# Pharmacotherapy of Asthma: Part 3

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# Why Are ICS Preferred Controllers for Persistent Asthma?

- Population Level Studies
  - Decrease in urgent care and hospitalization rates
  - Reduction in asthma mortality
- Clinical Efficacy Studies
  - Reduction or elimination of systemic corticosteroids
  - Reduction in asthma symptoms and exacerbations
  - Improved lung function
  - Decreased bronchial hyperresponsiveness
  - Improved exercise tolerance
  - Reduced airway inflammation

# Glucocorticoid Effects in Asthma

- Reduce recruitment, activation, retention, and survival of lymphocytes, macrophages, mast cells, and eosinophils at the site of inflammation in the airways
- Decrease microvasc. permeability, mucosal edema, subepithelial fibrosis, and mucous secretions
- Renew disrupted epithelium
- Normalize the epithelial goblet/cell ratio
- Upregulate $\beta$-adrenergic receptors
- Restore $\beta_2$-adrenergic responsiveness
- Reduce inducible nitric oxide production

# Factors Associated with a Diminished Dose Response to ICS

- Genetic polymorphisms (homozygous variant allele rs 37973, which maps to the glucocorticoid-induced transcript 1geneGLCC11)
- COPD
- Smoking
- Severe asthma
- Obesity
- Vitamin D insufficiency

Raissy HH et al. Am J Respir Crit Care Med 2013 (April 15) 187(8): 798-803

# Potential Adverse Effects of ICS Therapy

- **Local effects (irritation/cough, oropharyngeal candidiasis, dysphonia) – counseling focused on prevention**
- Behavioral/psychiatric effects
- **Growth delay in children**
- HPA axis dysfunction and adrenal insufficiency
- **Osteoporosis**
- Dermal thinning and increased ease of skin bruising
- Posterior subcapsular cataracts or glaucoma
- Metabolic changes (elevated glucose or lipids)
- Disseminated Varicella
- Interaction with potent CYP 3A4 inhibitors such as ritonavir, ketoconazole, itraconazole
- Increased risk of pneumonia (primarily COPD)

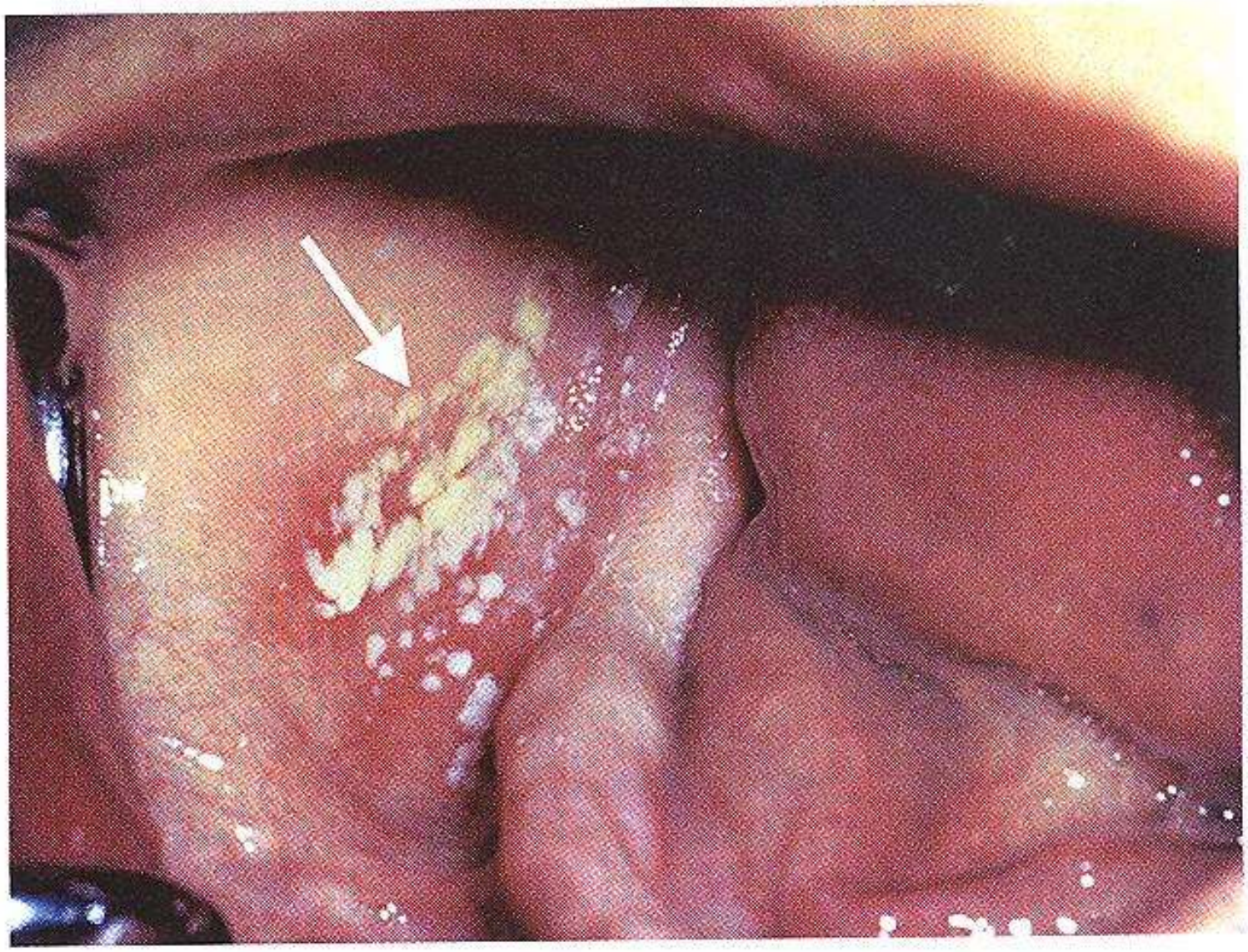


**FIGURE 1.** Pseudomembranous candidiasis lesions of the palate.

# Are All ICS Drug and Delivery Systems Alike?

# Therapeutic Issues Related to ICS

- The most important determinant of appropriate dosing is the clinician's judgment of the patient's response to therapy. The clinician must monitor the patient's response on several clinical parameters and adjust the dose accordingly. Once control of asthma is achieved, the dose should be carefully titrated to the minimum dose required to maintain control.

