postnasal drip, headache, facial pain and cough.
- MFNS has been found to be an effective monotherapy in cases of uncomplicated acute rhinosinusitis that are usually secondary to a viral infection; its use could decrease the overuse of antibiotics in this disease.

Nasal polyposis

- Nasal polyps are benign growths that develop in the nose and sinuses, causing obstruction and interfering with breathing. They often lead to impairment or loss of sense of smell.
- MFNS has been shown to reduce nasal polyp size, but a longer duration of therapy than that used for acute rhinosinusitis may be required.
- MFNS 200 µg twice-daily significantly improves nasal congestion/obstruction, rhinorrhea, postnasal drip and sense of smell in nasal polyposis.
- It has a rapid onset and provides lasting relief of most of the major symptoms of nasal polyposis within 2–5 days of initiating therapy.
- Local adverse events associated with MFNS in patients from all age groups are mild in intensity, self-limiting and usually resolve without discontinuation of therapy.

acute bacterial rhinosinusitis. By using MFNS in acute rhinosinusitis, inappropriate antibiotic use will be decreased, leading to lower costs and, most importantly, reduced bacterial resistance to antibiotics. MFNS has also been shown to reduce nasal polyp size and improve the troubling associated symptoms of nasal congestion/obstruction and loss of sense of smell. It has a rapid onset of action and provides lasting relief, thereby reducing or delaying the need for nasal polyp surgery. Future studies are needed to determine if MFNS prophylaxis is necessary to prevent the recurrence of nasal polyposis.

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Bibliography

1 Benninger MS: The development of the rhinosinusitis disability index. *Arch. Otolaryngol. Head Neck Surg.* 123, 1175–1179 (1997).

2 Dykewicz MS, Fineman S: Diagnosis and management of rhinitis: complete guidelines of the Joint Task Force on Practice Parameters in Allergy, Asthma, and Immunology. *Ann. Allergy Asthma Immunol.* 81, 478–518 (1998).

3 Fokkens W, Lund V, Mullol J: European position paper on rhinosinusitis and nasal polyps 2007. *Rhinology* (Suppl. 20), 1–136 (2007).

4 Meltzer EO, Hamilos DL, Hadley JA *et al.*: Rhinosinusitis: establishing definitions for clinical research and patient care. *J. Allergy Clin. Immunol.* 114, S155–S212 (2004).

5 Bousquet J, Khaltaev N, Cruz AA *et al.*: Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA²LEN and AllerGen). *Allergy* 63(Suppl. 86), 8–160 (2008).

6 Barlan IB, Erkan E, Bakir M *et al.*: Intranasal budesonide spray as an adjunct to oral antibiotic therapy for acute sinusitis in children. *Ann. Allergy Asthma Immunol.* 78, 598–601 (1997).

7 Meltzer EO, Orgel HA, Backhaus JW *et al.*: Intranasal flunisolide spray as an adjunct to oral antibiotic therapy for sinusitis. *J. Allergy Clin. Immunol.* 92, 812–823 (1993).

8 Slavin RG, Spector SL, Bernstein IL *et al.*: The diagnosis and management of sinusitis: a practice parameter update. *J. Allergy Clin. Immunol.* 116, S13–S47 (2005).

9 Wallace DV, Dykewicz MS, Bernstein DI, *et al.*: The diagnosis and management of rhinitis: an updated practice parameter. *J. Allergy Clin. Immunol.* 122 (suppl), S1–S84 (2008).

10 Onrust SV: Mometasone furoate: a review of its intranasal use in allergic rhinitis. *Drugs* 56, 725–745 (1998).

11 Smith CL, Kreutner W: *In vitro* glucocorticoid receptor binding and transcriptional activation by topically active glucocorticoids. *Arzneimittelforschung* 48, 956–960 (1998).

12 Berkowitz RB, Roberson S, Zora J *et al.*: Mometasone furoate nasal spray is rapidly effective in the treatment of seasonal allergic rhinitis in an outdoor (park), acute exposure setting. *Allergy Asthma Proc.* 20, 167–172 (1999).

13 Bronsky EA, Aaronson DW, Berkowitz RB *et al.:* Dose ranging study of mometasone furoate (Nasonex) in seasonal allergic rhinitis. *Ann. Allergy Asthma Immunol.* 79, 51–56 (1997).

