

Effective aerosol therapy

Bruce Rubin, MEngr, MD, MBA, FRCPC
Distinguished Professor and Chair Emeritus of Pediatrics
Professor of Biomedical Engineering
Virginia Commonwealth University, Richmond, VA

Disclosures:

I have no apparent conflicts of interest.

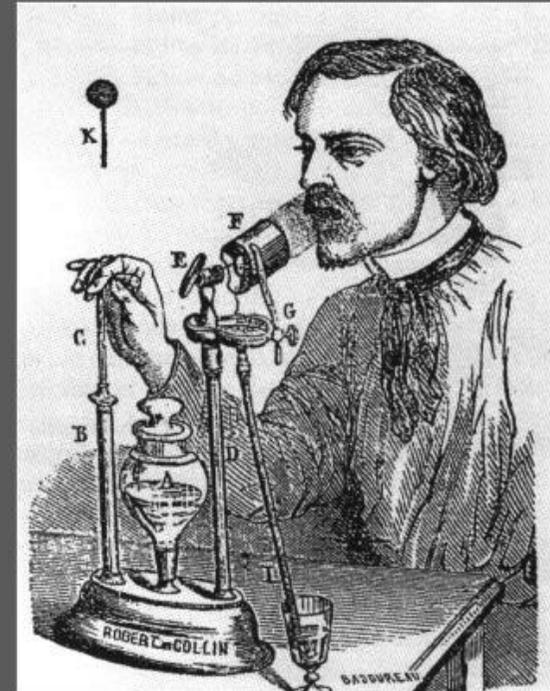
Aerosol therapy history



The Mudge inhaler, invented by Dr John Mudge in 1778,



The Sales-Girons "pulverisateur," which won the 1858 silver prize of the Paris Academy of Science

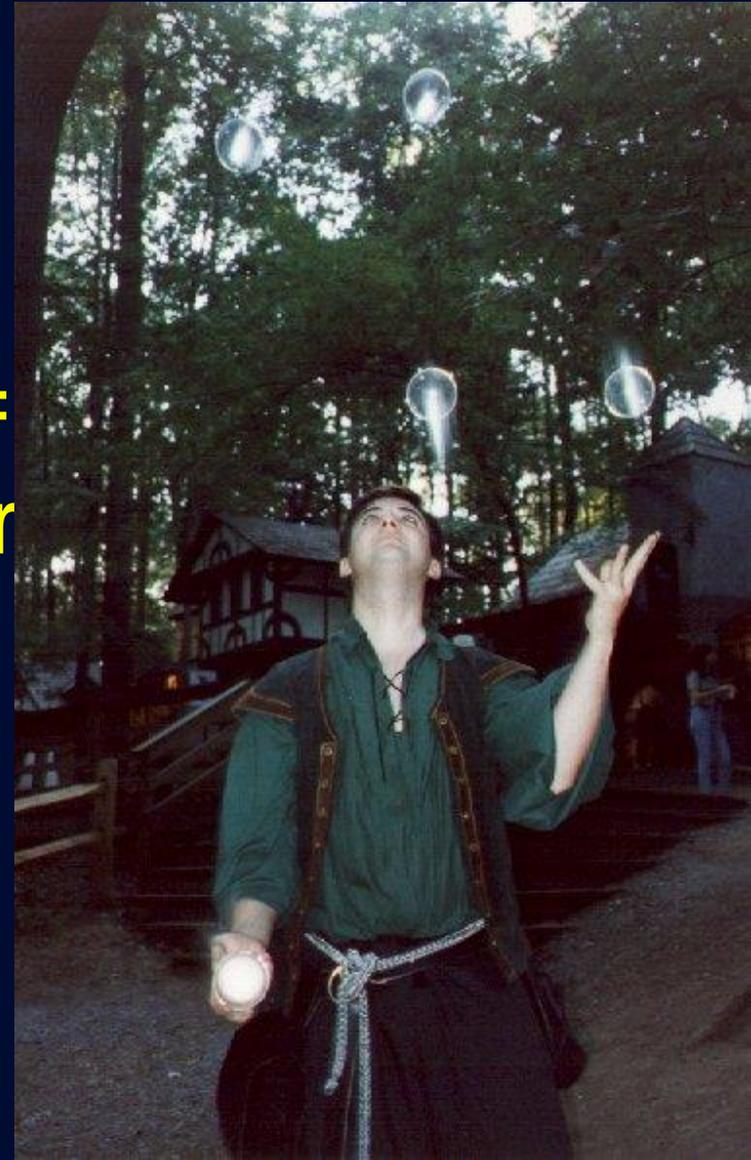


Aerosols

A group of particles that remains suspended in air because of low terminal settling velocity

For a *spherical particle*: $MMAD = d\sqrt{r}$ where d is particle diameter and r is density

Geometric standard deviation (GSD) describes the particle size distribution.



Size matters

Large particles $> 5 \mu\text{m}$

Inertial impaction in oral pharynx can lead to:

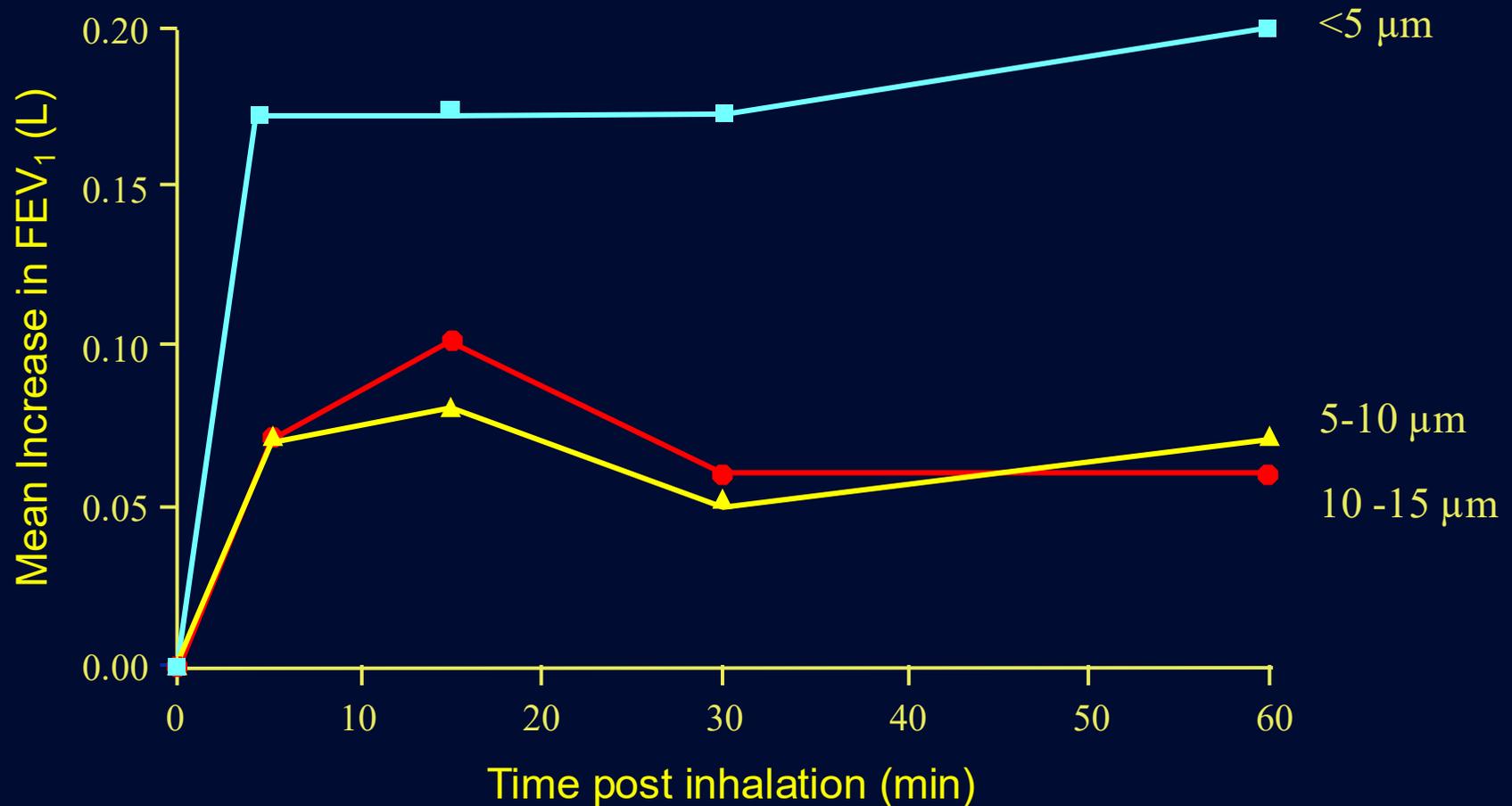
Thrush, laryngeal dysfunction (steroids)

Swallowing, systemic effects, loss of drug



<http://arkonline.com/banjo.html>

Effect of particle size on FEV₁ in patients with asthma



Adapted from Rees et al. *Eur J Respir Dis.*1982.

*Terbutaline administered to 10 patients with asthma via MDI.

Effective deposition of aerosols

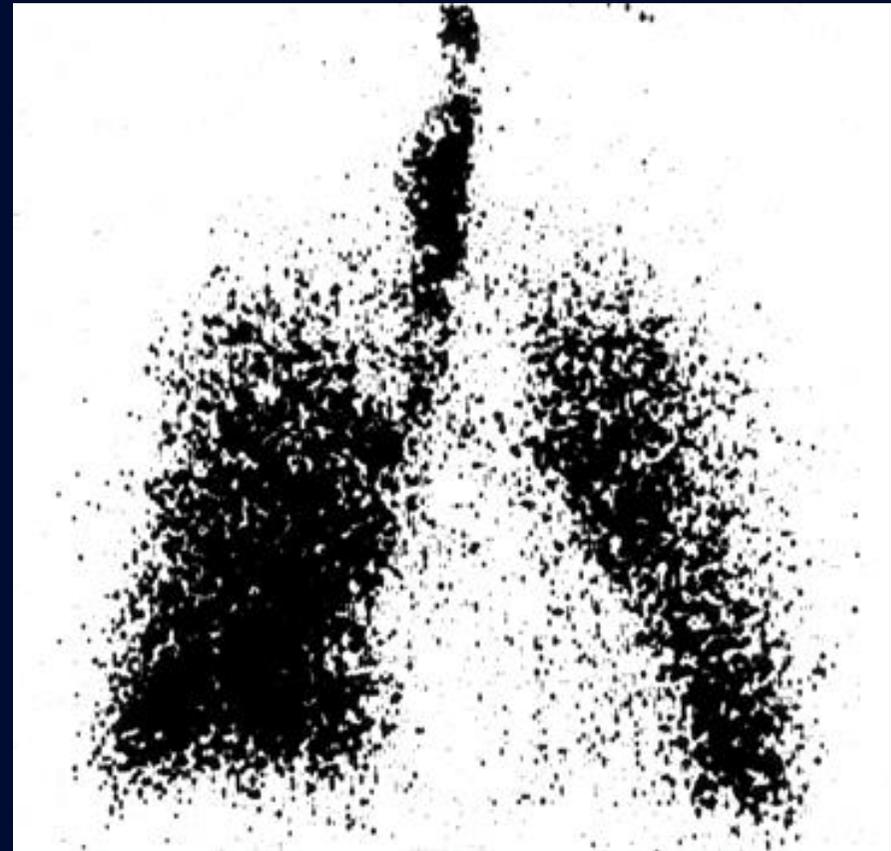
Slow inspiratory flow

Deep inhalation and breath hold

Lower inspired flow = Improved peripheral deposition



80 liters/minute



30 liters/minute

Aerosol delivery is negligible to a crying infant



The effect of crying on lung deposition



Not Crying



Crying

Aerosol therapy works best if
the patient is breathing quietly

Limited Special Offer!