- **Preparations are <u>not</u> interchangeable on a mcg or per-puff basis.**

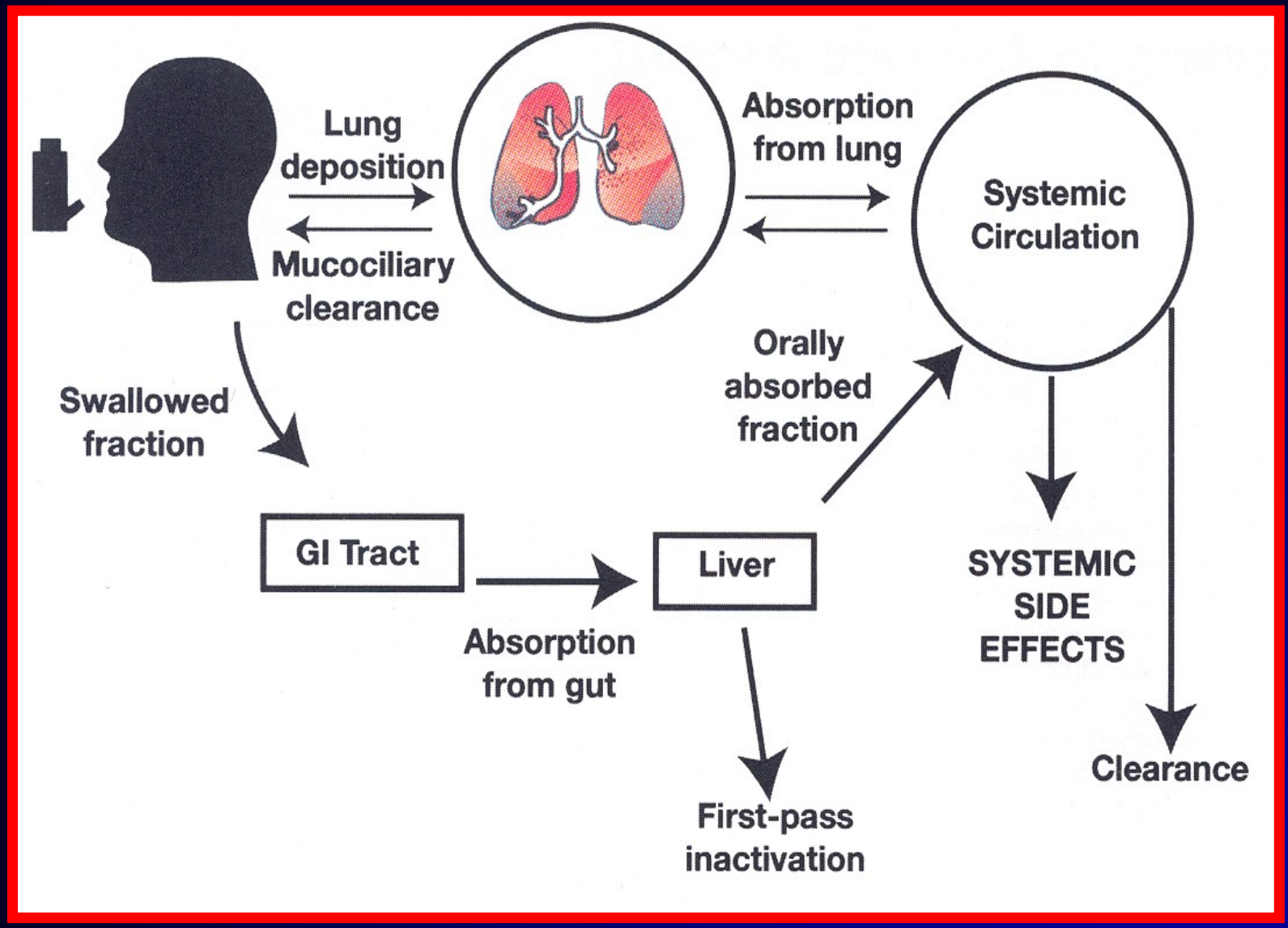
# Therapeutic Issues Related to ICS

(Cont'd)

- Budesonide nebulizer suspension is the only ICS with FDA-approved labeling for children < 4 years of age.

- For children < 4 years of age: The safety and efficacy of ICSs in children < 1 year has not been established. Children < 4 years of age generally require delivery of ICS (budesonide respules or fluticasone HFA) through a face mask that should fit snugly over nose and mouth and avoid nebulizing in the eyes. Wash face after each treatment to prevent local corticosteroid side effects. For budesonide, the dose may be administered 1-3 times daily. Budesonide suspension is compatible with albuterol, ipratropium, and levalbuterol nebulizer solutions in the same nebulizer. Use only jet nebulizers. For fluticasone HFA, the dose should be divided 2 times daily.

# Events Involved in Pulmonary Targeting




Hochhaus G. *Proc Am Thorac Soc* 2004; 1:269-274.

# A Successful ICS Formulation Should…..

- Provide a high pulmonary deposition efficiency
- Have a low oral bioavailability to ↓ systemic absorption
- Be subject to high systemic clearance for efficient removal of absorbed drug
- Possess a prolonged lung residence time to maximize the effect (lipophilicity, liposomes, prodrugs)

Hochhaus G. *Proc Am Thorac Soc* 2004; 1:269-274.

# Issues Related to ICS Oral Bioavailability

- Oral bioavailability is determined mainly by the degree to which swallowed drug is inactivated during the 1st pass through the liver
- Hepatic metabolism of newer ICS is very efficient
- Negligible bioavailabilities of fluticasone, mometasone, ciclesonide

Hochhaus G. *Proc Am Thorac Soc* 2004; 1:269-274.

# ICS Lung Delivery and Oral Bioavail.

| ICS Product | Lung Delivery | Bioavail. |
|---|---|---|
| Beclomethasone (BDP) DPI Redihaler | 50-68% | 40% |
| Budesonide (BUD) DPI Flexhaler | 15-30% | 11% |
| Nebules | 5-8% | |
| Ciclesonide (CIC) HFA MDI | 50% | < 1% |
| Fluticasone furoate (FF) DPI | 80% | ≤ 1% |
| Fluticasone propionate (FP) HFA MDI | 20% | ≤ 1% |
| DPI Diskus | 15% | |
| Mometasone furoate (MF) DPI | 11% | < 1% |

