

Background on Safety Issues with Long-Acting Beta Agonists for Asthma

**Joint Advisory Committee
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Outline

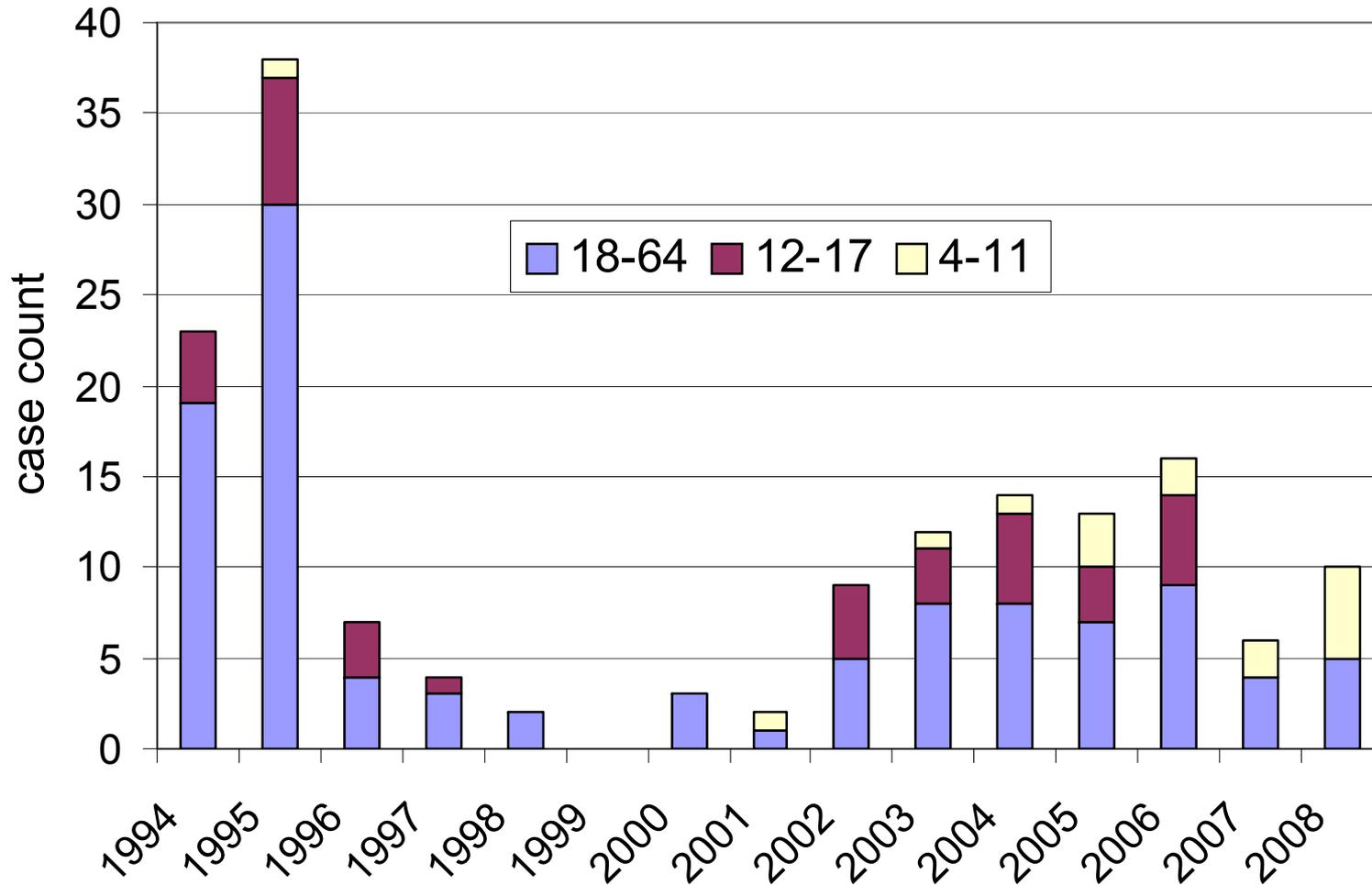
- **History and postmarketing surveillance data on long-acting beta agonists (LABAs)**
- **Observational pharmacoepidemiology studies**
- **Data from large safety trials of salmeterol**
- **Overview of clinical trial meta-analyses**
- **Current use patterns for LABAs**
- **Summary/Conclusions**

What Have Postmarketing Surveillance Data Shown for LABAs?

Beta agonists and asthma deaths: Experience with isoproterenol and fenoterol

- In the 1960's, an epidemic of asthma deaths in younger patients (aged 5-34 y.o.) occurred in countries which marketed high-dose isoproterenol inhalers
 - Stolley PD. Why the United States was spared an epidemic of deaths due to asthma. *Am Rev Respir Dis* 1972;105:883-90
- In the early 1990's, asthma deaths (among patients 5-34 y.o.) in New Zealand decreased when the inhaled short acting beta agonist fenoterol was removed from the market
 - Beasley R.A historical perspective of the New Zealand asthma mortality epidemics. *J Allergy Clin Immunol.* 2006;117:225-8

Trends in receipt of domestic, spontaneous cases of death in association with LABAs among reports with both age (4 - 64 years) and indication ("asthma"), 1994 through November 2008.



