Pharmacy Benefits Management Strategic Healthcare Group
Medical Advisory Panel
Drug Class Review: Intranasal Corticosteroids

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Objectives

To review the efficacy, safety, and administration of currently available intranasal corticosteroids for the management of allergic rhinitis (AR).

Table 1: Currently Available Intranasal Corticosteroids

Generic Name	Beclomethasone	Budesonide	Flunisolide	Fluticasone	Mometasone	Triamcinolone
Brand Name	Vancenase* Vancenase AQ* Beconase** Beconase AQ**	Rhinocort Rhinocort Aqua	Nasalide Nasarel	Flonase	Nasonex	■Nasacort ■Nasacort AQ □Tri-Nasal Spray
Manufacturer	Schering-Plough* GlaxoWellcome**	Astra	Dura	GlaxoWellcome	Schering-Plough	Rhone-Poulenc Rorer Muro

*Manufactured by Schering-Plough **Manufactured by GlaxoWellcome, ■ Manufactured by Rhone-Poulenc Rorer, □ Manufactured by Muro Pharmaceuticals.

I. Introduction

Allergic rhinitis (AR) is a condition that affects up to 40 million Americans and is the sixth most prevalent chronic disease in the Unites States[1-2]. In 1995, it was estimated that the direct and indirect costs for the management of allergic rhinitis was 2.7 billion dollars excluding costs for accompanying asthma or sinusitis [1]. In 1996, Ray et al, estimated the direct medical costs for AR, as a primary or secondary diagnosis, at 5.9 billion dollars accounting for related airway diseases [3].

Allergic rhinitis is defined as inflammation of the nasal mucosa precipitated by exposure to inhaled allergens producing a specific immunologic response [1,2]. Usual symptoms occurring in response to those aeroallergens include sneezing, nasal pruritis and congestion, rhinorrhea, palatal pruritis, and itchy, red, watery eyes. In more severe circumstances, mucous membranes of the ears and paranasal sinuses can be involved producing symptoms of ear fullness and popping, itchy throat and pressure in the area above the cheeks and forehead. Fatigue, weakness and malaise can also be present. Patients with AR may be limited in their ability to perform daily activities and often note disturbances in sleep, work performance concentration, and quality of life. It is now considered crucial to optimally treat an individual with AR since chronic inflammation of the nasal mucosa and nasal obstruction, if left untreated, can lead to more serious conditions of the upper and lower airways including asthma, sinusitis, chronic otitis media with effusion and nasal or sinus polyps[1,4].

There are two types of AR: seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR). Seasonal AR is seasonal and is usually caused by pollens or molds. Perennial AR tends to be present for more than 9 months of the year and can be attributed to dust mites, molds, animal dander, or pollen in areas where high pollen counts are present for much of the year[1].

Intranasal steroids are considered first line therapy for the management of AR. Since AR is an inflammatory condition, it follows that it should be treated with anti-inflammatory medications. Two recent articles reviewed studies examining the effectiveness of intranasal steroids compared to second-generation antihistamines for the treatment of AR. Both reviews concluded, from the evidence, that intranasal steroids should be considered as first-line therapy for AR based on their superiority in decreasing nasal allergy symptoms compared to second-generation antihistamines[5,6].

II. Pharmacology

The exact mechanism of action of the corticosteroids for the management of symptoms of allergic rhinitis is not known. However, corticosteroids have a broad range of effects on the cells (mast cells, eosinophils, neutrophils, and lymphocytes) and mediators (histamine, eicosanoids, leukotrienes, and cytokines) of inflammation.

III. Indications

Table 2: FDA Approved Indications for Intranasal Corticosteroids[7-12]

Indication	Beclomethasone	Budesonide	Flunisolide	Fluticasone	Mometasone	Triamcinolone
SAR	X*	X	X*	X	X+	X
PAR	X*	X	X*	X	X	X
Nasal polyps	Prevention of recurrence after surgery					
Nonallergic Rhinitis	X**	X				
Pediatric SAR/PAR	SAR and PAR 6 years and older	SAR and PAR 6 years and older	SAR and PAR 6 years and older	SAR and PAR 4 years and older	SAR and PAR 3 years and older	■SAR and PAR 6 years and older □ SAR and PAR 12 years or older

SAR-seasonal allergic rhinitis, PAR-perennial allergic rhinitis
* Nasalide, Beconase, Vancenase Pockethaler indicated when conventional therapy has failed.
** Beconase AQ, Vancenase AQ
+ Indicated for prophylaxis and treatment of nasal allergy symptoms, ■ Rhone-Poulenc Rorer product, □ Muro Product

IV. Pharmacokinetics

Table 3: Pharmacokinetic Properties of the Intranasal Corticosteroids[7-13]

Parameter	Beclomethasone	Budesonide	Flunisolide	Fluticasone	Mometasone	Triamcinolone
Systemic Bioavailability (%)†**	17	20	20-50*	2 or less	<0.1	22
Onset of action* **	Within a few days	24 hours to a few days	Within a few days	12 hours to several days	7 to 12 hours to 2 days	12 hours to a few days
Metabolism	Lung and liver	Liver (CYP3A)	Liver	Liver (CYP3A4)	Liver	Liver and kidney

*Absorption of Nasarel was 25% less than Nasalide. 20% is absorbed from GI tract vs. 50% via the intranasal route.
**All available intranasal steroids undergo significant first-pass metabolism. † Bioavailability is based upon an oral dose. With nasal administration, the percent bioavailability is difficult to determine based upon multiple factors including small surface area of the nasal mucosa, mucocilliary clearance, portion of swallowed dose and technique of drug delivery.
***A response may be seen as soon as several hours, as stated above, to several days.

V. Clinical Efficacy

In seasonal and perennial allergic rhinitis, intranasal corticosteroids are useful in decreasing nasal congestion, itching, sneezing, and runny nose. In clinical trials, the beneficial effects of these agents are measured primarily by subjective reports from patients and clinicians using the total nasal symptom score (TNSS-nasal blockage, rhinorrhea, sneezing, and nasal itching) to assess mean percent improvement from baseline. Non-nasal symptoms (e.g. itchy/burning eyes, tearing/watery eyes, redness of eyes, itchy ears or palate) may also be assessed. The severity of symptoms (nasal and non-nasal) is graded on a scale of 0 to 3 (e.g. 0: no symptoms, 1: mild, 2: moderate, 3: severe symptoms). At the completion of most of these clinical trials, patients and or physicians are asked to provide their overall global assessment of efficacy based upon a 5-point scale (o=no relief, 1=slightly effective, 2=noticeably effective, 3=very effective, 4=totally effective).). In some studies, the total points assigned when adding together the TNSS and the non-nasal scores is referred to as the total symptom score (TSS) [14]. Although most studies utilize subjective improvements to measure efficacy, certain objective measurements such as presence of

inflammatory cells within the nasal mucosa, evaluation of nasal fluids, nasal patency, and evaluation of ability to recognize odors are being added to determine effectiveness[15].

