Patient adherence to inhaled therapy
A clinical perspective

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Disclosures

- Aerocrine
- Almirall
- AstraZeneca
- Boehringer Ingelheim
- Chiesi
- Cipla
- GlaxoSmithKline
- Meda Pharmaceuticals
- Mundipharma
- Novartis
- Nycomed
- Pfizer
- Roche
- Teva
In asthma and COPD, disease control remains suboptimal despite the availability of effective treatment strategies.

Adherence and inhaler technique are strong determinants of treatment effectiveness.
- But misuse and poor adherence are frequent and inter-related.

Education is crucial but not always effective.

Patients are very different in terms of:
- Adherence profile
- Ability / capacity (handling, fast inhalation...) and spontaneous inhalation mode
- Satisfaction/preference

There is no ideal device; available inhalers differ in terms of:
- General characteristics (volume, weight, aspect, counter)
- Handling requirements and optimal inhalation profile
In asthma and COPD, disease control remains suboptimal despite the availability of effective treatment strategies

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Asthma control in real life

- General asthma population: not all patients are controlled!

Poor control is associated with:
- impaired health status
- more exacerbations
- impaired work productivity

*\(p = 0.035\); NS, non-significant
What can we expect?

- Patients (n = 1690) received fluticasone/salmeterol 100/50–500/50 μg b.i.d. for 1 year

Definitions of asthma control were derived from the treatment goals of the GINA/National Institutes of Health guidelines at the time of the study.

b.i.d., twice daily; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; LABA, long-acting β₂-agonist


*GINA guidelines do not advocate ICS/LABA use in steroid-naïve patients; Seretide is not licensed for use in steroid-naïve patients
### Possible explanations

#### On the doctor’s side
- Wrong diagnosis
- Poor disease assessment
- Inadequate treatment
- Insufficient follow-up
- Comorbidities
- Complications

#### On the patient’s side
- Poor adherence
- Inappropriate inhalation technique
- Persistent exposure to risk factors
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Determinants of inhaled treatment effectiveness

- Device (internal resistance...)
- Content (pharmacological agents, excipients, propellants)

Adherence

Inhalation technique

Preference

Adequate particle size (MMAD) & respirable dose/fine particle fraction

Appropriate treatment delivery

Poor handling and poor adherence reduce treatment effectiveness

<table>
<thead>
<tr>
<th>Variables (n = 727)</th>
<th>$p$ value</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker (vs non-smoker)</td>
<td>0.026</td>
<td>1.53</td>
<td>1.05–2.22</td>
</tr>
<tr>
<td>Inhalation technique</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-optimal (vs optimal)</td>
<td>0.008</td>
<td>1.89</td>
<td>1.31–2.75</td>
</tr>
<tr>
<td>Adherence (according to Morisky score)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor or very poor (vs moderate or very good)</td>
<td>0.002</td>
<td>1.68</td>
<td>1.21–2.33</td>
</tr>
</tbody>
</table>

Frequency of inhaler misuse

Various MDIs (incl. BAI & spacer) and DPIs (capsule and multidose)

Patients (%)
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>COPD</th>
<th>Asthma</th>
<th>OR±SE; p level&lt;sup&gt;a,b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least a critical inhaler error</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Hospital admissions, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>62</td>
<td>55</td>
<td>86</td>
</tr>
<tr>
<td>1</td>
<td>23</td>
<td>26</td>
<td>9</td>
</tr>
<tr>
<td>2–3</td>
<td>11</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td>&gt;3</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Emergency department visits, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>71</td>
<td>64</td>
<td>81</td>
</tr>
<tr>
<td>1</td>
<td>22</td>
<td>24</td>
<td>11</td>
</tr>
<tr>
<td>2–3</td>
<td>4</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>&gt;3</td>
<td>3</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Antimicrobial courses, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>30</td>
<td>20</td>
<td>41</td>
</tr>
<tr>
<td>1</td>
<td>29</td>
<td>31</td>
<td>30</td>
</tr>
<tr>
<td>2–3</td>
<td>26</td>
<td>33</td>
<td>18</td>
</tr>
<tr>
<td>&gt;3</td>
<td>15</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>Corticosteroid courses, %</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Never</td>
<td>37</td>
<td>29</td>
<td>35</td>
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<tr>
<td>1</td>
<td>22</td>
<td>19</td>
<td>30</td>
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<tr>
<td>2–3</td>
<td>30</td>
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<td>22</td>
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<tr>
<td>&gt;3</td>
<td>11</td>
<td>26</td>
<td>13</td>
</tr>
</tbody>
</table>

n=1664; COPD: 52%
Intricated outcomes

### Inhalation technique

- **Patients remaining suboptimal**
  - Baseline: 1.8 ± 1.2
  - Follow-up: 1.4 ± 1.1
  - $p < 0.001$

