

Variation in access to epilepsy surgery evaluation across Europe

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How common is refractory epilepsy in Europe?

- ▶ Prevalence of epilepsy: 8.93 / 1,000 (WHO¹)
- ▶ Europe population in 2010: 711 million²
- ▶ People with epilepsy in Europe: 6,350,000
- ▶ 25 to 30% are refractory²: **1.6 to 1.9 million patients**

1. Epilepsy atlas. WHO 2005
2. Wikipedia
3. Kwan and Brodie. *New Engl J Med* 2000

Burden of epilepsy

- ▶ Beyond seizure recurrence, epilepsy poses a burden in multiple aspects of life:
 - Biological
 - Psychological
 - Educational
 - Social
 - Employment, ...
- ▶ This burden is **more severe in refractory epilepsy**

Depression in epilepsy

Type of study	Authors	Rate of depression
General population	Boyd, Weissman. 1982	Men: 1–3% Women: 2–9%
<u>Epilepsy patients:</u> Community based studies	Jacoby et al. 1996 Edeh, Toone. 1987 and 1990	9–22%
Hospital based studies	Roy. 1979 Robertson et al. 1994 Victoroff et al. 1994	27–58%

The rate of depression is higher in patients with refractory compared to controlled epilepsy¹

Concomitant depression is a risk factor for refractory epilepsy²

Depression but not seizure frequency predicts QOL in refractory epilepsy³

1. Victoroff et al; Arch Neurol 1994
2. Hitiris et al; Epilepsy Res 2007
3. Boylan et al; Neurology 2004

Mortality in epilepsy

- ▶ 1.6–9.3 times higher than general population¹
- ▶ Epilepsy related causes of death account for 40%². These include:
 - Accidents
 - Status epilepticus
 - Sudden Unexpected Death in Epilepsy: 17% deaths, 1% every year in severe cases
- ▶ 50.000 deaths per year in the USA directly related to epilepsy

1. Cockerell et al, *Lancet* 1994

2. Téllez-Zenteno JF, et al; *Epilepsy Res* 2005

Sudden unexpected death

- ▶ Incidence (per 1,000 persons–year) in prospective studies:
 - Medically refractory epilepsy^{1,2}: 3.5 to 3.8
 - Epilepsy surgery referrals³: 9.0
 - Surgical candidates not operated⁴: 6.3
 - Persisting seizures after surgery⁵: 6.3

1. Leestma et al. Epilepsia 1997
2. Racoosin et al. Neurology 2001
3. Dasheiff et al. J Clin Neurophys 1991
4. Nilsson et al. Epilepsia 2003
5. Sperling et al. Epilepsia 2005

Refractory epilepsy can be identified early

- ▶ Patients who fail their first drug due to inefficacy have a low probability of future success (32%)¹
- ▶ Other risk factors^{1,2,3}:
 - Partial/focal epilepsy (80%)
 - High seizure frequency before diagnosis
 - Abnormal EEG
 - Abnormal MRI
 - Generalised symptomatic epilepsy
 - Developmental delay