Table 4: Clinical Efficacy of the Intranasal Corticosteroids in Seasonal and Perennial Allergic Rhinitis (Abbreviation key: page 14)

ADE=adverse effects, AQ=aqueous, BDP=beclomethasone dipropionate, BUD=budesonide, DB=double-blind, FLU=flunisolide, FP=fluticasone propionate, MC=multicenter,, MF=mometasone furoate, O=open-label, PAR=perennial allergic rhinitis, PLA=placebo, PC=placebo-controlled, PE=physical exam, R=randomized, SAR=seasonal allergic rhinitis, SB=single-blind, sx=symptom, TAA=triamcinolone acetonide, VAS=visual analogue scale

Clinical Trial	Treatment Groups	Results	Adverse Events/comments
Beclomethasone (BDP) aerosol vs. aqueous (AQ)			
Orgel, et al [16] Compared BDP aerosol to BDP aqueous in SAR DB,R,Parallel, Double-dummy 44 patients 3 weeks (Glaxo)	BDP 84 mcg in each nostril bid (336 mcg/day) (BDP aqueous or aqueous PLA) followed in 5 minutes by (BDP aerosol or aerosol PLA) Each patient received delivery of active drug or PLA by each device.	Nasal and ocular sx ↓ similarly in both groups. Combined mean total sx scores significantly ↓ from baseline at day 4: Nasal: $p<0.01$ Ocular: $p<0.05$ and continued to decrease by day 15. **BDP=BDP AQ**	34 patients complained of burning, pressure or sneezing immediately after using the devices (6 pts-aqueous pump or 28 pts-metered dose aerosol). Adverse effects were attributed to the device used. 84% of patients preferred aqueous spray 11% preferred aerosol spray 4% had no preference
Dunn, et al [17] Compared BDP aerosol to BDP aqueous in SAR DB,R,Parallel, Double-dummy 40 patients 2 weeks (Glaxo)	BDP 200 mcg bid (400 mcg/day) (Each patient received active aerosol and PLA aqueous or PLA aerosol and active aqueous)	No significant differences were noted for any nasal or non-nasal symptom between groups. Physician's assessment of symptom control was rated as very effective or good in at least 70% of patients in each group. **BDP=BDP AQ**	Nose bleeding was reported in 3 of the aerosol versus none of the aqueous treated patients. Stinging was reported by 11 patients receiving the aqueous versus none of the aerosol treated patients ($p<0.05$).

Beclomethasone (BDP) BID vs. QD			
Prenner, et al [18] Compared aqueous BDP-rs regular strength (42 mcg/spray) bid to BDP- ds double strength (84 mcg/spray) qd in SAR. MC, DB, R, PC, Parallel 438 patients 4 weeks (Schering-Plough)	-BDP 42 mcg/spray 2 sprays in each nostril bid (336 mcg/day) (n=111) -BDP 84 mcg/spray 2 sprays in each nostril qam (336 mcg/day) and PLA q pm (n=107) - PLA 2 sprays in each nostril bid (n=111). -BDP-hs high strength 336 mcg/spray 2 sprays in each nostril qam (1344 mcg/day) and PLA qpm was included for safety comparisons.	TNSS ↓ in all 3 active treatment groups compared to PLA ($p<0.03$). BDP-rs and BDP-ds were not different from each other at any time. TSS ↓ in all 3 active treatment groups compared to PLA ($p<0.05$) except for BDP-rs on day 29. BDP-rs and BDP-ds did not differ from each other at any time. Response to treatment was rated as good or excellent in a larger percent of the 3 active groups compared to PLA ($p<0.01$). **BDP-rs bid=BDP-ds qd>PLA**	There was no difference with regard to ADE noted in any of the 4 treatment groups. Overall, use of rescue medication (chlorpheniramine 4 mg) was less in all 3 active treatment groups compared to PLA On days 3 and 8 BDP-hs was more effective than BDP-ds and more effective than BDP-rs on day 8. Authors noted that linear trend analysis demonstrated significant linear trend among the 4treatment groups indicating a treatment dose response (PLA, BDP-rs, BDP-ds, BDP-hs).
Beclomethasone (BDP) vs. Budesonide (BUD)			
McArthur JG [19] Compared BDP aqueous to BUD aqueous in SAR. SB, R, Parallel 88 patients 3 weeks (Astra)	-BDP 2 sprays in each nostril bid (400 mcg/d) (n=38). -BUD 2 sprays in each nostril bid (400 mcg/d) (n=50).	BUD ↓ nasal symptoms of sneezing, runny and itchy nose more than BDP (p 0.0001-0.01) Symptom of blocked nose was not different between groups. Overall patient evaluation of response was noticeably, very or totally effective in 82% of BDP vs. 85% of BUD subjects. (no p value given) **BUD>BDP for sneezing, itchy and runny nose, but not blocked nose.**	25% (22/88) of patients withdrew from the study (21% BDP vs. 28% BUD). Primary reason for withdrawal: lack of efficacy and refusal to cooperate. Adverse effects were reported by 7.9% BDP vs. 14% BUD patients. (no p value given). Two patients in the BUD group withdrew due to ADE (sneezing and wheezing) vs. none in the BDP group. The use of eye drops was allowed and was not different between groups. **Criticism:** Single-blinded, no statistical values were given for overall efficacy assessment, just individual improvement in symptoms. Dose of BUD used is approximately 60% higher than the maximum recommended daily dose of 256 mcg.

Adamopoulos G, et al [20] Compared BDP aqueous to BUD aqueous in PAR. OL, R, Cross-over 37 patients 12 weeks (6 weeks each treatment) (Astra)	-BDP 1 spray in each nostril qid (400 mcg/d). -BUD 2 sprays in each nostril bid (400 mcg/d). Patients were crossed-over to the alternate treatment after 6 weeks of treatment.	TNSS improved more in the BUD group compared to BDP (p=0.001). Blocked and runny nose improved to a greater extent with BUD, but there was not a significant difference for sneezing, itchy nose, and runny eyes. A greater number of subjects preferred BUD (28) compared to BDP (4). Four patients rated them as equally effective. (p=0.0001) **BUD>BDP for blocked and runny nose and patient preference.**	Number of symptom free days was greater in those receiving BUD compared to BDP. (no p value given). A significantly greater number of patients preferred BUD to BDP overall and with regard to side effects. No serious ADE were reported by patients with either BDP or BUD. **Criticism:** Open-label study. Dose of BUD was 60% higher than the maximum recommended daily dose of 256 mcg. BDP was given qid and could have contributed to patient preference of BUD over BDP.
Al-Mohaimeid [21] Compared BDP to BUD in PAR SB, R, Parallel 120 patients 3 weeks (Astra)	-BDP 2 sprays in each nostril bid (400 mcg/d) (n=62) -BUD 2 sprays in each nostril bid (400 mcg/d) (n=58)	Mean TNSS for weeks 1, 2 and 3 were not different between groups with the exception of runny nose at week 1 (p=0.04) and sneezing at week 3 (p=0.04) favoring BUD. At the end of the study, 26% on BDP vs. 35% on BUD reported no symptoms (no p value given). Patients global evaluation of treatment was noticeably, very or totally effective in 58% on BDP and 72% on BUD (no p value given). **BUD slightly greater than BDP although no p value provided for 2 measures in the study.**	10 subjects receiving BDP reported non-serious ADE compared to 3 receiving BUD and may or may not have been related to the study drug. **Criticism:** Single-blinded. Dose of BUD used was 60% higher than the maximum recommended daily dose of 256 mcg. Individual symptoms (runny nose and sneezing) improved with BUD vs BDP at only 2 time points. No p value was provided for measures of patients reporting no symptoms and patients global assessment of efficacy.