Conclusions regarding postmarketing surveillance data for LABAs

- Causality assessment from spontaneous postmarketing reports is difficult when there is confounding by indication
 - Events of interest (serious asthma events) are related to condition being treated with the drug
 - Not possible to reliably estimate incidence because number of reports received reflects an unknown degree of under-reporting
 - Must turn to more systematic data sources

What are the Findings from Observational Pharmacoepidemiology Studies of LABAs in the Treatment of Asthma?

LABA Observational Safety Studies

A number of observational epidemiology studies of LABAs have been conducted

1. *Williams et al. Thorax 1998;53:7-13*
2. *Meier and Jick. Thorax 1997;52:612-617*
3. *Lanes et al. Am J Respir Crit Care Med 1998;158:857-861*
4. *Anderson et al. BMJ 2005;330:117*
5. *Lanes SF et al. Thorax 2002; 57:683-686*
6. *Davis et al. Pharmacoepidemiol Drug Safe 2007;16:S169*
7. *Gomez Dinger et al., AAAAI 2008 Annual Meeting*

LABA Observational Safety Studies: Comments

- Despite large sample sizes, problems include
 - Inconsistent findings regarding catastrophic asthma outcomes
 - Limited data relevant to pediatric population
 - Difficulty obtaining adequate statistical power for outcomes of interest
 - Difficulty accounting for differences in asthma severity between groups being compared
- On balance, of less inferential value than controlled clinical trial data

What Do Clinical Trial Data Show Regarding Risk of Serious Asthma Outcomes with LABAs?

- Large, randomized, safety trials
 - Salmeterol: SNS and SMART
 - Formoterol: No comparable studies
- Meta-analyses of controlled clinical trial data

Definitions: Risk Difference (RD) and Number Needed to Harm (NNH)

- Exposing how many patients will produce one excess adverse event?
- Calculation: NNH = inverse of RD
 - If study incidence is 5% on drug and 3% on placebo
 - Risk difference = $0.05 - 0.03 = 0.02$
 - Or, two excess events per 100 study subjects
 - Number Needed to Harm (NNH) is reciprocal of risk difference
 - $1/0.02 = 50$
 - One excess adverse event for every 50 patients given drug in the study

Serevent Nationwide Surveillance (SNS) study

Castle et al. BMJ. 1993;306: 1034-7

- Large, randomized, double blind, 16-wk safety trial
- Location: UK
- Purpose: assess safety; no a priori primary endpoint
- Salmeterol 50 mcg BID versus Albuterol 200 mcg QID
- 2:1 randomization ratio salmeterol:albuterol
- Mostly adults, 6% of subjects under 18 y.o., mild asthma
- Data on concomitant ICS use during trial lacking
- Investigators followed up dropouts to determine vital status

Serevent Nationwide Surveillance (SNS) study

Castle et al. BMJ. 1993;306: 1034-7

Outcome	Number of pts.		Relative Risk (p-value)
	Salmeterol (N=16,787)	Albuterol (N=8,393)	
Asthma-related Withdrawals	488	318	0.8 (0.0002)
Asthma-related death	12	2	3.0 (0.105)
All cause death	54	20	1.4 (0.250)

SMART trial

Sources: Serevent, Advair labeling, Nelson et al. Chest 2006; 129: 15-26,
www.gsk-clinicalstudyregister.com

- Large, randomized, 28 week trial
- Location: US
- Salmeterol 42 mcg BID versus placebo
- Randomization ratio 1:1
- Mostly adults, 12% of subjects 12-18 y.o.
- Data on concomitant ICS use lacking
- National Death Index used to complete data on vital status
- Study terminated early, did not meet enrollment target