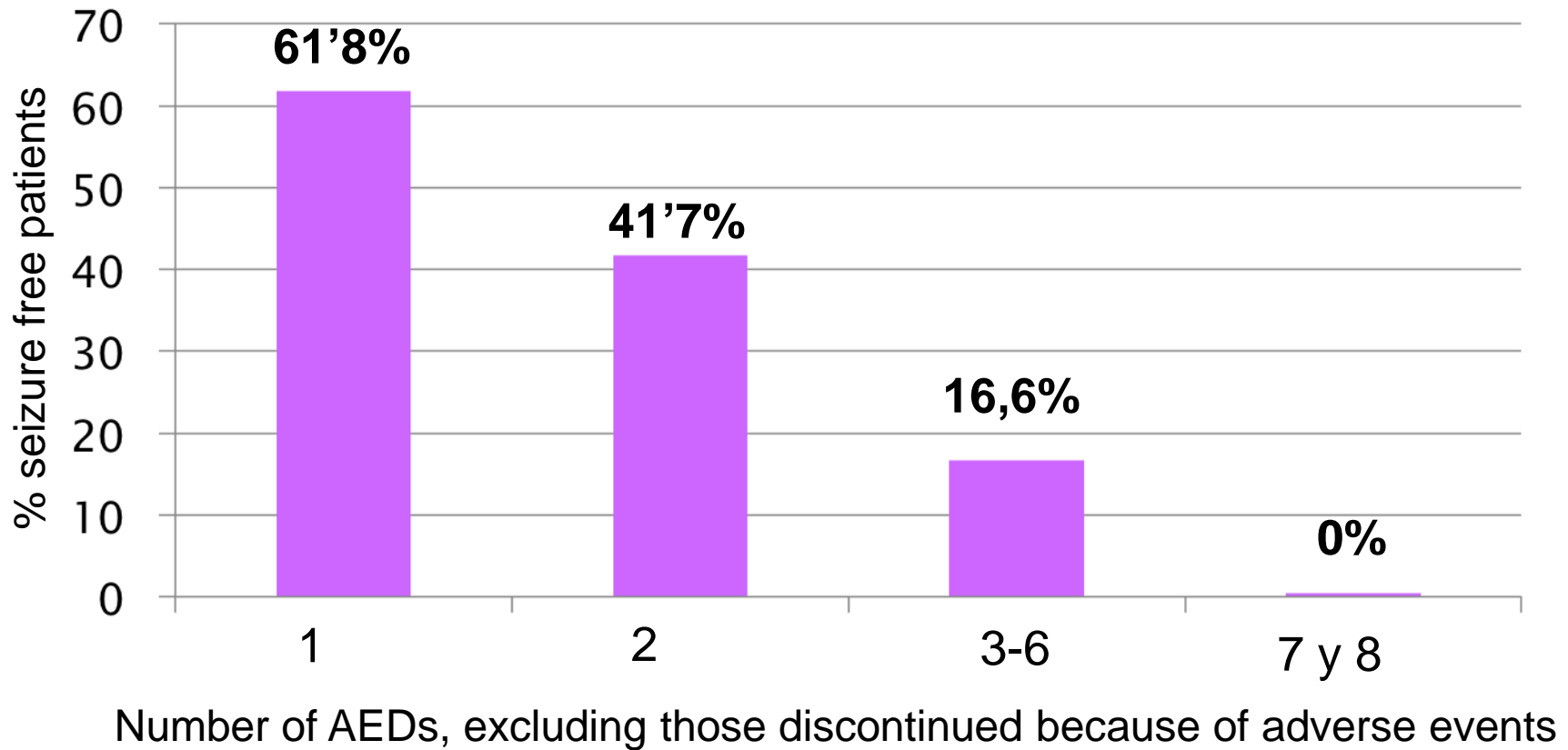
1. Kwan and Brodie. *New Engl J Med* 2000