Beclomethasone (BDP) vs. Flunisolide (FLU)			
Welsh, et al [22] Compared BDP aqueous to flunisolide and cromolyn in SAR DB (PLA, BDP) SB (flunisolide and cromolyn), R, PC 120 patients Approx. 8 week duration (Jul-Sept) (Glaxo)	-BDP 84 mcg in each nostril bid (336 mcg/day) (n=26). -Flunisolide 50 mcg bid each nostril bid (200 mcg/day) (n=26) -Cromolyn 1 spray in each nostril qid (41.6 mg/day) (n=24). -PLA 2 sprays in each nostril bid (n=22).	All active treatments were superior to PLA ($p<0.001$) and BDP and FLU were significantly better than cromolyn in reducing total hay fever scores ($p<0.001$). At peak season, PE showed that drug treated patients had less severe symptoms (($p<0.001$) and BDP and FLU were better than cromolyn ($p<0.05$), but not different from each other. **BDP=FLU>Cromolyn**	Of the 30 patients receiving flunisolide, 10 noted nasal burning (2 withdrew from the study due to burning). Common cold was noted in a greater number of patients receiving BDP than any other group. During peak season, patients in the PLA group reported a 10-fold increase in asthma symptoms compared to those receiving glucocorticoids ($p<0.001$). The expected increase in seasonal asthma symptoms did not occur in the intranasal steroid group.
Beclomethasone (BDP) vs. Fluticasone (FP)			
Ratner, et al [23] Compared BDP aqueous to FP in SAR (moderate to severe). MC, DB, R, PC, Parallel 313 patients 2 weeks (Glaxo)	-BDP 84 mcg in each nostril bid (n=103) -FP 100 mcg in each nostril qd and 2 sprays of PLA vehicle in each nostril qhs (n=106). -PLA 2 sprays in each nostril bid (n=104). Rescue medication: chlorpheniramine	**Clinician-rated nasal symptom score (VAS):** Similar significant improvement was noted in BDP and FP groups compared to PLA ($p<0.001$) at the first visit (day 7). **Patient-rated nasal symptom score (VAS):** Similar significant improvement was noted in BDP and FP compared to PLA ($p<0.01$). **Clinician-rated overall assessment:** BDP and FP achieved significant or moderate improvement more often than PLA. -Use of rescue medication was ↓ in both active groups compared to PLA ($p<0.05$). **BDP=FP>PLA**	No significant differences in ADE were noted across all 3 groups. More patients receiving FP noted episodes of epistaxis or blood in the nasal mucosa. Mean morning cortisol concentrations were within the normal range before and after treatment in all groups. Improvement in symptoms was noted by day 1 in the BDP group and day 2 in the FP group.

Van As, et al [24] Compared BDP aqueous to FP in PAR (moderate to severe) MC, DB, R, PC, Parallel 466 patients 6 months (Glaxo)	-BDP 84 mcg in each nostril bid (n=85). -FP 50 mcg in each nostril bid (n=92). -FP 100 mcg in each nostril qd and 2 sprays of PLA vehicle in each nostril qhs (n=102). -PLA 2 sprays in each nostril bid (n=81). Rescue medication: chlorpheniramine	**Clinician-rated nasal symptom score (VAS):** Similar significant improvement was noted in BDP and both FP groups compared to PLA ($p<0.05$) at the first visit (day 7). **Patient-rated nasal symptom score (VAS):** Similar significant improvement was noted in active treatment groups compared to PLA ($p<0.05$), except for FP qd at week 8 ($p=0.105$) compared to PLA. **Clinician-rated overall assessment:** Nearly twice as many patients receiving BDP or either dose of FP achieved significant or moderate improvement during the study compared to PLA. Rescue medication ↓ in both active groups but this ↓ was not significant at all visits. Nasal eosinophilia was reduced 64-79% in patients on FP or BDP but only 39% with PLA **BDP=FP qd/bid>PLA**	-No difference was observed in withdrawal due to ADE between groups or frequency of ADE reported. However, blood in the nasal mucous was reported more often in the BDP and FP bid groups compared to FP qd or PLA. Although not statistically significant, epistaxis was reported more often in both FP groups compared to BDP or PLA. -No difference was noted for mean morning plasma cortisol concentrations or response to cosyntropin stimulation testing for any group. -Nasal candidiasis was noted in 1 patient receiving FP bid and 1 patient receiving BDP. Oral candidiasis was noted in 1 patient receiving PLA. -Patients received ophthalmologic testing at 12 and 24 weeks. It was reported that 3% of patients in the active treatment and PLA groups had ocular changes, however none of these changes were the type attributed to systemic steroid therapy (posterior subcapsular cataracts and increased intraocular pressure) except 1 patient in the PLA group was noted to have a small subcapsular lenticular opacity in each eye. -Of the 466 patients enrolled in the study, 360 completed the 6 month follow-up. The number of subjects withdrawn were not different between groups, however more patients treated with PLA withdrew due to lack of effect.

Haye R [25] Compared BDP aqueous to FP in PAR MC, DB, R, Parallel 251 patients 1 year (Glaxo)	-BDP 200 mcg bid (n=63) -FP 200 mcg bid (n=116) -Treatment randomization 2:1 Rescue medication: terfenadine	Nasal blockage and rhinorrhea were significantly improved in the FP group vs. BDP group (p=0.002). Watery eyes/irritation improved more in the FP vs. BDP group (p=0.048). The symptoms of nasal itching and sneezing were not statistically different between BDP and FP. Use of rescue medication was not provided. **FP=or slightly >BDP** (see comment section)	Percent of reported ADE were similar between groups. Epistaxis was reported by 14% of the FP vs. 5% of those receiving BDP. Headache was reported by 8% vs 4% of the FP vs. BDP groups, respectively. Plasma cortisol levels were not significantly changed in either group. Only 179 patients were included in the efficacy analysis. Details of reasons for withdrawal were not given. **Criticism:** Dose of FP was double that of the maximum recommended daily dose of 200 mcg. One of the 2 lead authors was employed by Glaxo.
Beclomethasone (BDP) vs. Mometasone (MF)			
Graft D, et al [26] Compared BDP aqueous to MF in SAR beginning prior to ragweed season. MC, DB, R, PC, Parallel 347 patients 8 weeks (Schering-Plough)	-BDP 168 mcg bid (n=116) -MF 200 mcg qam and PLA spray qpm (n=116) -PLA 2 sprays in each nostril bid (n=115).	Primary comparison was between MF and PLA, other comparisons (BDP vs. MF) were considered secondary. Average number of days with minimal or no allergy symptoms was the primary efficacy endpoint. BDP and MF were associated with a higher number of minimal symptom days compared to PLA (p< or = 0.01). From the start of ragweed season, there was a prolonged period of days to worsened symptoms in both active groups compared to PLA (27 vs. 10 days, respectively) (p<0.01). TNSS were lower in both active groups compared to PLA (p<0.01) **BDP=MF>PLA**	330 patients were included in the efficacy analysis. 17 patients were excluded for: failure to meet entrance criteria, unacceptable baseline severity, noncompliance with dosing regimen and follow up visits. ADE were reported by 51% of those receiving BDP, 63% of those receiving MF, and 52% of those in the PLA group. The most common ADE that was felt to be at least possibly related to treatment was headache occurring in 7% MF, 3% BDP, and 6% PLA. Withdrawal due to ADE occurred in 5 subjects on BDP, 1 on MF, and 4 in the PLA group. The only group reporting serious related ADE was the PLA group.