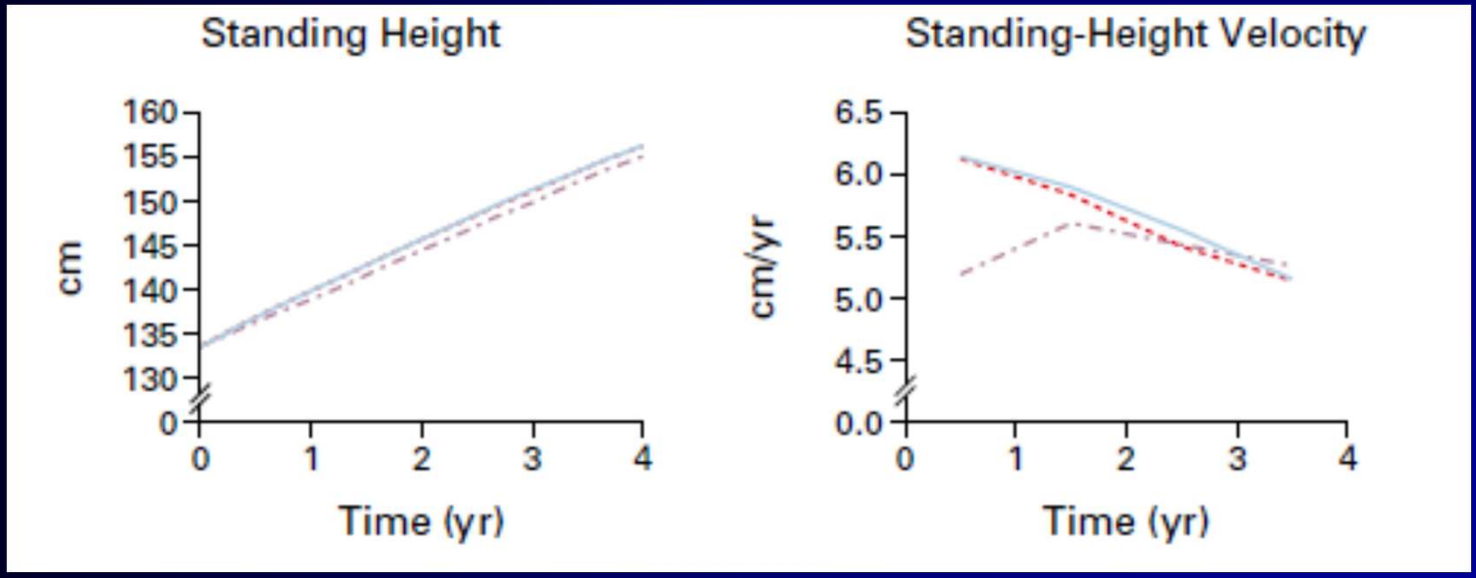
# FDA Label Requirements For ICS

"Corticosteroids, including intranasal and orally inhaled corticosteroids, have been shown to cause a reduction in growth velocity when administered to children and adolescents."

". . . The long-term effects of the observed reduction in growth velocity in children and adolescents using intranasal and/or orally inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for 'catch-up' growth following discontinuation of treatment with intranasal and/or orally inhaled corticosteroids has not been adequately studied. The growth of children and adolescents receiving intranasal and/or orally inhaled corticosteroids, including (Product Name), should be monitored, and the potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of treatment alternatives."

# ICS and Growth

- CAMP Trial
  - 1041 children, 5-12 years of age with mild-moderate asthma
    - 200 mcg budesonide, 8 mg of nedocromil or placebo BID for 4-6 years
    - Secondary outcomes: physical growth
  - Mean increase in  height difference was 1.1cm less than the placebo group
    - Evident mostly in the first year

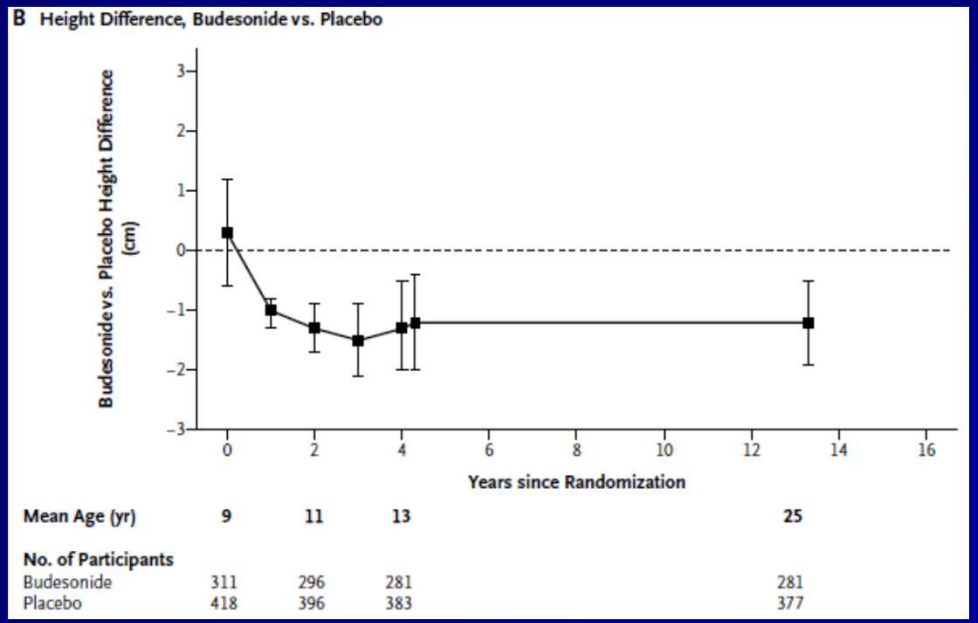



P=0.005 budesonide vs placebo

*N Engl J Med* 2000;343:1054-63

# ICS and Growth – CAMP Trial Adult Height

- Observational cohort – avg 4.3 years post-CAMP
  - Height measured 1-2 x/year for 8 years
- Mean adult height 1.2 cm less in budesonide group (p=0.001)
  - Larger daily ICS dose in first 2 years correlated with lower adult height (-0.1cm for each mcg/Kg body weight)
  - Reduction in height was NOT progressive or cumulative
  - ↓ growth velocity primarily in prepubertal children




*N Engl J Med* 2012;367:904-12

# ICS and Growth

- CARE Trial
  - 254 children ages 5-11 years with mild-moderate persistent asthma
    - Fluticasone 44 mcg 2 puffs bid with same dose or quintupled dose (220 mcg 2 puffs bid) for 7 days at early signs of loss of asthma control
    - Secondary outcome – linear growth
  - Growth rate in children in high-dose group was .23 cm/year less than children in the low dose group
    - Children < 8 years of age in high-dose group 0.12 cm/year lower growth per yellow zone treatment

*N Engl J Med* 2018;378:891-901

# ICS and Growth

- TREXA Trial
  - 843 children ages 5-18 years with mild persistent asthma
    - 4 treatment groups: BID beclomethasone with rescue beclomethasone/albuterol; BID beclomethasone with rescue placebo/albuterol; BID placebo with rescue beclomethasone/albuterol; BID placebo with rescue placebo/albuterol
    - Secondary outcome: measured growth
  - Children in the combined and daily Beclomethasone groups grew 1.1cm less

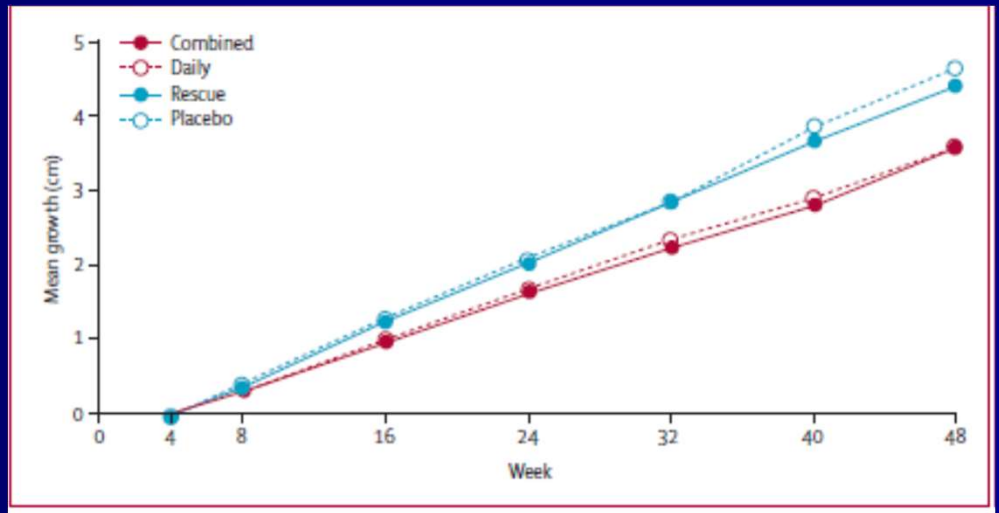



*Figure 4:* Linear growth by treatment group
Randomisation took place at week 4.