- **Patients remaining optimal**
  - Baseline: 1.4 ± 1.3
  - Follow-up: 1.1 ± 1.3
  - $p < 0.001$

- **Patients becoming optimal**
  - Baseline: -0.2 ± 0.8
  - Follow-up: -0.4 ± 0.8
  - $p < 0.01$ vs becoming optimal

$n = 437$

### Control

- **Baseline**: 1.8 ± 1.2
- **Follow-up**: 1.4 ± 1.1
- $p < 0.001$

$n = 437$

### Adherence

- **Baseline**: 1.4 ± 1.3
- **Follow-up**: 1.1 ± 1.3
- $p < 0.001$

$n = 436$

Asthma training was provided by a Pharmacist

ACQ, asthma control questionnaire

Determinants of inhaler use

<table>
<thead>
<tr>
<th>Determinant</th>
<th>&lt;60</th>
<th>1.00</th>
<th>95% CI</th>
<th>≥60</th>
<th>1.40</th>
<th>0.67–2.94</th>
<th>Low</th>
<th>2.01</th>
<th>0.67–4.61</th>
<th>Middle</th>
<th>1.84</th>
<th>0.73–4.61</th>
<th>High</th>
<th>1.00</th>
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<tbody>
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<td>Age (years)</td>
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<tr>
<td>Educational level$^a$</td>
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<tr>
<td>FEV$_1$/VC$^b$</td>
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<tr>
<td>Received inhalation instruction$^c$</td>
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<td>1.00</td>
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<tr>
<td>no</td>
<td></td>
<td>2.22</td>
<td>1.02–4.80</td>
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<tr>
<td>Device</td>
<td>single</td>
<td>1.00</td>
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<tr>
<td>multiple</td>
<td></td>
<td>2.23</td>
<td>1.07–5.02</td>
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Rootmensen, JAMPDD 2010 ; n=156
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Effect of training

Percentage incorrect users of each inhaler device at baseline and at 4-month follow-up (n = number of patients using inhaler type). Inhaler technique was assessed at baseline by a trained pulmonary nurse specialist.

Patients completed a validated asthma control questionnaire (ACQ). At follow-up 3–4 months later, inhaler technique was re-assessed and the ACQ repeated.

Adapted from Harnett CM et al. J Asthma 2014;51:440–5
Training does not solve everything

Hardwell PCRJ 2011

Do we educate properly?

- Proportion of patients who received education
- Among 727 patients visiting a pharmacy for delivery of an inhaled treatment (MDI or BAI)

*INSUFFICIENT!* 63% !

Switching without consultation...

Data are based on a 2-year retrospective matched-cohort study using the UK General Practice Research Database. Graph shows outcome of asthma treatment during year 2 of study for patients whose ICS device was switched without an accompanying consultation (switched cohort) and controls.

Treatment success was defined based on a composite measure including mean short-acting $\beta_2$-agonist dose, oral corticosteroid use/year, controller therapy and hospitalization.

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Patients’ preferences

Preference

Device handling

Compliance with treatment regimen

Control

Haughney J et al. Respir Med 2010;104:1237–45
Determinants of adherence

- Patient
  - Health beliefs
  - Cognitive ability
  - Self-efficacy
  - Comorbidities
  - Psychological profile
  - Conscientiousness

- Treatment
  - Method of administration
  - Dosing regimen
  - Polypharmacy
  - Side effects

- Society
  - Patient-prescriber relationship
  - Social support
  - Access to medication
  - Device training
  - Follow-up