SMART trial

Sources: Serevent, Advair labeling, Nelson et al. Chest 2006; 129: 15-26

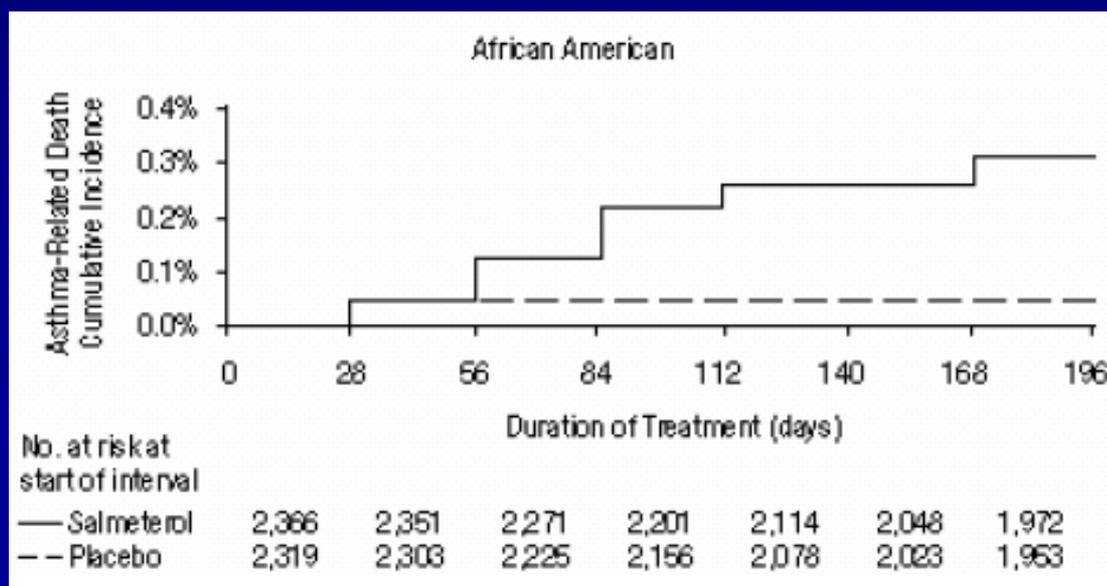
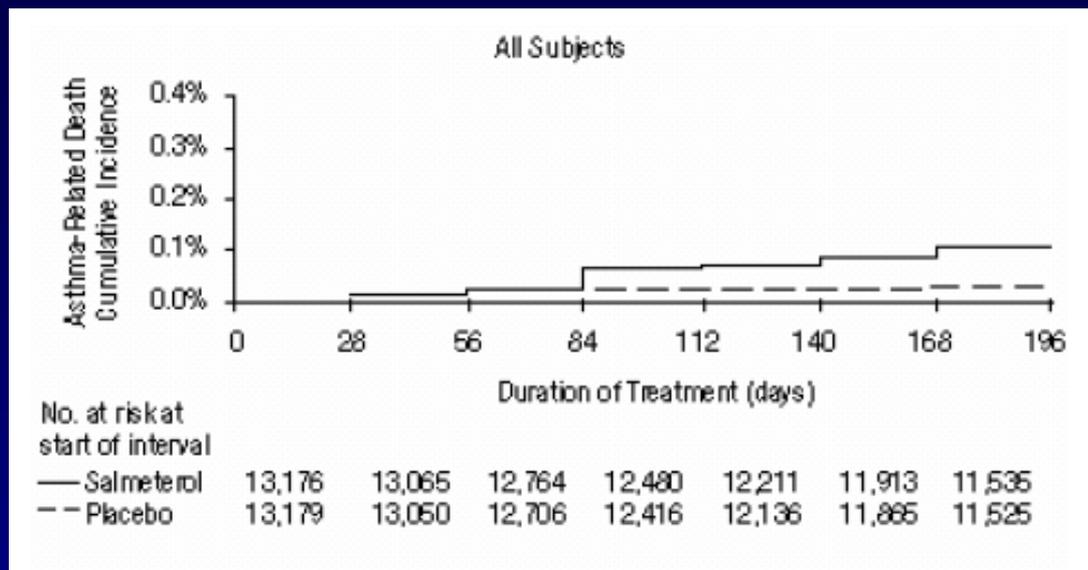
Outcome	Number of pts.		Relative Risk (95% c.i.)	Number needed to harm (95% c.i.)
	Salmeterol (N=13,176)	Placebo (N=13,179)		
Primary outcome: Combined resp- related death or life-threatening experience	50	36	1.4 (0.9-2.1)	-
Asthma death	13	3	4.4 (1.3-15.3)	1317 (739-6086)
Respiratory-related death	24	11	2.2 (1.1-4.4)	1013 (536-9302)
All-cause death	24	15	1.6 (0.8-3.1)	

Comparison of selected outcomes from SNS and SMART

Sources: Nelson et al. 2006, Castle et al. 1993, QSPG meta-analysis

	No LABA	LABA	Relative risk (unadjusted)
SMART			
N	13179	13176	
Asthma death	3	13	4.3
Asthma intubations	20	31	1.6
Asthma hospitalizations	153	176	1.2
Withdrawals for lack of efficacy	535	343	0.6
SNS			
N	8393	16787	
Asthma death	2	12	3.0
Asthma intubations	1	8	4.0
Asthma hospitalizations	102	196	1.0
Asthma-related withdrawals	318	488	0.8

From Serevent & Advair Labels



Conclusions from salmeterol large, randomized controlled trials

“In view of the results of the two studies, both of the highest evidence class (Ib), the existence of salmeterol-related excess mortality has to be assumed with near certainty.”

– Hasford and Virchow, Eur Respir J 2006; 28: 900–902

Combined odds ratio for asthma mortality (SNS and SMART) = 3.7 (1.4-9.8), p-value = 0.0074

– Cates and Cates, Cochrane Database of Systematic Reviews, 2008

Conclusions from salmeterol large, randomized controlled trials (2)

“One death was attributable to salmeterol for every 700 patient-years of treatment [in SMART], a result strikingly similar to that in the United Kingdom study...Unfortunately, the limitations of the trials...preclude definitive conclusions regarding the potential for inhaled corticosteroids to limit or prevent these adverse outcomes.”