*Lancet* 2011;377:650-57

# Oral Corticosteroid (OCS) Sparing Effect of High Dose ICS

- Systematic review & meta-analysis of RCTs of OCS-sparing effects of high-dose ICS in OCS-dependent asthma (n=1,283, 11 studies)
- Prednisone dose ↓ per 1000mcg increase in ICS varied from 2.1-4.9mg, depending on type of ICS
- Ratio of prednisone-sparing effect due to systemic effects per 1000mcg of FP was 1.02 (95% CI 0.66-2.08) and for budesonide was 0.93 (95% CI 0.63-1.89)
- At least 60% of OCS dose ↓ can be attributed to effects from ICS systemic absorption

Maijers I et al. Eur Respir J 2020 Jan 2; 55(1)

# OCS Exposure & Adverse Effects (AE) in Asthmatic Patients

Market Scan Data

- Retrospective cohort study (≥ 18 yrs) in 2000-2014 Market Scan Data
- F/U 24 months-10 yrs after index date = first OCS use (n=72,063 OCS cohort and 156,373 in no OCS cohort)
- ≥ 4 OCS Rx's within the year had 1.29 (1.04) times the odds of a new AE within the year
- Each year of OCS exposure to ≥ 4 Rx's (current & past) resulted in 1.20 x the odds of an AE in the current year
- ≥ 4 Rx's → ↑ AE odds for osteoporosis, HTN, obesity, Type 2 DM, GI ulcers/bleeds, fractures, & cataracts (odds 1.21-144, depending on AE)
- Conclusion: each OCS Rx may result in cumulative burden on current & future health regardless of dose & duration. OCS sparing strategies essential.

Sullivan P W et al. J Allergy Clin Immunol 2018; 141:110-6

# Recommendations for Lifestyle Mods./Assessment: Glucocorticoids at any dose ≥ 3 months

- Lifestyle: exercise (weight-bearing), smoking ↓, nutrition
- Calcium intake 1200-1500 mg/day & Vitamin D
- Baseline measures
  - Height
  - BMD & Radiography (esp. if post-menopausal or risks)

Buehring B et al. J Allergy Clin Immunol 2013; 132:1019-30.

# Inhaled Long-Acting Beta-Agonists

- Not recommended as monotherapy for long-term control of persistent asthma
- Not currently recommended to treat acute symptoms or exacerbations
- May be used to prevent EIB
- Adjunct to ICS for long-term control as a combination ICS/LABA device; preferred adjunctive for ≥ 12 yrs

NAEPP Expert Panel Report 3, 2007

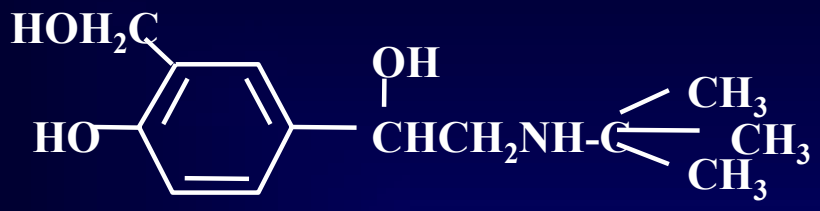
# General Safety of LABAs

- Sustained relaxation of airway smooth muscle, conducive to twice-daily administration
- FDA approved LABA for asthma
  - Salmeterol (Serevent®) and salmeterol with fluticasone (Advair® or AirDuo®)
  - Formoterol (with budesonide or mometasone)
  - Vilanterol (with fluticasone furoate, as Breo®)
- Highly selective beta-2 agonists
- Relevant cardiovascular effects at doses 4-5x those recommended
- Safety questioned in the SNS* and SMART** trials → black-box warning

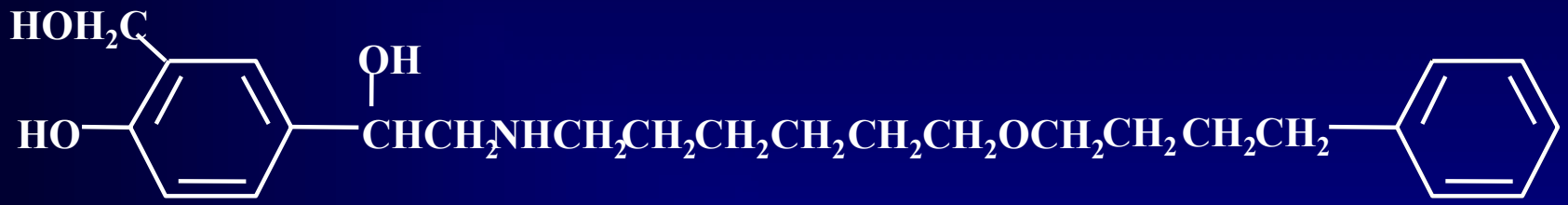
- *SNS = Serevent Nationwide Surveillance (1993)
- **SMART = Salmeterol Multicenter Asthma Research Trial (2006)