To CATARRH, BRONCHITIS,
ASTHMA and LUNG TROUBLE
SUFFERERS.

Pillow-Inhaler

Reduced from \$5 to \$3.

Although thousands upon thousands have used the Pillow-Inhaler, yet there are many thousands still suffering who want to be cured. In order to place the Pillow-Inhaler within their reach and to widen and extend our business, we make a LIMITED SPECIAL OFFER from now UNTIL FEBRUARY 24th—reducing the price from \$5 to \$3.

This is an extraordinary chance but it must be taken advantage of at once.

Reader, do you know what the Pillow-Inhaler is? It is the greatest boon ever granted to catarrh, bronchitis and asthma sufferers. Scattered all over America are the living witnesses of this fact **cured and well** by means of the Pillow-Inhaler. It applies medicated air (tar, iodine, carbolic and other healing properties) to the inflamed parts of the air passages whilst sleeping as usual 7 to 10 hours at a time. It is this **night after night inhaling** that **conquers and cures**. If you would be again **free** from any of the above troubles, try the Pillow-Inhaler. It is safe, easy and simple to use. It can be sent to all parts of the world by express. Explanatory pamphlet and testimonials sent if requested.

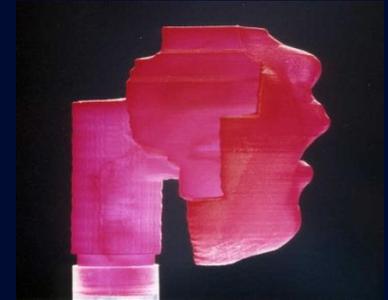
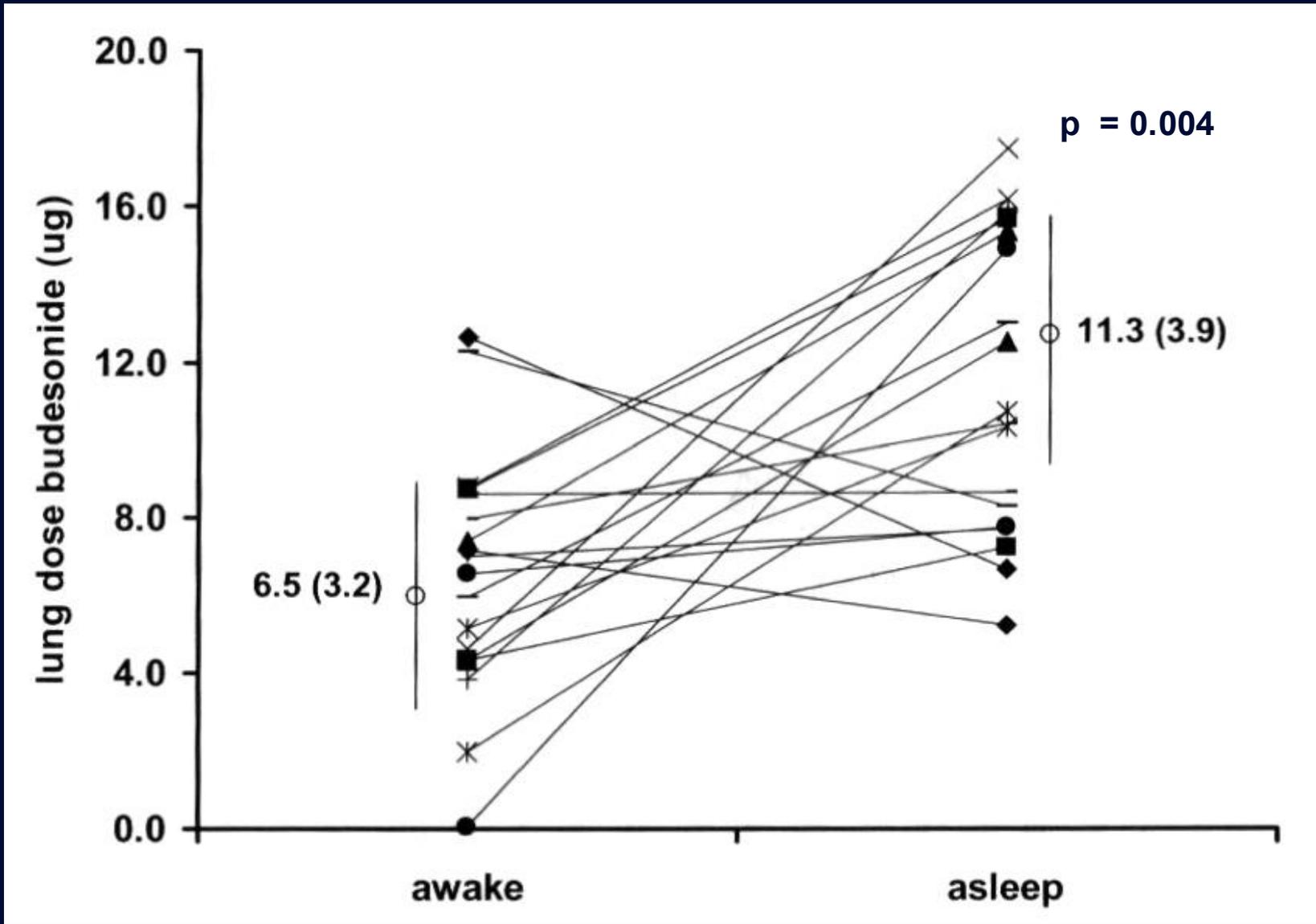


When ordering state the disease you wish the Inhaler for and write name and address plainly. Send money with order, and by P. O. or Express Money Order, Registered Letter or New York Draft. Kindly do not fail to mention THE PURITAN.

PILLOW-INHALER CO., 1407 Chestnut Street, Philadelphia, Pa.



Aerosol delivery is 74% greater to a “sleeping” infant



pMDI-VHC (*in vivo*) in sleeping infants

N=30 ages 6-23 mo

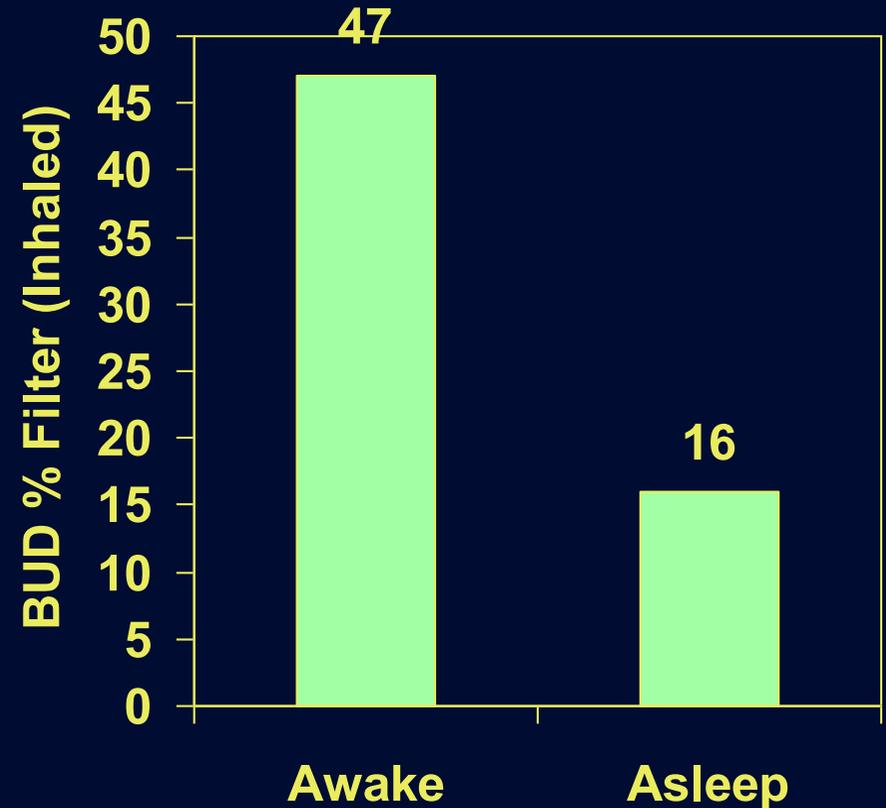
Tested awake and asleep

Filter dose (inhaled dose)

Budesonide by
Nebuchamber

Awake: 29% poor
cooperation

Asleep: 69% awoke with
3/4 “distressed”





SootherMask (InspiRx) is an infant mask designed for the facial structure of infants. It incorporates an oral pacifier to enhance the seal of the mask on the face and aerosol deposition as young infants are preferential nasal breathers.

Advantages of Nebulizers

- Tidal breathing at any age
- Use while sleeping (perhaps)
- Easy to use when sick
- Higher drug doses possible
but also problematic
- No propellant
- Little teaching required in clinic
- Mixing medications possible
but also problematic



Disadvantages of Nebulizers

Less portable than pMDI or DPI

Much more time consuming

Requires equipment maintenance and *cleaning*

Requires power source

Much more expensive than pMDI or DPI

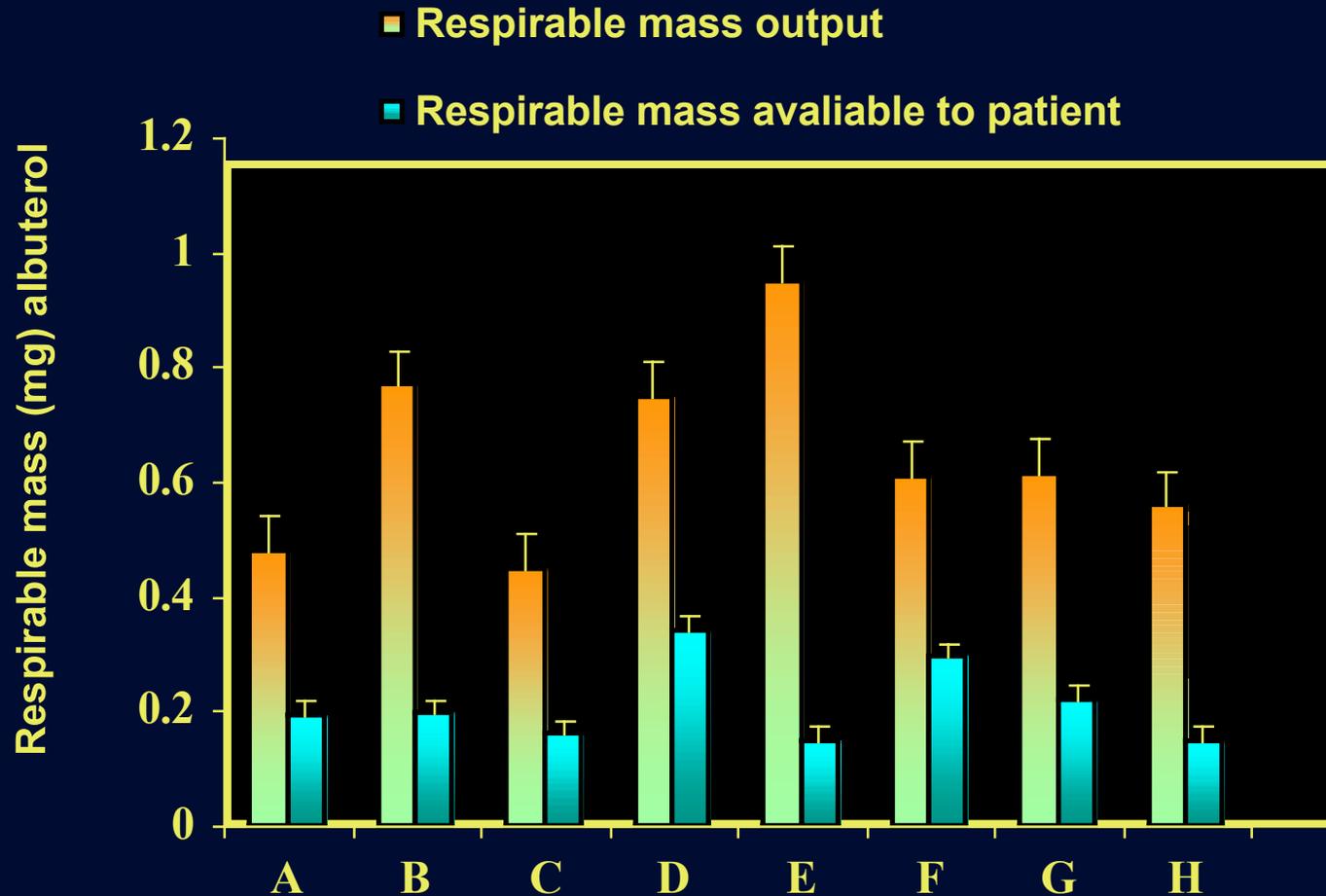
Requires some training

Poor efficacy for jet nebulizers – better for VMN

Variability of delivery

Poorest adherence

All nebulizers are not the same: Respirable mass



Data from each nebulizer brand are pooled from all flow settings.
Adapted from Hess, D. *CHEST* 1996;110: 498-505