-Martinez, NEJM 2005;353: 2637-9

- **Excess death rate of 1 per 700 patients per year will not be obvious to prescribers**

Formoterol

- No large sample safety trials comparable to SNS or SMART have been performed with formoterol
- In asthma clinical trials, formoterol 24 mcg BID was associated with higher frequency of serious asthma events, and so this dose was not approved

Serious asthma events in selected formoterol clinical trials

(Mann et al. Chest 2003, Wijesinghe et al. Postgrad Med J 2008)

Treatment group (pooled data)	Placebo (n=453)	Albuterol 180 mcg QID (n=272)	Formoterol 12 mcg BID (n=446)	Formoterol 24 mcg BID (n=442)
N (%) of patients with serious asthma events	2 (0.4%)	2 (0.7%)	9 (2.0%)	20* (4.5%)

*Includes one death and two intubations

Meta-analysis by Salpeter et al.

Ann Intern Med. 2006;144:904-912

Purpose: Assess risk for severe asthma exacerbations with LABAs (salmeterol or formoterol)

Data sources: 19 randomized, placebo controlled LABA trials \geq 3 months in duration (n=33,826)

6 of these were pediatric trials (3 with salmeterol, 3 with formoterol), combined n=1768

Analysis: Peto odds ratios and C.I. for outcomes

Results (for all ages): LABAs associated with

Asthma hospitalizations (odds ratio 2.6, 95% C.I. 1.6-4.3)

Asthma exacerbations requiring intubation and ventilation (odds ratio 1.8, 95% C.I. 1.1-2.9)

Salpeter et al.

Meta-analysis of LABA pediatric trials which provided data on asthma hospitalizations

(All trials except SMART had mean subject ages between 8 and 10 y.o.)

Comparison: Long-acting beta-agonists (LABA) and hospitalizations for asthma exacerbations - children

