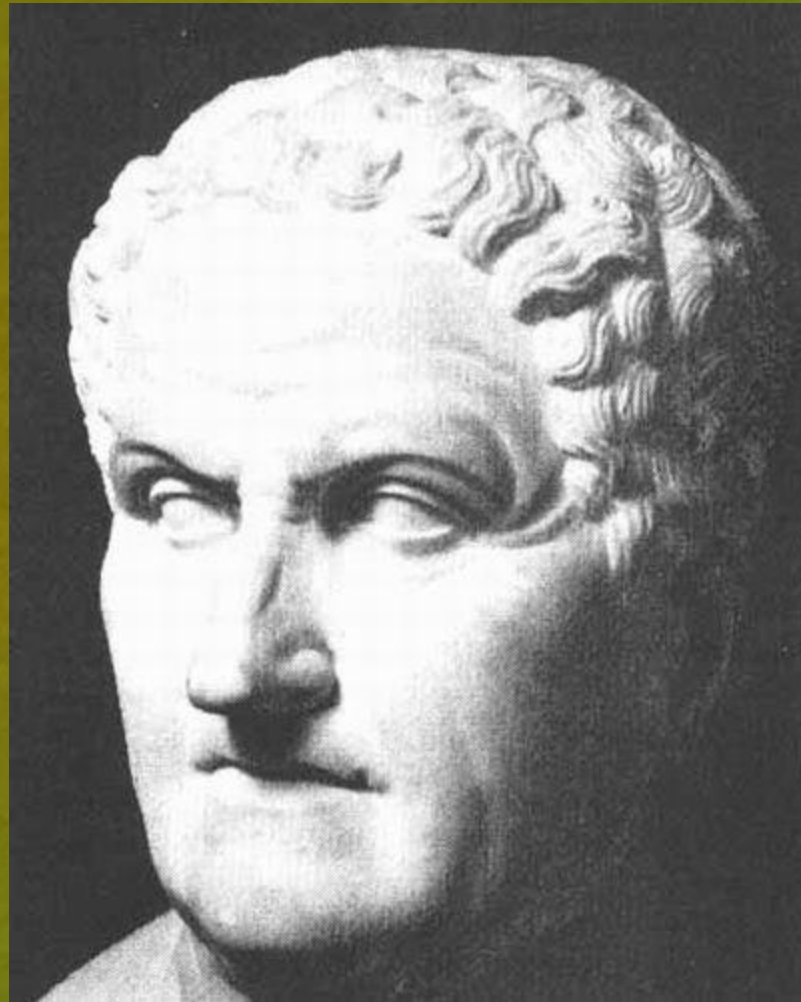


Does long acting beta agonists
increase asthma related death
or intubation?

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Galen “The Infallible Master”

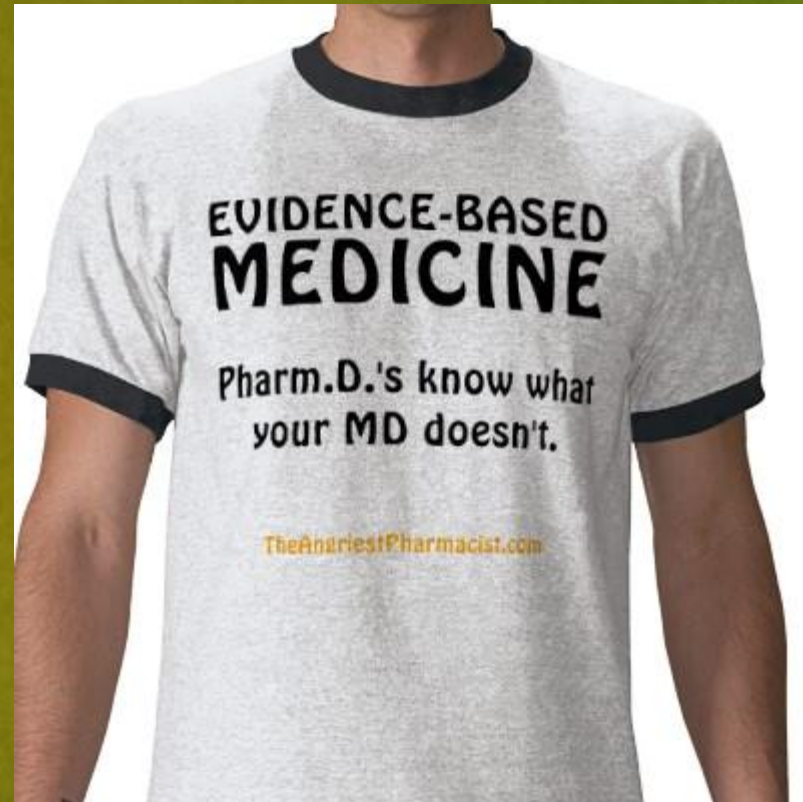


Galen “The Infallible Master”