Myth: Jet nebulization of albuterol is more effective than other pMDI delivery in the Emergency Department

β-AGONISTS THROUGH METERED-DOSE INHALER WITH VALVED HOLDING CHAMBER VERSUS NEBULIZER FOR ACUTE EXACERBATION OF WHEEZING OR ASTHMA IN CHILDREN UNDER 5 YEARS OF AGE: A SYSTEMATIC REVIEW WITH META-ANALYSIS

JOSÉ A. CASTRO-RODRIGUEZ, MD, AND GUSTAVO J. RODRIGO, MD

Six RCTs found (1966-2003) n=491

Found beta-agonists by MDI+VHC more effective than nebulizers for decreasing admission rate (OR = 0.42) and symptom score (mean diff = -0.44)

Data from 21 trials, including 880 Children. [mild & moderate]

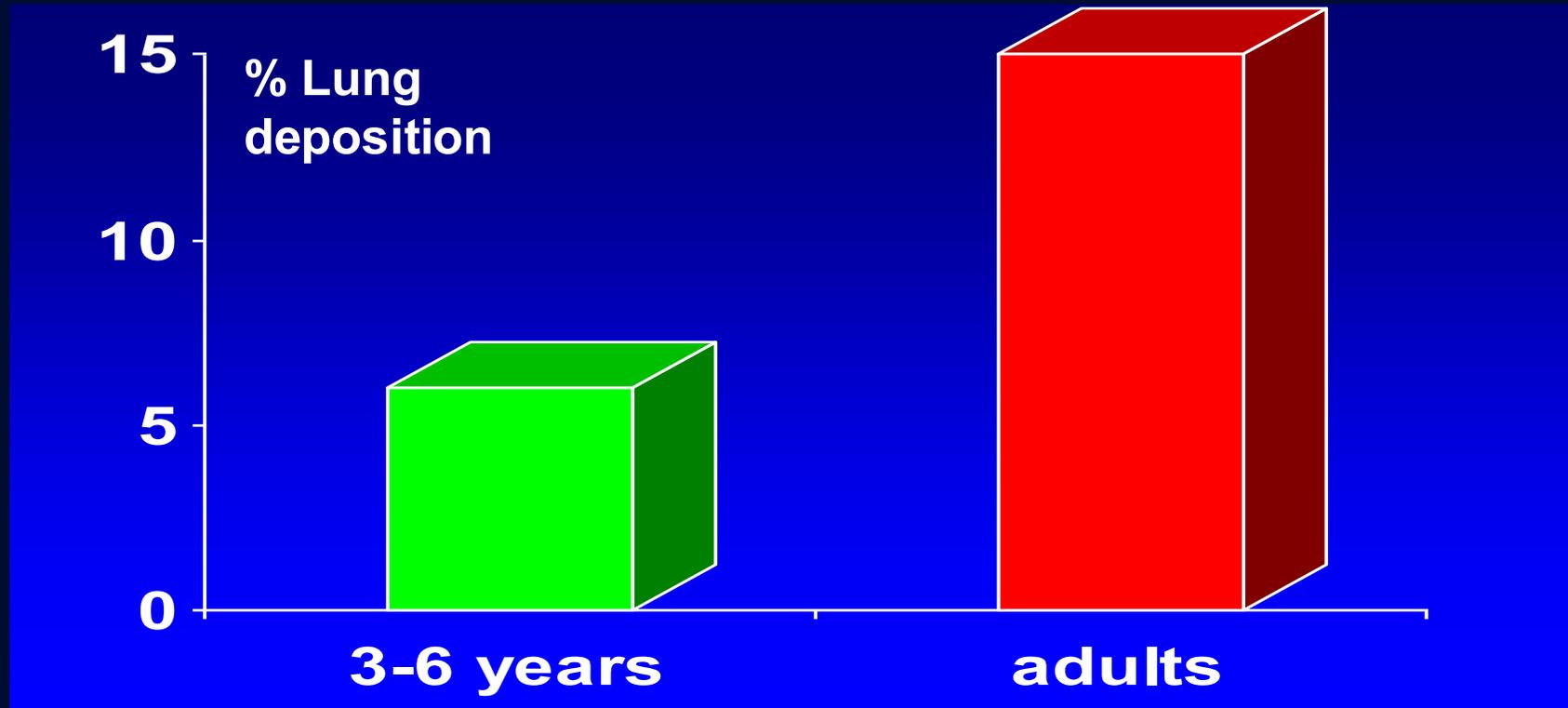
No significant difference in:

- admission rates
- PEF or FEV1 30 minutes after treatment
- change in respiratory rate or oxygen saturation
- development of tremor
- children needing oral corticosteroid treatment

Significant Differences:

- Average 35 minutes shorter time in A&E department with VHC treatment. (One Study, n=152)
- Heart rate on average 7% lower with VHC at end of treatment.

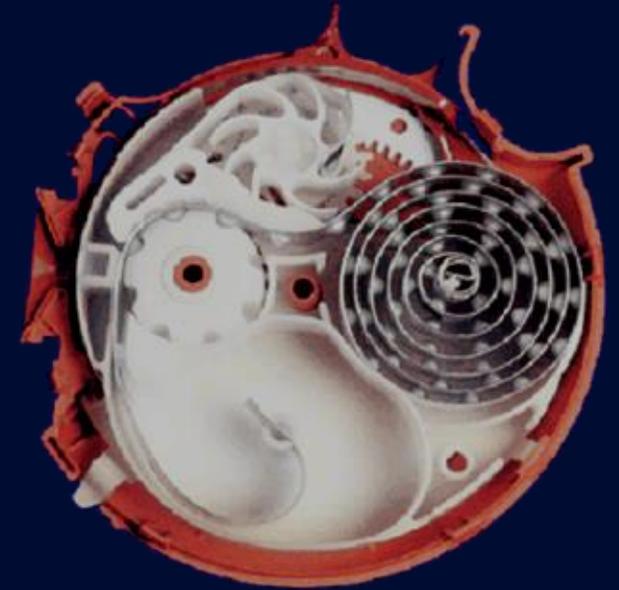
Lung deposition: Jet nebulizer



Agertoft. Systemic availability and pharmacokinetics of nebulised budesonide in preschool children. Arch dis Child 1999; 80: 241-247.

Dahlström. Lung deposition and systemic availability of budesonide inhaled as nebulised suspension from different nebulisers. J Aerosol Med 1995; 8: 79.

Dry powder inhalers (DPI)



Dry powder inhalers (DPI)

No propellants, portable

Very quick

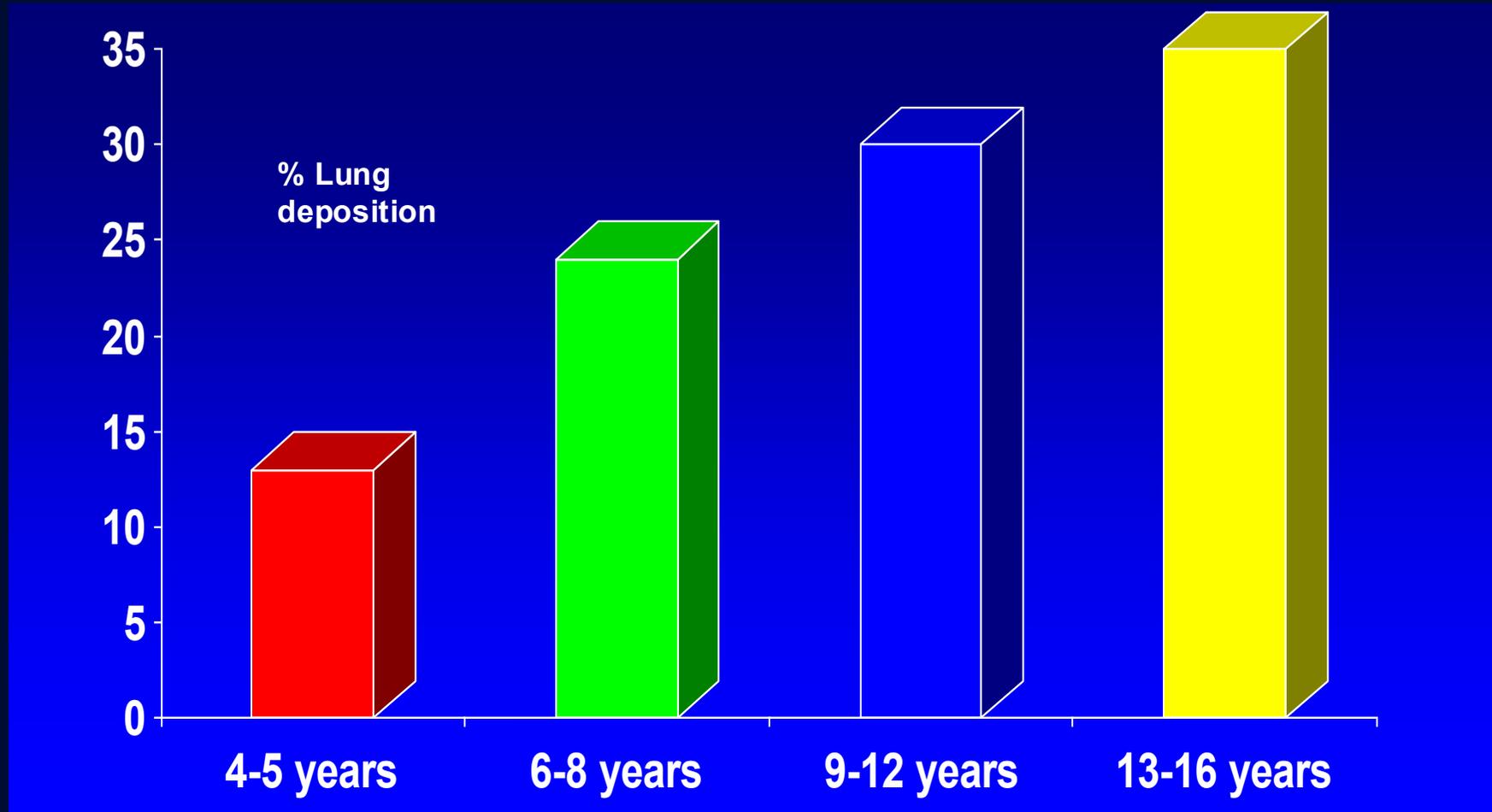
Breath actuated (never exhale into DPI)

Higher inspiratory flow (age > 4-5 yr.)