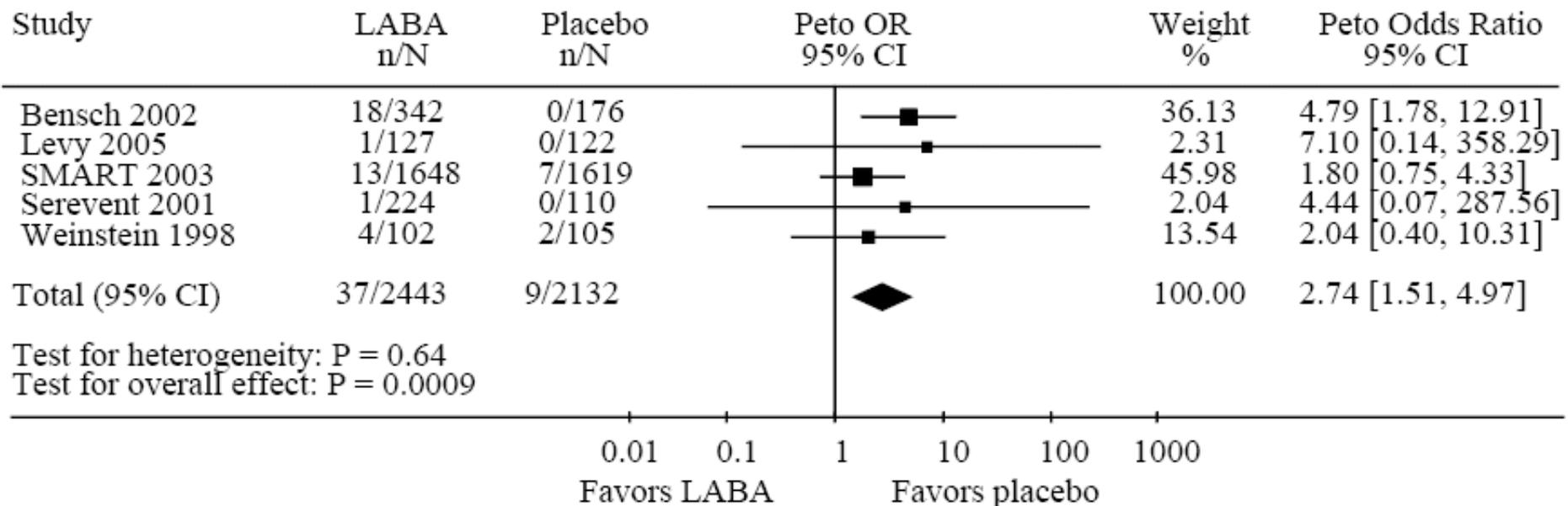


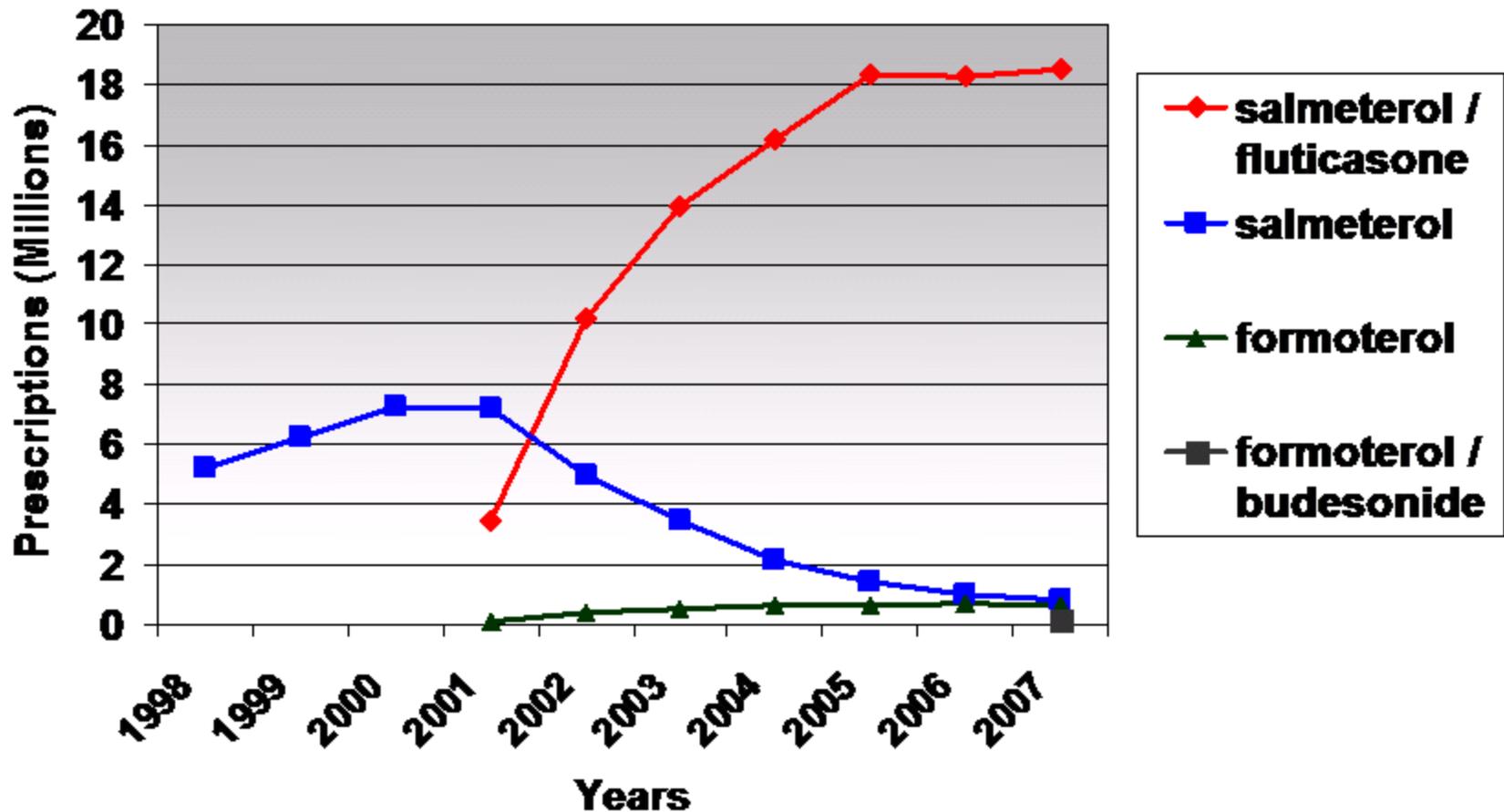
Figure courtesy of Dr. S. Salpeter

Proposed Mechanisms for Paradoxical Association of Severe Asthma Events with LABAs

1. Masking of progression of asthma by LABA bronchodilation
 - McIvor et al. Am J Respir Crit Care Med 1998;158:924–930.
2. A specific genetic variant of the beta adrenergic receptor may worsen clinical outcomes
 - Palmer et al. Thorax 2006;61:940-944.
3. Desensitization/Downregulation/Tolerance
 - Tolerance demonstrated with salmeterol in pediatric exercise induced asthma
 - Simons et al. Pediatrics 1997;99:655– 659