# Chemical Structures of Albuterol, Salmeterol, and Formoterol

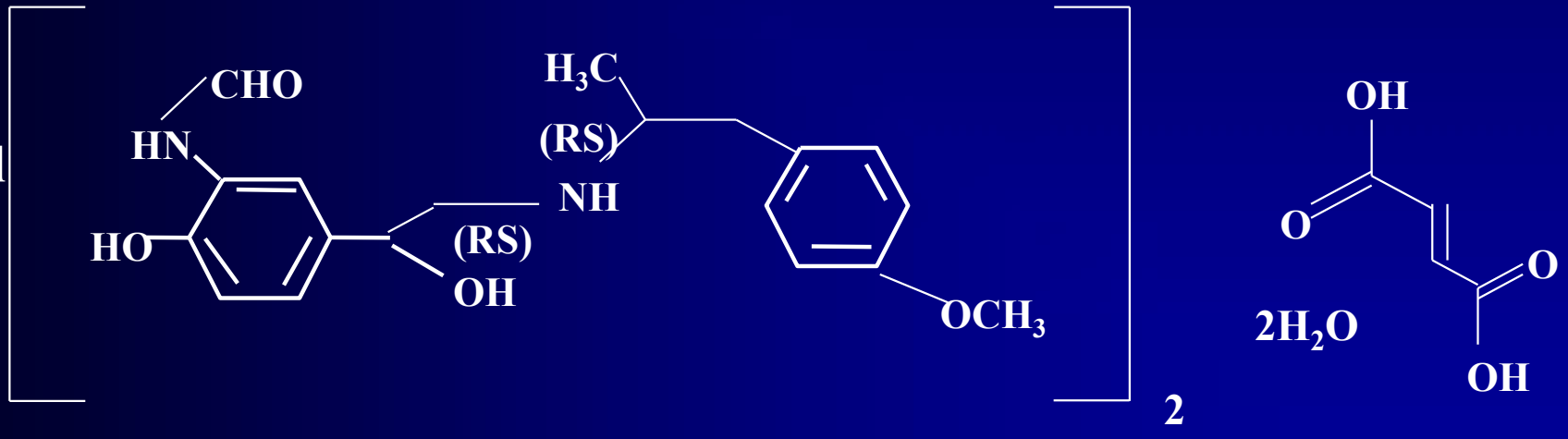
**Albuterol**




**Salmeterol**




**Formoterol**




Prescribing Information, GlaxoSmithKline.
Prescribing Information, Novartis.

# Relative Selectivity, Potency, Onset and Duration of Action of the β-Adrenergic Agonists

| Agent | $\beta_2$ Activity | | Agonist at $\beta_2$ (full/partial) | Onset and Duration of Action[a] | | |
|---|---|---|---|---|---|---|
| | $\beta_2$ Intrinsic Efficacy | $\beta_2$ Selectivity over β1 | | Bronchodilation (hours) | Protection (hours)[a] | Onset of bronchodilation |
| Isoproterenol | 1 | 0.24 | Full | 0.5–2 | 0.5–1 | 1-2 minutes |
| Albuterol/levalbuterol | Not done | 27 | Partial | 4–8 | 2–4 | 1-2 minutes |
| Formoterol | 0.95 | 150 | Full | ≥12 | **≥12** | 1-2 minutes |
| Salmeterol | 0.41 | 3000 | Partial | ≥12 | **≥12** | 10 minutes |
| Indacaterol | 0.86 | 16 | Nearly full | ≥24 | **≥24** | 1-2 minutes |
| Olodaterol | not done | not done | Nearly full | ≥24 | **≥24** | 1-2 minutes |
| Vilanterol | 0.70 | 2400 | Nearly full | ≥24 | not studied | 1-2 minutes |

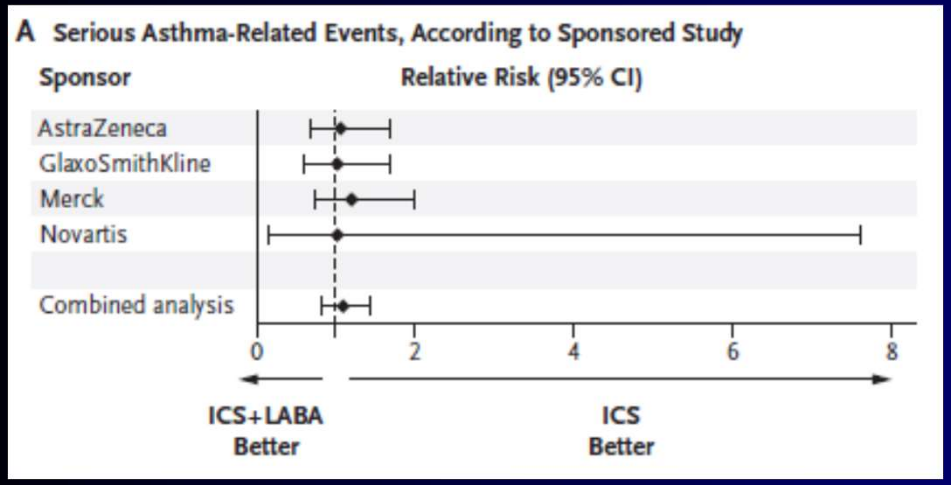
[a]Protection refers to the prevention of bronchoconstriction induced by exercise or nonspecific bronchial challenges.

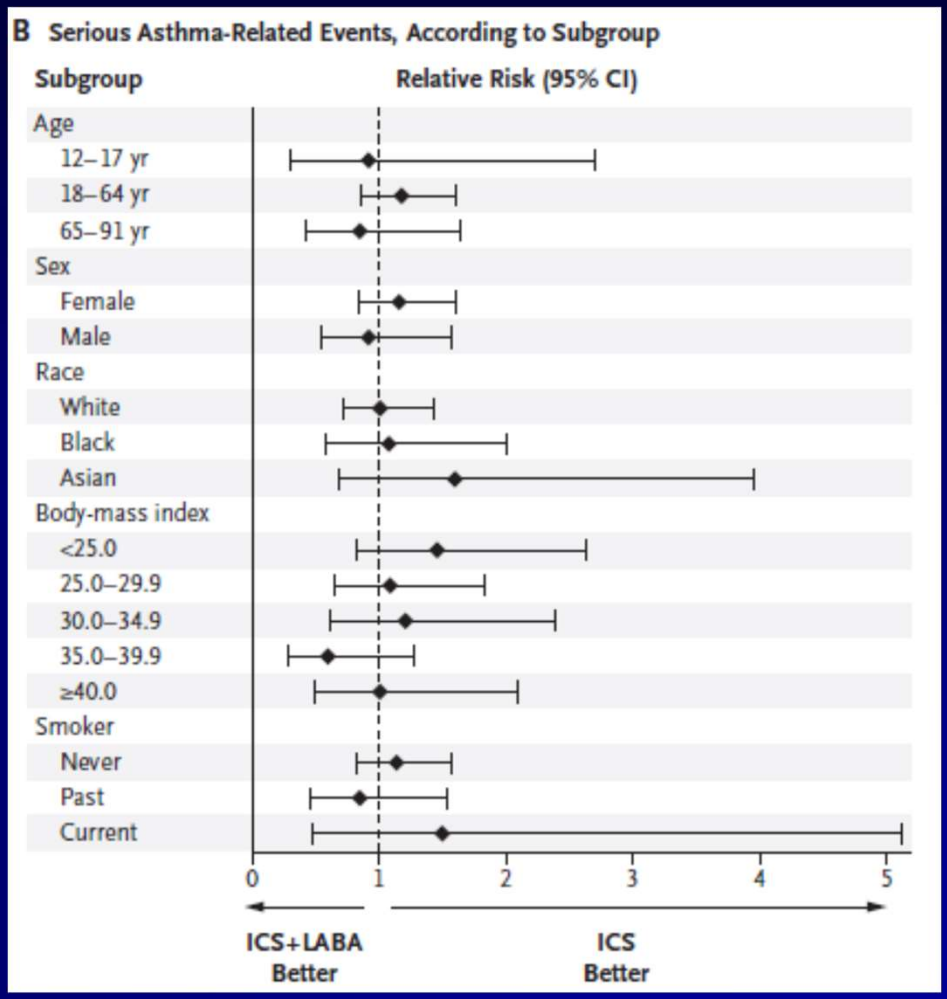
# Safety & Efficacy of LABA's in Asthma

- FDA mandated safety trials (2010)
  - 4 trials, 36,010 adolescents and adults (≥ 12 years) with persistent asthma
    - Multicenter, parallel, randomized, double-blind, noninferiority trial
    - 90% power, hazard ratio of 2.0
    - ICS plus LABA or ICS alone and prn unblinded SABA
  - Primary outcome – composite of asthma-related intubation or death
  - Secondary outcomes – serious asthma-related events and exacerbations in subgroups of patients at potential increased risk
  - Conclusion: combination therapy with a LABA plus ICS was noninferior to an ICS alone with respect to the risk of asthma-related intubation or death
    - No significant between subgroup differences in the frequency of serous asthma-related events (Lower relative risk of asthma exacerbations with combination therapy)