Dose counters (multi-dose)

Easy to teach technique

Lung deposition: DPI



Devadason. Lung deposition from the Turbuhaler in children with cystic fibrosis. Eur Respir J 1997; 10: 2023-2028.

pressurized metered dose inhalers pMDI

First pMDI – Riker Labs 1956

Vol. 141, No. 4 43

At Last...
UNIFORM DOSAGE NEBULIZATION
in Asthma

MEDIHALER™

with Your Favorite
Bronchodilator*

- NO RUBBER BULBS TO DETERIORATE
- NO BREAKAGE OF COSTLY GLASS NEBULIZERS
- NO SPILLING OF SOLUTION IN POCKET OR PURSE




MediHALER Oral Adapter is nonbreakable. Vial of MediHALER medication is leakproof, spillproof, provides 200 applications. Economical.

True nebulization—80% of particles from $\frac{1}{2}$ to 4 microns radius. Amount of medication released does not depend on pressure applied—dosage always the same. One application usually sufficient for most patients.

Notably safe for use with children. One application usually aborts attack.



*** MEDIHALER-EPI™**
0.5% solution of epinephrine HCl U.S.P.

*** MEDIHALER-ISO™**
0.25% solution of isoproterenol HCl U.S.P.

On your prescriptions be sure to write "MediHALER-ISO (or MediHALER-Epi) AND MediHALER Oral Adapter," since medication cannot be used without Adapter. For refills write for medication only.

Rx MediHALER-ISO
and
MediHALER Oral
Adapter

Another First from
Riker LOS ANGELES

22½% More
Vital Capacity
Right Now

FOR YOUR ASTHMATICS
NOTHING IS QUICKER • NOTHING IS MORE EFFECTIVE

PREMETERED FOR
OPTIMAL EFFICACY



MediHALER-EPI
Epinephrine Hydrochloride Solution

MediHALER-ISO
Isoproterenol Hydrochloride Solution

MEDIHALER™
substantially metered-dose nebulized nebulizations
nonbreakable • spillproof • leakproof • economical

Riker

pMDI Advantages

Small, portable

Higher lung deposition

Quick

Lower expense (except ED?)

Easy to clean

More effective than most nebs or DPI



pMDI problems

Not shaking pMDI (suspensions - ICS)

Rapid inhalation

Delay between actuation and inhalation

HC is less portable than MDI alone

Multiple actuations into HC

Poor mask fit

Difficult to learn and teach

Contrivance

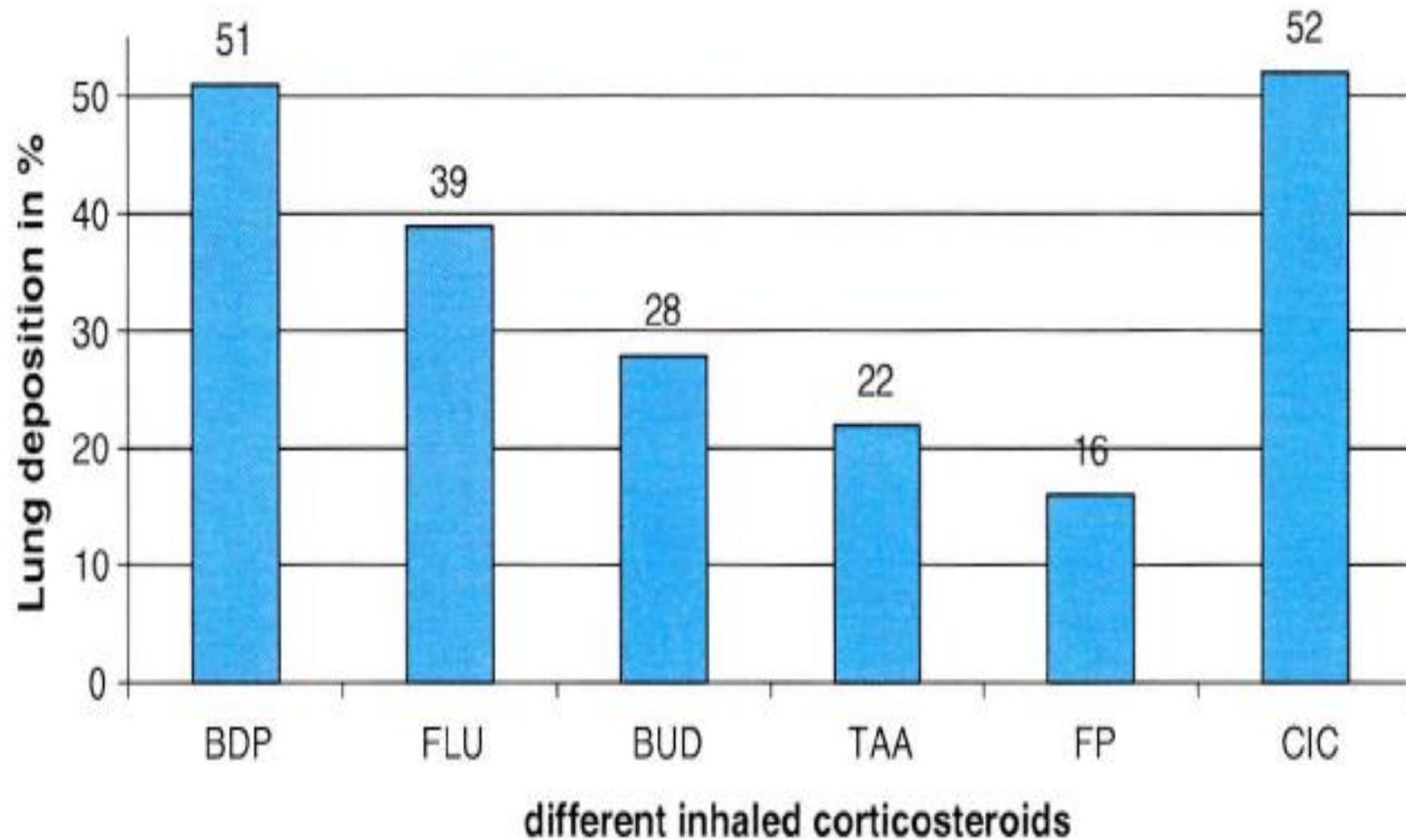
Myth: HFA-carrier pMDIs have a smaller particle size than CFC equivalents

Fact:

Only those ICS that go into solution with ethanol solvent and use a modified valve will have a smaller particle size (eg ciclesonide, beclomethasone, flunisolide)

Other aerosol medications are approximately the same size particle regardless of carrier

Lung deposition of HFA ICS



Myth: Finer particles (smaller particle size) improves asthma outcome

Fact:

While fine particles (MMAD < 2.5 mcm) are better able to deposit in the small airway, there is no clinical evidence that this leads to better outcomes.

Fine particles are more likely to be exhaled



THE COCHRANE LIBRARY

Independent high-quality evidence for health care decision making

Fluticasone versus 'extrafine' HFA-BDP for chronic asthma in adults and children

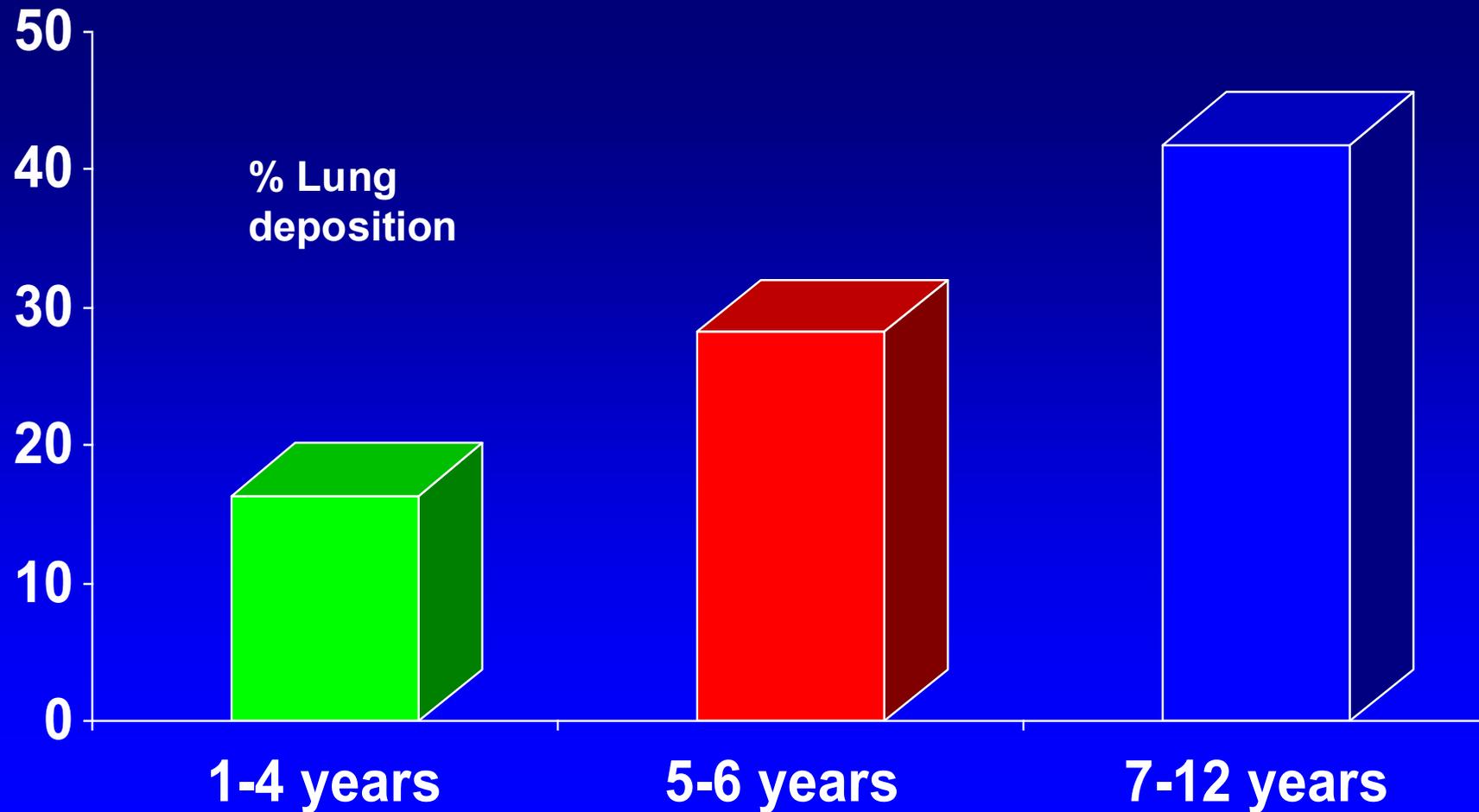
Toby J Lasserson^{1,*}, Christopher J Cates², Emma H Lasserson³, John White⁴

Editorial Group: Cochrane Airways Group

Nine studies (1265 subjects) met inclusion criteria. Two studies were in children. Study quality was fair, but all studies were of short duration (3-12 weeks).

