

PROBLEMS OF DRUG ADHERENCE IN EPILEPSY

**Professor Martin J Brodie
Director, Epilepsy Unit
Western Infirmary
Glasgow, Scotland**



DRUG ADHERENCE

Definition

“Taking the exact prescribed amount of medication at the precise times of every day for an extended period of time”

DRUG ADHERENCE

Methods of measurement

- ❖ Direct questioning
- ❖ Patient calendars
- ❖ Counting pills
- ❖ Electronic bottle tops
- ❖ Serum drug levels

MORISKY MEDICATION ADHERENCE SCALE

1. Do you ever forget to take your medication?
2. Do you ever have problems remembering to take your medication?
3. When you feel better do you sometimes stop taking your medication?
4. Sometimes if you feel worse when you take the medicine, do you stop taking it?

YES= 0, NO=1, RANGE 0-4, 1-2 LOW ADHERENCE

DRUG ADHERENCE

My method

Look the patient straight in the eye at the clinic and ask sweetly –

“How often do you forget to take your tablets?”



DRUG ADHERENCE

Effect of dosing schedules

Adherence decreases with the number of antiepileptic drugs and drug doses prescribed each day

**EVEN ONCE DAILY DOSING DOES NOT
RESULT IN PERFECT ADHERENCE!**

Cramer J et al. *Epilepsy and Behavior* 2002; 3: 338-42

DRUG ADHERENCE

Teenagers

“If I don’t take my pills regularly, I won’t need to tell people I have epilepsy”.

