

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?



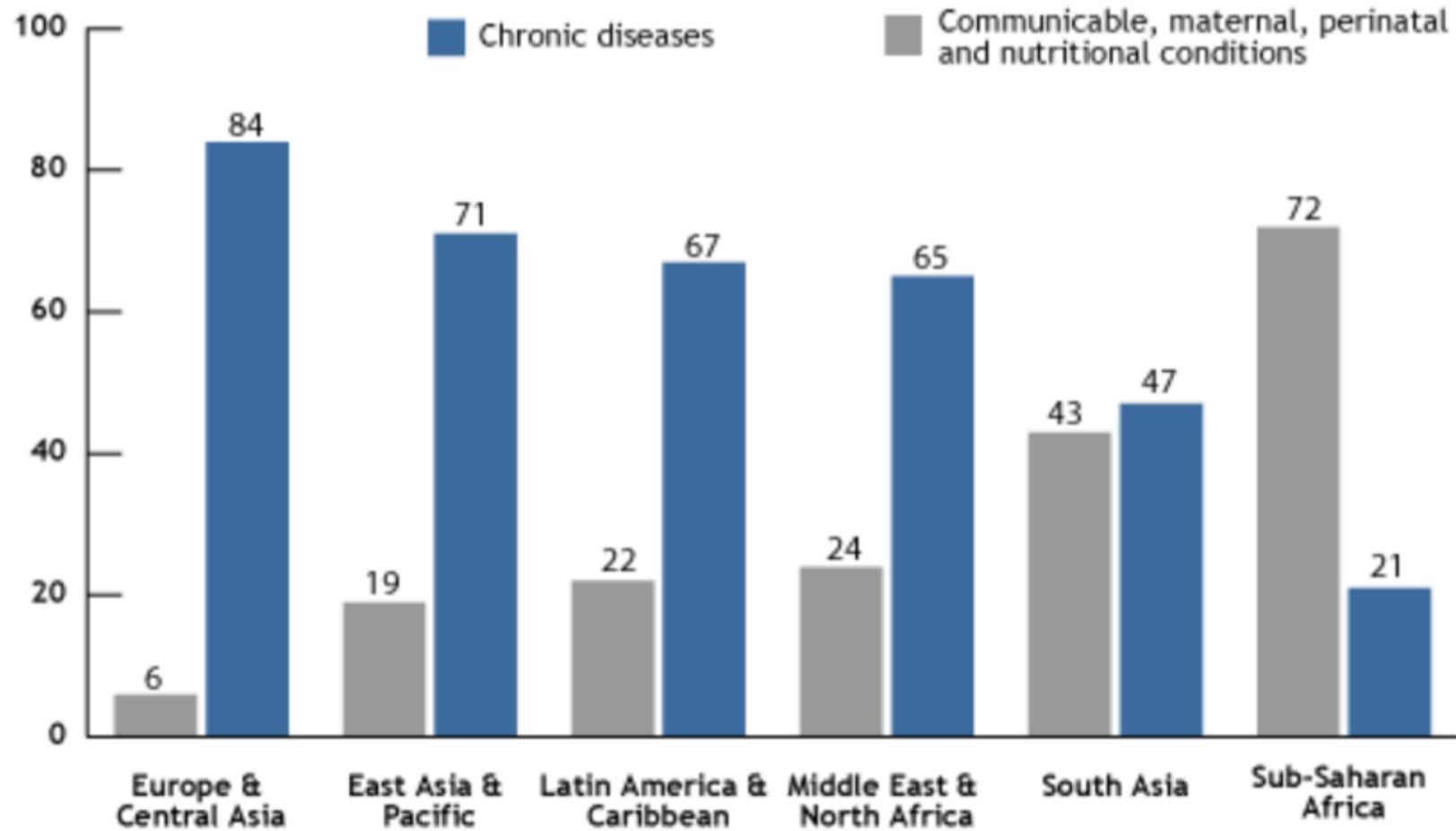
C Everett Koop
US Surgeon General

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

— *C. Everett Koop* —

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

Worldwide Share of Deaths, by Cause



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.