- One of the most colorful and authoritarian character of Medicine.
- **NO ONE DARED TO EVER DIFFER WITH HIM!**



Evidence based medicine vs. Authoritarian medicine



Long-acting Beta-Agonists with and without Inhaled Corticosteroids and Catastrophic Asthma Events

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ABSTRACT

BACKGROUND: It is unclear whether long-acting β -agonists with concomitant inhaled corticosteroids increase asthma-related intubations and deaths. We pooled data on long-acting β -agonists with variable and concomitant inhaled corticosteroids to evaluate the risk for catastrophic asthma events.

METHODS: We conducted searches of electronic databases, the US Food and Drug Administration website, clinical-trials registries, and selected references through December 2008. We analyzed randomized controlled trials in patients with asthma, which lasted at least 3 months, evaluated long-acting β -agonists compared with placebo or long-acting β -agonists with inhaled corticosteroids compared with corticosteroids alone, and included at least 1 catastrophic event, defined as asthma-related intubation or death.

RESULTS: In pooled trial data that included 36,588 participants, long-acting β -agonists increased catastrophic events 2-fold (Peto odds ratio [OR] 2.10; 95% confidence interval [CI], 1.37-3.22). Statistically significant increases were seen for long-acting β -agonists with variable corticosteroids compared with placebo (OR 1.83; 95% CI, 1.14-2.95) and for concomitant treatment with corticosteroids compared with corticosteroids alone (OR 3.65; 95% CI, 1.39-9.55). Similar increases in risk were seen for variable and concomitant corticosteroid use, salmeterol and formoterol, and children and adults. When the analysis was restricted to trials with controlled corticosteroid use, given as part of the study intervention, concomitant treatment still increased catastrophic events compared with corticosteroids alone (OR 8.19; 95% CI, 1.10-61.18).

CONCLUSION: Long-acting β -agonists increase the risk for asthma-related intubations and deaths, even when used in a controlled fashion with concomitant inhaled corticosteroids.

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KEYWORDS: Asthma; Inhaled corticosteroids; Intubation; Long-acting beta-agonists; Meta-analysis; Mortality

Introduction

- There has been growing concern about asthma-related morbidity and mortality associated with the long-acting beta-agonists salmeterol and formoterol, given with or without concomitant inhaled corticosteroids.
- To evaluate this issue, a meta analysis was carried by Shelley R. Salpeter et al.



Materials and methods

- The researcher performed a search of the MEDLINE, EMBASE, and Cochrane databases; the US FDA website; clinical-trials registries of drug manufacturers; and previous meta-analyses to identify trials on long-acting beta-agonist use in patients with asthma published through December 2008.



Materials and methods

- Studies included in this meta analysis were
 - randomized controlled trials of long-acting beta-agonists compared with placebo
 - or long-acting beta-agonists with inhaled corticosteroids compared with inhaled corticosteroids alone
 - of at least 3 months duration
 - that reported at least 1 asthma related intubation or death.



Materials and methods

- Subgroup analyses were performed to evaluate the difference in results between trials
 - with variable corticosteroids (use in <100% of participants) versus concomitant corticosteroids (use in 100% of participants),
 - salmeterol versus formoterol,
 - children (aged 12 years) versus adults,
 - and fatal versus nonfatal events.



Materials and methods

- Further subgroup analysis compared results between
 - trials with no corticosteroid use at all and
 - trials with the use of corticosteroid in combination with a long acting beta - agonist (either in a single inhaler or separate inhalers).



Materials and methods

- The meta-analysis included a total of 36,588 participants followed for 21,343 patient-years.
- The mean trial duration was 7.0 months.



Result

- The meta analysis showed that , There is a 3-fold increase in asthma related intubations and deaths in those taking long-acting beta-agonists with concomitant corticosteroids compared with corticosteroids alone.



Result

- Similar increases in risk were seen for variable and concomitant corticosteroid use, salmeterol and formoterol, and children and adults.



Conclusion

- Long-acting beta-agonists increase the risk for asthma-related intubations and deaths, even when used in a controlled fashion with concomitant inhaled corticosteroids.



Proposed mechanism for increased adverse events of salmeterol and formoterol

- Regular use of short- and long-acting beta-agonists is associated with down-regulation and desensitization of beta-receptors, an increase in airway hyperreactivity, and thus an increase in asthma deaths and near-deaths.