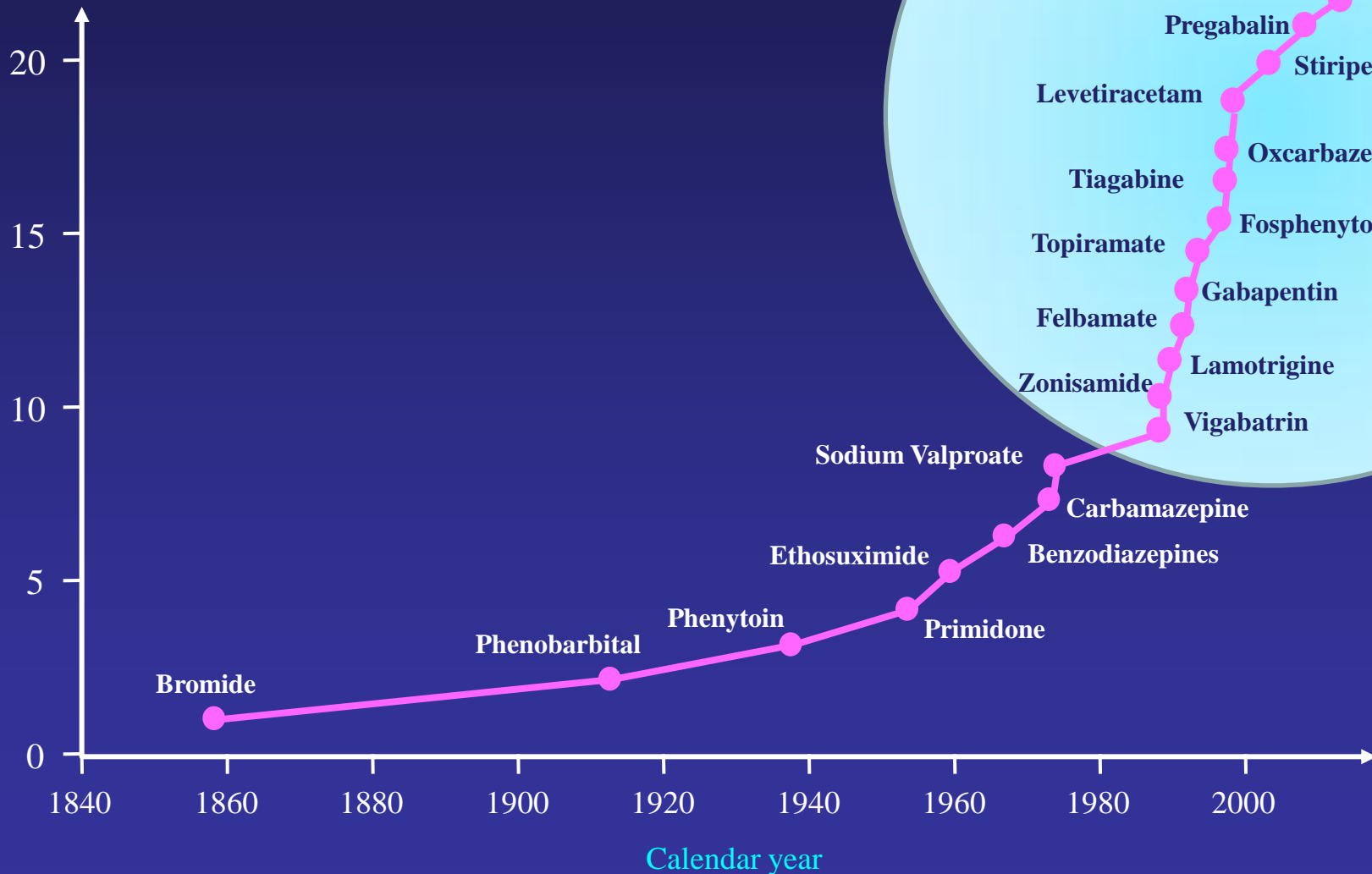
Melissa, aged 15

“No teenager prescribed 3 antiepileptic drugs is adherent to their treatment schedule”.

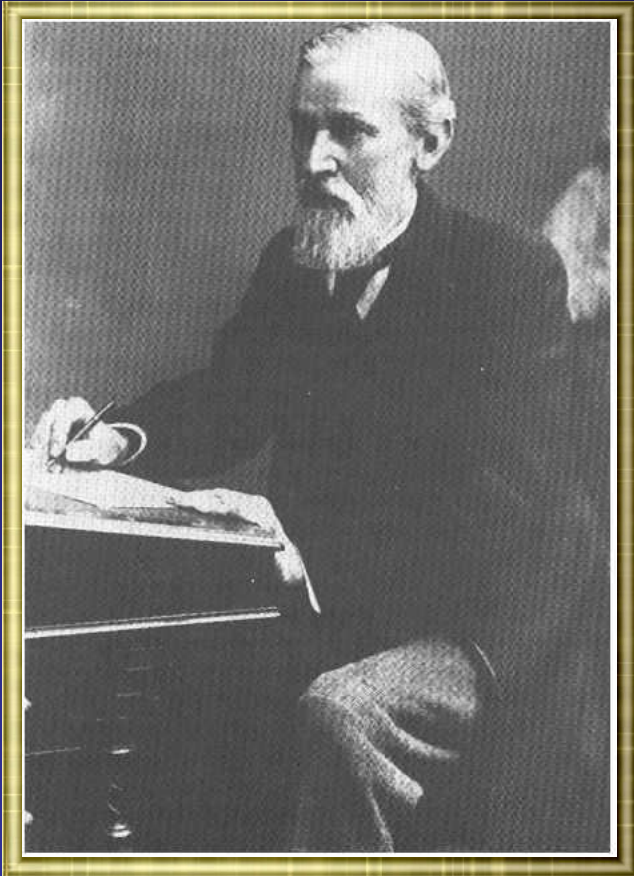
Martin, aged 60+

DRUG ADHERENCE

Antiepileptic drugs



DRUG ADHERENCE



W.R. Gowers
1845-1915

“ What is the prospect, in any given case, that an arrest of the fits can be obtained by treatment? **The indications of the prognosis have been materially changed by the introduction of the bromides as remedies for epilepsy.** Not only do they arrest fits far more frequently than any other remedy, but they are effective in many cases which, according to experience previous to the introduction of these remedies, would have been regarded as most unpromising. Hence, by their use, the conditions of the prognosis have been essentially changed”.