Why it (should) matter to pharma

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Adherence: Addressing Pharma's Last-Mile Problem

Jun 05, 2018 By Tom Kottler

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

"I'd love to see the day when our research specialists... are just as big"



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

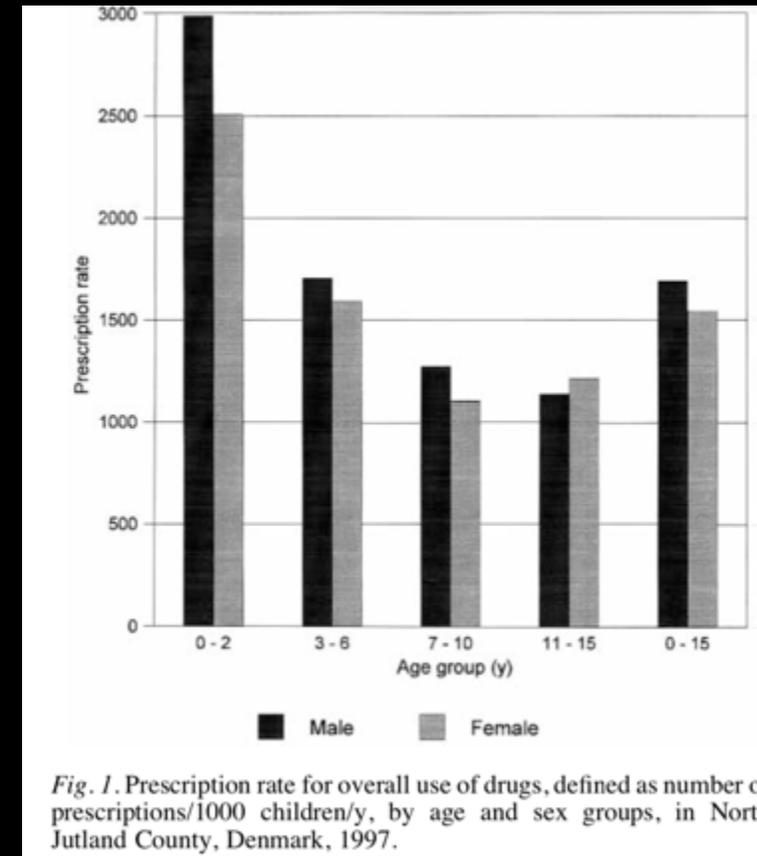
- Subjective
 - patient reporting
 - Scaled questionnaires
- Objective
 - Remaining pill counts
 - Electronic pill monitoring
 - Medication possession ratio
 - Clinical population data-linkage
 - Biochemical – drug levels
- Defining thresholds
 - “Good” v “Poor” adherence
 - Varying thresholds 80 – 95%



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

Prescribing in children

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



Thrane, Sørensen, 1999

Childhood asthma

Table 1 Mean adherence rates to inhaled corticosteroids when measured electronically

Study	Population	Age	Type of EMD	Study duration	Mean	Notes
Gibson <i>et al</i> ¹⁵	26 children, Glasgow, UK	15 months–5 years	Nebulizer chronolog NC300*	2 months	71%	
Milgrom <i>et al</i> ¹⁴	24 children, USA	8–12 years	MDI chronolog*	13 weeks	Median=58%	'Non compliant' children excluded
Bender <i>et al</i> ²	27 children, USA	7–12 years	Doser CT†	6 months	50%	
Mcquaid <i>et al</i> ²¹	106 children, USA	8–16 years	MDILog‡	1 month	48%	
O'Connor <i>et al</i> ¹⁸	16 children, USA	8–18 years	Doser CT†	3 months	54%	
Burgess <i>et al</i> ³⁹	21 children, Australia	18 months–7 years	Smartinhaler§	3 months	Median=65%	
Bender and Zhang ²⁶	104 children, USA	8–18 years	MDILog‡	4 months	40%	
Burgess <i>et al</i> ⁶	51 children, Australia	18 months–7 years	Smartinhaler§	1 month	Median=71%	Poorly controlled asthma
Jentzsch <i>et al</i> ⁸	102 children, Brazil	3–14 years	Doser CT†	1 year	52%	Low-income families
McNally <i>et al</i> ²⁷	63 children, USA	5–17 years	MDILog‡	1 year	34%	African–American children
Burgess <i>et al</i> ²⁸	26 children, Australia	6–14 years	Smartinhaler§	4 months	58%	
Celano <i>et al</i> ²⁹	1433 children, USA	6–11 years	MDILog-II‡	1 year	57%	Low-income African-American
Nikander <i>et al</i> ²⁴	115 children, USA	5–10 years	Vitalograph Spirometer¶	18 months	73%	Peak flow, competence and adherence monitored
Jentzsch <i>et al</i> ³⁰	102 children, Brazil	5–14 years	Doser CT†	1 year	47%	'steroid naïve patients'

Childhood diabetes

Published in final edited form as:

Curr Diab Rep. 2015 August ; 15(8): 621. doi:10.1007/s11892-015-0621-6.

