



LONG-ACTING BETA AGONISTS

AND ICS/LABA COMBINATIONS



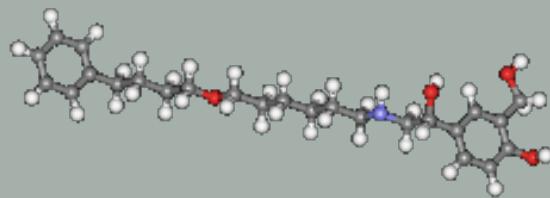
DISCLOSURE

- Dr. Francisco has no financial interest in any commercial entity discussed in this presentation
- Dr. Francisco will not discuss experimental or off-label use of medications or devices

OBJECTIVES

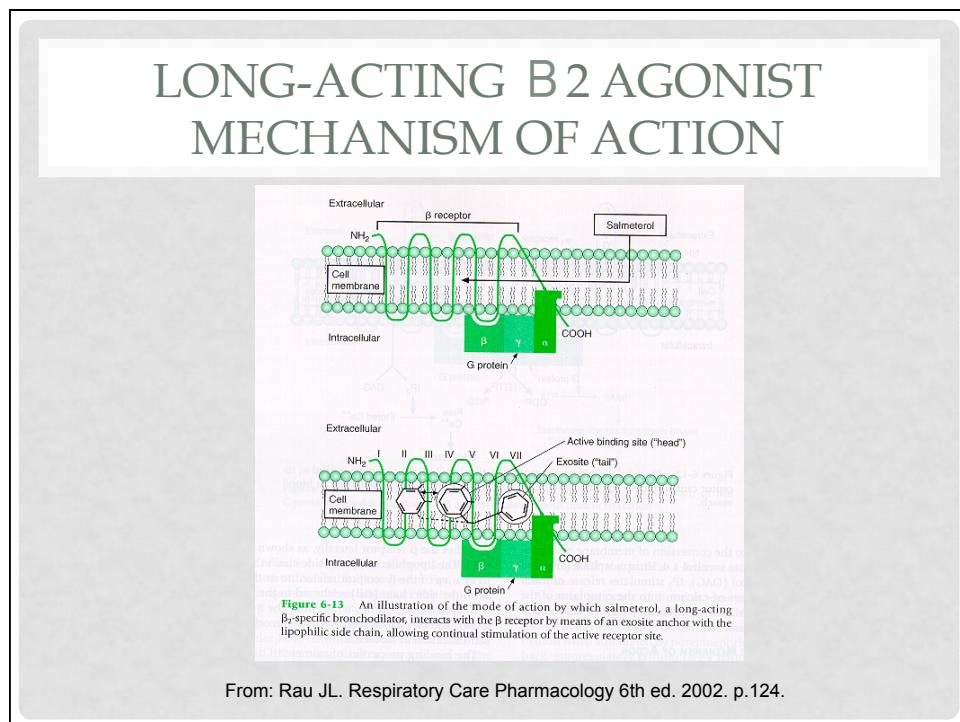
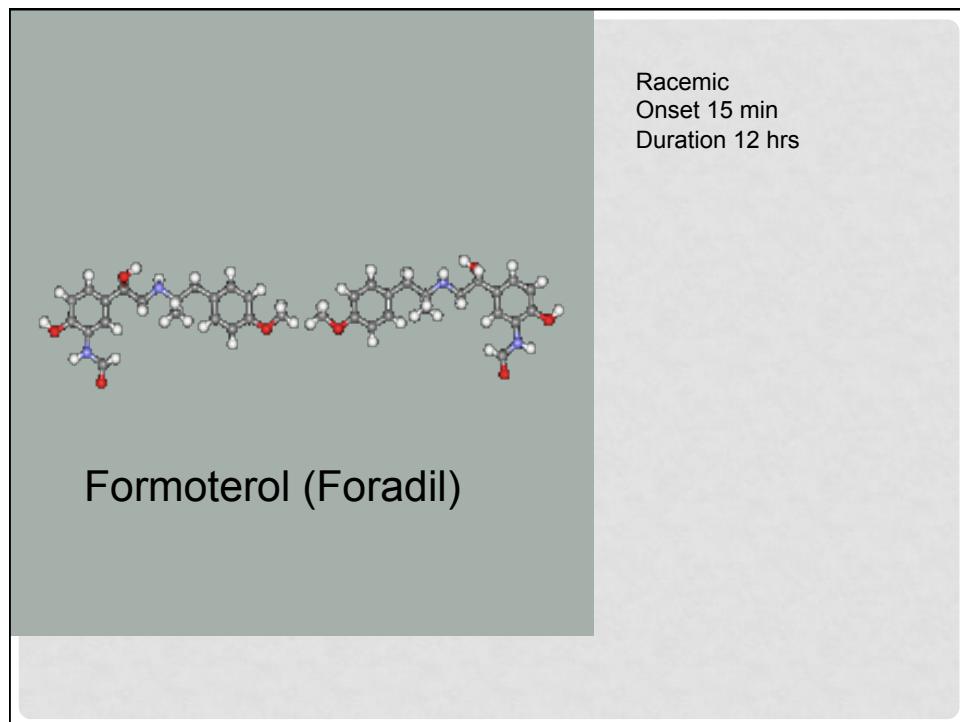
- 1) Describe the mode of action, therapeutic value and role in the management of asthma.
- 2) Identify potential adverse effects and strategies for managing patients to minimize side effects
- 3) Evaluate the cost, barriers and potential benefit of this class of medications.