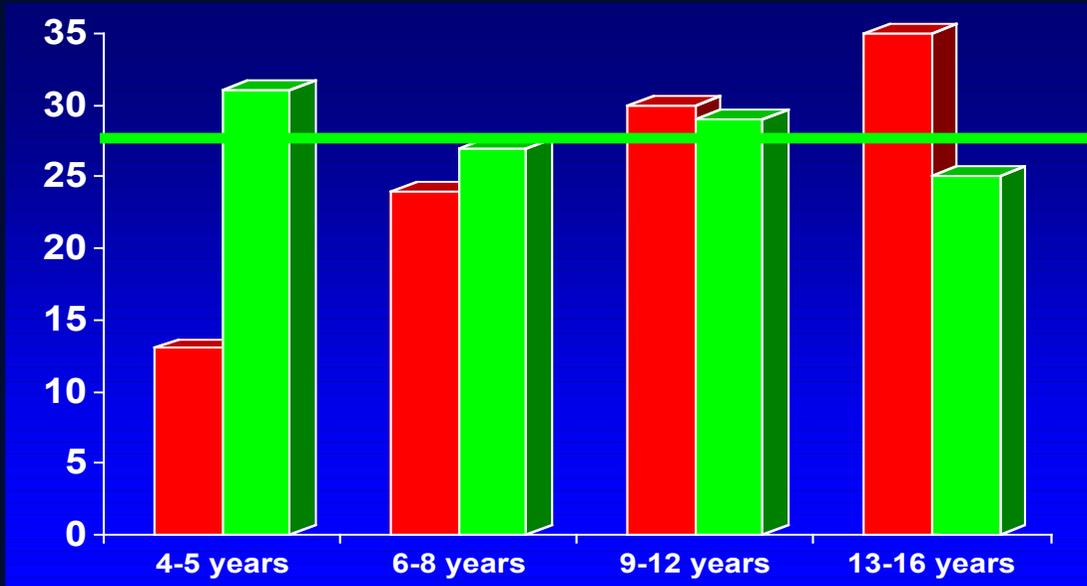
PFT was not significantly different between extrafine BDP and FP when compared at the same dose in parallel studies

Lung deposition: pMDI + VHC



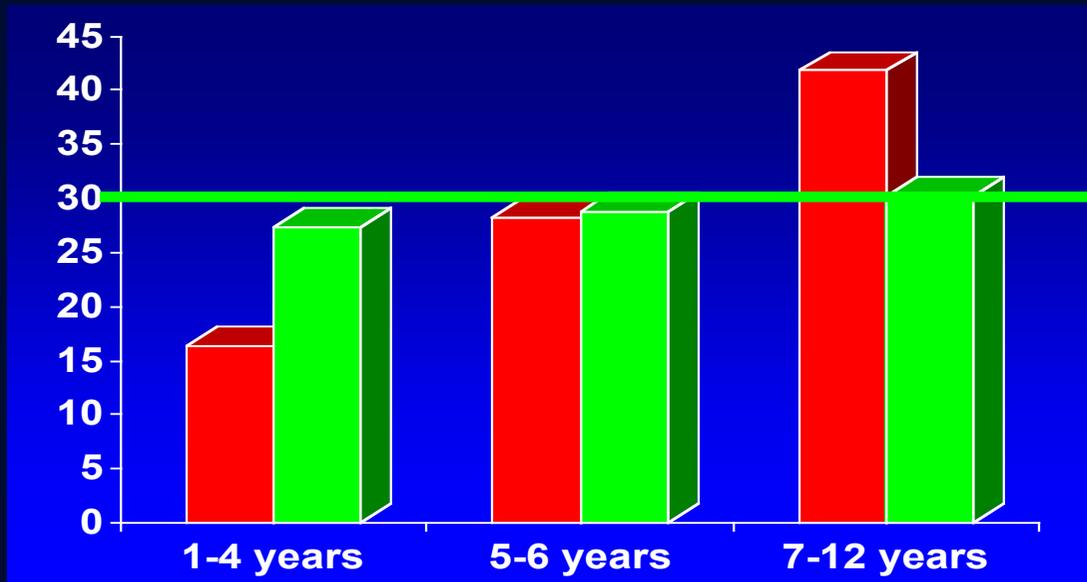
Wildhaber. High percentage lung delivery in children from detergent-treated spacers. *Pediatr Pulmonol* 2000; 29: 389-393.

Lung deposition: Corrected for BW



■ % Lung deposition
■ % Lung deposition (corrected for BW)

Devadason. Lung deposition from the **Turbuhaler** in children with cystic fibrosis. *Eur Respir J* 1997; 10: 2023-2028.



■ % Lung deposition
■ % Lung deposition (corrected for BW)

Wildhaber. High percentage lung delivery in children from **detergent-treated spacers**. *Pediatr Pulmonol* 2000; 29: 389-393.

Newer delivery systems

Respimat soft mist inhaler

Vibrating mesh nebulizers

eFlow

AeroNeb Go

Omron NE-U022

“Smart” nebulizers

AerX

Halolite/ProDose

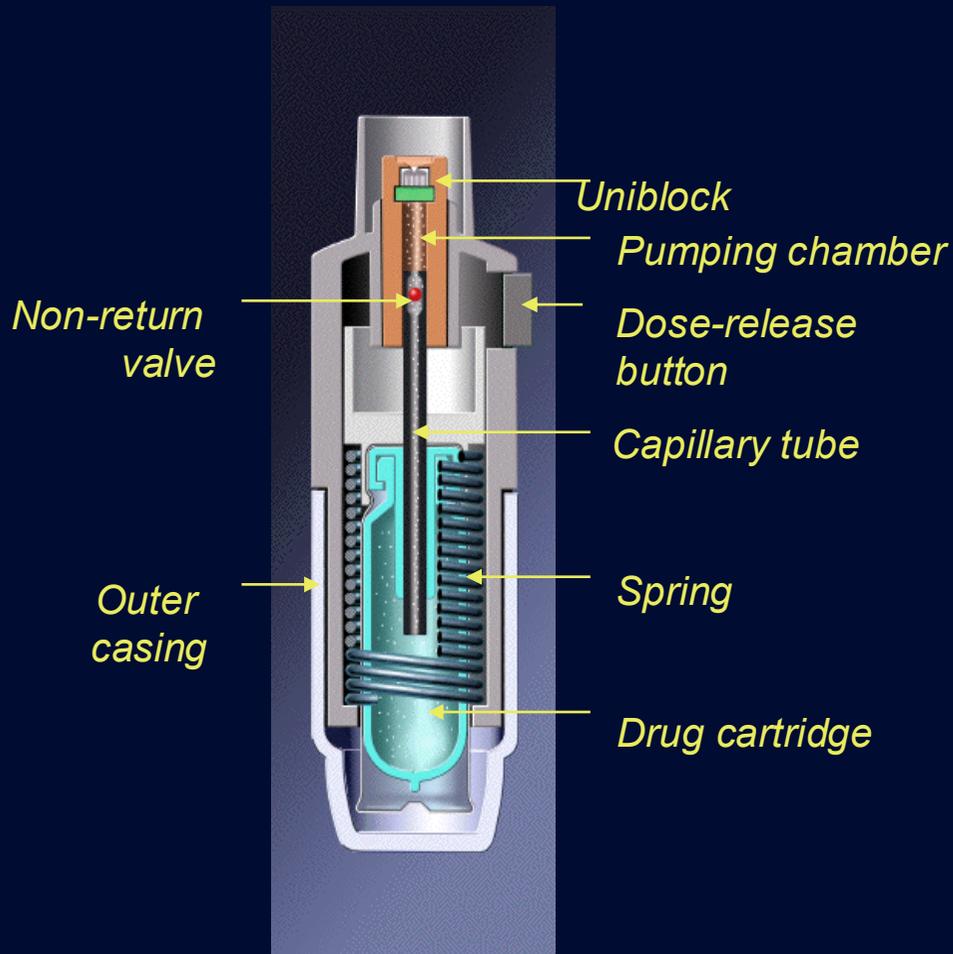
Breath-Control nebulizers

iNeb

Akita

Small volume liquid inhalers

Respimat - soft mist inhaler (SMI)



Propellant-free system
Not electronic



Respimat

Disposable device

Energy produced by spring compression

Aerosol properties

-1.2 seconds, 10 m/s velocity

Used for β -agonists and anti-cholinergics

Advantages

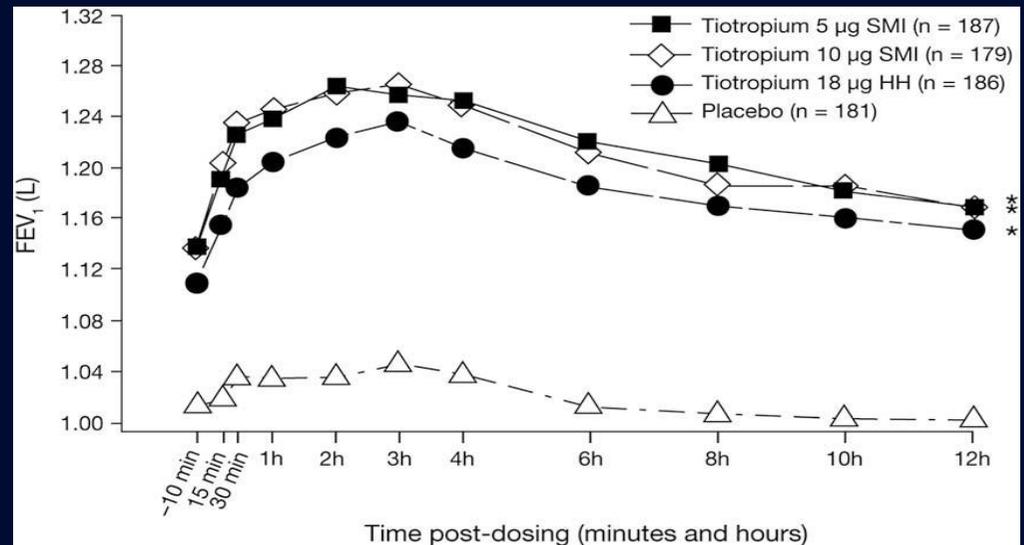
Slow mist improves coordination, easier than pMDI

Higher efficiency of lung delivery (~ 40%)

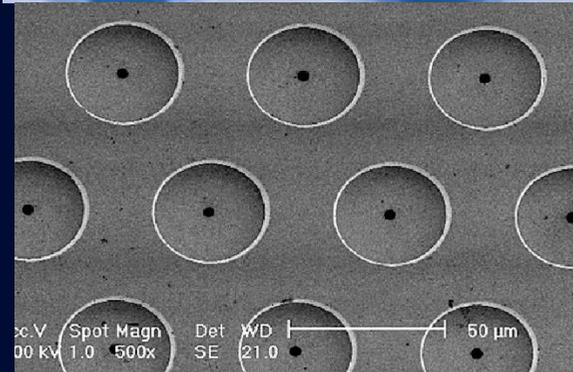
Disadvantages

Small dose chamber (11-15 μ L) limits microgram quantities

Need to coordinate actuation-inhalation



Vibrating mesh devices



Piezo-element vibrates a mesh or horn in contact with drug to create aerosol

Small

Portable

Battery or AC-powered

Silent operation

Faster than jet neb

High doses possible

Vibrating mesh devices: Challenges

Viscous drugs

May disrupt drug-carrier complexes (eg, liposomes)