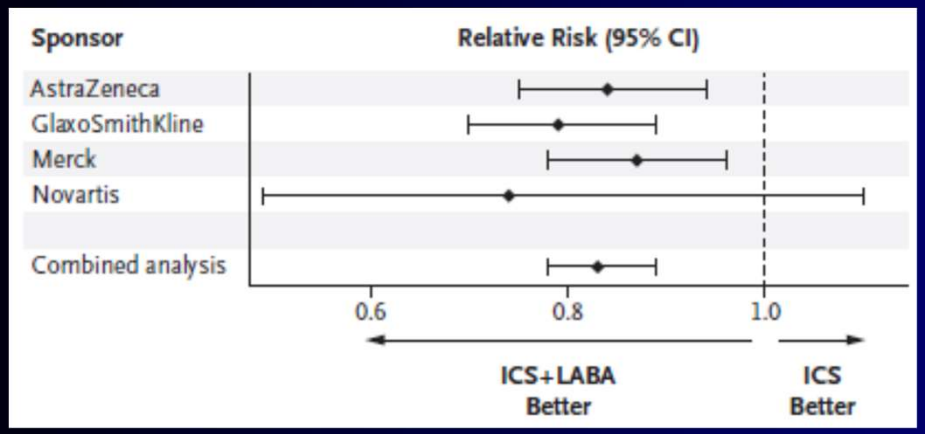
Busse, WW, et al. *NEJM* 2018:378:2497-505

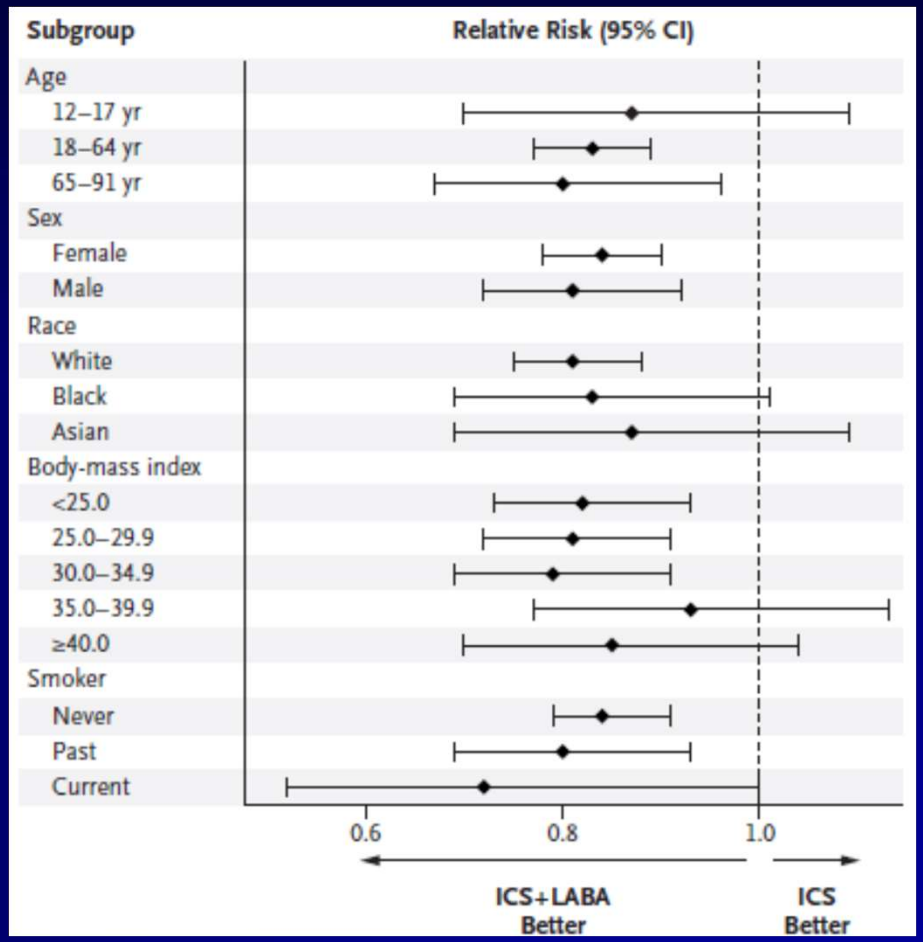
# Serious asthma-related events



# Asthma Exacerbations



# Pediatric LABA Safety & Efficacy Trial

- Multicenter, randomized, double-blind, active comparator
  - 6,208 children ages 4-11 years requiring daily asthma controller medications
  - Noninferiority trial with 95% confidence interval to 2.675 hazard ratio
  - 1:1 to fluticasone or fluticasone plus salmeterol
- Primary endpoint – 1st severe asthma-related event
  - Death, intubation, hospitalization
- Efficacy endpoint – time to 1st exacerbation requiring systemic CS
- Secondary efficacy endpoints – changes in baseline therapy, rescue-free days, asthma control
- Conclusion: Fluticasone alone vs fluticasone/salmeterol did not result in a higher risk of severe asthma events in children

Stempel DA, et al. NEJM 2016;375:840-9

# FDA Drug Safety Update on LABAs

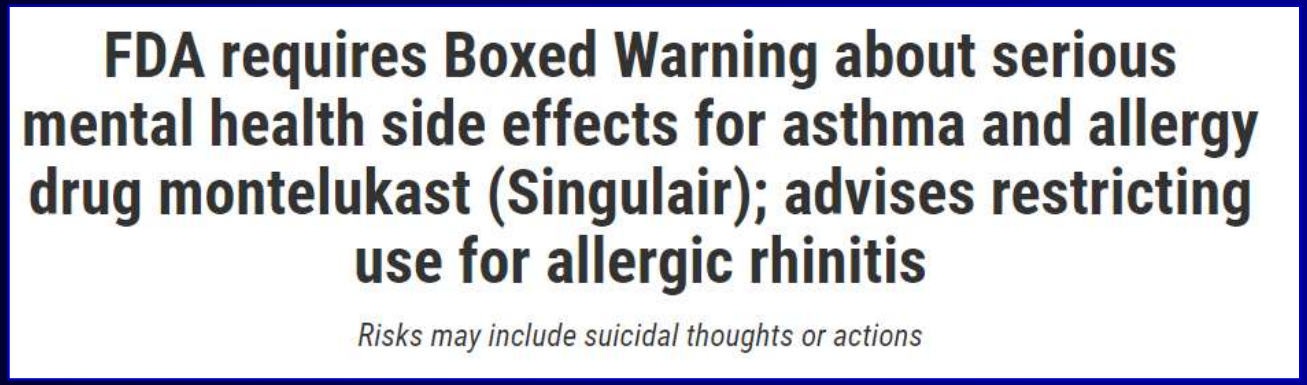
- New Study Results
  - ICS/LABA reduced exacerbations compared to ICS
  - Efficacy information added to ICS/LABA drug labels
  - Combination of ICS/LABA more effective in decreasing asthma attacks
- Boxed Warning about risk of asthma-related deaths removed from labels of ICS/LABA combos
- Boxed Warning will remain on single-ingredient LABA products approved for asthma, EIB, or COPD