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

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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

Adherence to insulin treatment, glycaemic control, and ketoacidosis in insulin-dependent diabetes mellitus

Andrew D Morris, Douglas I R Boyle, Alex D McMahon, Stephen A Greene, Thomas M MacDonald, Ray W Newton, for the DARTS/MEMO Collaboration

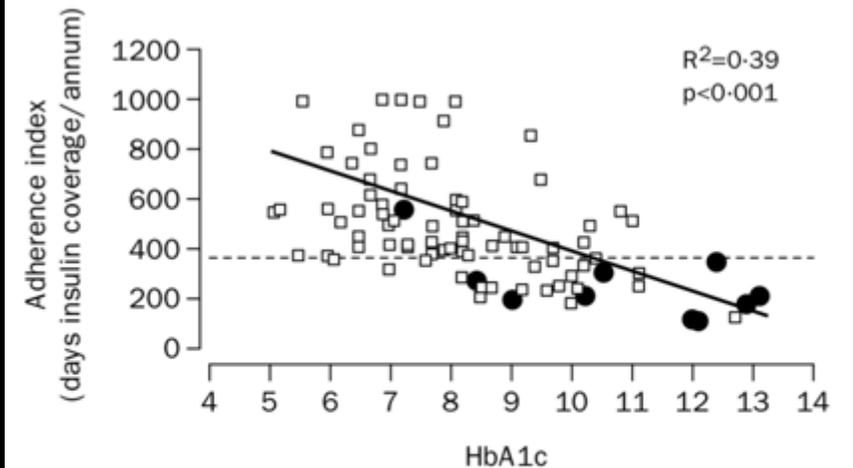


Figure 1: Linear regression of the association between glycaemic control (HbA_{1c}) and adherence index

Morris et al, Lancet 1997

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?



All children <16 years with epilepsy in 2 one year cohorts

Mean duration of epilepsy - 4 years



$$\text{Adherence Index} = \frac{\text{Encashed AED (HIC data)} \times 100}{\text{Recommended AED (Clinical data)}}$$