14 Graft D, Aaronson D, Chervinsky P *et al.*: A placebo- and active-controlled randomized trial of prophylactic treatment of seasonal allergic rhinitis with mometasone furoate aqueous nasal spray. *J. Allergy Clin. Immunol.* 98, 724–731 (1996).

15 Hebert JR, Nolop K, Lutsky BN: Once-daily mometasone furoate aqueous nasal spray (Nasonex) in seasonal allergic rhinitis: an active- and placebo-controlled study. *Allergy* 51, 569–676 (1996).

16 Meltzer EO, Jalowayski AA, Orgel HA *et al.*: Subjective and objective assessments in patients with seasonal allergic rhinitis: effects of therapy with mometasone furoate nasal spray. *J. Allergy Clin. Immunol.* 102, 39–49 (1998).

17 Drouin M, Yang WH, Bertrand B *et al.*: Once daily mometasone furoate aqueous nasal spray is as effective as twice daily beclomethasone dipropionate for treating perennial allergic rhinitis patients. *Ann. Allergy Asthma Immunol.* 77, 153–160 (1996).

18 Mandl M, Nolop K, Lutsky BN: Comparison of once daily mometasone furoate (Nasonex) and fluticasone propionate aqueous nasal sprays for the treatment of perennial rhinitis. *Ann. Allergy Asthma Immunol.* 79, 370–378 (1997).

19 Bende M, Carrillo T, Vóna I *et al.*: A randomized comparison of the effects of budesonide and mometasone furoate aqueous nasal sprays on nasal peak flow rate and symptoms in perennial allergic rhinitis. *Ann. Allergy Asthma Immunol.* 88, 617–623 (2002).

20 Meltzer EO, Charous BL, Busse WW *et al.*: Added relief in the treatment of acute recurrent sinusitis with adjunctive mometasone furoate nasal spray. *J. Allergy Clin. Immunol.* 106, 630–637 (2000).

21 Nayak AS, Settipane GA, Pedinoff A *et al.*: Effective dose range of mometasone furoate nasal spray in the treatment of acute rhinosinusitis. *Ann. Allergy Asthma Immunol.* 89, 271–278 (2002).

22 Bachert C, Meltzer EO: Effect of mometasone furoate nasal spray on quality of life in patients with acute rhinosinusitis. *Rhinology* 45, 190–196 (2007).

23 Meltzer EO, Bachert C, Staudinger H: Treating acute rhinosinusitis: comparing efficacy and safety of mometasone furoate nasal spray, amoxicillin, and placebo. *J. Allergy Clin. Immunol* 116, 1289–1295 (2005).

24 Small CB, Hernandez J, Reyes A *et al.*: Efficacy and safety of mometasone furoate nasal spray in nasal polyposis. *J. Allergy Clin. Immunol.* 116, 1275–1281 (2005).

25 Stjärne P, Blomgren K, Cayé-Thomasen P *et al.*: The efficacy and safety of once-daily mometasone furoate nasal spray in nasal polyposis: a randomized, double-blind, placebo-controlled study. *Acta Oto-Laryngologica* 126, 606–612 (2006).

26 Stjärne P, Mosges R, Jorissen M *et al.*: A randomized controlled trial of mometasone furoate nasal spray for the treatment of nasal polyposis. *Arch. Otolaryngol. Head Neck Surg.* 132, 179–185 (2006).

27 Small CB, Stryszak P, Danzig M, Damiano A: Onset of symptomatic effect of mometasone furoate nasal spray in the treatment of nasal polyposis. *J. Allergy Clin. Immunol.* 121, 928–932 (2008).

28 Dahl R, Andersen PS, Chivato T *et al.*: National prevalence of respiratory allergic disorders. *Respir. Med.* 98, 398–403 (2004).

29 Bauchau V, Durham SR: Prevalence and rate of diagnosis of allergic rhinitis in Europe. *Eur. Respir. J.* 24, 758–764 (2004).

30 Wright AL, Holberg CJ, Martinez FD *et al.*: Epidemiology of physician-diagnosed allergic rhinitis in childhood. *Pediatrics* 94, 895–901 (1994).