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Salmeterol (Serevent)

Racemic
Lipophilic: anchors in the cell wall to prolong effect
Onset 20-40 min
Duration 12 hours



Long-acting β_2 adrenergic receptor agonists

- Relax airway smooth muscle
- Cause bronchodilation
- Same mechanisms as SABA

Chronic treatment with a receptor agonists often leads to receptor desensitization and a diminution of effect.

Goodman & Gilman's The Pharmacological Basis of Therapeutics - 11th Ed. (2006)

LABA POTENTIAL ADVERSE EFFECTS

- Tachycardia, skeletal muscle tremor, hypokalemia
- Diminished broncho-protective effect within 1-6 weeks of chronic therapy
- Increase risk of severe, life-threatening exacerbations

LABA CONTROVERSY

- Increased risk of life-threatening and fatal exacerbations related to LABA in asthma
 - Castle et al, BMJ 1993;306:1034
- Respiratory related death or life-threatening experiences in all patients (1.98/1000 person-years)
 - 0.48/1000 for all persons with asthma
- Disparate increase in combined asthma-related death or life-threatening experience
 - Increase in respiratory related deaths and life threatening experiences in African-Americans (5.8 vs. 1.2 /1000 person-years for Caucasians)
 - Nelson et al Chest 2006;129:15-26.
 - (SMART study)

CAUSE OF DEATH RELATED TO LABAS

- Worsened asthma control
 - Repeated stimulation of β receptors results in desensitization
 - Uncoupling and internalization of receptors
 - Followed by downregulation
 - Decrease in receptor density and receptor gene expression
 - Increased bronchial hyperreactivity
 - Reduced response to rescue inhaler

LABA CONTROVERSY: WHY THE RACIAL DIFFERENCE?

At screening, African Americans:

- Had a lower PEF (78% vs. 85%)
- Had more nocturnal sx. (59% vs. 67%)
- Had increased hospitalizations, ED visits
- Had less ICS use (38% vs. 49%)
- Different patient behaviors?
- Genetic variation in β adrenergic receptor?

β_2 -ADRENOCEPTOR POLYMORPHISM

- Variant of the β_2 adrenergic receptor in which glycine replaces arginine at position 16 (Gly 16) shows an increased rate of down-regulation in response to agonist exposure.
- Polymorphism occurs with equal frequency in asthmatic and non-asthmatic populations.
- Some evidence that asthmatics who are homozygous for Gly 16 receptors are less responsive to β_2 -agonist therapy than wild-type controls

Martinez, F.D., Graves, P.E., Baldini, P.E., et al. Genetic polymorphisms of the β_2 adrenergic receptor and response to albuterol in children with and without a history of wheezing. *J. Clin. Invest.*, 1997, 100:3184-3188.

Tan, S., Hall, I.P., Dewar, J., et al. Association between β_2 -adrenoceptor polymorphism and susceptibility to bronchodilator desensitization in moderately severe stable asthmatics. *Lancet*, 1997, 350:995-999.

β_2 -adrenoceptor polymorphism

- Polymorphism of the β_2 receptor did not appear to determine the response to long-term inhaled β_2 -agonist treatment¹
- The complexity of the genotype by response effects makes clinical application of the ADRbeta₂ variations limited²

¹ Hancox, R.J., Sears, M.R., and Taylor, D.R. Polymorphism of the β_2 -adrenoceptor and the response to long-term β_2 -agonist therapy in asthma. *Eur. Respir. J.*, 1998, 11:589-593.