2. Callaghan *et al. Epilepsia* 2005

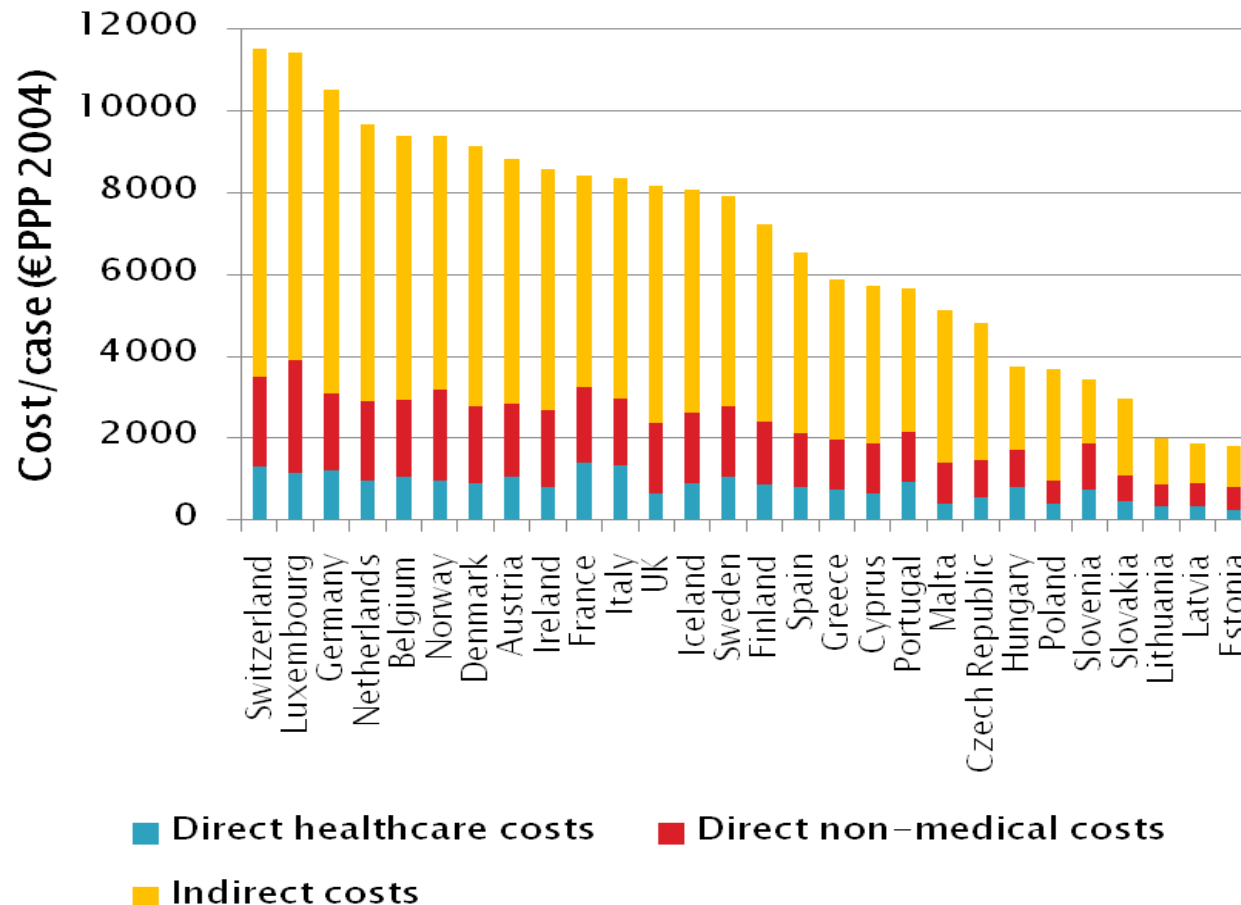
3. Semah *et al, Neurology* 1998

Antiepileptic drugs have limited impact on refractory epilepsy

Efficacy of sequential therapies



Cost of epilepsy in Europe



- ▶ No of people with active epilepsy: 3.4 million
- ▶ Estimated cost: 2,000 to 11,500€ per patient/year
- ▶ Estimated total cost of epilepsy in Europe in 2004: €15.5 billion

Cost in € adjusted for Purchasing Power Parity (PPP)