Drouin, et al [27] Compared BDP aqueous to MF in PAR (moderate to severe) MC, DB, R, Double-dummy, Parallel 427 patients 3 months (Schering-Plough)	-BDP 100 mcg in each nostril bid (400 mcg/d) plus MF PLA bid (n=116). -MF 100 mcg in each nostril qam (200 mcg/d) and MF PLA qpm and BDP PLA bid (n=111). -PLA 2 sprays from each PLA bottle bid (n=101). -Each patient received a total of 16 sprays/day comprised of active drug and PLA. Rescue medication: loratadine	**Patient-rated total nasal symptom score:** Mean ↓ in TNSS for the first 15 days of treatment was the primary efficacy variable. Secondary variables included TNSS averaged over 15 day intervals beyond initial 15 days. BDP and MF ↓ TNSS similarly and greater than PLA ($p<0.01$) **Physician-rated total nasal symptom score:** Mean ↓ in TNSS ranged from 40-64% for BDP and 34-58% for MF for the 5 office visits. BDP was statistically better than PLA at all visits, however MF was numerically better but not statistically better than PLA at 2 visits (day 29 and week 8). There was no statistical difference between BDP and MF at any time. **Physicians Evaluation of patient response:** BDP and MF were statistically better than PLA at 60% of the office visits and similar to each other. The use of rescue medications did not differ between groups. **BDP=MF>PLA**	Numbers of patients reporting ADE were not different among the 3 groups. However, epistaxis or blood in nasal discharge was reported more frequently in the active treatment groups. Eight patients in the MF, 6 in the BDP, and 2 in the PLA groups withdrew from the study due to ADE. The most common reason for withdrawal was epistaxis in 3 of the MF and 5 in the BDP group. 328 patients were included in the efficacy analysis. 55 patients withdrew due to treatment failure (14 BDP, 15 MF, 26 PLA). Other reasons for discontinuation were similar among groups except for ADE (see above).

Beclomethasone (BDP) vs. Triamcinolone (TAA)			
Winder J, et al [28] Compared BDP aqueous to TAA aerosol in PAR MC, SB (investigator blind), R, Parallel 169 patients 4 weeks (Rhone-Poulenc-Rorer)	-BDP 168 mcg bid (n=83) -TAA 220 mcg qd (n=86)	Individual and total nasal scores were reported by patients on a daily basis and were not different between groups. Physicians and patients were asked to provide global efficacy evaluations of their treatment. Patients rated TAA as more efficacious overall (p-0.035), however physicians global rating was not different between BDP and TAA. **TAA= or slightly >BDP**	The authors provided thoughts on reasons for higher global efficacy in those patients receiving TAA which included improved compliance with once daily dosing, anti-inflammatory potency or a combination of both. The authors concluded that the differences in efficacy observed were most likely not clinically important. ADE were mild and significant differences included a higher incidence of sneezing with TAA and a higher rate of nose and throat "runoff" with BDP. **Criticism**: Single-blinded study (patients not blinded)
Budesonide (BUD) aerosol vs. Budesonide (BUD) aqueous			
Day J, et al [29] Compared BUD aerosol to BUD aqueous in SAR MC, DB, R, PC, Parallel 318 patients 4 weeks (Astra)	-BUD aerosol 100 mcg in each nostril bid (400 mcg/day) (n=76) -BUD aqueous 256 mcg qam (n=78) -BUD aqueous 400 mcg qam (n=79) -PLA qam (n=70) Rescue medication: terfenadine	TNSS in all 3 active BUD groups improved to a greater extent than the PLA group ($p<0.001$). No difference was seen between the 3 BUD groups. Overall assessment of treatment by patients was also better in all 3 BUD groups compared to PLA ($p<0.001$) and similar to each other. The use of rescue medications (terfenadine) was significantly ↓ in all 3 BUD groups compared to PLA ($p<0.001$). **BUD aerosol=BUD aqueous>PLA**	Reported ADE were not different between active treatment groups or PLA. Urine cortisol was not changed significantly from baseline and end of treatment in any group.

Budesonide (BUD) vs. Flunisolide FLU)			
Pipkorn, U [30] Compared BUD to FLU in SAR. SB, R, Parallel 60 patients 3 weeks (AB Draco)	-BUD aerosol 400 mcg/d (n=30) -FLU aqueous 200 mcg/d (n=28)	TNSS ↓ from baseline in both groups but were not different from each other. Overall patient assessment of treatment was good to very good in 79% of those using BUD and 71% of those using FLU. Physician overall assessment was rated as good to very good by 82% receiving BUD vs. 72% receiving FLU. (no p value given). **BUD=FLU**	2 patients in the FLU were withdrawn from the study due to not following instructions because of intense stinging of FLU at the time of administration. A significantly higher number of subjects reported ADE with FLU compared to BUD (FLU 59% vs. BUD 18%). Most common ADE in the FLU group was nasal stinging and irritation. **Criticism:** No p values provided for patient or physician overall assessment of efficacy.
Budesonide (BUD) vs. Fluticasone (FP)			
Stern MA, et al [31] Compared BUD aqueous to FP in SAR MC, DB, SB (FP to the investigator), R, PC, Parallel 635 patients 4-6 weeks (Astra)	-BUD 128 mcg qam (n=181). -BUD 256 mcg qam (n=182). -FP 200 mcg qam (n=180). -PLA 2 sprays qam (n=59) Rescue medication: terfenadine	Individual nasal symptom scores were significantly ↓ from baseline for all 3 active treatment groups compared to PLA ($p<0.001$). Sneezing was ↓ to a greater extent in the BUD 256 mcg group compared to FP 200 mcg ($p=0.04$). **TNSS were ↓ significantly in the 3 active treatment groups compared to PLA ($p<0.001$) and similar to each other.** On days in which the pollen count was >10 grains/m^3, a greater ↓ from baseline was observed for those in the BUD 256 mcg group compared to FP 200 mcg ($p=$or<0.04) for sneezing, runny nose, and TNSS. BUD 256 mcg was better than BUD 128 mcg in ↓ Sneezing. No difference was observed for BUD 128 mcg and FP 200	ADE were reported by 32% BUD 128 mcg, 34% BUD 256 mcg, 24% FP, 25% PLA and were not clinically significant. **Criticism:** FP group was not blinded for the patient.