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

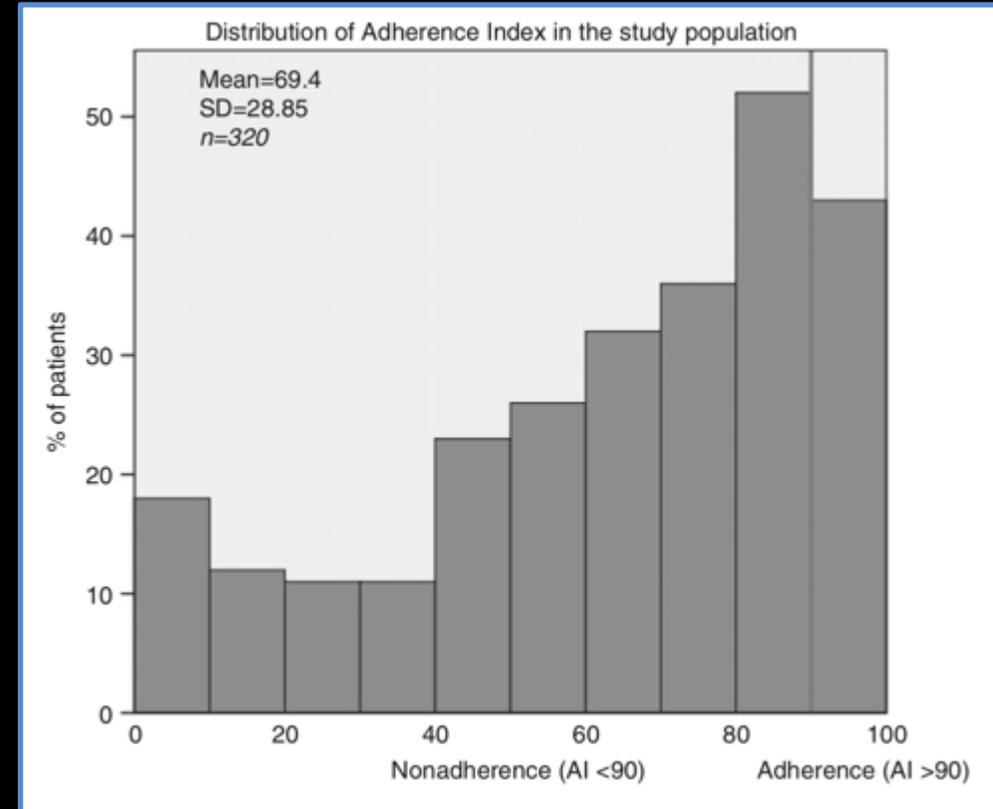
Table I: Patient characteristics

Clinical variable	Total	Adherence	Non-adherence
Median age in years (IQR)	10 (7–14)	9 (6–13)	11 (8–14)
Med age of seizure onset, y (IQR)	4 (1–9)	3 (1–8)	4 (1–9)
Median duration of epilepsy, y (IQR)	4 (2–7.6)	3 (1–8)	4 (1–9)
Male (%)	181 (57)	54 (54)	127 (58)
Female (%)	139 (43)	45 (46)	94 (42)
Children with other chronic health problems (%)	194 (61)	63 (33)	131 (67)
Regular medication other than AED (%)	72 (23)	24 (33)	48 (67)
Seizure frequency (%)			
Seizure free for >12mo	86 (27)	33 (34)	53 (24)
1–12 seizures per y	75 (23)	24 (24)	51 (23)
2–4 seizures per mo	45 (14)	12 (12)	33 (15)
1–7 seizures per wk	37 (12)	12 (12)	25 (11)
Daily seizures	77 (24)	18 (18)	59 (27)
Antiepileptic drugs (%)			
Carbamazepine	79	27 (34)	52 (66)
Ethosuximide	15	4 (27)	11 (73)
Lamotrigine	67	17 (25)	50 (75)
Levetiracetam	13	4 (31)	9 (69)
Topiramate	14	8 (57)	6 (43)
Valproate	186	69 (37)	117 (63)
Vigabatrin	5	5 (100)	0
Monotherapy (%)	239 (75)		
Polytherapy (%)	81 (25)		

IQR, interquartile range; AED, anti-epilpetic drugs

Results

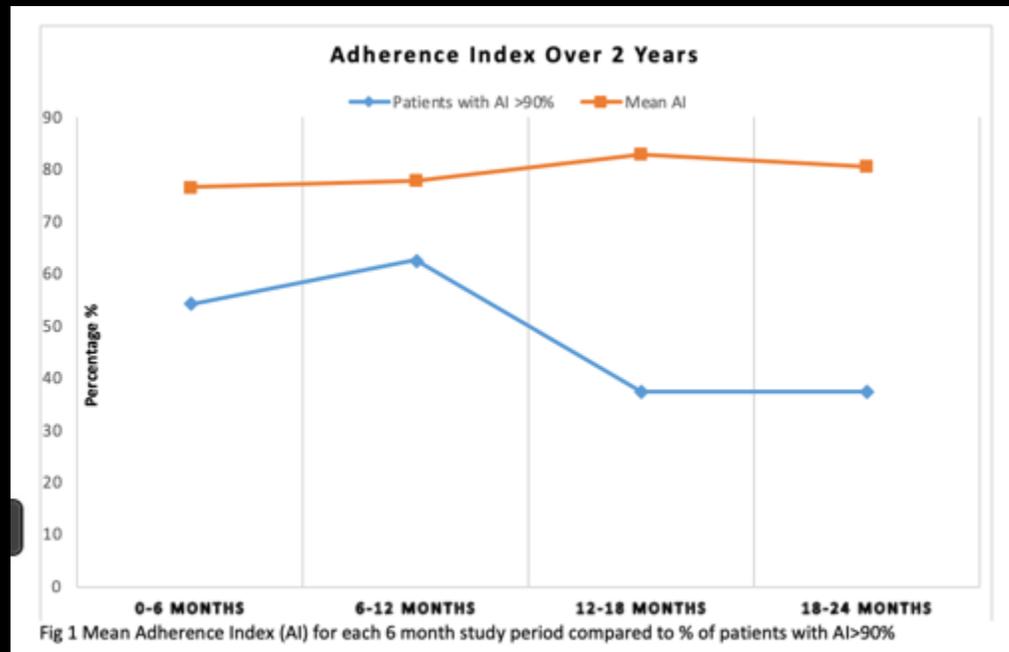
- Mean adherence 69.4%
 - >90% adherence – 31%
 - <50% adherence – 25%
- No effect on adherence:
 - epilepsy duration
 - seizure frequency
 - AED type, polytherapy
 - co-morbidity
- Adherence falls with age