Gowers W R, *Epilepsy and Other Chronic Convulsive Diseases*, 1881, p201

NEWLY DIAGNOSED EPILEPSY

Responder rates (%) in an expanding cohort

<u>Recruitment</u>	<u>N</u>	<u>One AED</u>	<u>Multiple</u>	<u>Total</u>
1982-1997 ¹	470	61	3.0	64.0
1982-2001 ²	780	59	5.4	64.4
1982-2005 ³	1098	62	6.4	68.4

¹Kwan P, Brodie MJ. N Engl J Med 2000; 342: 314-9

²Mohanraj R, Brodie MJ. Eur J Neurol 2006; 13: 277-82

³Brodie MJ et al. Neurology 2012; 78: 1548-54

DRUG-RESISTANT EPILEPSY



SPECIAL REPORT

Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies

*¹Patrick Kwan, †Alexis Arzimanoglou, ‡Anne T. Berg, §Martin J. Brodie, ¶W. Allen Hauser, #²Gary Mathern, **Solomon L. Moshé, ††Emilio Perucca, ‡‡Samuel Wiebe, and §§²Jacqueline French *Division of Neurology, Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China ; †Institute for Children and Adolescents with Epilepsy-IDEE, University Hospital of Lyon (HCL) and Inserm U821, Lyon, France ; ‡Department of Biology, Northern Illinois University, DeKalb, Illinois, U.S.A. ; §Epilepsy Unit, Western Infirmary, Glasgow, United Kingdom ; ¶GH Sergievsky Center, Columbia University, New York, New York, U.S.A. ; #Department of Neurosurgery, David Geffen School of Medicine, University of California, Los Angeles, California, U.S.A. ; **The Saul R. Korey Department of Neurology, Dominick P. Purpura Department of Neuroscience and Department of Pediatrics, Albert Einstein College of Medicine, Bronx, New York, U.S.A. ; ††Clinical Trial Center, Institute of Neurology IRCCS C. Mondino Foundation, and Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy ; ‡‡Department of Clinical Neurosciences, University of Calgary, and Hotchkiss Brain Institute, Calgary, Alberta, Canada ; and §§NYU Comprehensive Epilepsy Center, New York, New York, U.S.A