31 Howarth PH: Mediators of nasal blockage. *Allergy* 52(Suppl. 40), 12–18 (1997).

32 Fireman P: Treatment of allergic rhinitis: effect on occupation productivity and work force costs. *Allergy Asthma Proc.* 18, 63–67 (1997).

33 Prenner BM, Schenkel E: Allergic rhinitis: treatment based on patient profiles. *Am. J. Med.* 119, 230–237 (2006).

34 Cockburn IM, Bailit HL, Berndt ER, Rinkelstein SN: Loss of work productivity due to illness and medical treatment. *J. Occup. Environ. Med.* 41, 948–953 (1999).

35 Bousquet J, Bullinger M, Fayol C, Marquis P, Valentin B, Burtin B: Assessment of quality of life in patients with perennial allergic rhinitis with the French version of the SF-36 Health Status Questionnaire. *J. Allergy Clin. Immunol.* 94, 182–188 (1994).

36 Spaeth J, Klimek L, Mosges R: Sedation in allergic rhinitis is caused by the condition and not by antihistamine treatment. *Allergy* 51, 893–906 (1996).

37 Kremer B, Den Hartog HM, Jolles J: Relationship between allergic rhinitis, disturbed cognitive functions and psychological well-being. *Clin. Exp. Allergy* 32, 1310–1315 (2002).

38 Simons FE: Learning impairment and allergic rhinitis. *Allergy Asthma Proc.* 17, 185–189 (1996).

39 Vuurman EF, van-Veggel LM, Uiterwijk MM, Leutner D, O'Hanlon JF: Seasonal allergic rhinitis and antihistamine effects on children's learning. *Ann. Allergy* 71, 121–126 (1993).

40 Fineman SM: The burden of allergic rhinitis: beyond dollars and cents. *Ann. Allergy Asthma Immunol.* 88, 2–7 (2002).

41 Crystal-Peters J, Crown WH, Goetzel RZ *et al.*: The cost of productivity losses associated with allergic rhinitis. *Am. J. Manag. Care.* 6, 373–378 (2000).

42 Bousquet J, Demarteau N, Mullol J: Costs associated with persistent allergic rhinitis are reduced by levocetirizine. *Allergy* 60, 788–794 (2005).

43 Barton BE: Cytokine inhibition by a novel steroid, mometasone furoate. *Immunopharm. Immunotox.* 13, 251–261 (1991).

44 Umland SP, Narhebne DK, Razac BS *et al.*: Effects of mometasone furoate and other glucocorticoids on cytokine production from cultured peripheral blood $CD4^+$ T cells. *J. Allergy Clin. Immunol.* 97, 288 (1996) (Abstract).

45 Therattil J, Chavarria V, Cosachov J *et al.*: The effect of mometasone furoate on early and late phase inflammation in patients with seasonal allergic rhinitis (SAR). *Ann. Allergy Asthma Immunol.* 78, 129 (1997) (Abstract).

46 Mazzari P, Nolop K, Lutsky BN *et al.*: Prophylactic use of once-daily mometasone furoate (Nasonex) aqueous nasal spray in patients with seasonal allergic rhinitis. *J. Allergy Clin. Immunol.* 99(Pt 2), S440 (1997).

47 Nasonex, package insert. Schering-Plough Inc, Kenilworth, NJ, USA (2005).

48 Brannan MD: Lack of systemic activity with intranasal mometasone furoate. *J. Allergy Clin. Immunol.* 198, 62 (1996) (Abstract).

49 Brannan MD: Safety and tolerability of once-daily mometasone furoate aqueous nasal spray in children. *Clin. Ther.* 19, 1330–1339 (1997).

50 O'Brien F, Minshall E, Nolop K *et al.*: Histological and immunocytochemical assessment by nasal biopsy of mometasone furoate nasal spray in perennial rhinitis. *J. Allergy Clin. Immunol.* 99(Pt 2), S498 (1997).

51 Meltzer EO, Berger WE, Berkowitz RB *et al.*: A dose-ranging study of mometasone furoate aqueous nasal spray in children with seasonal allergic rhinitis. *J. Allergy Clin. Immunol.* 104, 107–114 (1999).

52 Gawchik S, Goldstein S, Prenner B *et al.*: Relief of cough and nasal symptoms associated with allergic rhinitis by mometasone furoate nasal spray. *Ann. Allergy Asthma Immunol.* 90, 416–421 (2003).