Newly diagnosed epilepsy

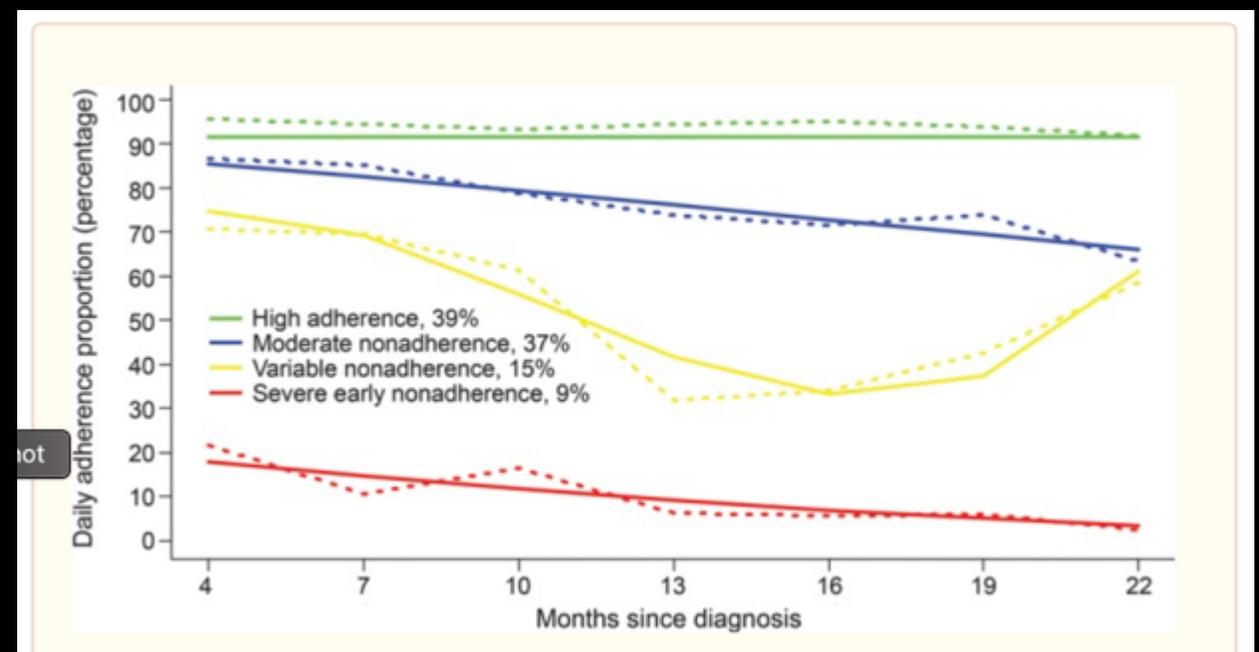
- Pooled adherence data – 58% for all v. 65% for new diagnosis

Yang, Ep Res, 2018



Even if initial adherence was good, 27% became non-adherent after 12 months

Fuchs, 2019, (submitted)



Modi, Neurology, 2014

Does adherence affect outcome in paediatric epilepsy?

Antiepileptic drug nonadherence predicts pediatric epilepsy seizure outcomes

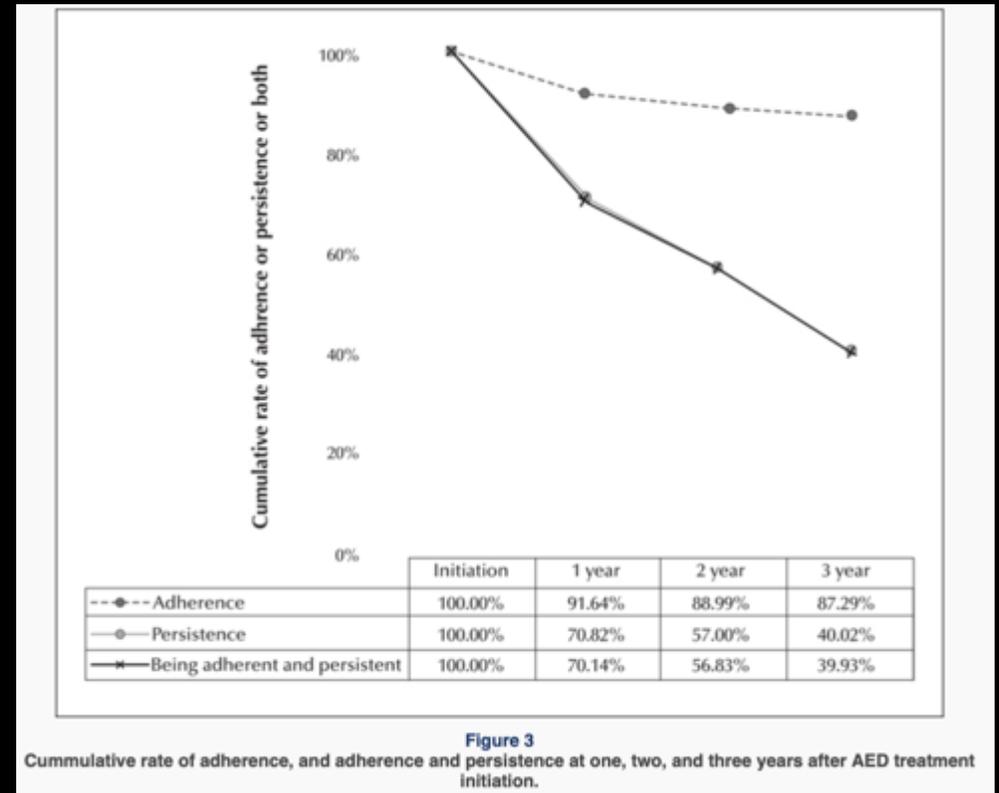
Avani C. Modi, PhD
Yelena P. Wu, PhD
Joseph R. Rausch, PhD
James L. Peugh, PhD
Tracy A. Glauser, MD