² Hawkins GA, Weiss ST, Bleeker ER. Clinical consequences of ADRbeta2 polymorphisms. *Pharmacogenomics*. 2008 Mar;9(3):349-58

LABA CONTROVERSY

- Meta-analysis of 19 trials and 33,826 participants
- LABA increases risk for hospitalization for an asthma exacerbation (OR=2.6), life-threatening asthma attack (OR=1.8), and asthma-related death (OR=3.5)
- Increase in asthma-related death of 0.06% - 0.07%/6 months
- Salmeterol may be responsible for 4000 of the 5000 asthma deaths/year!

Salpeter et al. *Ann Int Med* 2006;144:904-912.

LABA CONTROVERSY

Pro

- Reduction in asthma exacerbations
- Widely-used to treat COPD as well
 - Still, β agonists increased respiratory deaths (rr=2.5) vs. decreased respiratory deaths with anticholinergics (rr=0.3)

Con

- Increase asthma deaths after LABAs were introduced
- Similar risks for morbidity and mortality exist for salmeterol vs formoterol
- Associated with unnecessary hospitalization, ICU admission and death

SALMETEROL WARNING

WARNING

Long-acting beta₂-adrenergic agonists, such as salmeterol, the active ingredient in SEREVENT DISKUS, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, SEREVENT DISKUS should only be used as additional therapy for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies, including SEREVENT DISKUS. Data from a large placebo-controlled US study that compared the safety of salmeterol (SEREVENT® Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo) (see WARNINGS and CLINICAL TRIALS: Asthma: *Salmeterol Multi-center Asthma Research Trial*).

"This information could be used to reassess whether these agents should be withdrawn from the market" Salpeter et al.

EPR-3 CONCLUSIONS ABOUT LABA USE

- **ALWAYS** use adjunctively to ICS
- **DO NOT** use as monotherapy for asthma
- Not to be used for quick relief
- May be used before exercise to prevent EIB

EPR-3: SAFETY OF LABA

- Addition of LABA when asthma is not well controlled on low-medium dose ICS decreases symptoms, exacerbations and SABA use
- Black box warning warranted
- Recognize the risk
- Give equal weight to increasing ICS or addition of LABA (note step 3 in age group 0-4 years)

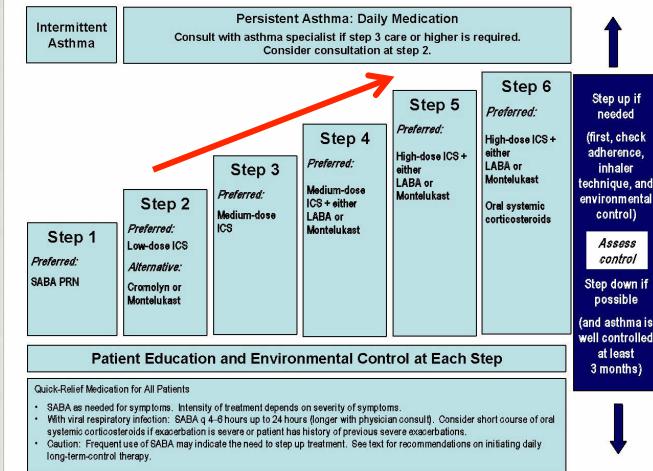
EPR3 Guide to Stepping Therapy Up or Down