- Disease

Lareau, Int J Chron Obstruct Pulmon Dis. 2010
## Improving adherence

<table>
<thead>
<tr>
<th>Type of nonadherence</th>
<th>Adherence interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erratic</td>
<td>Simplify and tailor regimen</td>
</tr>
<tr>
<td></td>
<td>Implement behavioral strategies such as cueing (e.g., storing medication next to toothbrush), reminders and reinforcement</td>
</tr>
<tr>
<td></td>
<td>Self-monitoring and support, with monitoring from others</td>
</tr>
<tr>
<td>Unwitting</td>
<td>Review of adherence behavior</td>
</tr>
<tr>
<td></td>
<td>Written or visual medication plans</td>
</tr>
<tr>
<td></td>
<td>Patient education in disease management</td>
</tr>
<tr>
<td>Intelligent</td>
<td>Patient education and counseling</td>
</tr>
<tr>
<td></td>
<td>Negotiate therapy</td>
</tr>
<tr>
<td></td>
<td>Link therapy with personal goals</td>
</tr>
</tbody>
</table>

Lareau, Int J Chron Obstruct Pulmon Dis. 2010
What do they want - Patient/Physician ranking of device features

Patient rank order

11 10 9 8 7 6 5 4 3 2 1 0

- High physician importance
- Low patient importance

- Minimal effort needed to inhale drug
- No need to coordinate breathing and pressing the inhaler
- Device lock out when empty
- Easy to hold and carry
- Easy to hold and carry
- Easy and simple instructions
- Signal to indicate correct inhalation
- Has dose counter/indicator
- Robust and Durable
- Same lung delivery every time
- No need to load the drug before inhaling
- No need to clean
- High patient importance
- Low physician importance
Patient’s satisfaction ➔ increased compliance/adherence

Based on data from the Adelphi Respiratory Disease Specific Programme (Adelphi, Macclesfield, UK), a cross-sectional study of consulting patients in five European countries. Data shown for patients (n = 1345) who answered the inhaler attribute satisfaction section of their form and physicians (n = 582) who provided patient record forms.

Preference ➔ better control?

- Fluticasone/salmeterol fixed-dose combination
  - Retrospective, 2-year (1 baseline year, 1 outcome year), matched-cohort study using data the UK General Practice Database
  - 3134 patients (n = 1567 in each group)

Outcomes in the pMDI cohort (vs DPI), 1 year after prescription of fixed-dose fluticasone propionate/salmeterol

Primary measure of asthma control
Unadjusted OR (95% CI) 1.19 (1.01–1.40)

Exacerbations
Adjusted RR (95% CI) 0.82 (0.66–1.00)

Treatment success
Unadjusted OR (95% CI) 1.23 (1.07–1.42)

Asthma control was a composite measure comprising no recorded hospital attendance for asthma, oral corticosteroids or antibiotics for lower respiratory infection. Treatment success was defined as no exacerbations (an unscheduled hospital admission or emergency department attendance for asthma, or acute use of oral corticosteroids) and no change in asthma therapy.

CI, confidence interval; DPI, dry powder inhaler; FP, fluticasone propionate; OR, odds ratio; pMDI, pressurized metered-dose inhaler; RR, relative risk

Adapted from Price D et al. Respir Med 2011;105:1457–66
Patients’ participation ➔ increased compliance/adherence

- Adherence to ICS (n = 612, randomized)

Patients with poorly controlled asthma were randomized to SDM, CDM or UC. Cumulative controller medication dose was measured as beclametasone canister equivalents. Adherence was measured by fill/refill continuous medication acquisition indices.

CDM, clinician decision making; SDM, shared decision making; UC, usual care

Adapted from Wilson SR et al. Am J Resp Care Med 2010;181:566–77
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Diverse patients need diverse inhalers
## Advantages and limitations of available devices