ABSTRACT

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

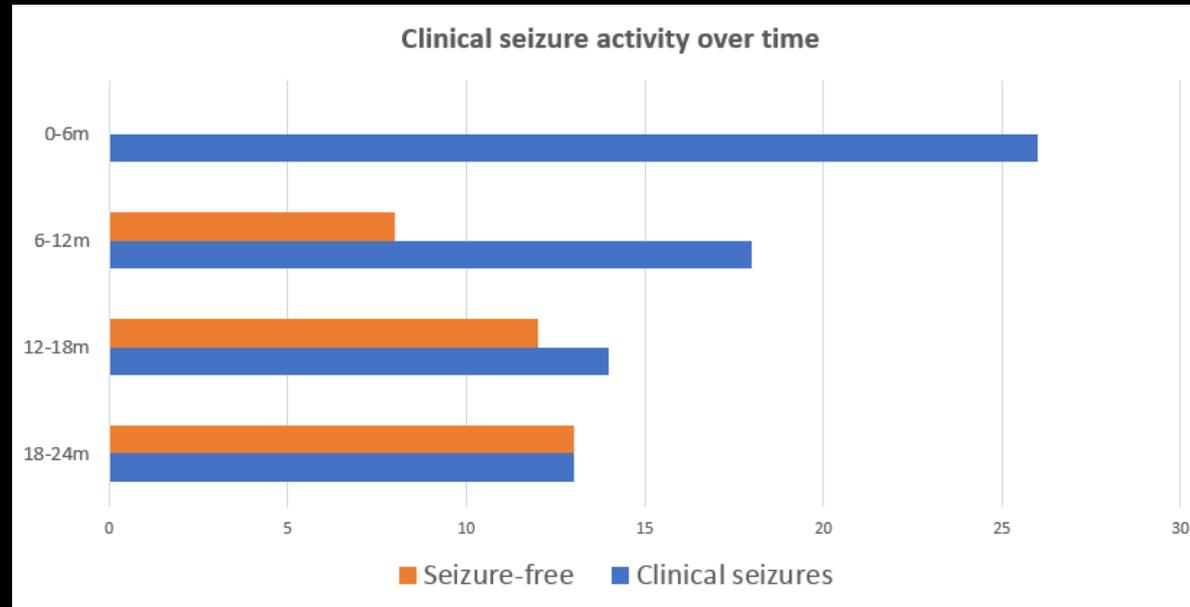
Methods: This study is a prospective, longitudinal, observational study of antiepileptic drug (AED) adherence and seizure outcomes in children with newly diagnosed epilepsy. Patients were