53 Schenkel E, LaForce C, Gates D: Mometasone furoate nasal spray in seasonal allergic rhinitis effective in relieving ocular symptoms. *Allergy Clin. Immunol. Int.* 19, 50–53 (2007).

54 Bielory L: Ocular symptom reduction in patients with seasonal allergic rhinitis treated with the intranasal corticosteroid mometasone furoate. *Ann. Allergy Asthma Immunol.* 100, 272–279 (2008).

55 Naclerio RM, Pinto J, deTineo M, Baroody FM: Elucidating the mechanisms underlying the ocular symptoms associated with allergic rhinitis. *Allergy Asthma Proc.* 29, 24–28 (2008).

56 Meltzer EO, Bardelas J, Goldsobel A *et al.*: A preference evaluation study comparing the sensory attributes of mometasone furoate and fluticasone propionate nasal sprays by patients with allergic rhinitis. *Treat. Respir. Med.* 4, 289–296 (2005).

57 Bachert C, El-Akkad T: Patient preferences and sensory comparisons of three intranasal corticosteroids for the treatment of allergic rhinitis. *Ann. Allergy Asthma Immunol.* 89, 292–297 (2002).

58 Stokes M, Amorosi SL, Thompson D *et al.*: Evaluation of patients' preferences for triamcinolone acetonide aqueous, fluticasone propionate, and mometasone furoate nasal sprays in patients with allergic rhinitis. *Otolaryngol. Head Neck Surg.* 131, 225–231 (2004).

59 Hickner JM, Bartlett JG, Besser RE *et al.*: Principles of appropriate antibiotic use for acute rhinosinusitis in adults: background. *Ann. Intern. Med.* 134, 498–505 (2001).

60 International Rhinosinusitis Advisory Board: Infectious rhinosinusitis in adults: classification, etiology and management. *Ear Nose Throat J.* 76(Suppl. 12), 1–22 (1997).

61 Poole MD: Acute bacterial rhinosinusitis: clinical impact of resistance and susceptibility. *Am. J. Med.* 117(Suppl.), 29S–38S (2004).

62 Sande MA, Gwaltney JM: Acute community-acquired bacterial sinusitis: continuing challenges and current management. *Clin. Infect. Dis.* 39(Suppl. 3), S151–S158 (2004).

63 Lau J, Zucker D, Engels EA *et al.*: Diagnosis and treatment of acute bacterial rhinosinusitis. *Evid. Rep. Technol. Assess. (Summ.)* 9, 1–5 (1999).

64 Sinus and Allergy Health Partnership: Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. *Otolaryngol. Head Neck Surg.* 130(Suppl. 1), 1–45 (2004).

65 Gonzales R, Bartlett JG, Besser RE *et al.*: Principles of appropriate antibiotic use for treatment of acute respiratory tract infections in adults: background, specific aims and methods. *Ann. Intern. Med.* 134, 479–486 (2001).

66 Ray NF, Baraniuk JN, Thamer M *et al.*: Healthcare expenditures for sinusitis in 1996: contributions of asthma, rhinitis, and other airway disorders. *J. Allergy Clin. Immunol.* 103, 408–414 (1999).

67 Yilmaz G, Baran B, Yilmaz T *et al.*: Intranasal budesonide spray as an adjunct to oral antibiotic therapy for acute sinusitis in children. *Eur. Arch. Otorhinolaryngol.* 257, 256–259 (2000).

68 Qvarnberg Y Kantola O, Salo J *et al.*: Influence of topical steroid treatment on maxillary sinusitis. *Rhinology* 30, 103–112 (1992).

69 Small CB: Judicious antibiotic use and intranasal corticosteroids in acute rhinosinusitis. *Am. J. Med.* 120, 289–294 (2007).

70 Hedman J, Kaprio J, Poussa T *et al.*: Prevalence of asthma, aspirin intolerance, nasal polyposis and chronic obstructive pulmonary disease in a population-based study. *Int. J. Epidemiol.* 28, 717–722 (1999).

71 Bachert C, Hörmann K, Mösges R *et al.*: An update on the diagnosis and treatment of sinusitis and nasal polyposis. *Allergy* 58, 176–191 (2003).

72 Delank KW, Stoll W: Sense of smell before and after endonasal surgery in chronic sinusitis with polyps. *HNO* 42, 619–623 (1994).