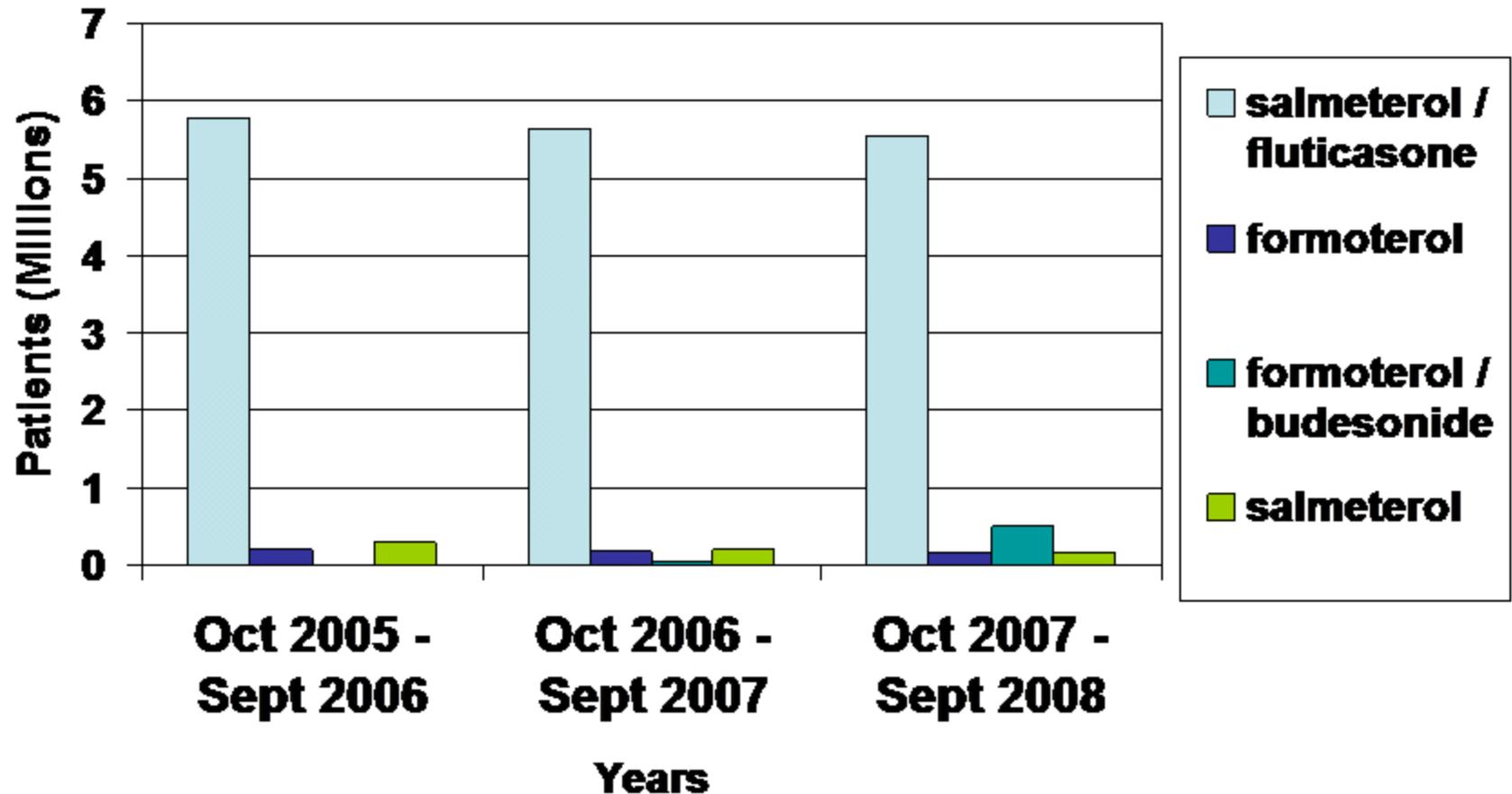
How are LABAs Being Used Currently?

Ten Year Trend of Projected Number of LABA Prescriptions Dispensed by U.S. Retail Pharmacies, Years 1998 - 2007