- *Salpeter SR, Ormiston TM, Salpeter EE. Meta-analysis: respiratory tolerance to regular beta2-agonist use in patients with asthma. Ann Intern Med. 2004;140:802-813.*

US FDA recommendation

- In December 2008 a follow-up FDA advisory committee meeting concluded that the risks of using salmeterol and formoterol alone outweighed the benefits and should be banned for use in asthma for all ages.



US Food and Drug Administration. Summary minutes of the joint Pulmonary-Allergy Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee, and Pediatric Advisory Committee, December 10-11, 2008. Available at: <http://www.fda.gov/ohrms/dockets/AC/08/minutes/2008-4398m1-final.pdf>. Accessed February 6,2009.

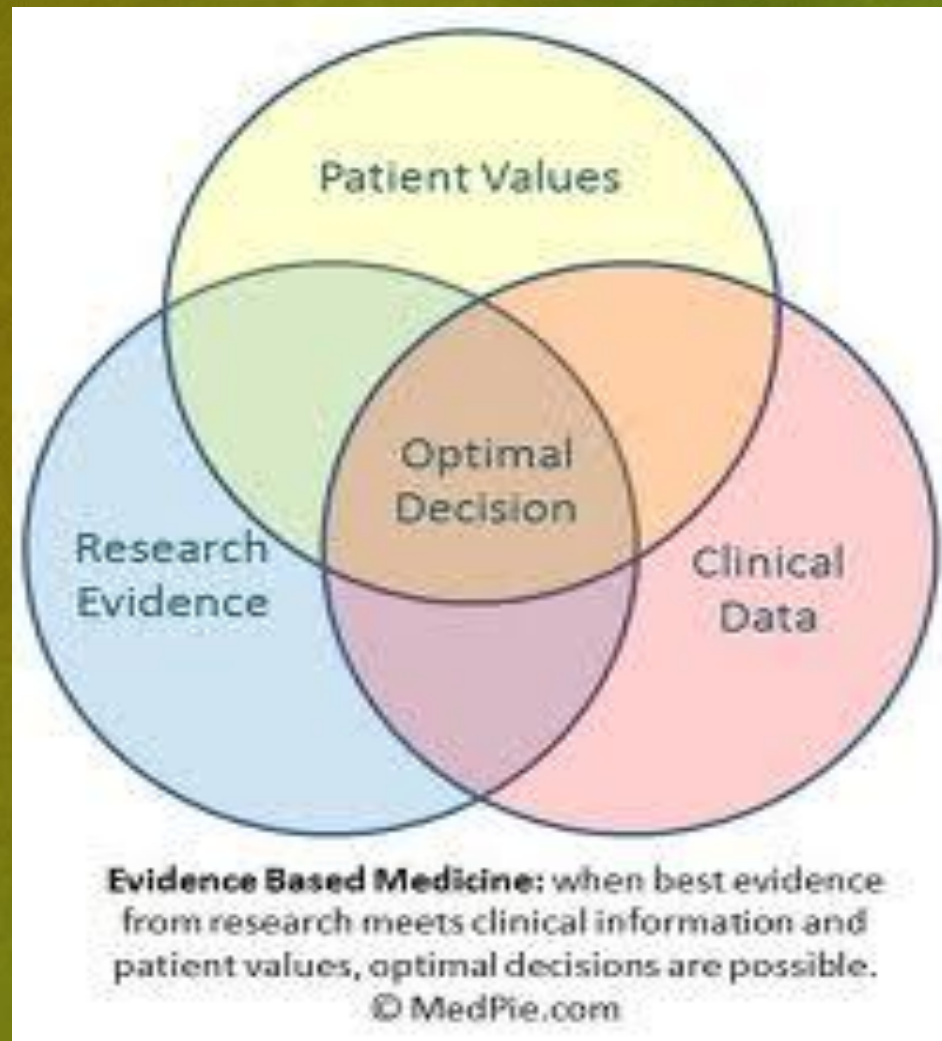
US FDA recommendation

- The committee separately evaluated long acting beta-agonists combined with a corticosteroid in a single inhaler, such as salmeterol with fluticasone and formoterol with budesonide, and concluded that further safety studies were needed to assess risk.



US Food and Drug Administration. Summary minutes of the joint Pulmonary-Allergy Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee, and Pediatric Advisory Committee, December 10-11, 2008. Available at: <http://www.fda.gov/ohrms/dockets/AC/08/minutes/2008-4398m1-final.pdf>. Accessed February 6, 2009.

Making an optimal decision





THANK YOU