Clogging of pores

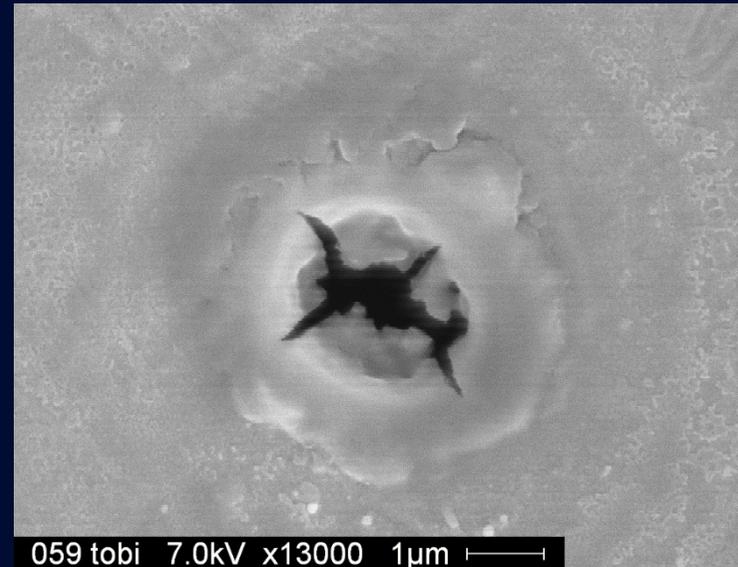
Suspensions

Drug or soap residues

Cleaning process

Many parts

Handling of mesh



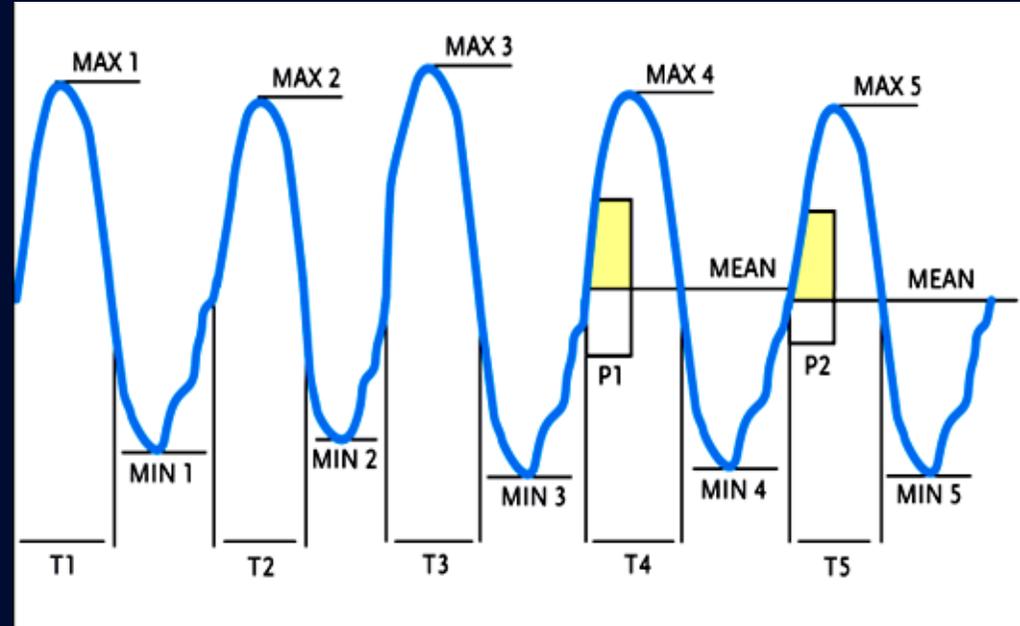
Adaptive Aerosol Delivery [AAD]

Pre-programmed with Inhalation dose

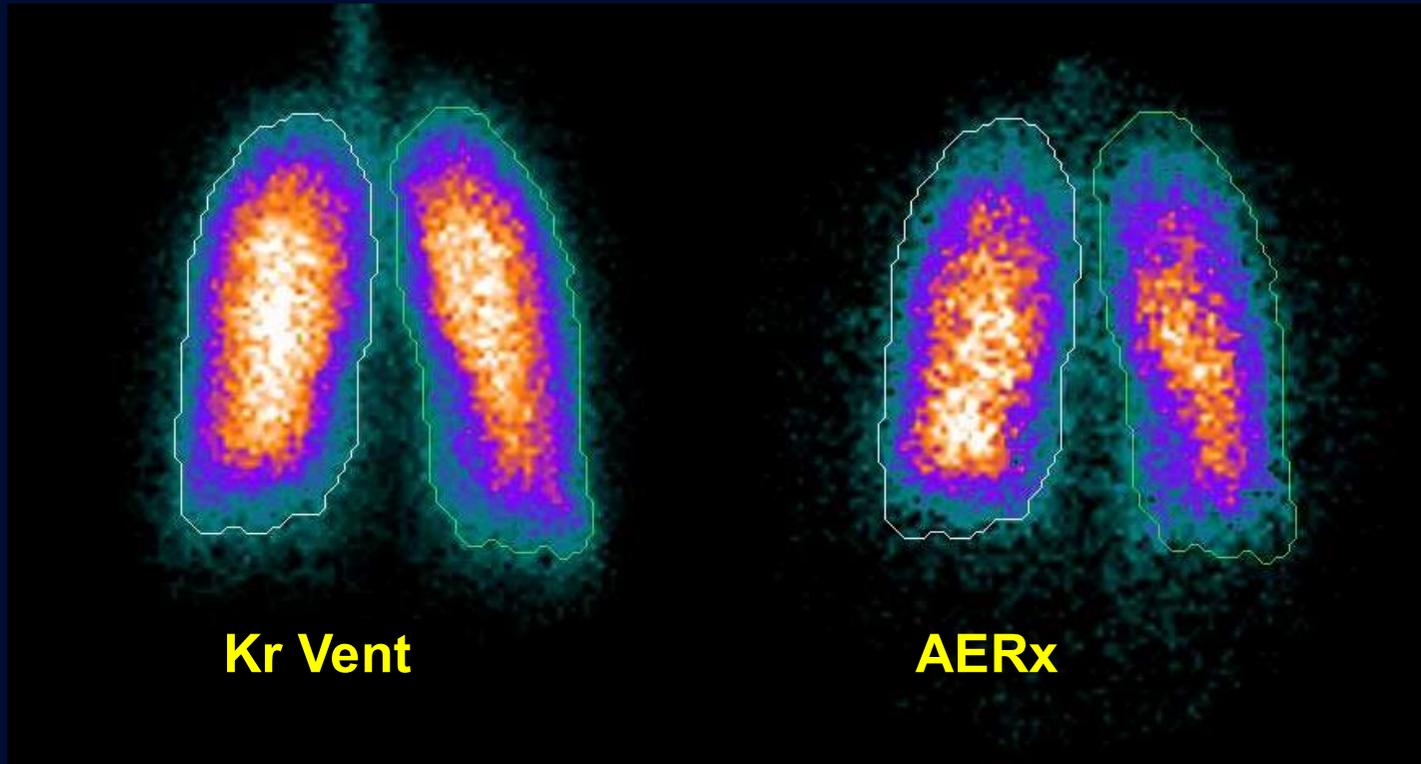
'Learns' how the patient is breathing and adapts to changes in breathing pattern

Feedback given when dose delivered

Datalogger



Small volume liquid inhalers - AERx[®]



lung deposition 64–88% (emitted dose) Intra subject lung dose CV11%

Breath-controlled nebulizers

Advantages

- Improved dose precision

 - Avoids upper airway

 - Better dispersion pattern in lungs

- Larger particles possible with slow inhalation

- Can reduce delivery time

- Very low residual volumes

Disadvantages

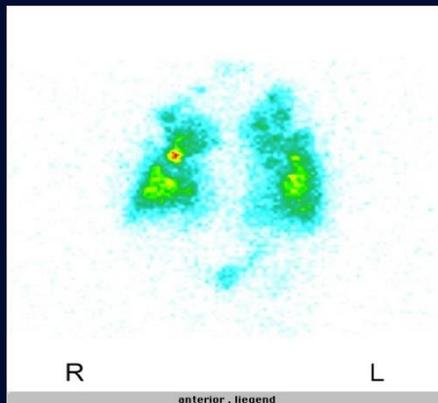
- Very expensive

- Cost may be absorbed with expensive drugs

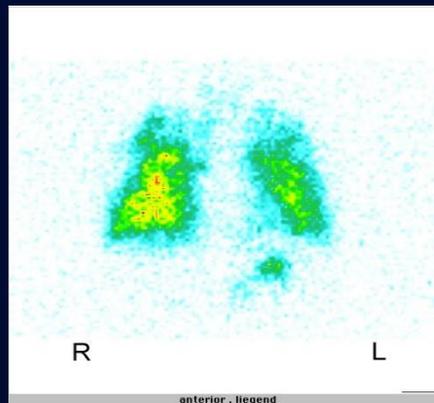
- Mesh clogging

Inspiratory control : AKITA

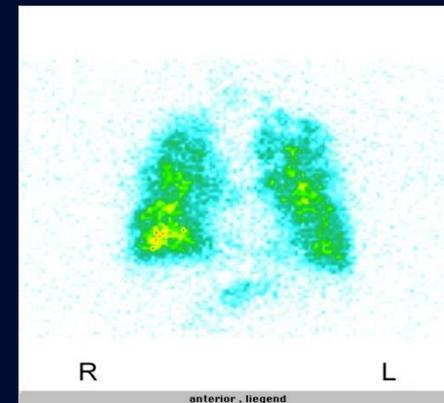
Limits inspiratory flow (12-15 lpm)
Larger particles can navigate to lung
Bypasses areas of obstruction
Coupled with PARI LC jet or mesh