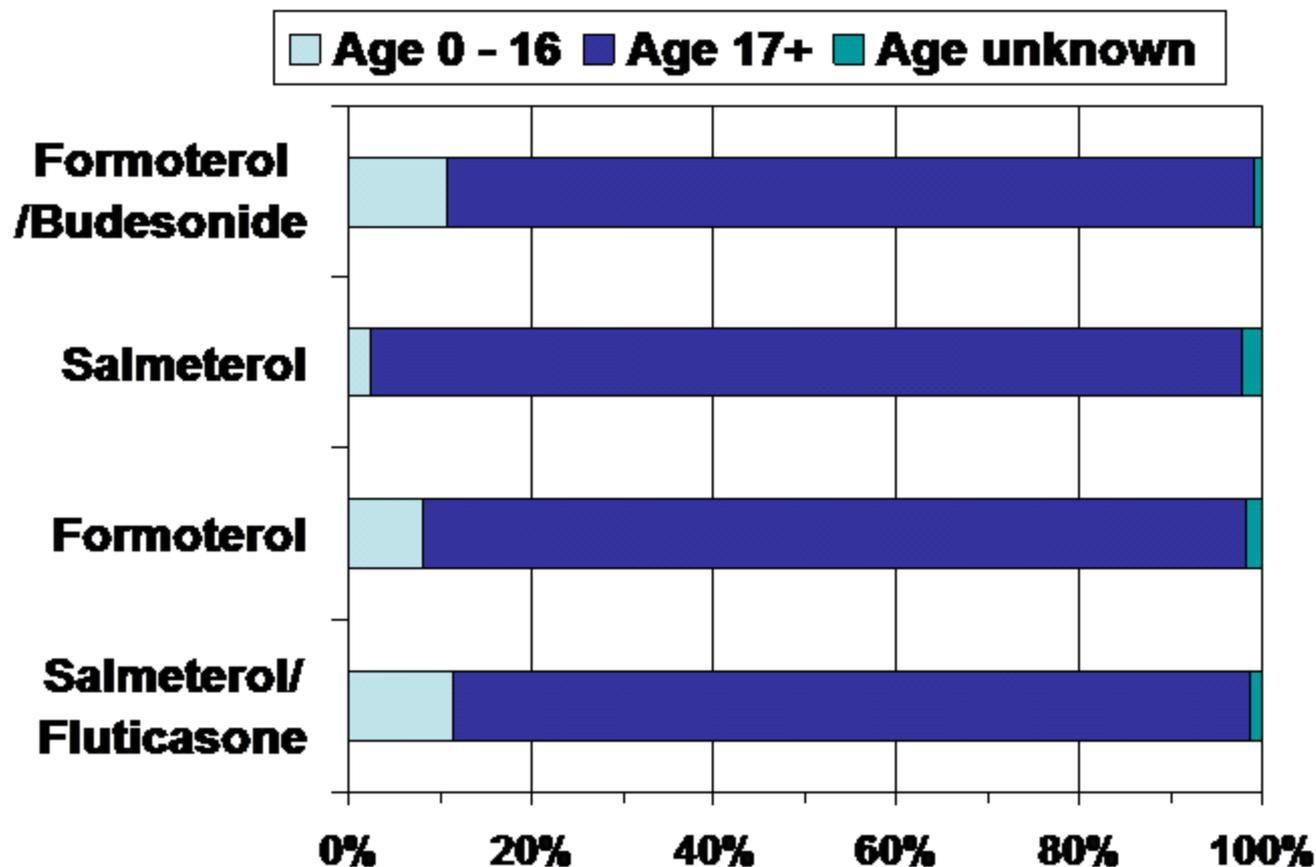
Source: SDI Vector One® National, Data Extracted 11-2008

Projected Number of Patients Receiving LABA Prescriptions Through U.S. Retail Pharmacies Oct 2005 - Sept 2008



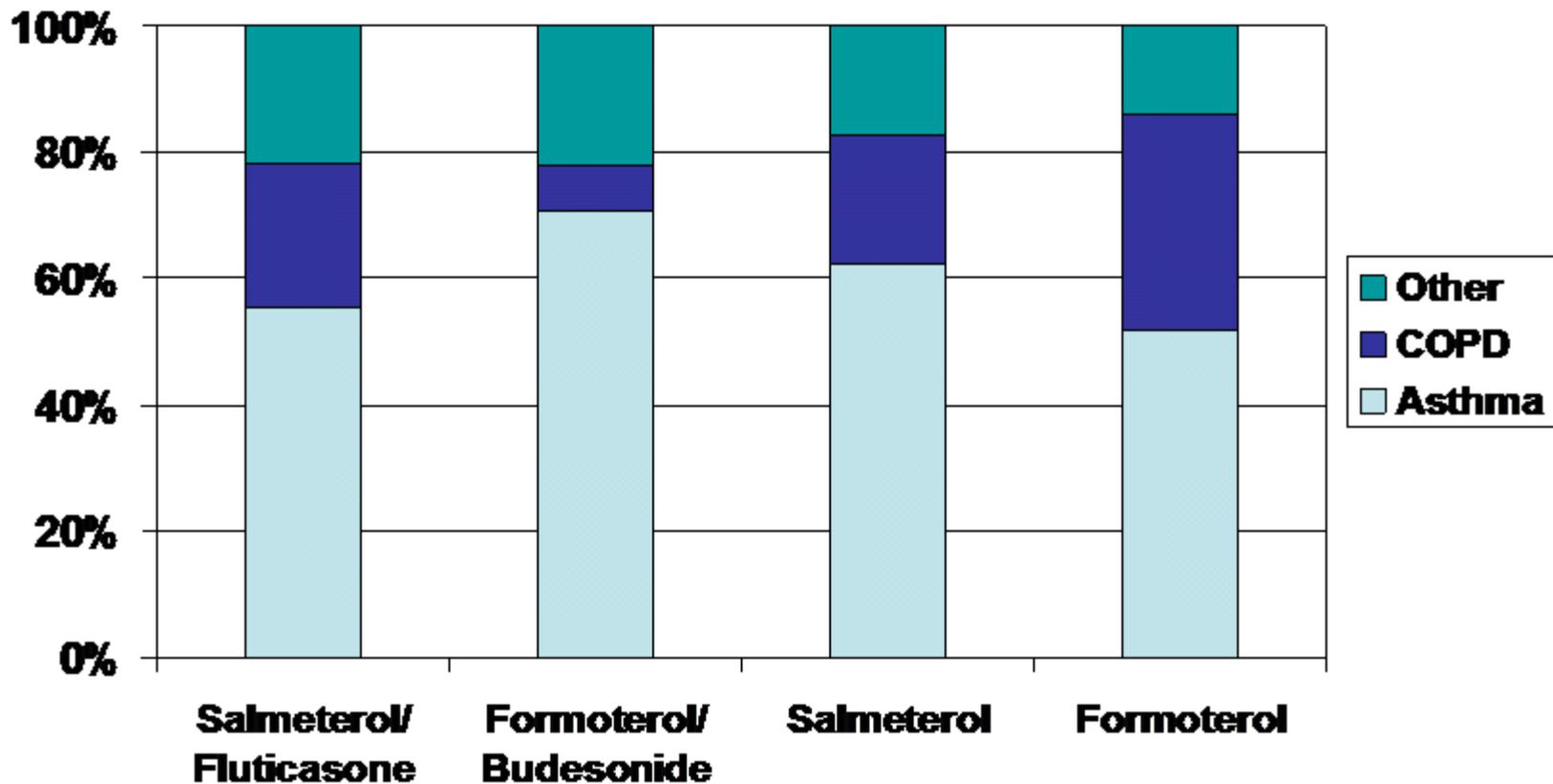
Source: SDI Total Patient Tracker, Extracted 11-2008