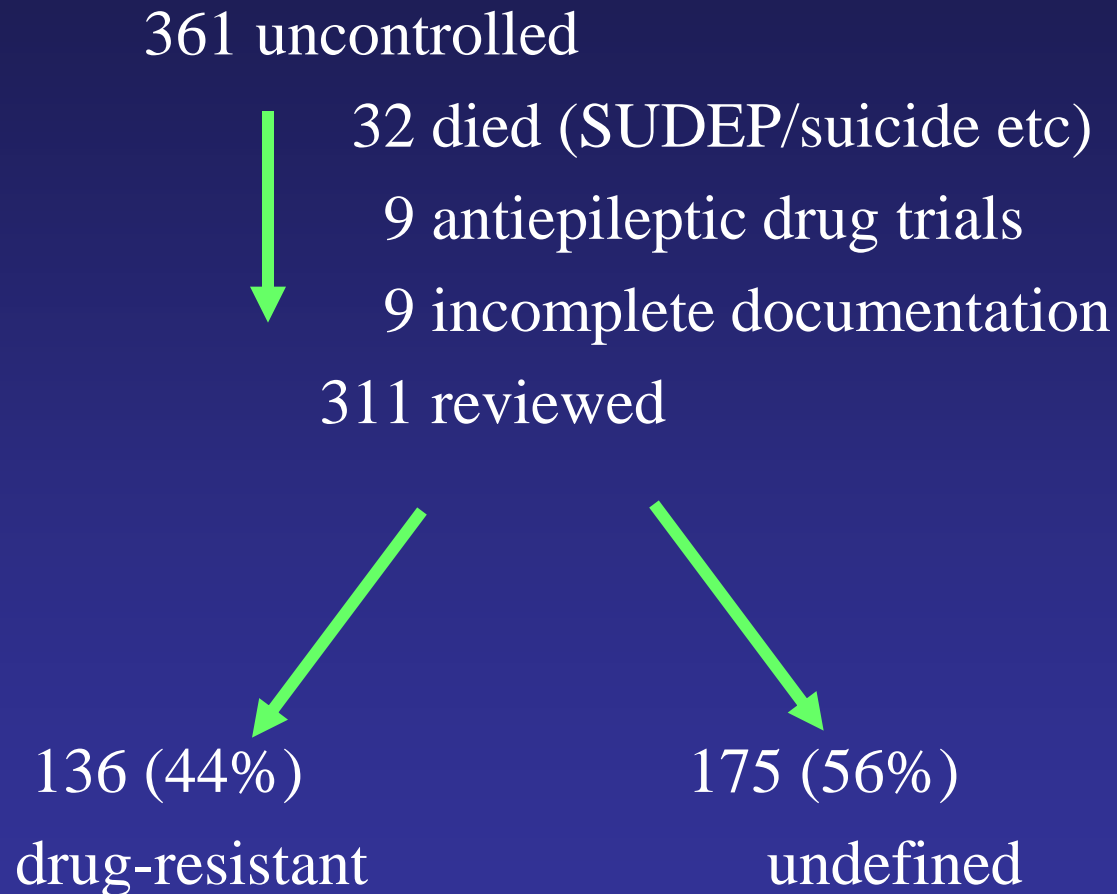
DEFINITION OF DRUG-RESISTANT EPILEPSY

Failure of adequate trial of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.

PROPOSAL BY THE AD HOC TASK FORCE OF THE ILAE
COMMISSION ON THERAPEUTIC STRATEGIES

DRUG-RESISTANT EPILEPSY

Newly diagnosed cohort (n=1098)



DRUG-RESISTANT EPILEPSY

Reasons for being undefined (n=175)

Single agent only

Inadequate drug dosing

Intermittent adherence (34%)

Adverse effects at low dose

Poor patient documentation

Erratic clinic attendance

Alcohol or recreational drug use

Social issues such as imprisonment

Patient choice

Median reasons 2, range 1-4

DRUG ADHERENCE

MW FEMALE DOB 16th MARCH 1990

JANUARY 2004

Generalised tonic-clonic seizure at school
Seen at seizure clinic same week
Family history + few myoclonic jerks

FEBRUARY 2004

EEG – bursts of polyspikes/photosensitivity
Started lamotrigine after discussion with family

JULY 2004

Seizure free on lamotrigine 200 mg b.d.

DECEMBER 2004

Still seizure-free – discharged from clinic

DRUG ADHERENCE

MW FEMALE DOB 16th MARCH 1990

JANUARY 2008 - Mother switched her to homoeopathic remedy

MARCH 2008 - Found dead in bed with teeth through tongue

**WE DISCUSS SUDEP
WITH ALL NEWLY DIAGNOSED PATIENTS!**

DRUG ADHERENCE

Blood and hair AED levels

Poor adherence



More seizures



SUDEP¹⁻⁵

1. Leestma JE et al. *Epilepsia* 1997; 38; 47-51
2. Davis GG, George JR. *J Forens Sci* 1998; 43: 598-603
3. Opeskin K et al. *Epilepsia* 1999; 40: 1795-8
4. Kloster R, Engelskjon T. *JNNP* 1999; 67: 439-44
5. Williams J et al. *JNNP* 2006; 77: 481-4

DRUG ADHERENCE

Study population of 33,658 patients

Nonadherence was associated with

- ❖ increased risk of mortality (HR 3.32, 95% CI 3.11 to 3.54)
- ❖ more emergency department visits (IRR 1.50, 95% CI 1.49 to 1.52)
- ❖ more hospital admissions (IRR 1.86, 95% CI 1.84 to 1.88)
- ❖ more motor vehicle accidents (IRR 2.08, 95% CI 1.81 to 2.39)
- ❖ greater likelihood of fractures (IRR 1.21, 95% CI 1.18 to 1.23)

RETROSPECTIVE OPEN COHORT DESIGN USING MEDICAID CLAIMS DATA

DRUG ADHERENCE

Economic consequences

Nonadherence to drug regimens makes epilepsy care much more expensive

- poorer work performance
 - higher disability payments
 - more emergency department visits
 - more hospital admissions
 - more antiepileptic drugs at higher doses
- etc, etc, etc.