Patient A



Patient B

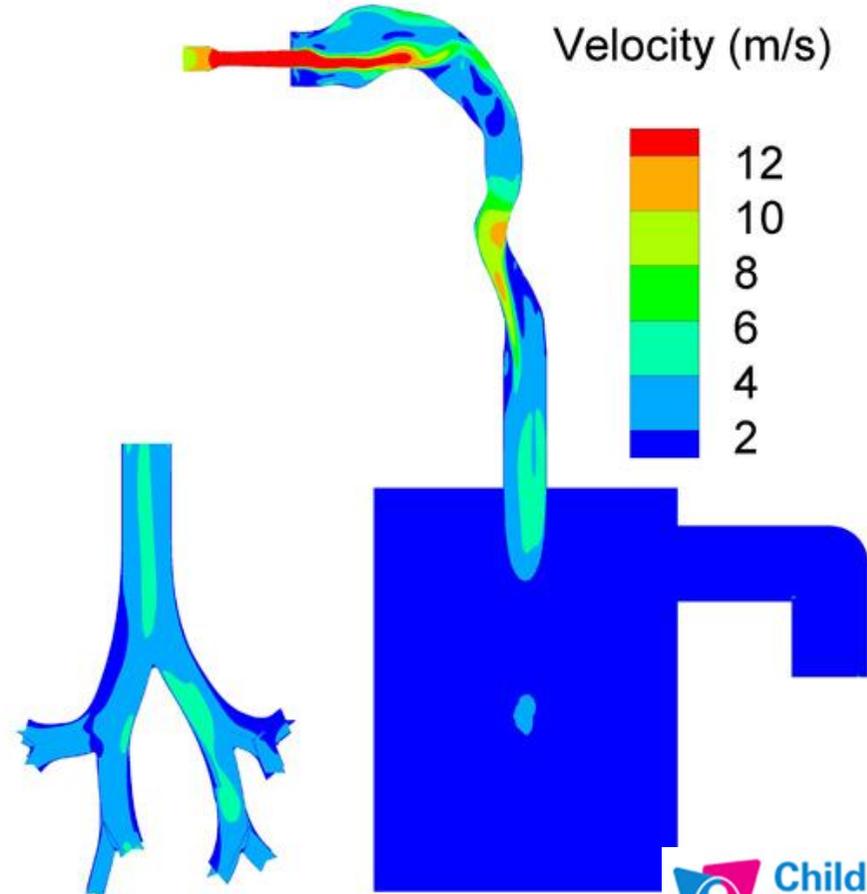
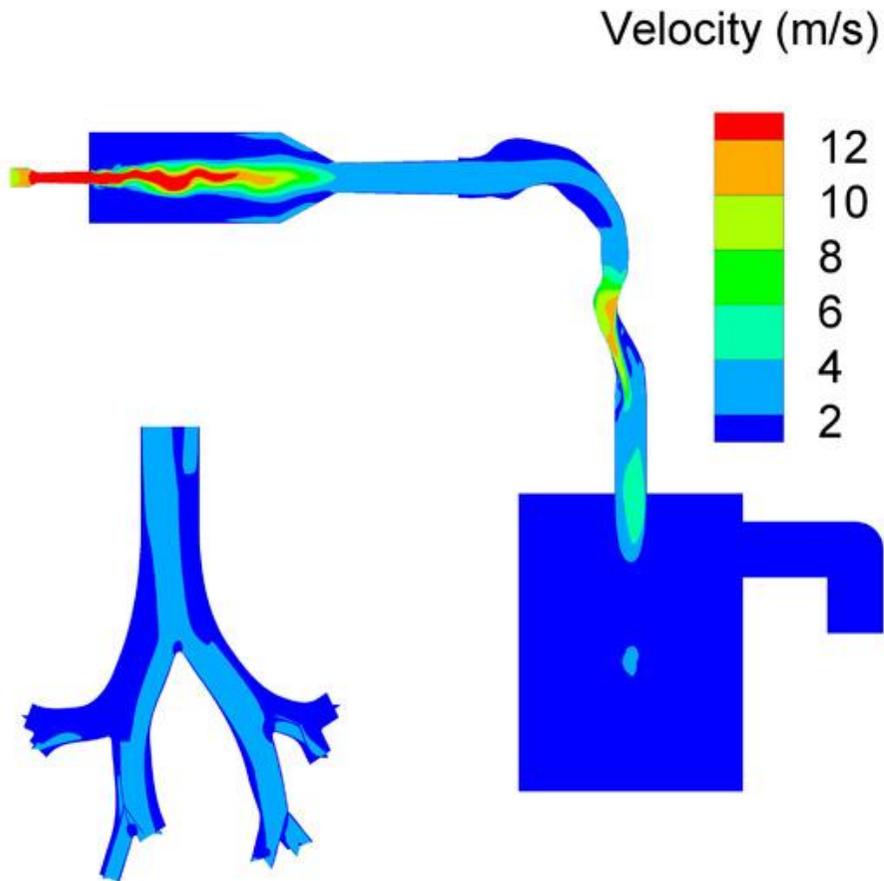


Patient C

Enhanced excipient growth (EEG)

(a) HandiHaler with spacer: 45 LPM

(b) HandiHaler: 45 LPM



Systemic delivery by aerosol

General considerations

- Expensive medication

- Can be delivered intact to acinus and absorbed

- Safe and effective - Not inactivated at airway

- Systemic effects are desired

Patients

- Chronic use

- Administration unpleasant by other routes

Gonda I. J Aerosol Med. 2006;19:47-53

Laube BL. Respir Care. 2005;50:1161-76.

Systemic delivery by aerosol

“Novel” use e.g. peptides

Diabetes affects 200 million people globally and growing

Insulin has a narrow therapeutic index

Insulin - first by aerosol in 1925

Gannslen M. Über inhalation von insulin. Klin. Wochenschr. 1925;4:71.

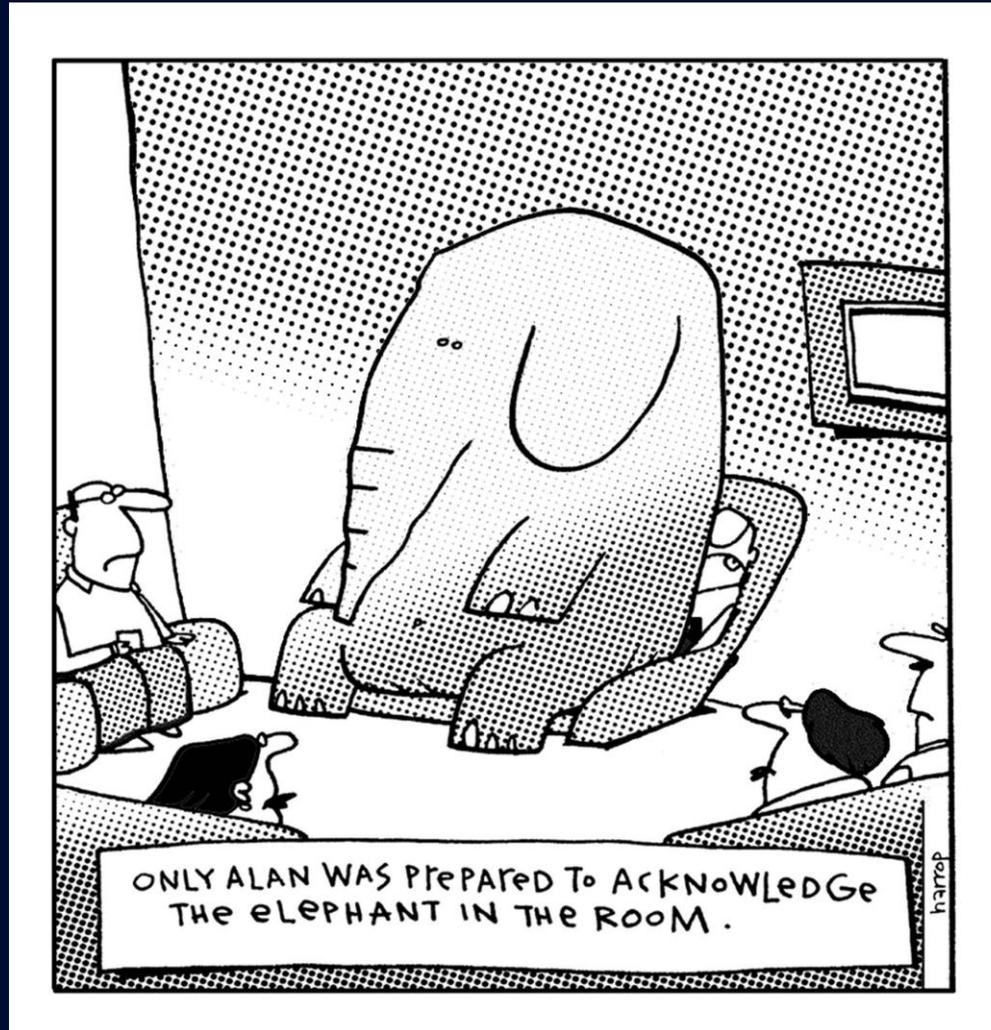
Harsch IA. Inhaled insulins: their potential in the treatment of diabetes mellitus. Treat Endocrinol 2005; 4: 131–138.