Proportion of Patients 0-16 Years and 17 Years and Older Who Received a LABA Prescription Through U.S. Retail Pharmacies for Year 2007



Source: SDI Total Patient Tracker, Extracted 11-2008

Proportion of LABA Drug Mentions Associated with Diagnoses of Asthma, COPD or Other by Office Based Physicians, for Year 2007



Source: SDI Physician Drug and Diagnosis Audit, extracted 11/2008

What proportion of patients taking single ingredient LABA (salmeterol or formoterol) without concurrent use of ICS?

Study Population

- Patients with asthma diagnosis who did not have COPD
- Enrollment in managed care organization ≥ 1 year before LABA exposure
- Prescriptions for single-ingredient LABAs between 2005-2007

Concurrency/Non-concurrency with ICS

- # of all single-ingredient LABA users: 11,912
- LABA concurrent with ICS: 11%
- LABA sometimes concurrent with ICS: 40%
- LABA never concurrent with ICS: 48%

Source: IMS Health, Health Plan Claims database, 2005-2007, extracted November 26, 2008

Does concomitant ICS therapy
protect against catastrophic
asthma events associated with
LABAs?

Overview of Data Regarding Concomitant ICS

- Two recent clinical trial meta-analyses examined serious asthma events for LABAs administered with ICS
 - Salmeterol with ICS: Bateman et al. Ann Intern Med 2008
 - OR for asthma hospitalizations 1.1 (0.7-1.7)
 - One asthma death and one asthma intubation, both salmeterol subjects
 - Formoterol or salmeterol with ICS: Jaeschke et al. AJRCCM Sept 2008
 - OR for asthma hospitalizations 0.7 (0.5-1.0)
 - All 5 asthma deaths and/or intubations were among LABA subjects

Overview of Data Regarding Concomitant ICS (2)

- For data on asthma mortality, must refer again to SNS and SMART
 - However, data on ICS concomitant use was not collected during either trial
 - Can only examine effect of ICS use at entry into study

SNS and SMART: asthma deaths by baseline ICS use

SNS

Source: Cates and Cates, Cochrane Database of Systematic Reviews, 2008

Subgroup (some data missing)	Salmeterol + baseline ICS	Albuterol+ baseline ICS	Salmeterol, no baseline ICS	Albuterol, no baseline ICS
N	9809	4895	3704	1887
Asthma deaths	7	2	4	0

SMART

Source: Nelson et al. Chest, 2006

Subgroup	Salmeterol + baseline ICS	Placebo + baseline ICS	Salmeterol, no baseline ICS	Placebo, no baseline ICS
N	6127	6138	7049	7041
Asthma deaths	4	3	9	0

ORs for asthma mortality, by available data on baseline ICS use, SNS and SMART

(Dr. C. Cates, personal communication)

Subgroup	Combined Peto Odds Ratio	95% c.i.
ICS use at baseline	1.5	0.5-4.1
No ICS use at baseline	6.4	2.1-19.4

Chi² test for subgroup differences $p = 0.06$

Conclusions

- Postmarketing surveillance data include reports of asthma deaths with LABAs, but causal interpretation difficult
- Observational safety studies of LABAs for asthma have shown mixed results, and are of limited inferential value because of methodological issues with non-randomized data
- Large, randomized controlled trials with salmeterol (SNS and SMART) showed an increase in asthma mortality
- Comparable trials with formoterol are lacking, but clinical trials showed a dose-related imbalance of serious asthma events, favoring placebo

Conclusions (2)

- Clinical trial meta-analyses may be useful to improve sample size and statistical power, especially for pediatric age group
- Use of LABAs with concomitant ICS has become widespread, but evidence that ICS nullifies LABA-related risks is lacking