73 Radenne F, Lamblin C, Vandezande L-M *et al.*: Quality of life in nasal polyposis. *J. Allergy Clin. Immunol.* 103, 79–84 (1999).

74 Bachert C, van Zele T, Gevaert P *et al.*: Superantigens and nasal polyps. *Curr. Allergy Asthma Rep.* 3, 523–531 (2003).

75 Simon HU, Yousefi S, Schranz C, Schapowal A, Bachert C, Blaser K: Direct demonstration of delayed eosinophil apoptosis as a mechanism causing tissue eosinophilia. *J. Immunol.* 158, 3902–3908 (1997).

76 Bachert C, Wagenmann M, Hauser U, Rudack C: IL-5 synthesis is upregulated in human nasal polyp tissue. *J. Allergy Clin. Immunol.* 99, 837–842 (1997).

77 Garcia-Zepeda EA, Rothenberg ME, Ownbey RT, Celestin J, Leder P, Luster AD: Human eotaxin is a specific chemoattractant for eosinophil cells and provides a new mechanism to explain tissue eosinophilia. *Nat. Med.* 2, 449–456 (1996).

78 Ebisawa M, Liu MC, Yamada T *et al.*: Eosinophil transendothelial migration induced by cytokines. II. Potentiation of eosinophil transendothelial migration by eosinophil-active cytokines. *J. Immunol.* 152, 4590–4596 (1994).

79 Blaiss MS: Expanding the evidence base for medical treatment of nasal polyposis. *J. Allergy Clin. Immunol.* 116, 1272–1274 (2005).

80 Lund VJ, MacKay IS: Outcome assessment of endoscopic sinus surgery. *J. R. Soc. Med.* 87, 70–72 (1994).

81 Blomqvist E, Lundblad L, Anggard A *et al.*: A randomized controlled study evaluating medical treatment versus surgical treatment in addition to medical treatment of nasal polyposis. *J. Allergy Clin. Immunol.* 107, 224–228 (2001).

82 Alobid I, Benítez P, Bernal-Sprekelsen M *et al.*: Nasal polyposis and its impact on quality of life: comparison between the effects of medical and surgical treatments. *Allergy* 60, 452–458 (2005).

83 Benitez P, Alobid I, de Haro J *et al.*: A short course of oral prednisone followed by intranasal budesonide is an effective treatment of severe nasal polyps. *Laryngoscope* 116, 770–775 (2006).

84 Albu S, Tomescu E, Mexca Z *et al.*: Recurrence rates in endonasal surgery for polyposis. *Acta Otorhinolaryngol. Belg.* 58, 79–86 (2004).

85 Jiang RS, Hsu CY: Revision functional endoscopic sinus surgery. *Ann. Otol. Rhinol. Laryngol.* 111, 155–159 (2002).

86 Wynn R, Har-El G: Recurrence rates after endoscopic sinus surgery for massive sinus polyposis. *Laryngoscope* 114, 811–813 (2004).

87 Mygind N, Lildholdt T: Medical management. In: *Nasal polyps: Epidemiology, Pathogenesis and Treatment.* Settipane GA, Lund V (Eds). Oceanside Publications, Inc., Providence, RI, USA (1997).

88 Ruhno J, Andersson B, Denburg J *et al.*: A double-blind comparison of intranasal budesonide with placebo for nasal polyposis. *J. Allergy Clin. Immunol.* 86, 946–953 (1990).

89 Holmberg K, Juliusson S, Balder B *et al.*: Fluticasone propionate aqueous nasal spray in the treatment of nasal polyposis. *Ann. Allergy Asthma Immunol.* 78, 270–276 (1997).

90 Lund V, Flood J, Sykes A *et al.*: Effect of fluticasone in severe polyposis. *Arch. Otolaryngol. Head Neck Surg.* 124, 513–518 (1998).

91 Vendelbo-Johansen L, Illum P, Kristensen S, Winther L, Petersen SV, Synnerstad B: The effect of budesonide (Rhinocort®) in the treatment of small and medium-sized nasal polyps. *Clin. Otolaryngol.* 18, 524–527 (1993).

92 Lildholdt T, Rundcrantz H, Lindqvist N: Efficacy of topical corticosteroid powder for nasal polyps: a double-blind, placebo-controlled study of budesonide. *Clin. Otolaryngol. Allied Sci.* 20, 26–30 (1995).