Other peptides

Human growth hormone - of special interest to pediatricians

Asthma resistant to therapy

... is often resistance to taking therapy



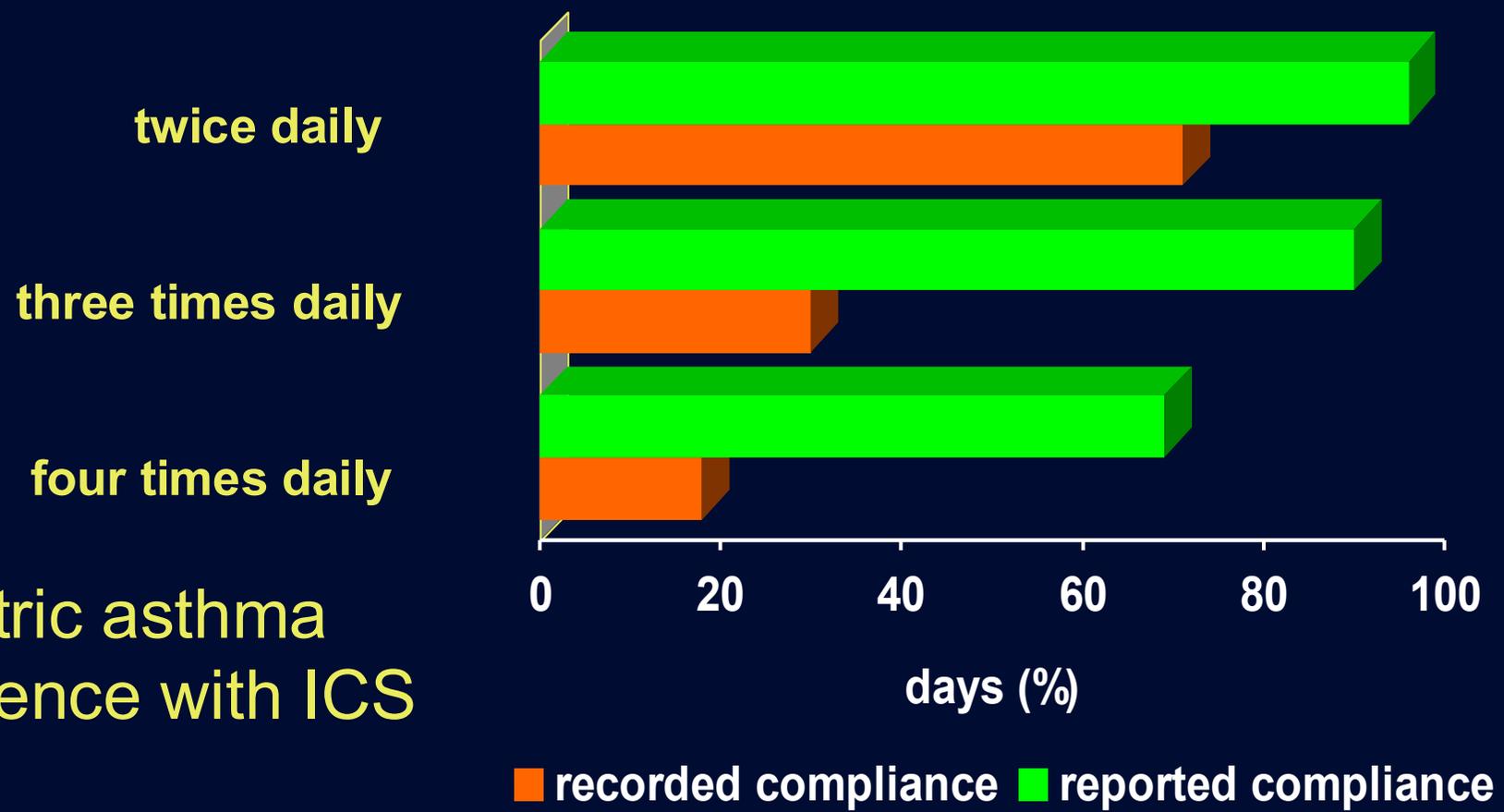
Compliance: Do as I say

Adherence: Do what is right

Contrivance: I do what I want, when
I want, and how I want it

Myth: Non-adherent patients can be recognized by health care providers

Pediatric asthma adherence with ICS



Adherence in pre-school children

29 pre-school children 'Chronolog' monitoring

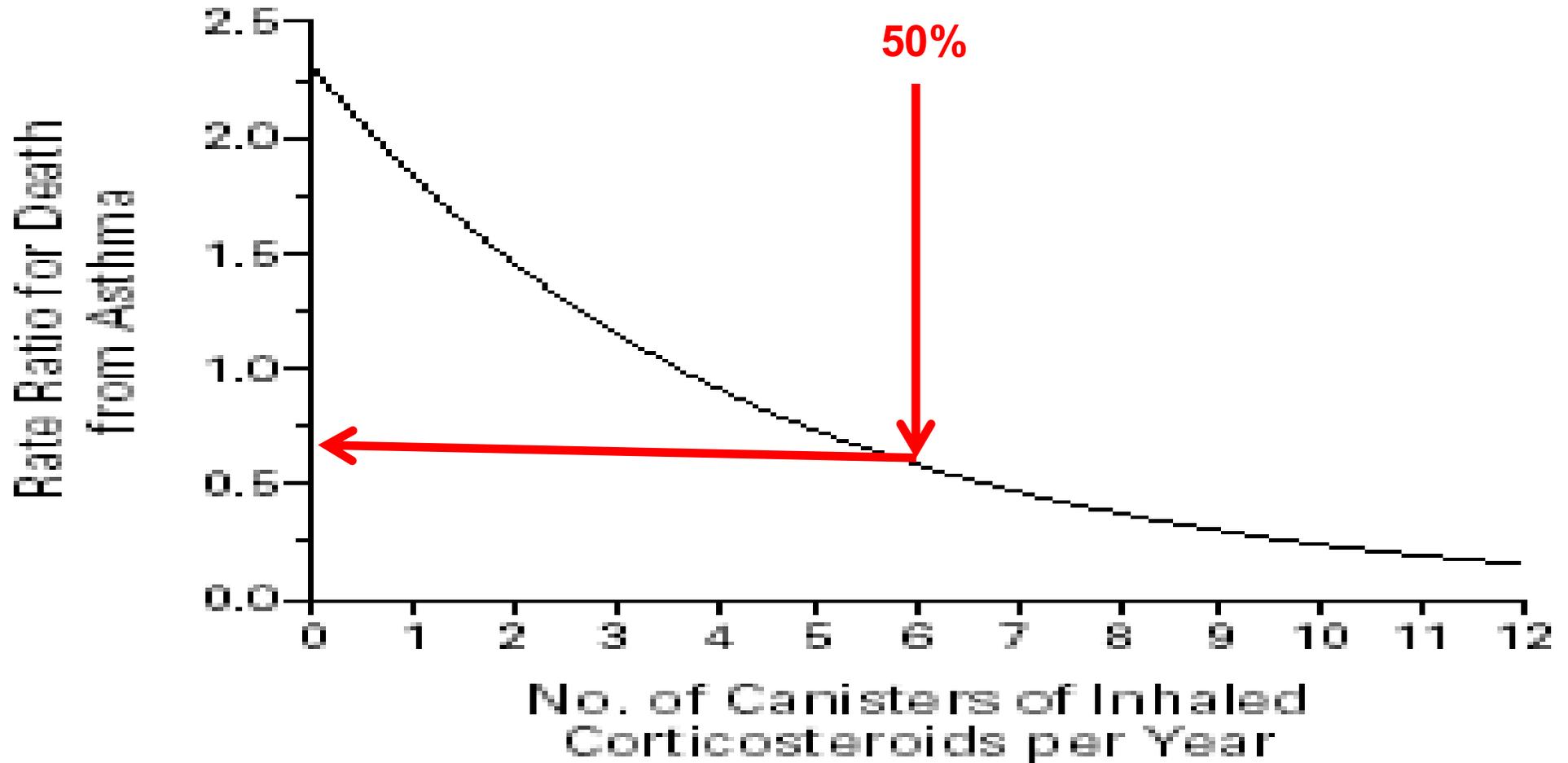
Median of 50% study days with full adherence

Very variable patterns of usage (elevator dumping)

'Compliance' greater in weeks after clinic

Gibson et al. Thorax 1995; 50: 1274

ICS use lowers risk of death from asthma



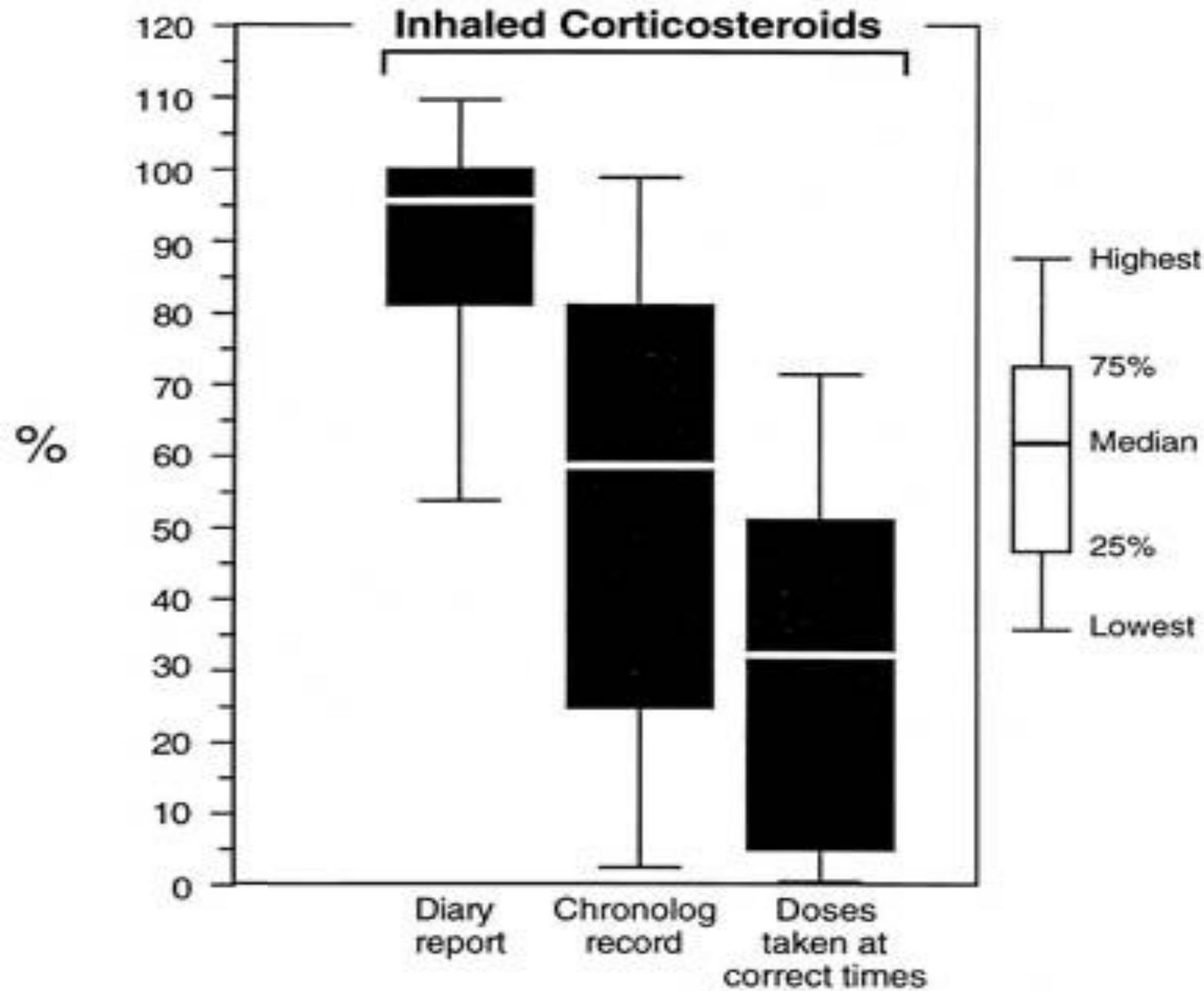
Suissa S et al. N Engl J Med 2000; 343: 332-336

Adherence

Median adherence

diary cards: 95.4%

Electronic counter: 58.4%



Milgrom et al. JACI

1996;98:1051-7

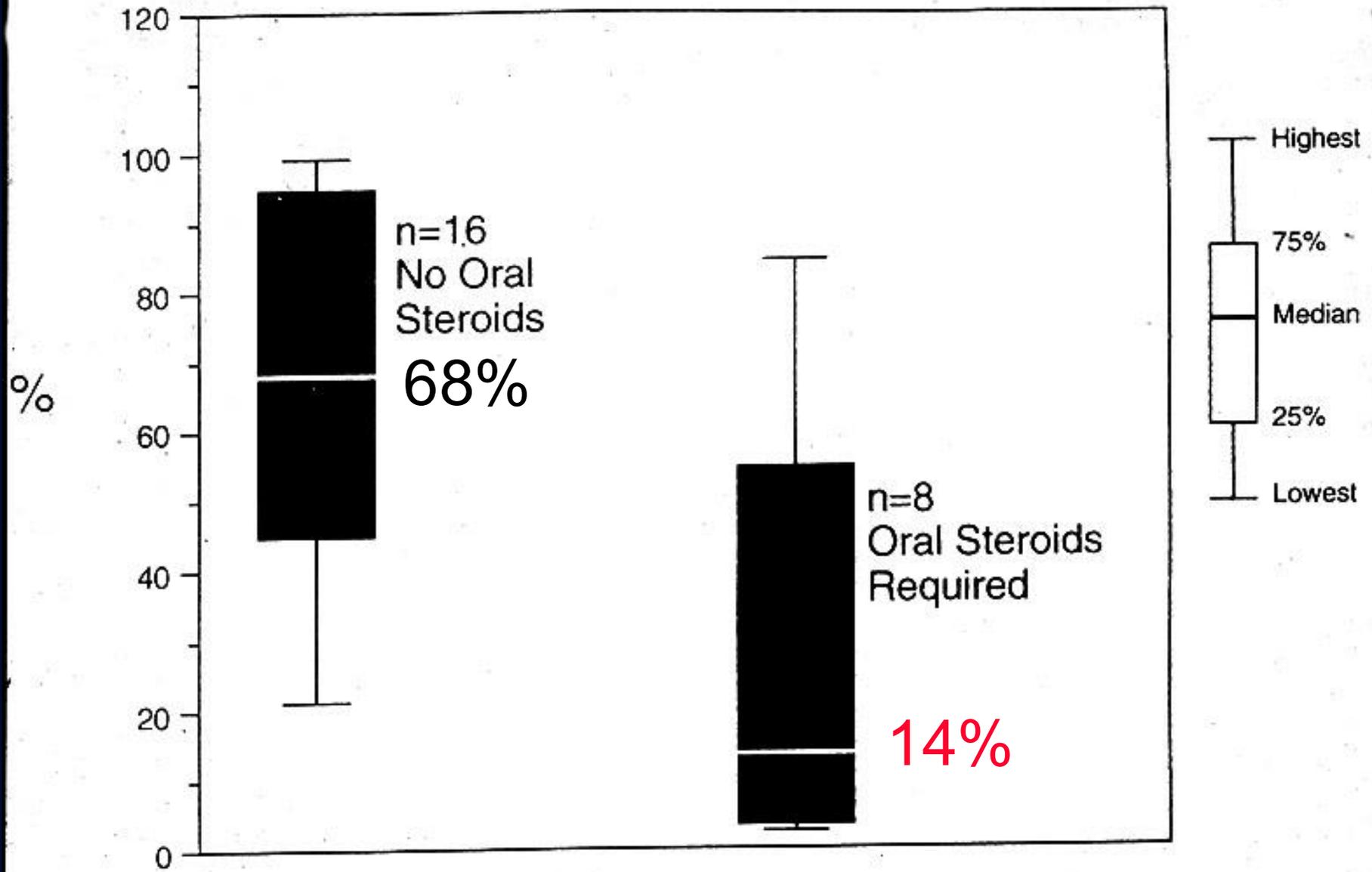


Figure 1. Distribution of percentages of prescribed doses.

CHALLENGES

Fool proof, efficient, low cost, portable,
and safe aerosol devices

Fool proof patients

