The Elephant in the Room - Medication adherence

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Medication adherence - Outline

- Why is it an elephant?
- Adherence in long-term disease management
- Adults v children
- Adherence in epilepsy?
- Does adherence affect clinical outcome?
- What factors influence adherence?
- What interventions work?
Adherence – what is it?

- Compliance v adherence v concordance
- Adherence – “the extent to which the patient’s action matches the agreed recommendations of the prescriber”

Drugs don't work in patients who don't take them.

— C. Everett Koop —
Worldwide Share of Deaths, by Cause

<table>
<thead>
<tr>
<th>Region</th>
<th>Chronic diseases</th>
<th>Communicable, maternal, perinatal and nutritional conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe &amp; Central Asia</td>
<td>84</td>
<td>6</td>
</tr>
<tr>
<td>East Asia &amp; Pacific</td>
<td>71</td>
<td>19</td>
</tr>
<tr>
<td>Latin America &amp; Caribbean</td>
<td>67</td>
<td>22</td>
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<tr>
<td>Middle East &amp; North Africa</td>
<td>65</td>
<td>24</td>
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<tr>
<td>South Asia</td>
<td>43</td>
<td>47</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>72</td>
<td>21</td>
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</tbody>
</table>
Medication adherence in adult long-term disease

• Diabetes - CODE2
  – <30% good glycaemic control.
  – 2% adhered fully to agreed management.

• Hypertension
  – Increases risk of ischaemic heart disease by 3-fold and stroke by 8-fold.
  – UK - <25% have optimum BP control.
  – 60% of hypertension relates to poor adherence

• Asthma
  – Adherence 30% – 70%;
  – Poor adherers - 6 fold risk of ICU admission
Why adherence is important

• Health outcomes
  – Morbidity and mortality
  – Apparent drug ineffectiveness
  – Adverse effects
  – Multiple changes of medication

• Costs
  – Relates to 33-69% of medication related hospital admissions – USA $100 billion
  – UK - £750million p.a.

Cutler & Everett, 2010; Maidment, 2017
Why it (should) matter to pharma

Adherence: Addressing Pharma's Last-Mile Problem

Pharmaceutical manufacturers have done more to save lives over the past century than any other industry. They have developed

Adherence in a financial perspective

Up to 30 percent of prescriptions to treat chronic conditions are never filled, and across major indications, more than 50 percent of patients stop taking their medications within the first year. In financial terms, nonadherence costs the pharmaceutical industry $637 billion in lost revenue each year, according to Capgemini.
Measuring adherence

• Subjective
  – patient reporting
  – Scaled questionnaires

• Objective
  – Remaining pill counts
  – Electronic pill monitoring
  – Medication possession ratio
  – Clinical population data-linkage
  – Biochemical – drug levels

• Defining thresholds
  – “Good” v “Poor” adherence
  – Varying thresholds 80 – 95%

MPR = \left( \frac{\text{Sum of days' supply for all fills in period}}{\text{Number of days in period}} \right) \times 100\%
Prescribing in children

• 15% of children age 11-15 have a chronic illness (NHS-E, 2018)