		mcg. **Overall assessment of efficacy was similar and significantly better in all3 active groups compared to PLA (p<0.001).** The use of rescue medications ↓ by 50% in all 3 active groups, but ↑ in the PLA group. **BUD 256= or slightly > in certain parameters than BUD 128 mcg and FP>PLA**	
Day J, et al [32] Compared BUD aqueous to FP in PAR MC, DB, SB (FP to the investigator), R, PC, Parallel 314 patients 6 weeks (Astra)	-BUD 256 mcg qd (n=111) -FP 200 mcg qd (n=109) -PLA qam (n=53) Treatment randomization: 2:2:1 (BUD:FP:PLA) Rescue medication: loratadine	TNSS ↓ significantly in both active treatment groups compared to PLA (p<0.001 BUD, p<0.001 FP). BUD was associated with a greater improvement in TNSS compared to FP (p=0.031). For individual nasal symptom scores, BUD was better than FP in ↓ the symptom of blocked nose (p=0.009). FP was no better than PLA in improving blocked nose. For sneezing and rhinorrhea, there was no difference. After 6 weeks, there was no difference noted in overall patient assessment of treatment efficacy between active groups, both active groups were better than PLA. Rescue loratadine was ↓ significantly in both active treatment groups compared to PLA. **BUD=or> for certain parameters than FP>PLA**	ADE were reported by 46% of BUD, 37% FP, and 36% of PLA recipients. There was no statistical difference between active groups or PLA. Two patients in each active treatment group withdrew due to ADE. Onset of significant symptom relief, compared to PLA was noted within 36 hours for the BUD group and 60 hours for the FP group. However, this study did not set out to evaluate onset of action. Therefore, differences represent 24-hour intervals instead of data obtained at shorter specified time points. **Criticism:** FP group was blinded only to the investigator.
Andersson M, et al [33] Compared BUD dry powder to FP in PAR MC, DB, SB (FP to the investigator), R, PC	-BUD 200 mcg qd (n=24) -BUD 400 mcg qd (n=22) -FP 200 mcg qd (n=25)	TNSS ↓ significantly in all 3 active treatment groups compared to PLA (p<0.05). No difference was noted between active groups.	24 hour urinary cortisol did not change significantly from baseline and were not different from each other. No significant findings were observed on rhinoscopy.

Parallel 98 patients 6 weeks (Astra Draco)	-BUD PLA (n=27) Urinary cortisol and rhinoscopy were performed to assess safety Rescue medication: terfenadine or antazoline/naphazoline eye drops	For patient overall assessment of efficacy, more patients receiving BUD 400 mcg/d experienced substantial or total control of symptoms compared to BUD 200 or FP although no statistical analysis was done to compare active treatment groups. **BUD 200 mcg=FP** **BUD 400 slightly better than BUD 200 and FP>PLA**	Use of rescue medications was less in all 3 active groups compared to PLA. **Criticism:** FP was blinded only to the investigator. Small sample size. Compliance was 89.6% in FP, 98.3% in BUD 400 mcg, and 111.2% in the BUD 200 mcg group.
Fluticasone (FP) vs. Mometasone (MF)			
Mandl M, et al [34] Compared FP to MF in PAR (moderate to severe) MC, DB (double-dummy), R, PC, Parallel 548 patients 12 weeks, 13th week off treatment (Schering-Plough)	-FP 200 mcg qd followed by MF PLA qd (n=183) -MF 200 mcg/d followed by FP PLA qd (n=181) -FP PLA plus MF PLA qd (n=184) Rescue medication: Loratadine	TNSS improved from baseline in both active groups compared to PLA ($p<0.01$) at all time points during the study. Following 1 week off treatment, TNSS were still improved more than PLA in both active groups ($p<$ or $=0.01$). Number of symptom-free days were similar in the active groups, but greater than PLA ($p<0.01$). Individual symptoms were better with MF at day 29 and week 8 for nasal congestion ($p=0.04$) and nasal discharge at weeks 8 and 12 ($p=0.03$). **FP=MF overall**	474 patients completed the trial. Withdrawn due to inefficacy: PLA 14, FP 6, MF 4 Withdrawn due to ADE: PLA 2, FP 4, MF 3 Use of rescue medication was similar in both active treatment groups but greater in the PLA group.

Fluticasone (FP) vs. Triamcinolone (TAA)			
Small P, et al [35] Compared FP aqueous to TAA aerosol in SAR. MC, SB, R, Parallel 233 patients 3 weeks (Rhone-Poulenc Rorer)	-FP 200 mcg qd (n=117) -TAA 220 mcg qd (n=116)	TNSS ↓ similarly in both groups. There was also no difference with regard to individual nasal symptoms. Differences between groups occurred with regard to patient acceptance (e.g. medication runs down throat or out of nose more often in those receiving FP. However, medication caused dry nostril or stuffy nose more in the TAA group). **FP=TAA with some differences in patient acceptance for both products.**	223 patients completed the trial. 10 were excluded for primarily administrative reasons. Only 1 withdrew due to ADE (severe headache in the TAA group). ADE were similar between groups with the most common being epistaxis and headache. **Criticism:** Single-blinded.

ADE=adverse effects, AQ=aqueous, BDP=beclomethasone dipropionate, BUD=budesonide, DB=double-blind, FLU=flunisolide, FP=fluticasone propionate, MC=multicenter,, MF=mometasone furoate, O=open-label, PAR=perennial allergic rhinitis, PLA=placebo, PC=placebo-controlled, PE=physical exam, R=randomized, SAR=seasonal allergic rhinitis, SB=single-blind, sx=symptom, TAA=triamcinolone acetonide, VAS=visual analogue scale
N, in the study group section, refers to those patients included in the efficacy analysis.
Studies in table 4 included a run-in period of 4-14 days to assess severity of allergy symptoms on no allergy medications.
Parenthesis in the first column indicate the study's sponsor.

After review of clinical trials, evaluating the efficacy of the intranasal corticosteroids, differences between agents are minimal. Therefore, these agents can be considered equally effective for the management of seasonal and perennial allergic rhinitis.

VI. Safety and Adverse Effects

Local Adverse Effects:
The most common adverse effects, associated with the use of intranasal corticosteroids, result from local irritation of the nasal mucosa and include burning, stinging, and sneezing in approximately 10% of patients. Bloody nasal discharge/epistaxis can be observed in about 2% of patients and rare case reports of perforated septum exist in patients using nasal steroids [36]. Therefore, patients should be advised to direct the spray of their nasal steroid away from the nasal septum in order to decrease the risk of perforation. It is recommended that patients prescribed long-term intranasal steroids have their nasal mucosa evaluated periodically to identify erosions that may precede septal perforation.

Long-term studies in patients with perennial allergic rhinitis have demonstrated, using nasal biopsies, that no evidence of tissue atrophy or change occur in patients receiving long-term treatment with beclomethasone or mometasone [37,38].

Systemic Adverse Effects:
The systemic bioavailability of each intranasal corticosteroid is made up of the swallowed portion of the dose as well as the amount absorbed via the nasal mucosa. All of the commercially available intranasal steroids undergo significant first-pass hepatic metabolism resulting in relatively low bioavailability for all agents. Mometasone and fluticasone have the lowest reported bioavailability from the gastrointestinal tract (<2%) vs. approximately 20% for the other agents. Since drugs absorbed via the nasal mucosa do not undergo first-pass metabolism, bioavailability is

thought to be nearly 100%. However, as a result of rapid mucocilliary clearance and limited nasal surface area for drug deposition, actual bioavailability is probably significantly less than 100%[39].

