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.

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

Salmeterol (Serevent)
Formoterol (Foradil)

Long-Acting β₂ Agonist

Long-acting $\beta_2$ 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.

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

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

CAUSE OF DEATH RELATED TO LABAS

- Worsened asthma control
  - Repeated stimulation of $\beta$ 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 $\beta$ adrenergic receptor?

B$_2$-ADRENOCEPTOR POLYMORPHISM

- Variant of the B$_2$ 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 B$_2$-agonist therapy than wild-type controls.

β₂–adrenoceptor polymorphism

- Polymorphism of the β₂ receptor did not appear to determine the response to long-term inhaled β₂-agonist treatment.
- The complexity of the genotype by response effects makes clinical application of the ADRβ₂ variations limited.

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!

# LABA CONTROVERSY

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<th><strong>Pro</strong></th>
<th><strong>Con</strong></th>
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<tr>
<td>- Reduction in asthma exacerbations</td>
<td>- Increase asthma deaths after LABAs were introduced</td>
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<td>- Widely-used to treat COPD as well</td>
<td>- Similar risks for morbidity and mortality exist for salmeterol vs formoterol</td>
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<td>- Still, β agonists increased respiratory deaths (rr=2.5)</td>
<td>- Associated with unnecessary hospitalization, ICU admission and death</td>
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<td>vs. decreased respiratory deaths with anticholinergics (rr=0.3)</td>
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# 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 (SEEREVENT® 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

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**FIGURE 4–1a, STEPWISE APPROACH FOR MANAGING ASTHMA IN CHILDREN 0–4 YEARS OF AGE**

- **Step 1**: Preferred: SABA, PRN
- **Step 2**: Preferred: Medium-dose ICS
  - Alternative: Cromolyn or Mometasone
- **Step 3**: Preferred: Medium-dose ICS + either LABA or Montelukast
- **Step 4**: Preferred: High-dose ICS + either LABA or Montelukast
- **Step 5**: Preferred: High-dose ICS + Oral systemic corticosteroids
- **Step 6**: Step up if needed
  - (and asthma is well controlled for 3 months)
  - Step down if possible
  - (and asthma is well controlled for at least 3 months)

Key: Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy. ICS, inhaled corticosteroid; LABA, inhaled long-acting beta₂-agonist; SABA, inhaled short-acting beta₂-agonist.

Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma
NIH Publication No. 08-4051
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 ≥ 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