Thrane, Sørensen, 1999
Childhood asthma

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Age</th>
<th>Type of EMD</th>
<th>Study duration</th>
<th>Mean</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gibson et al&lt;sup&gt;15&lt;/sup&gt;</td>
<td>26 children, Glasgow, UK</td>
<td>15 months--5 years</td>
<td>Nebulizer chronolog&lt;sup&gt;*&lt;/sup&gt;</td>
<td>2 months</td>
<td>71%</td>
<td>Median=58% ‘Non compliant’ children excluded</td>
</tr>
<tr>
<td>Milgrom et al&lt;sup&gt;14&lt;/sup&gt;</td>
<td>24 children, USA</td>
<td>8–12 years</td>
<td>MDI chronolog&lt;sup&gt;*&lt;/sup&gt;</td>
<td>13 weeks</td>
<td>50%</td>
<td>Median=58% ‘Non compliant’ children excluded</td>
</tr>
<tr>
<td>Bender et al&lt;sup&gt;2&lt;/sup&gt;</td>
<td>27 children, USA</td>
<td>7–12 years</td>
<td>Doser CT&lt;sup&gt;†&lt;/sup&gt;</td>
<td>6 months</td>
<td>48%</td>
<td></td>
</tr>
<tr>
<td>Mcquaid et al&lt;sup&gt;3,1&lt;/sup&gt;</td>
<td>106 children, USA</td>
<td>8–16 years</td>
<td>MDILog&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>1 month</td>
<td>54%</td>
<td></td>
</tr>
<tr>
<td>O’Connor et al&lt;sup&gt;4,8&lt;/sup&gt;</td>
<td>16 children, USA</td>
<td>8–18 years</td>
<td>Doser CT&lt;sup&gt;†&lt;/sup&gt;</td>
<td>3 months</td>
<td>54%</td>
<td></td>
</tr>
<tr>
<td>Burgess et al&lt;sup&gt;33&lt;/sup&gt;</td>
<td>21 children, Australia</td>
<td>18 months--7 years</td>
<td>Smartinhaler&lt;sup&gt;§&lt;/sup&gt;</td>
<td>3 months</td>
<td>65%</td>
<td>Median=65%</td>
</tr>
<tr>
<td>Bender and Zhang&lt;sup&gt;26&lt;/sup&gt;</td>
<td>104 children, USA</td>
<td>8–18 years</td>
<td>MDILog&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>4 months</td>
<td>40%</td>
<td>Poorly controlled asthma</td>
</tr>
<tr>
<td>Burgess et al&lt;sup&gt;36&lt;/sup&gt;</td>
<td>51 children, Australia</td>
<td>18 months--7 years</td>
<td>Smartinhaler&lt;sup&gt;§&lt;/sup&gt;</td>
<td>1 month</td>
<td>71%</td>
<td>Median=71%</td>
</tr>
<tr>
<td>Jentzsch et al&lt;sup&gt;8&lt;/sup&gt;</td>
<td>102 children, Brazil</td>
<td>3–14 years</td>
<td>Doser CT&lt;sup&gt;†&lt;/sup&gt;</td>
<td>1 year</td>
<td>52%</td>
<td>Low-income families</td>
</tr>
<tr>
<td>McNally et al&lt;sup&gt;27&lt;/sup&gt;</td>
<td>63 children, USA</td>
<td>5–17 years</td>
<td>MDILog&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>1 year</td>
<td>34%</td>
<td>African–American children</td>
</tr>
<tr>
<td>Burgess et al&lt;sup&gt;38&lt;/sup&gt;</td>
<td>26 children, Australia</td>
<td>6–14 years</td>
<td>Smartinhaler&lt;sup&gt;§&lt;/sup&gt;</td>
<td>4 months</td>
<td>58%</td>
<td>Low-income African-American</td>
</tr>
<tr>
<td>Celano et al&lt;sup&gt;29&lt;/sup&gt;</td>
<td>1433 children, USA</td>
<td>6–11 years</td>
<td>MDILog-II&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>1 year</td>
<td>57%</td>
<td>Peak flow, competence and adherence monitored</td>
</tr>
<tr>
<td>Nikander et al&lt;sup&gt;34&lt;/sup&gt;</td>
<td>115 children, USA</td>
<td>5–10 years</td>
<td>Vitalograph Spirometer&lt;sup&gt;¶&lt;/sup&gt;</td>
<td>18 months</td>
<td>73%</td>
<td></td>
</tr>
<tr>
<td>Jentzsch et al&lt;sup&gt;30&lt;/sup&gt;</td>
<td>102 children, Brazil</td>
<td>5–14 years</td>
<td>Doser CT&lt;sup&gt;†&lt;/sup&gt;</td>
<td>1 year</td>
<td>47%</td>
<td>‘steroid naïve patients’</td>
</tr>
</tbody>
</table>
A Review of Adolescent Adherence in Type 1 Diabetes and the Untapped Potential of Diabetes Providers to Improve Outcomes

Karishma A. Datye¹, Daniel J. Moore¹, William E. Russell¹, and Sarah S. Jaser¹

¹Ian M. Burr Division of Pediatric Endocrinology and Diabetes, Vanderbilt University Medical Center, Nashville, TN 37232, USA

Abstract

Only 21% of adolescents with type 1 diabetes (T1D) meet glycemic goals set forth by the American Diabetes Association. Adherence to therapy is a particular concern in this population, and the association between poor adherence and worsening glycemic control indicates that there is a critical need to improve adherence to therapy in adolescents with T1D. In this article, we review...
Childhood cystic fibrosis

- Poor adherence:
  - Enzyme supplements – 72%
  - Vitamins – 59%
  - Chest physio 49%
Childhood epilepsy

• 50% onset as child/young adult
• Common chronic condition (c.8 per 1000)
• 1 in 20 acute admissions and outpatient consultations
• 70% can become seizure free with appropriate treatment
• Adherence to medication?
Medication adherence in childhood epilepsy

How common is poor adherence?
What clinical variables might be associated with good or poor adherence?