The use of intranasal corticosteroids for the management of SAR and PAR has generally been regarded as safe and effective without significant concern for systemic adverse effects. However, investigators have demonstrated decreased serum and urinary cortisol levels in short-term studies in patients and/or volunteers using fluticasone, beclomethasone, budesonide, or triamcinolone. Alternatively, in these studies, hypothalamic-pituitary-adrenal (HPA) axis was found to be unaffected using insulin tolerance testing (ITT) or adrenocorticotropic hormone (ACTH) stimulation testing, suggesting intact adrenal reserve with the use of these agents.

The following tests have been used in controlled clinical trials to evaluate systemic bioactivity of intranasal corticosteroids **(The clinical relevance of these findings is not known) [39].** Since the clinical relevance of these test are unknown, we are not recommending that any of these tests be used routinely to detect systemic side effects of the intranasal corticosteroids.

Screening Tests (basal cortisol secretion)	**Stimulation Tests (assess adrenal reserve)**
Overnight urinary free cortisol	Low dose ACTH test (0.5 mcg) a.k.a. tetracosactrin
24 hour urinary free cortisol	CRH-corticotrophin releasing hormone test (100 mcg)
24 hour plasma cortisol	High dose ACTH test (250 mcg)
8 am plasma cortisol	

Other tests:

Osteocalcin: Osteocalcin is produced by osteoblasts and is a specific surrogate marker of their activity and is used to measure effects on bone growth.

Blood eosinophil count: Can be used as a surrogate marker of systemic allergy burden.

Insulin tolerance test (ITT): Insulin-induced hypoglycemia causes increases in plasma cortisol levels and suggests whether hypoglycemic stress leads to a normal or impaired increase in cortisol. It is another method for measuring the adrenal glands ability to respond to physiologic stress (intact HPA axis). Obviously, it should be used with caution since its effects can be hazardous (hypoglycemia).

Screening tests can be used to assess basal cortisol secretion and are simply a marker for potential systemic bioactivity. Long-term exposure to systemic corticosteroids can lead to depressed ACTH levels and adrenal atrophy. Therefore a stimulation test is necessary to assess adrenal reserve and the bodies ability to respond to physiologic stress.

Table 5. Clinical Trials Evaluating Systemic Bioactivity of the Intranasal Corticosteroids (Abbreviation key: page 18)
AR=allergic rhinitis, BUD=budesonide, BDP=beclomethasone dipropionate, DB=double-blind, FP=fluticasone propionate, MF=mometasone furoate, MC=multicenter, O=open-label, PLA=placebo, PC=placebo-controlled, R=randomized, SB=single-blind, TAA=triamcinolone acetonide

Clinical Trial; Adult or child	Number of Patients	Drug/Dose	Duration	Assessment Test	Results
Wilson AM, et al [40] Adult, SB, R, PC, 4-way crossover design	16 volunteers	PLA FP 200 mcg/d TAA 220 mcg/d BDP 336 mcg/d	Each arm consisted of 4 days of treatment	**Overnight:** -urinary cortisol -urinary cortisol/ creatinine ratio **-ACTH 0.5 mcg Stimulation Test**	**Overnight urinary cortisol:** PLA=no change FP=↓ significantly compared to PLA ($p<0.05$). TAA and BDP=change not significant compared to PLA. **Overnight urinary cortisol/creatinine:** Not significant for any agent. **ACTH Stim. Test:** No significant adrenal suppression for any agent.
Wilson AM, et al [41] Adult, SB, R, PC, 4-way crossover design	20 patients with AR	PLA BUD 200 mcg/d MF 200 mcg/d TAA 220 mcg/d	Each arm consisted of 4 days of treatment	**Overnight, 8 am, Daytime, and 24-hour:** -plasma cortisol -urinary cortisol /creatinine ratio -urinary cortisol **Serum osteocalcin** **Blood eosinophil count**	No significant differences were observed in any of the active treatment groups compared to PLA for any screening test used.
Knutsson U, et al [42] Adult, O, R	14 volunteers	FP 200 mcg/d BUD 400 mcg/d	2 weeks (Drug doses were doubled for the 2nd week)	**24-hour:** -urine cortisol -plasma cortisol **Serum osteocalcin** **Insulin tolerance test (ITT)**	**24-hour urinary and plasma cortisol levels:** Both FP and BUD were associated with a significant decrease in urinary and plasma cortisol levels. **Serum osteocalcin** Significantly decreased for both agents during the first week compared to baseline. No further reduction was seen during the 2nd week. **ITT:** No significant

					change, indicating intact HPA axis.
Nayak AS, et al [43] Children, MC, DB, R, PC, parallel design	80 children with AR	PLA TAA 220 mcg/d TAA 440 mcg/d	6 weeks	**ACTH 250 mcg Stimulation Test** **Pharmacokinetic testing of TAA in randomly selected patients.**	**ACTH:** No difference was noted in plasma cortisol levels between either dose of TAA or PLA, suggesting intact HPA axis. **TAA plasma concentrations:** 67% of patients had no detectable plasma concentrations of TAA 24 hours after dosing suggesting a rapid decline in TAA from the blood with little or no accumulation even at the highest doses.
Wihl JA, et al [44] Adult, O, R, PC, crossover design	14 volunteers (single-dose) 30 volunteers (4 day study)	PLA BDP 200, 400, 800 mcg single dose or qd BUD 200, 400, 800 mcg single dose or qd	Single dose or 4 days	**Overnight:** Plasma and urinary cortisol (single-dose study) **24-hour urinary cortisol** (4 day study)	**Single dose study:** No treatment altered plasma cortisol. Urinary cortisol levels were significantly decreased compared to PLA for BUD 400 and 800 mcg but not for any dose of BDP. **Multiple dose study:** A significant decrease in urinary cortisol was observed with all doses of BUD and only the 800 mcg dose of BDP. BUD had a significantly greater effect on cortisol levels than BDP at all dose levels ($p<0.03$).
Brannan MD, et al [45] Adult, 3rd party blind, R, parallel design	64 patients with AR	PLA Prednisone 10 mg qd BDP 42 mcg, 2 sprays in each nostril bid BDP 84 mcg, 2	36 days	**ACTH 250 mcg Stimulation Test**	Significant difference in response of plasma cortisol with prednisone compared to PLA ($p<0.01$). No

		sprays in each nostril qd			difference was noted in plasma cortisol between either BDP and PLA or from the 2 doses of BDP.
Howland WC, et al [46] Adult, MC, DB, PC, parallel design	64 patients with AR	PLA TAA 220 mcg/d TAA 440 mcg/d Prednisone 10 mg qd	6 weeks	**ACTH 250 mcg Stimulation Test**	No difference in plasma cortisol occurred in either TAA group compared to PLA. However, the prednisone group has a significant reduction in plasma cortisol compared to PLA ($p<0.001$). These data suggest an intact HPA axis with TAA.
Brannan MD, et al [47] Children, R, PC, parallel design	96 children with AR (3-12 years of age)	PLA MF 50, 100, 200 mcg qd	14 days	**Plasma cortisol and 24-hour urinary cortisol** **ACTH 250 mcg Stimulation Test**	No difference in urinary or plasma cortisol was detected in any MF group compared to PLA. **ACTH Stim. Test:** Normal response to stimulation test was observed in all MF groups compared to PLA suggesting intact HPA axis.