# Leukotriene Modifiers

- 2 cysteinyl leukotriene receptor antagonists (montelukast and zafirlukast) and one 5-lipoxygenase inhibitor zileuton)
- Less effective than ICS as monotherapy; not as effective as LABAs as add-on
- Oral therapy, administered 1-2x/day
- Side effects
  - Headaches
  - ↑LFTS with zileuton
  - Neuropsychiatric events (FDA label change 8/09), including nightmares, depression, and aggression
  - Ongoing concern about Rx in very young children, & for non-asthma indications, eg. cough
  - ? Linked to Churg-Strauss syndrome (allergic granulomatous angiitis); rare

# Adverse Effects with Montelukast

- FDA boxed warning in March 2020 about risk of serious neuropsychiatric events, including suicidality, with montelukast
  - Includes suicidality in adults and adolescents
  - Nightmares and behavioural problems in children
- Before prescribing montelukast, health professionals should consider its benefits and risks, and patients should be counselled about the risk of neuropsychiatric events

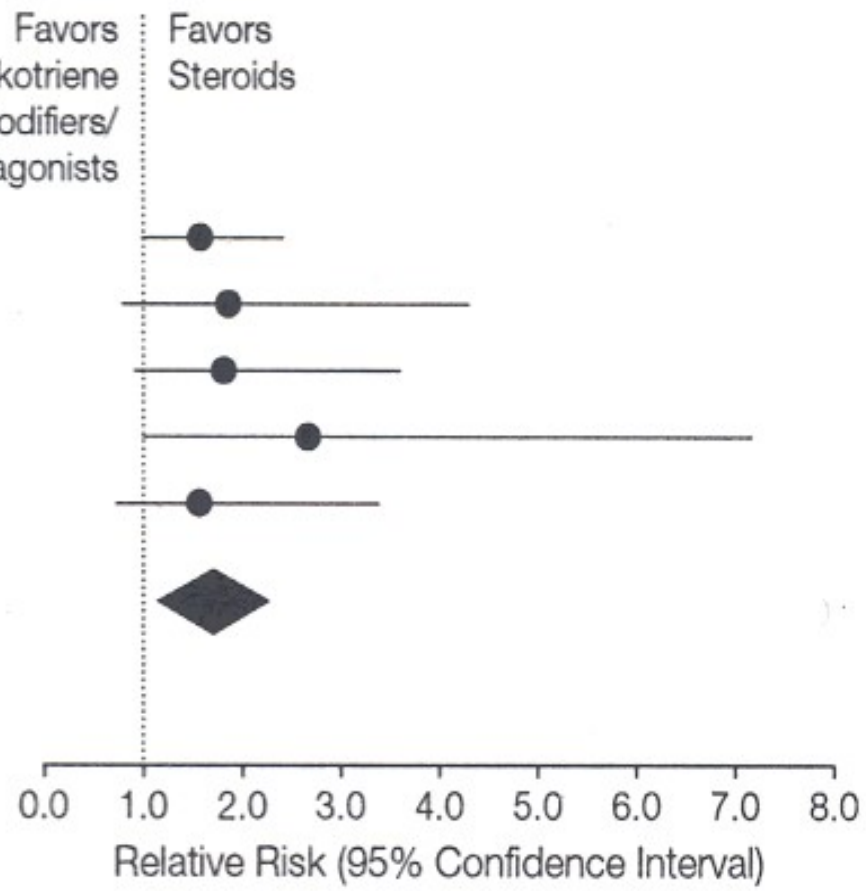


# Effects of LTRAs on Exacerbations

B vs Inhaled Corticosteroids

| Study | Participants, No. | Age, y, Mean (SD)* | FEV, % Predicted, Mean (SD)* |
|---|---|---|---|
| Malmstrom,[27] 1999 | 638 | 35 | 65 (10) |
| Bleeker,[81] 2000 | 451 | 31 | 67 |
| Busse,[82] 2001 | 533 | 35 | 65 (9) |
| Busse,[26] 2001 | 224 | NR | 66 |
| Meltzer,[42] 2002 | 522 | 36 | 66 |

Pooled Summary
(RR, 1.72; 95% CI, 1.28-2.31;
Test for Heterogeneity: $\chi^2 = 1.02$, $P = .91$)



# Long-Acting Anticholinergics in Asthma

- FDA approved for asthma ≥ 12 years
- TALC trial in adults (Peters SP, N Engl J Med 2010; 363: 171S)
  - Tiotropium & ICS superior to doubling ICS & equivalent to LABA & ICS
- Tiotropium trial in adults with poorly controlled asthma on ICS/LABA (Kerstjens HA, N Engl J Med 2012; 367: 1198)
  - Increased time to 1$^{st}$ severe exac. & improved lung function

# Recommendations for Use of LAMA's for Asthma (≥ 12 yrs)

- In ≥ 12 yrs with uncontrolled persistent asthma, NAEPP conditionally recommends against adding LAMA to ICS compared to adding LABA to ICS (moderate certainty evidence)
- In ≥ 12 yrs with uncontrolled persistent asthma, NAEPP conditionally recommends adding LAMA to ICS controller therapy compared to continually the same dose of ICS alone (moderate certainty evidence)
- Individuals with urinary retention or glaucoma should not receive LAMA

J Allergy Clin Immunol 2020;146:1217-70

# Supplemental Reference Info.

# Quick-Relief Asthma Medications Short-Acting Inhaled Beta$_2$-Agonists

| MEDICATION | DOSAGE FORM | ADULT DOSE | CHILD DOSE |
|---|---|---|---|
| Albuterol HFA MDI | 90 mcg/puff, 200 puffs | 2 puffs tid-qid prn | 2 puffs tid-qid prn |
| Albuterol Respi Click | 90 mcg/puff, 200 puffs | 2 puffs tid-qid prn | Not approved < age 12 |
| Levalbuterol HFA MDI | 45 mcg/puff | 2 puffs tid-qid pm | 2 puffs tid-qid pm |