Adherence to antiepileptic drugs in children with epilepsy in a Scottish population cohort

Jayakara Shetty1,2 | Stephen A Greene3 | Oscar Mesalles-Naranjo1 | Martin Kirkpatrick1

1 Tayside Children’s Hospital, NHS Tayside; Ninewells Hospital and Medical School, Dundee; 2 Ninewells Hospital and Medical School, University of Dundee, Dundee; 3 Bespoke Specialist Services, ISD, NHS National Services Scotland, Edinburgh, UK.

All children <16 years with epilepsy in 2 one year cohorts
Mean duration of epilepsy - 4 years

Community dispensing dataset
“Adherence Index”
Clinical dataset (plus prescribing data)
Adherence Index = \frac{\text{Encashed AED (HIC data)} \times 100}{\text{Recommended AED (Clinical data)}}

- Clinical data – demography, seizure frequency, AED Rx, comorbid disorders

<table>
<thead>
<tr>
<th>Table: Patient characteristics</th>
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</thead>
<tbody>
<tr>
<td><strong>Clinical variable</strong></td>
</tr>
<tr>
<td>Median age in years (IQR)</td>
</tr>
<tr>
<td>Med age of seizure onset, y (IQR)</td>
</tr>
<tr>
<td>Median duration of epilepsy, y (IQR)</td>
</tr>
<tr>
<td>Male (%)</td>
</tr>
<tr>
<td>Female (%)</td>
</tr>
<tr>
<td>Children with other chronic health problems (%)</td>
</tr>
<tr>
<td>Regular medication other than AED (%)</td>
</tr>
<tr>
<td>Seizure frequency (%)</td>
</tr>
<tr>
<td>Seizure free for &gt;12mo</td>
</tr>
<tr>
<td>1-12 seizures per y</td>
</tr>
<tr>
<td>2-4 seizures per mo</td>
</tr>
<tr>
<td>1-7 seizures per wk</td>
</tr>
<tr>
<td>Daily seizures</td>
</tr>
<tr>
<td>Antiepileptic drugs (%)</td>
</tr>
<tr>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Ethosuximide</td>
</tr>
<tr>
<td>Lamotrigine</td>
</tr>
<tr>
<td>Levetiracetam</td>
</tr>
<tr>
<td>Topiramate</td>
</tr>
<tr>
<td>Valproate</td>
</tr>
<tr>
<td>Vigabatrin</td>
</tr>
<tr>
<td>Monotherapy (%)</td>
</tr>
<tr>
<td>Polytherapy (%)</td>
</tr>
</tbody>
</table>

IQR, interquartile range; AED, anti-epileptic drugs
Results

• Mean adherence 69.4%
  – >90% adherence – 31%
  – <50% adherence – 25%

• No effect on adherence:
  – epilepsy duration
  – seizure frequency
  – AED type, polytherapy
  – co-morbidity

• Adherence falls with age
Newly diagnosed epilepsy

• Pooled adherence data – 58% for all v. 65% for new diagnosis
  Yang, Ep Res, 2018
Does adherence affect outcome in paediatric epilepsy?

**Abstract**

Objective: The aim of the study was to determine sociodemographic, biological epilepsy-specific, and adherence predictors of long-term pediatric seizure outcomes.

Methods: This is a prospective, longitudinal, observational study of antiepileptic drug (AED) adherence and seizure outcomes in children with newly diagnosed epilepsy. Patients were followed up to 2 years post AED initiation.

Results: Adherence trajectory group status was a significant predictor of seizure outcome. Non-adherence at 2 years doubled the risk of emergency admission (HR 2.1).

Lee YK, Epileptic Disord. 2016

**Figure 3**

Cumulative rate of adherence, and adherence and persistence at one, two, and three years after AED treatment initiation.

Non-adherence at 2 years doubled the risk of emergency admission (HR 2.1)

Lee YK, Epileptic Disord. 2016
Seizure frequency v adherence in new diagnosis

Falling adherence vs rising seizure freedom rates!??