<table>
<thead>
<tr>
<th>Device</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>pMDI</td>
<td>• Portable and compact&lt;br&gt;• Multi-dose device&lt;br&gt;• Quick to use&lt;br&gt;• Relatively cheap&lt;br&gt;• Cannot contaminate contents&lt;br&gt;• Available for most inhaled medications</td>
<td>• Contains propellants&lt;br&gt;• Not breath actuated&lt;br&gt;• Many patients cannot use it correctly (e.g. coordination difficulties)&lt;br&gt;• Cold Freon effect&lt;br&gt;• High oropharyngeal deposition</td>
</tr>
<tr>
<td>pMDI+spacer</td>
<td>• Easier to coordinate inhaler actuation with inspiration than pMDI alone&lt;br&gt;• Large drug doses delivered more conveniently than pMDI alone&lt;br&gt;• Less oropharyngeal deposition&lt;br&gt;• Higher lung deposition than a pMDI</td>
<td>• Bulkier and less portable than pMDI alone&lt;br&gt;• Plastic spacers may acquire static charge</td>
</tr>
<tr>
<td>BA-MDI</td>
<td>• Portable and compact&lt;br&gt;• Multi-dose device&lt;br&gt;• Quick to use&lt;br&gt;• Breath-actuated (no coordination needed)&lt;br&gt;• Cannot contaminate contents</td>
<td>• Contains propellants&lt;br&gt;• &quot;Cold Freon&quot; effect&lt;br&gt;• Require moderate inspiratory flow to be triggered&lt;br&gt;• More bulky and noisy than pMDI</td>
</tr>
<tr>
<td>DPI</td>
<td>• Portable and compact&lt;br&gt;• Quick to use&lt;br&gt;• Breath actuated (no coordination needed)&lt;br&gt;• Usually higher lung deposition than a pMDI&lt;br&gt;• Does not contain propellants</td>
<td>• Require high inspiratory flow to be triggered&lt;br&gt;• May not be appropriate for emergency situations&lt;br&gt;• Many patients cannot use them correctly (e.g. capsule handling problems for elderly)&lt;br&gt;• Most types are moisture sensitive</td>
</tr>
<tr>
<td>SMI (Respimat)</td>
<td>• Portable and compact&lt;br&gt;• Multi-dose device&lt;br&gt;• Probably easier to use correctly than pMDI&lt;br&gt;• High lung deposition&lt;br&gt;• Does not contain propellants</td>
<td>• Not breath actuated&lt;br&gt;• Not currently available in most countries&lt;br&gt;• Relatively expensive</td>
</tr>
</tbody>
</table>

Lavorini F et al. Breathe 2008;5:121-31
## Crucial differences between device types

<table>
<thead>
<tr>
<th>MDI</th>
<th>DPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shaking (+/-)</td>
<td>Device preparation</td>
</tr>
<tr>
<td>Actuation</td>
<td>No actuation, i.e. no need to coordinate</td>
</tr>
<tr>
<td><strong>Coordinated</strong> with inspiration, except</td>
<td>No manipulation during inhalation</td>
</tr>
<tr>
<td>- BAI</td>
<td>- Fast inhalation from the beginning</td>
</tr>
<tr>
<td>- MDI + Spacer</td>
<td></td>
</tr>
<tr>
<td><strong>Slow</strong> inhalation</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions: make it:

- Easy to use
- Ready to use
- Robust
- Reproductible dose
- Dose counter
- No need to inhale hard
- Indicates correct dose delivery
## Factors to consider when choosing an inhaler

<table>
<thead>
<tr>
<th><strong>Patient-related factors</strong></th>
<th>ability to inhale consciously, handle the device and coordinate the use of the device and the inspiratory effort, preference, adherence and compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease-related factors</strong></td>
<td>severe and/or acute airflow obstruction may compromise the ability to generate an adequate inspiratory flow therapeutic strategy and indications not the same for asthma and COPD.</td>
</tr>
<tr>
<td><strong>Device-related factors</strong></td>
<td>the optimal inhalation profile differs between pMDIs (slow inspiration is preferable) and DPIs (high-flow inhalation in required, with fast acceleration especially for reservoir devices).</td>
</tr>
<tr>
<td><strong>Caregivers-related factors</strong></td>
<td>accounting for the availability and knowledge of professionals involved in information and education (general practitioners, specialists, nurses, physiotherapists, pharmacists).</td>
</tr>
</tbody>
</table>

Adapted from Dekhuijzen, Respir Med 2013;107:1817-21
Proposition

Can inhale voluntarily

YES

Able to inhale fast

NO

MDI + spacer BAI Respimat

YES

MDI + spacer BAI Respimat DPI

NO

MDI +/- spacer BAI Respimat

YES

MDI +/- spacer BAI Respimat DPI

NO

MDI + spacer Nebulizer

Adapted from Dekhuijzen, Respir Med 2013;107:1817-21
Thank you for your attention