AR=allergic rhinitis, BUD=budesonide, BDP=beclomethasone dipropionate, DB=double-blind, FP=fluticasone propionate, MF=mometasone furoate, MC=multicenter, O=open-label, PLA=placebo, PC=placebo-controlled, R=randomized, SB=single-blind, TAA=triamcinolone acetonide

Pediatric Adverse Effects: Bone Growth and Development

Recently, a double-blind, placebo-controlled, 12-month study enrolled 100 children (6-9 years) with PAR who were randomized to receive beclomethasone 336 mcg/d or placebo. In this study, bone growth was measured by standing height at 7 time-points during the 12-month period. A significant decrease in bone growth was observed at 1, 6, 8, and 12-month time periods, although the clinical significance of these findings is unclear [48]. In a similarly designed study, in children 6-9 years of age, treatment with mometasone furoate 100 mcg daily for 12 months compared to placebo did not slow growth rate [49]. However, as a result of these data and other findings, in late 1998, the Food and Drug Administration's Pulmonary and Allergy Drugs Committee instituted a class labeling change for all inhaled oral and intranasal corticosteroids regarding the potential for growth suppression in children.

Biochemical markers of bone metabolism (formation and resorption) include: osteocalcin, parathyroid hormone (PTH), alkaline phosphatase (AP), bone alkaline phosphatase (BAP), propeptide of type III procollagen (PIIINP), and telopeptide of type I collagen (ICTP). Markers of bone formation seem to be more sensitive than bone resorption for evaluation of systemic activity of the inhaled corticosteroids [39].

Bone formation: Osteocalcin, alkaline phosphatase, bone alkaline phosphatase (all of these markers decrease with decreased bone mineralization and formation).

Bone resorption: ICTP, PTH (these markers increase with increased bone resorption).

Knemometry: Technique in which lower leg growth is measured. Knemometry can accurately and reproducibly determine short-term growth velocity to within 2 mm in children.

Stadiometer: Standing height (long-term growth)

Table 6. Clinical Trials Evaluating Intranasal Corticosteroids Effect on Bone Metabolism and Growth (Abbreviation key: page 21)

AR=allergic rhinitis, BDP=beclomethasone dipropionate, BUD=budesonide, DB=double-blind, HPA=hypothalamic-pituitary-adrenal, MC=multicenter, MF=mometasone furoate, MPDA=methylprednisolone acetate, O=open-label, PLA=placebo, PC=placebo-controlled, R=randomized.

Clinical Trial: Children	Number of Subjects	Drug/Dose	Duration	Assessment Test	Results
Martinati LC, et al [50] R	39 children AR (6-14 years old)	-BDP 200 or 400 mcg/d -Sodium cromoglycate (SCG) 30 mg/d	8 weeks	**Biochemical markers of bone metabolism:** Osteocalcin, PTH, AP, BAP, ICTP	**Osteocalcin:** No change from baseline or from each other. **PTH:** No significant difference (tendency to ↓ in SCG group and ↑ in BDP 400 mcg group). **AP and BAP:** All groups showed a reduction after 2 months of treatment regardless of treatment assignment. No differences were seen between groups. **ICTP:** No differences within each group were noted during the study period. **Conclusion:** BDP in doses of 200 or 400 mcg/d did not significantly affect markers of bone metabolism. Canisters weighed before and after treatment suggested overuse since the change in canister weight averaged 108.5% (range 79-136%)of predicted values.
Wolthers OD, et al [51] DB, R, parallel design	38 children AR (7-15 years old)	-BUD 200 or 400 mcg/d (dry powder) -PLA qd	4 week run-in 4 weeks treatment	Knemometry	**Growth velocity** was nearly identical during the run-in and treatment phases for the PLA and BUD 200 mcg groups. For the PLA and 400 mcg groups, there was a nonsignificant ($p<0.11$) decrease in growth velocity. **Conclusion:** No differences in growth velocities were noted between the 3 groups during the run-in and treatment phases of the study. Results provide evidence that systemic activity is low in children receiving 200 or 400

					mcg/d for SAR or PAR.
Wolthers OD, et al [52] DB, O (MPDA) R, Parallel design	44 children AR (school age)	-BUD 200 mcg bid -Terfenadine 60 mg bid -MPDA 60 mg IM once	4 week run-in 6 weeks treatment	Knemometry	Compared with the run-in period, treatment with BUD and MPDA were associated with a significant reduction in lower leg growth velocity. Run-in and treatment growth velocity did not change significantly in the terfenadine group. **Conclusion:** Short-term lower leg growth velocity is decreased in children with AR receiving intranasal or depot steroids. However, conclusions regarding long-term statural growth cannot be drawn.
Agertoft L, et al [53] DB, R, PC, crossover design	22 children SAR or PAR (7-12 years old)	-BUD 400 mcg/d -MF 100 or 200 mcg/d -PLA	Two week treatment intervals, 2 week wash-out periods separated each treatment period	Knemometry	Although a greater growth velocity was observed in the MF 100 mcg group, compared to all other groups including PLA, there was no overall difference in growth velocities in any of the active treatment groups or PLA. **Conclusion:** No short-term effects on linear lower leg growth were observed after either dose of MF or BUD.
Skoner DP, et al [40] DB, R, PC, parallel design	100 children (6-9 years old)	-BDP 168 mcg bid -PLA bid	12 months	**Height measurement:** stadiometer at 1, 2, 4, 6, 8, 10, and 12 months. **8 am basal cortisol conc.** **ACTH 250 mcg Stimulation testing**	**Stadiometer:** Mean change in standing height was 5 cm in BDP group compared to 5.9 cm in the PLA group. The mean overall rate of growth was 0.13 cm/d in the BDP vs. 0.17 cm/d in the PLA group ($p<0.01$)). Difference was apparent after 1 month. Authors point out that baseline height was significantly greater in the BDP group, but comment that statistical testing ruled this difference out as a contributor to the difference in final height at 1 year. **8 am basal cortisol levels:** No differences were noted in plasma cortisol levels between BDP and PLA. **ACTH Stim. Test:** No difference between groups suggesting intact HPA axis. **Comment:** Adult doses of BDP were used.

Schenkel EJ, et al [41] MC, DB, R, PC, parallel design	98 children (6-9 years old)	-MF 100 mcg qd -PLA qd	12 months	**Height measurement:** stadiometer at 4, 8, 12, 26, 39, and 52 weeks. **ACTH 250 mcg Stimulation Testing**	**Stadiometer:** No difference in height at 1 year was seen between groups (p> or = to 0.20). At 8 and 52 weeks, mean height was greater in the MF group compared to PLA (p=0.02). However the rate of growth averaged for all time points was similar between groups. Mean change in height in the MF group was 6.95 cm vs. 6.35 cm in the PLA group. **ACTH Stim. Test:** No difference between groups at any time point suggesting intact HPA axis. **Comment:** Recommended dose in children 3-11 years was used (1/2 adult dose).

AR=allergic rhinitis, BDP=beclomethasone dipropionate, BUD=budesonide, DB=double-blind, HPA=hypothalamic-pituitary-adrenal, MC=multicenter, MF=mometasone furoate, MPDA=methylprednisolone acetate, O=open-label, PLA=placebo, PC=placebo-controlled, R=randomized.