# Quick-Relief Asthma Medications
# Short-Acting Nebulized Beta$_2$-Agonists

| MEDICATION | DOSAGE FORM | ADULT DOSE | CHILD DOSE | COMMENTS |
|---|---|---|---|---|
| Albuterol Neb. Sol. | 5 mg/mL (0.5%)<br>2.5 mg/3 mL<br>1.25 mg/3 mL<br>0.63 mg/3 mL | 1.25-5 mg in 3 cc of Saline q 4-8 hours | 0.05 mg/kg (min 1.25 mg, max 2.5 mg) in 3 cc of saline q 4-6 hours | May mix with cromolyn or ipratropium nebulizer solutions. May double dose for severe exacerbations. |
| Levalbuterol (R-albuterol) Neb. Sol. | 0.31 mg/3 mL<br>0.63 mg/3 mL<br>1.25 mg/3 mL | 0.63 mg-2.5 mg q 4-8 hours | 0.025 mg/kg (min. 0.63 mg, max. 1.25 mg) q 4-8 hours | 0.63 mg of levalbuterol is equivalent in efficacy and side effects to 1.25 mg of racemic albuterol. The product is a sterile-filled preservative-free unit dose vial. |

# Long-Term Control Asthma Medications
# Leukotriene Modifiers

| MEDICATION | DOSAGE FORM | ADULT DOSE | CHILD DOSE | COMMENTS |
|---|---|---|---|---|
| Montelukast (Singulair®) | 4 mg oral granules<br>4 mg or 5 mg chewable tablet<br>10 mg tablet | 10 mg qhs | •4 mg oral granules (12-23 months of age<br>4 mg qhs (2-5 years of age)<br>5 mg qhs (6-14 years of age)<br>10 mg qhs (>14 years of age) | •Montelukast exhibits a flat dose-response curve. Doses >10 mg will not produce a greater response in adults. |
| Zafirlukast (Accolate®) | 10 or 20 mg tablet | 40 mg daily (20 mg tablet bid) | •20 mg daily (5-11 years of age) (10 mg tablet bid) | •For zafirlukast, administration with meals decreases bio-availability; take at least 1 hr before or 2 hrs after meals. |
| Zileuton (Zyflo® CR) | 600 mg tablet | 1200 mg bid | | •For zileuton, monitor hepatic enzymes (ALT).<br>•Some drug interactions.(CYP3A4) (warfarin and theophylline) |

# Long-Term Control Asthma Medications
# Methylxanthines

| MEDICATION | DOSAGE FORM | ADULT DOSE | CHILD DOSE | COMMENTS |
|---|---|---|---|---|
| Theophylline | Liquids, sustained-release tablets, and capsules | Starting dose 10 mg/kg/day up to 300 mg max; usual max 800 mg/day | Starting dose 10 mg/kg/day; usual max:<br>•< 1 yr of age: 0.2 (age in weeks) + 5 = mg/kg/day<br>•≥1 yr of age: 16 mg/kg/day | •Adjust dosage to achieve serum concentration of 5-15 mcg/mL at steady-state (at least 48 hrs on same dosage).<br>•Due to wide interpatient variability in theophylline metabolic clearance, routine serum theophylline conc. monitoring is important.<br>•Many factors can affect theophylline concs. |

# Long-Term Control Asthma Medications
# Long-Acting Inhaled Beta$_2$-Agonists (LABA)

| MEDICATION | DOSAGE FORM | ADULT DOSE | CHILD DOSE | COMMENTS |
|---|---|---|---|---|
| Salmeterol | DPI 50 mcg/blister | 1 blister q 12 hrs | 1 blister q 12 hrs | •Should not be used for symptom relief or exacerbations. Use with corticosteroids.<br><br>•May use one dose nightly for symptoms. |

# Long-Term Control Asthma Medications
# Combined ICS and LABA

| MEDICATION | DOSAGE FORM | ADULT DOSE | CHILD DOSE | COMMENTS |
|---|---|---|---|---|
| Flutacasone/ Salmeterol (Advair®) | DPI 100 mcg, 250 mcg, or 500 mcg/50 mcg | 1 inhalation bid; dose depends on severity of Asthma | 1 inhalation bid; dose depends on severity of asthma | •Not FDA approved in children < 5 years of age. 100/50 for patient not controlled on low-to-medium dose ICS. 250/50 for patients not controlled on medium-to-high dose ICS. |
| | MDI HFA 45/21 mcg, 115/21 mcg, 230/21 mcg | 2 inhalations bid; dose depends on severity of asthma | 2 inhalations bid; dose depends on severity of Asthma | Not FDA approved in children < 12 years of age. |
| Air Duo ™ | DPI 55 mcg, 113 mcg or 232 mcg/14 mcg | 1 inhalation bid, dose depends on severity of asthma | N/A | Not FDA approved in children < 12 years of age |

# Long-Term Control Asthma Medications Combined ICS and LABA (Cont'd)

| MEDICATION | DOSAGE FORM | ADULT DOSE | CHILD DOSE | COMMENTS |
|---|---|---|---|---|
| Budesonide/ Formoterol (Symbicort) | HFA MDI<br>80 mcg/4.5 mcg<br>160 mcg/4.5 mcg | 2 puffs bid; dose depends on severity of asthma | 2 puffs bid; dose depends on severity of asthma | Not FDA approved in children < 12 years of age. |
| Mometasome/ Formeterol (Dulera) | HFA MDI<br>100 mcg/5 mcg<br>200 mcg/5 mcg | 2 puffs bid; dose depends on severity | 2 puffs bid; dose depends on severity | Not FDA approved in children < 12 years of age. |
| Fluticasone Furoate/ Vilanterol (Breo) | DPI<br>100 mcg/25 mcg<br>200 mcg/25 mcg | 1 inhalation daily; dose depends on severity | N/A | Not FDA approved in < 18 years of age. |

# Use of Systemic Corticosteroids for Long-Term Control

| MEDICATION | DOSAGE FORM | ADULT DOSE | CHILD DOSE | COMMENTS |
|---|---|---|---|---|
| Methyl-prednisolone | 2, 4, 8, 16, 32 mg tablets | •7.5-60 mg daily in a single dose in a.m. or qod as needed for control | •0.25-2 mg /kg daily in single dose in a.m. or qod as needed for control | •For long-term treatment of severe persistent asthma, administer single dose in a.m. either daily or on alternate days. |
| Prednisolone | 5 mg tablets, 5 mg/5 cc, 15 mg/5 cc | •Short-course "burst": to achieve control 40-60 mg per day as single or 2 divided doses for 3-10 days | •Short-course "burst": 1-2 mg/kg/day, max. 60 mg/day for 3-10 days | •Short courses or "bursts" are effective for establishing control when initiating therapy or during a period of gradual deterioration. |
| Prednisone | 1, 2.5, 5, 10, 20, 50 mg tablets; 5 mg/cc, 5 mg/5 cc | | | •The burst should be continued until patient achieves 80% PEF personal best or symptoms resolve. This usually requires 3-10 days but may require longer. No evidence that tapering the dose following improvement prevents relapse. |