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

Seizure frequency v adherence in new diagnosis



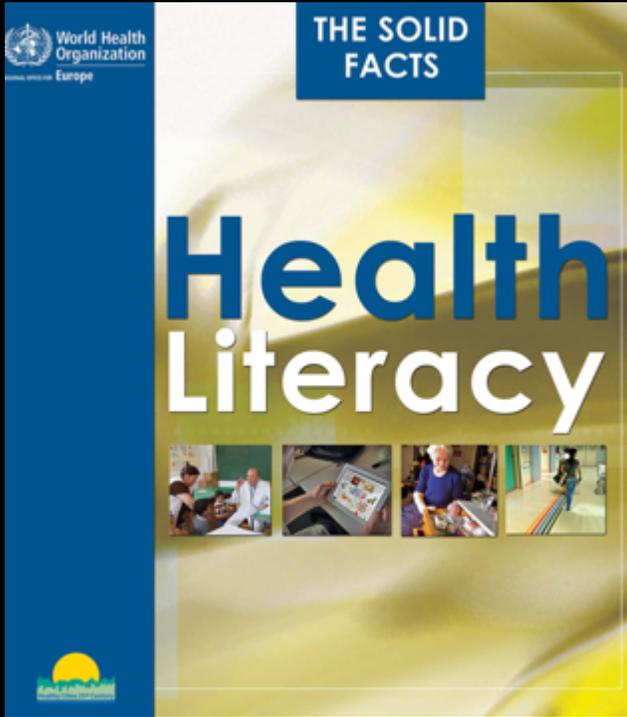
Falling adherence vs rising seizure freedom rates!?!

Epilepsy: Is children's adherence better?

- Pooled adherence rates in systematic reviews
 - Children - 58% (22 – 96%)
Yang, Ep Res, 2018
 - Adults - 40% (26 – 79%)
Malek, Acta Neur Scand, 2016
- 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”

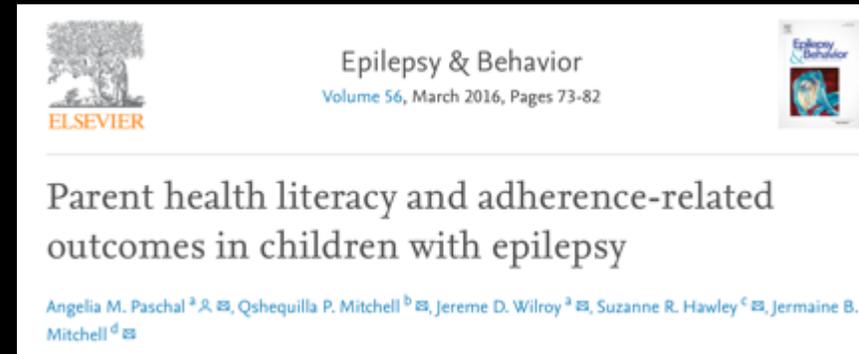


Health Literacy

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

UK population:

- 16% functionally illiterate
- 35% “health illiterate”



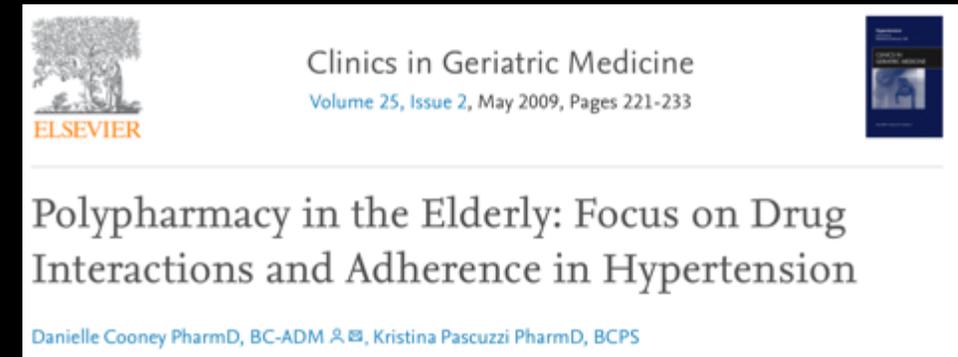
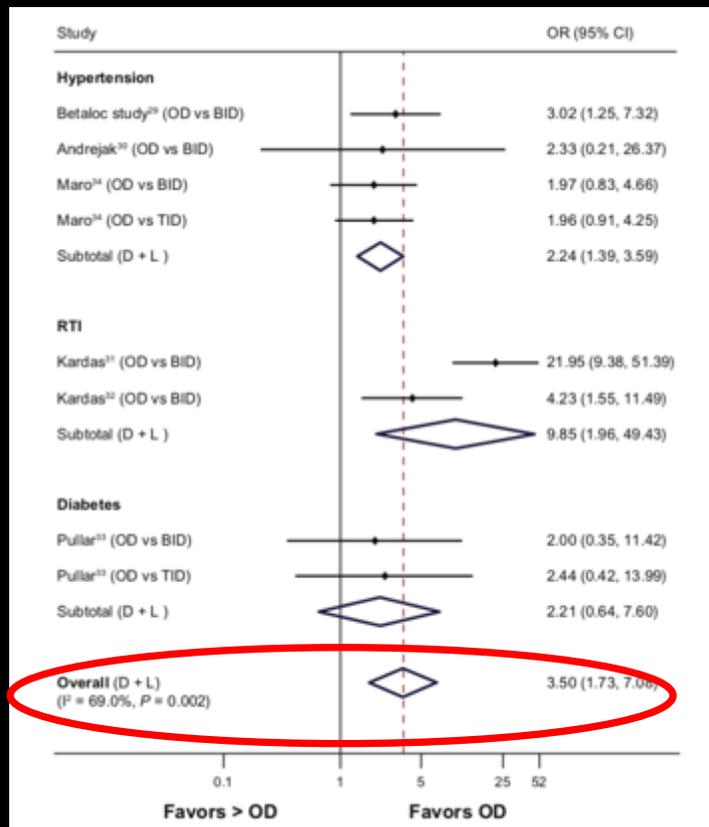
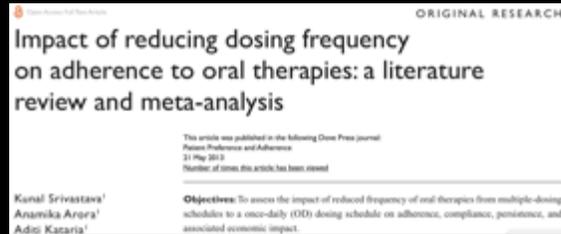
Highlights