Faught E et al. *Epilepsia* 2009; 50: 501-9

Zachry WM et al. *Epilepsy and Behavior* 2009; 16: 268-73

Ivanova JI et al. *Pharmacoeconomics* 2010; 28: 675-85

DRUG ADHERENCE

Dried blood spots in 100 children

“The overall rate of non-adherence in children with epilepsy was 33%. Logistic regression analysis indicated that children with generalised epilepsy (vs focal epilepsy) were more likely (odds ratio 4.7, 95% confidence interval 1.37 to 15.81) to be classified as non-adherent as were children whose parents have depressed mood (odds ratio 3.6%, 95% confidence interval 1.1 to 11.41)”

DRUG ADHERENCE

Survey of 99 patients in capital of Lao PDR

Hospital based – 57.1%

Community based – 58.0%

Total adherence – 57.6%

***HIGH LEVEL OF ADHERENCE ASSOCIATED WITH
FEW SEIZURES, MONOTHERAPY AND ILLITERACY***

DRUG ADHERENCE

Study of 385 Brazilians at tertiary centre

Non-adherence was highest in young males
with uncontrolled epilepsy taking a complex schedule

***NON-ADHERENCE RATE WAS 66.2
MEASURED BY THE MORISKY-GREEN TEST***

DRUG ADHERENCE

Prospective study in patients with refractory focal epilepsy admitted for 5 days without drug tapering

18 of 44 (41%) were non-adherent

12 overconsumers/4 underconsumers/2 others

OVERCONSUMPTION WAS THE MOST FREQUENT FORM NONADHERENCE!

DRUG ADHERENCE

Why don't people with epilepsy take their treatment?

1. They don't think they have epilepsy
2. They don't want to have epilepsy
3. They don't like taking pills in principle
4. They don't like the prescribed medication
5. They don't understand the need for treatment
6. The drug schedule is too complicated
7. They are disorganised, unfocused, forgetful
etc, etc, etc

DRUG ADHERENCE

What can we do to improve it?

1. Discuss history, diagnosis, investigations, and prognosis in detail with patient and family providing written material
2. Give plenty of time for subsequent discussions and answer all questions slowly, honestly and carefully
3. Allow everyone enough time to come to terms with the diagnosis, results of investigations, treatment and prognosis
4. Choose best treatment with specific focus on matching the side effect profile to the patient's lifestyle and clinical history
5. Ask specifically about individual side-effects such as dizziness, sedation, aggression, depression etc.

KEEP EVERYTHING FLEXIBLE – DON'T BE JUDGEMENTAL!

DRUG ADHERENCE

Causes of refractory nonadherence

- ❖ Misinformation on side effects
- ❖ Hidden alcohol or drug addiction
- ❖ Patient feels better off treatment
- ❖ Refusal to accept epilepsy diagnosis
- ❖ Inability to prioritise treatment cost



PIGHEADEDNESS IS NOT COMMON!

DRUG ADHERENCE

Antiepileptic drugs

What exactly is he/she taking  Patient?
GP?
Consultant?

***ASK PATIENT TO BRING ALL HIS MEDICATION
TO EVERY CLINIC APPOINTMENT***

DRUG ADHERENCE

What can we do to improve it?

- ❖ Involve family in management plan
- ❖ Provide dosette box for chronic offenders
- ❖ Check plasma levels when possible

IF THE PATIENT DOES NOT TAKE HIS/HER
MEDICATION, IT WON'T WORK!