Fuchs, 2019, (submitted)
Epilepsy: Is children’s adherence better?

• Pooled adherence rates in systematic reviews
  – Children  - 58% (22 – 96%)
    Yang, Ep Res, 2018
  – Adults - 40% (26 – 79%)

• Why so varied?
  – definitions, methodology, population heterogeneity
Factors affecting adherence

• Patient related
  – “Health Literacy”
  – Partnership working/ decision making

• Prescribers
  – Complex Rx regimes
  – Multiple changes of healthcare provider

• Health systems
  – Time
  – Access & “Contactability”
Health Literacy

UK population:
- 16% functionally illiterate
- 35% “health illiterate”

“the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions to prevent or treat illness.”

Highlights
- This study examined the relationship between parent health literacy and adherence-related outcomes in children with epilepsy.
- Parent health literacy was an overall significant predictor of missed doses and seizure frequency.
- Higher health literacy scores were associated with fewer missed medication doses and seizure occurrences.
- Household income was the only other predictor associated with few missed doses.
- None of the study variables, including health literacy, was associated with missed medical appointments.
Drug treatment regimes

Patient-Centred Pharmaceutical Design to Improve Acceptability of Medicines: Similarities and Differences in Paediatric and Geriatric Populations

Fang Liu, Sejal Ramnal, Hannah K. Batchelor

Adherence to Drugs That Prevent Cardiovascular Disease: Meta-analysis on 376,162 Patients
Sayed H. Naderi, BMedSci, Jonathan P. Beeston, MSc, David S. Wald, MD
Wolfson Institute of Preventive Medicine, Barts and the London School of Medicine, Queen Mary University of London, Charterhouse Square, London

Key Points
Appropriate pharmaceutical design of oral medicines can improve acceptability and patient outcomes in paediatric and geriatric populations.
Similar considerations should be given to physical characteristics affecting swallowability of tablets and capsules for use in children and older patients.
Whilst formulation factors such as taste and smell are important features for paediatric medicines, safe swallowing is the key formulation factor in designing medicines for older patients.

CLINICAL SIGNIFICANCE
- Approximately one third of patients with a history of myocardial infarction and approximately one half without do not adhere to effective cardiovascular preventive treatment.
- Nonadherence is not greatly influenced by the class of drug prescribed (aspirin, blood pressure-lowering drugs, or statins), suggesting that side effects are not the main cause.
Epilepsy in children

• Factors associated with good adherence
  – Family support
  – Smaller family size
  – Stable parental marriage status
  – Better socio-economic status
  – Healthcare provided support

• Inconsistent results
  – Age
  – Seizure frequency
  – Seizure type
  – Medication
  – Medication preparation
  – Polytherapy
  – Comorbidity
  – Adverse effects
Interventions to improve adherence
Systematic review:
Interventions to enhance adherence in chronic illness in children and young people

• **Education**
  – Phone, home visits, clinic settings
  – Benefit in 2/7 trials

• **Behavioural**
  – Goal setting, reward reinforcement, linking to established routines
  – Benefit in 4/7 trials

• **Conclusions**
  – Education plus behavioural likely to more effective
  – Need to select out poor adherers

Dean, Arch Dis Ch, 2010
Electronic media

- “Sweet Talk” – text messaging
- Randomised to:
  - Standard insulin
  - standard insulin + Sweet Talk
  - intensive insulin + Sweet Talk

Franklin, Diab Med, 2006
Reminders – wearable

E-gift cards!

Patients enrolled in the RespiPoints program participate in a variety of activities to earn points, which can be redeemed for e-gift cards. Activities include reporting daily medicine taking, verifying monthly refills, reading educational information and insightful tips and completing weekly quizzes and surveys. To sign-up, eligible patients should visit [www.MyRespiPoints.com](http://www.MyRespiPoints.com).
• Web-based educational programme
• Randomised to weekly email reporting or via social media forum with other subjects
• Subjective and objective adherence reporting
• All adherence improved (p<.001)
• Before and after intervention
  – Control group 58% to 67% (p=0.7)
  – SM group adherence 50% to 92% (p=0.03)
Conclusions

- Recognise the elephant!
- Adherence is a big issue
- Clinical outcomes and costs
- Professionals’ & societal education
- Need simple tools to identify good and poor adherence
- Health Literacy
- Choosing the right medicines
- Education packages and behavioural support
- Can we use electronic media to promote adherence?