- 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 fewer missed doses.
- None of the study variables, including health literacy, was associated with missed medical appointments.

Drug treatment regimes

Dosing frequency?

Polytherapy?



Drug treatment regimes

Medicine formulation?

Drugs (2014) 74:1871–1889
DOI 10.1007/s40265-014-0297-2

REVIEW ARTICLE

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

Fang Liu · Sejal Ranmal · Hannah K. Batchelor ·

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.

Adverse effects?

Adherence to Drugs That Prevent Cardiovascular Disease: Meta-analysis on 376,162 Patients

Sayed H. Naderi, BMedSci, Jonathan P. Bestwick, 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.

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

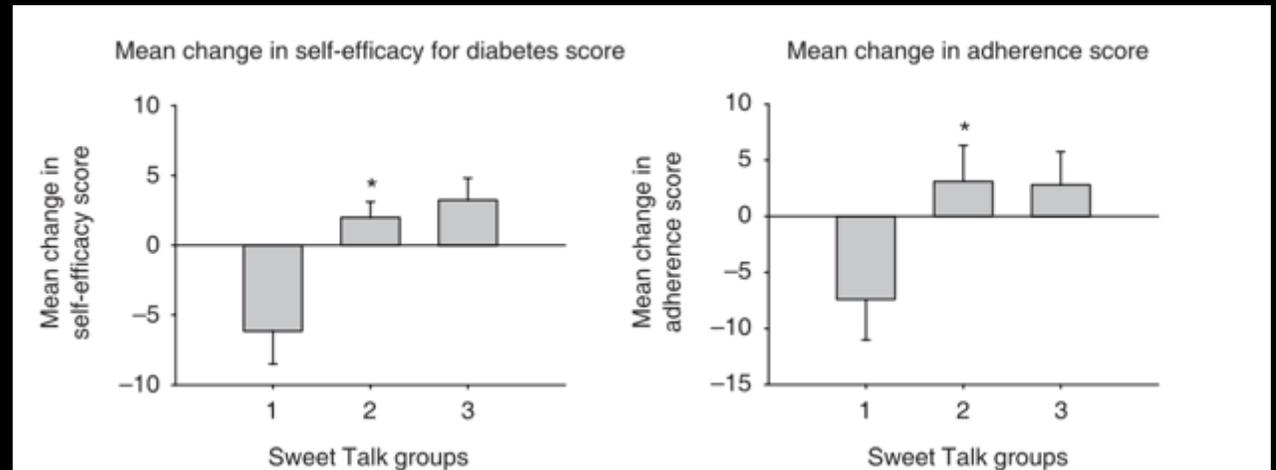
Systematic review:

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

Electronic media

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



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.



Improvement of medication adherence in adolescents and young adults with SLE using web-based education with and without a social media intervention, a pilot study

Lisabeth V. Scalzi , Christopher S. Hollenbeak, Emily Mascuilli and Nancy Olsen

- 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?