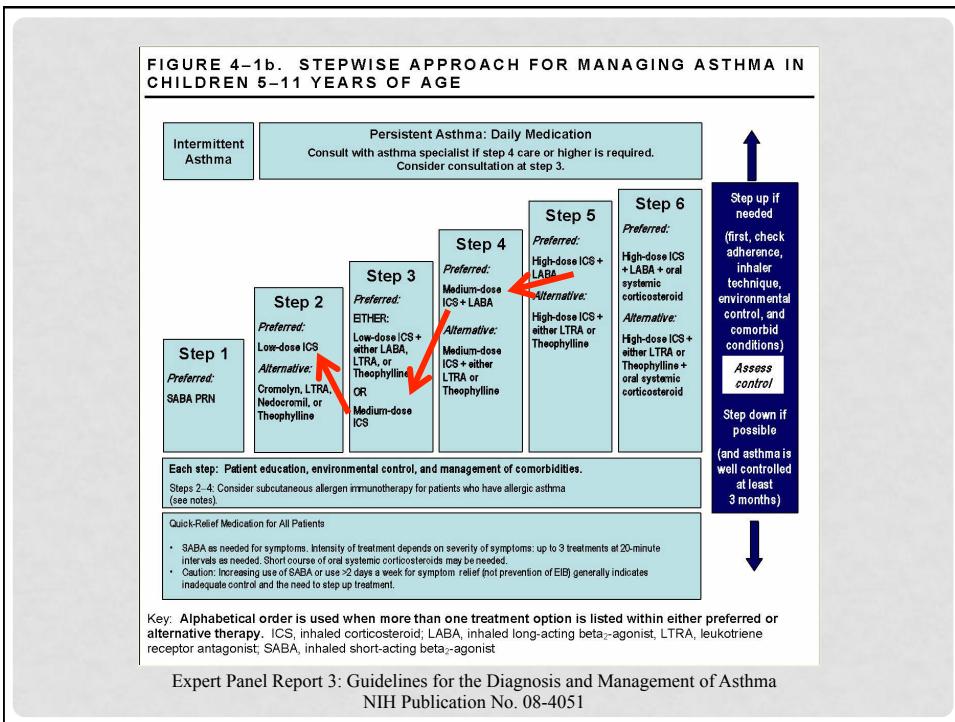
- **Step up IF** needed
- FIRST, check adherence
- THEN, check inhaler technique
- AND, check environmental control
- **Step Down**, IF asthma is well controlled for 3 months or longer

Must base therapy step changes on assessment of adherence, inhalation technique and triggers



FIGURE 4-1a. STEPWISE APPROACH FOR MANAGING ASTHMA IN CHILDREN 0-4 YEARS OF AGE





CHILDREN 5 TO 11 YEARS OLD

Moderate persistent asthma or asthma inadequately controlled by low dose ICS

Step 3 care equal weight given to:

- Increasing dose to medium dose ICS
- Add LABA to low dose ICS

CHILDREN 5 TO 11 YEARS OLD

LABA/ICS combinations are the preferred therapy for long term control in moderate to severe persistent asthma (Step 4 care or higher)

[Evidence B]

CHILDREN 5 TO 11 YEARS OLD

Severe persistent asthma or asthma inadequately controlled on Step 3 Care

The combination of LABA & ICS is preferred

YOUTHS \geq 12 YEARS AND ADULTS

LABA/ICS combinations are the preferred therapy for long term control in moderate to severe persistent asthma (Step 4 care or higher)

[Evidence A]

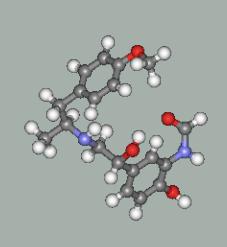
LABA/ICS ADVERSE REACTIONS

- Nasopharyngitis
- Dysphonia
- Headache
- Upper respiratory tract infection
- Pharyngo-laryngeal pain
- Sinusitis
- Stomach discomfort
- Tremor
- Dysrhythmias

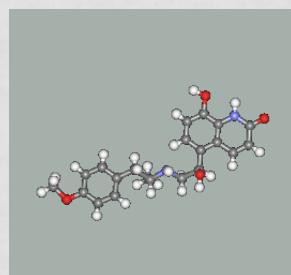
ICS/LABA THERAPY DOSING- APPLYING EPR3 GUIDELINES

- Which ICS/LABA products can be used in step 5 for ages 12 years and older
- Which ICS/LABA products can be used for step 4 for children ages 5-11?
- What other considerations are important in selecting an ICS/LABA product?

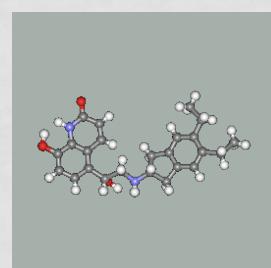
OTHER LABA AGENTS (COPD)



R,R Formoterol



Carmoterol



indacaterol

SUMMARY

- Anchorage of LABAs in lipophilic receptors gives them their long duration of action
- The addition of LABA to ICS should be given equal weight to increasing ICS
- Do not use LABA as monotherapy
- Several LABAs are under development that may offer once daily dosing lipophilic ICS



LEUKOTRIENE MODIFIERS: LEUKOTRIENE RECEPTOR ANTAGONISTS (LTRA) AND 5-LIPOXYGENASE INHIBITOR

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