VII. Dosage and Administration

Patients with AR should be advised to begin treatment with an intranasal corticosteroid prior to the beginning of allergy season, if possible, and to continue using on a daily basis until the season has passed. Once treatment has begun, it may take several days to notice a reduction in allergy symptoms and as long as 1-2 weeks for maximum benefit. If patients have not experienced improvement in their symptoms after 2 weeks, alternative treatment should be instituted. Although a delayed onset of action may be present in some individuals, investigators have observed that many patients experience some degree of symptom relief within 24 hours of the first dose [54-58]. In fact, evidence suggests that some patients may benefit from "as needed" use of the intranasal corticosteroids, while others require treatment on a regular basis [59, 60].

Although the clinical significance of data regarding the potential for systemic adverse effects from the use of intranasal corticosteroids is not yet known, it is generally recommended that the lowest effective dose of an intranasal corticosteroid be used for the shortest period of time, especially in children. One author suggested that once a canister of medication has been used (3-4 weeks), the patient should be advised to wait 1 week to determine if their symptoms are still present and whether another canister is necessary [61].

Table 7. Dosage and Administration of the Intranasal Corticosteroids in Adult Patients [7-12]

Generic Name	Brand Name	Dose per Actuation (# doses per unit)	Usual daily dose (possible number of sprays/month)	Usual daily dose in micrograms
Beclomethasone Dipropionate (BDP)	**Beconase**	42 mcg (80 or 200)	1-2 sprays in each nostril bid-qid (120-240)	168-336
	Beconase AQ	42 mcg (200 or >)	1-2 sprays in each nostril bid-qid (120-240)	168-336
	Vancenase	42 mcg (80 or 200)	1-2 sprays in each nostril bid-qid (120-240)	168-336
	Vancenase Pocket	42 mcg (200 or >)	1-2 sprays in each nostril bid-qid (120-240)	168-336
	Vancenase AQ	84 mcg (120 or >)	1-2 sprays in each nostril qd (60-120)	168-336
Budesonide (BUD)	**Rhinocort** **Rhinocort Aqua**	32 mcg (200 or >) 32 mcg 200 or >	2 sprays in each nostril bid or 4 sprays in each nostril qd (240)	256
Flunisolide (FLU)	**Nasalide**	25 mcg (200 or >)	2 sprays in each nostril bid-tid (240-360)	200-300 Max=400
	Nasarel	25 mcg (200 or >)	2 sprays in each nostril bid-tid (240-360)	
Fluticasone Propionate (FP)	**Flonase**	50 mcg (120)	2 sprays in each nostril qd (120)	200
Mometasone Furoate (MF)	**Nasonex**	50 mcg (120)	2 sprays in each nostril qd (120)	200
Triamcinolone Acetonide (TAA)	**Nasacort** **Nasacort AQ** **Tri-Nasal Spray**	55 mcg (100 or >) 55 mcg (30 or 120) 50 mcg (120)	2 sprays in each nostril qd (120) 2 sprays in each nostril qd (120)	220 Max=440 200 Max=400

VIII. Use Patterns of the Intranasal Corticosteroids in the VA

Table 8. Department of Veteran's Affairs Use of the Intranasal Corticosteroids

Generic Name	January 1999 (percentage of total RXs for intranasal steroids)	December 1999 (percentage of total RXs for intranasal steroids)	Percent of patients receiving 2 canisters per month (average and range FY99)
Beclomethasone Dipropionate (BDP)	92	88	**Aerosol:** 24.2 (range 22.2-26.2) **AQ:** 22.7 (range 20-26) **AQ double strength:** 16.5 (range 13.8-19.5)
Flunisolide (FLU)	0.7	0.6	24.7 (range 21-28.6)
Fluticasone Propionate (FP)	4.4	9.6	**9 gram size:** 41.1 (range 24.6-57)* **16 gram size:** 10.9 (range 9-12.6)
Triamcinolone Acetonide (TAA)	2.4	2.1	**Aerosol:** 26.8 (range 21.7-33.8) **Aqueous:** 33.2 (range 29-36)

Mometasone and budesonide are not included due to low prescribing volume
*****Less than 100 prescriptions per month

IX. Monthly Cost

Table 10. Estimated Monthly Cost per Canister Dispensed

Generic Name	Brand Name (strength/number of actuations)	Cost ($)/Canister/Month (assuming 1 canister/month)
Beclomethasone Dipropionate (BDP)	Beconase 42 mcg/200	18.53
	Beconase AQ 42 mcg/200 or >	25.60
	Vancenase 42 mcg/200	3.62*
	Vancenase Pocket 42 mcg/200 or >	3.62*
	Vancenase AQ 84 mcg/120 or >	27.73**
Budesonide (BUD)	Rhinocort 32 mcg/200 or >	19.60
	Rhinocort Aqua 32 mcg/ 200 or >	29.94
Flunisolide (FLU)	Nasalide 25 mcg/200 or >	5.79
	Nasarel 25 mcg/200 or >	11.89
Fluticasone Propionate (FP)	Flonase 50 mcg/120	11.18
Mometasone Furoate (MF)	Nasonex 50 mcg/120	26.84
Triamcinolone Acetonide (TAA)	Nasacort 55 mcg/100 or >	18.79
	Nasacort AQ 55 mcg/120	19.56
	Tri-Nasal Spray 50 mcg/120	19.40

*National contract price-expires 6/01
**Once daily-double strength product

X. Conclusions and Recommendations

All of the available intranasal corticosteroids have been shown to be beneficial for the management of SAR and PAR. Furthermore, a review of the literature failed to demonstrate any clinically significant benefit of one agent over another with regard to efficacy. All agents are effective when administered once or twice daily and can be considered equally effective when used in equipotent doses.

Local adverse effects (stinging, burning, dry nasal mucosa) are similar among agents, however may vary with the propellant used (aqueous vs. aerosol). In November 1998, the FDA modified prescribing information for the entire class of inhaled corticosteroids regarding the potential for growth suppression in children receiving either intranasal and/or orally inhaled corticosteroids. This change was made as a result of data from several studies in asthmatic children in which growth was inhibited. As for the intranasal corticosteroids, a study was recently published in which children, 6-9 years of age, were found to have a small, but significant, suppression of growth during a 12-month study with beclomethasone [48]. The authors of this study, along with the FDA, are unsure of the clinical significance of these findings. Authors of a similar study found no inhibition of growth when mometasone was administered intranasally for a period of 12 months [49]. Long-term studies, evaluating suppression of growth in children, with the intranasal corticosteroids fluticasone, budesonide, flunisolide, or triamcinolone have not been performed. Subsequently, it is not known whether certain agents are more likely to inhibit growth velocity than others; how rapidly growth velocity returns to normal once an agent is discontinued; or whether attainment of full adult height is in any way affected by the use of these agents. These questions will remain until long-term studies are undertaken to answer them.

In conclusion, the safety and efficacy of these agents in adult patients with SAR or PAR is similar. Therefore, the recommendation for choice of intranasal corticosteroid for the VA National Formulary should be based upon per patient cost. Furthermore, a contract should be sought for both an aerosol and an aqueous product, due to patient tolerability and preference for one mode of delivery over the other.

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