93 Keith P, Nieminen J, Hollingworth K, Dolovich J: Efficacy and tolerability of fluticasone propionate nasal drops 400 microgram once daily compared with placebo for the treatment of bilateral polyposis in adults. *Clin. Exp. Allergy* 30, 1460–1468 (2000).

94 Penttilä M, Poulsen P, Hollingworth K, Holmström M: Dose-related efficacy and tolerability of fluticasone propionate nasal drops 400 microg once daily and twice daily in the treatment of bilateral nasal polyposis: a placebo-controlled randomized study in adult patients. *Clin. Exp. Allergy* 30, 94–102 (2000).

95 Badia L, Lund V: Topical corticosteroids in nasal polyposis. *Drugs* 61, 573–578 (2001).

96 Adcock IM, Stevens DA, Barnes PJ: Interactions of glucocorticoids and β_2-agonists. *Eur. Respir. J.* 9, 160–168 (1996).

97 Lundblad L, Sipilä P, Farstad T *et al.*: Mometasone furoate nasal spray in the treatment of perennial nonallergic rhinitis: a Nordic, multicenter, randomized, double-blind, placebo-controlled study. *Acta Otolaryngol.* 121, 505–509 (2001).

98 Dibildox J: Safety and efficacy of mometasone furoate aqueous nasal spray in children with allergic rhinitis: results of recent clinical trials. *J. Allergy Clin. Immunol.* 108(suppl. 1), S54–S58 (2001).

99 Minshall E, Ghaffar O, Cameron L *et al.*: Assessment by nasal biopsy of long-term use of mometasone furoate aqueous nasal spray (Nasonex) in the treatment of perennial rhinitis. *Otolaryngol. Head Neck Surg.* 118, 648–654 (1998).

100 Schenkel E: Features of mometasone furoate nasal spray and its utility in the management of allergic rhinitis. *Expert Opin. Pharmacother.* 4, 1579–1591 (2003).

101 Allen DB: Systemic effects of intranasal steroids: an endocrinologist's perspective. *J. Allergy Clin. Immunol.* 106(Suppl. 4), S179–S190 (2000).

102 Benninger MS, Ahmad N, Marple BF: The safety of intranasal steroids. *Otolaryngol. Head Neck Surg.* 129, 739–750 (2003).

103 Allen A, Down G, Newland A *et al.*: Absolute bioavailability of intranasal fluticasone furoate in healthy subjects. *Clin. Ther.* 29, 1415–1420 (2007).

104 Corren J: Intranasal corticosteroids for allergic rhinitis: how do different agents compare? *J. Allergy Clin. Immunol.* 104, S144–S149 (1999).

105 Daley-Yates PT, Kunka RL, Yin Y *et al.*: Bioavailability of fluticasone propionate and mometasone furoate aqueous nasal sprays. *Eur. J. Clin. Pharmacol.* 60, 265–268 (2004).

106 Lee DKC, Robb FM, Sims EJ *et al.*: Systemic bioactivity of intranasal triamcinolone and mometasone in perennial allergic rhinitis. *Br. J. Clin. Pharmacol.* 55, 310–313 (2003).

107 Zitt M, Kosoglou T, Hubbell J: Mometasone furoate nasal spray. A review of safety and systemic effects. *Drug Saf.* 30, 317–326 (2007).

108 Schenkel EJ: Absence of growth retardation in children with perennial allergic rhinitis after one year of treatment with mometasone furoate aqueous nasal spray. *Pediatrics* 105, E22 (2000).

Websites

201 American Academy of Allergy, Asthma and immunology: the allergy report. II: diseases of the atopic diathesis (Accessed March 2008). www.aaaai.org/ar/volume2.pdf

202 Management of allergic and nonallergic rhinitis. Summary, evidence report/ technology assessment: number 54, May 2002. USA Department of Health and Human Services, Agency for Healthcare Research and Quality (Accessed February 2009). www.ahrq.gov/clinic/epcsums/rhinsum.htm.

203 National Center for Health Statistics: Health, USA, 2005, with chartbook trends in the health of Americans (Accessed March 2008). www.cdc.gov/nchs/data/hus/hus05.pdf