Superiority of surgical treatment in some epilepsies

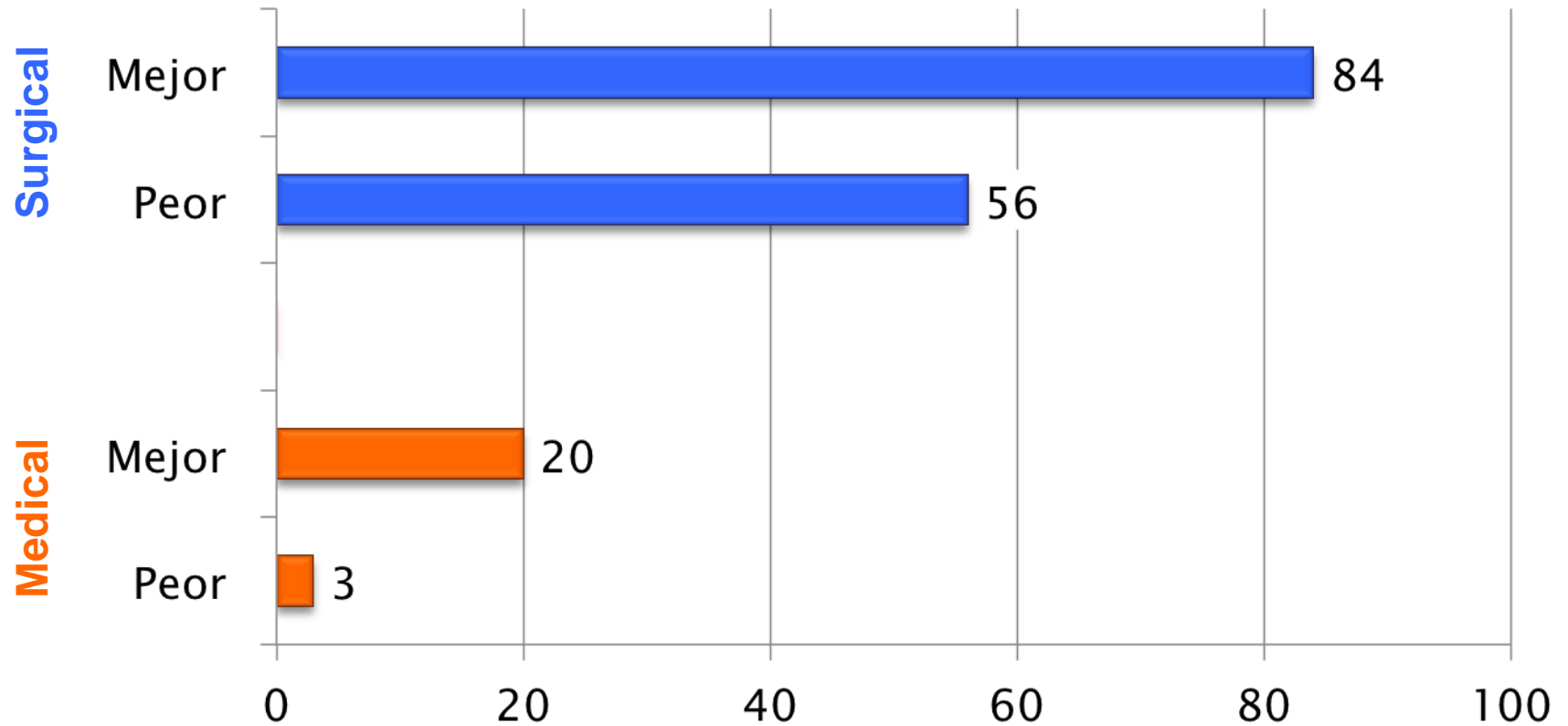
	Age	Follow-up (years)	Number of patients	Proportion seizure free after surgery
Al-Kaylani et al ²¹	Adult	>2 (mean 6)	150	78% (no difference with MTS)
Alpherts et al ²²	Adult	6	71	68%
Aszetely et al ²³	Adult	>8-6 (mean 12-2)	54	65%
Bien et al ²⁴	Adult	>2 yrs (mean 4-8)	148	62%
Cohen-Gadol et al ²⁵	3-69 years	Mean 6-2 years	372	79%
Dulay et al ²⁶	>17 years	1	90	61% overall, 61% MTS, 12% MTS+
Dupont et al ²⁷	Adult	1	110	73% (but 41% at 10 years post-op)
Gilliam et al ²⁸	>17 years	1	196	65%
Jeong et al ²⁹	9-51 years	18 months	93	84%
Jutila et al ³⁰	14-54 years	>1 (mean 5-4)	140	56%
Kellet et al ³¹	Adult	1	94	48% MTS, 65% tumour
Lee et al ³²	9-55 years	1	171	72%
Pintor et al ³³	Adult	1	70	68%
Radhakrishnan et al ³⁴	7-86 years	>2 (mean 3-6)	175	77%
Salanova et al ³⁵	8-57 years	>1 (mean 7)	215	69%
Sanyal et al ³⁶	>15 years	1	25	76% MTS, 74% lesional
So et al ⁹	7-86 years	>1	184	74%
Spencer et al ³⁷	>12 years	>2 (mean 4-6)	297	68%
Sperling et al ³⁸	Adult and adolescent	2	86	56%
Wiebe et al ³⁹	Adult	1	36	64%
Zaatreh et al ⁴⁰	8-76 years	>2 (mean 9)	68	65% (all tumoural)

MTS=mesial temporal sclerosis. MTS+=dual pathology.

Table 1: Studies of temporal lobectomy to treat epilepsy in adults

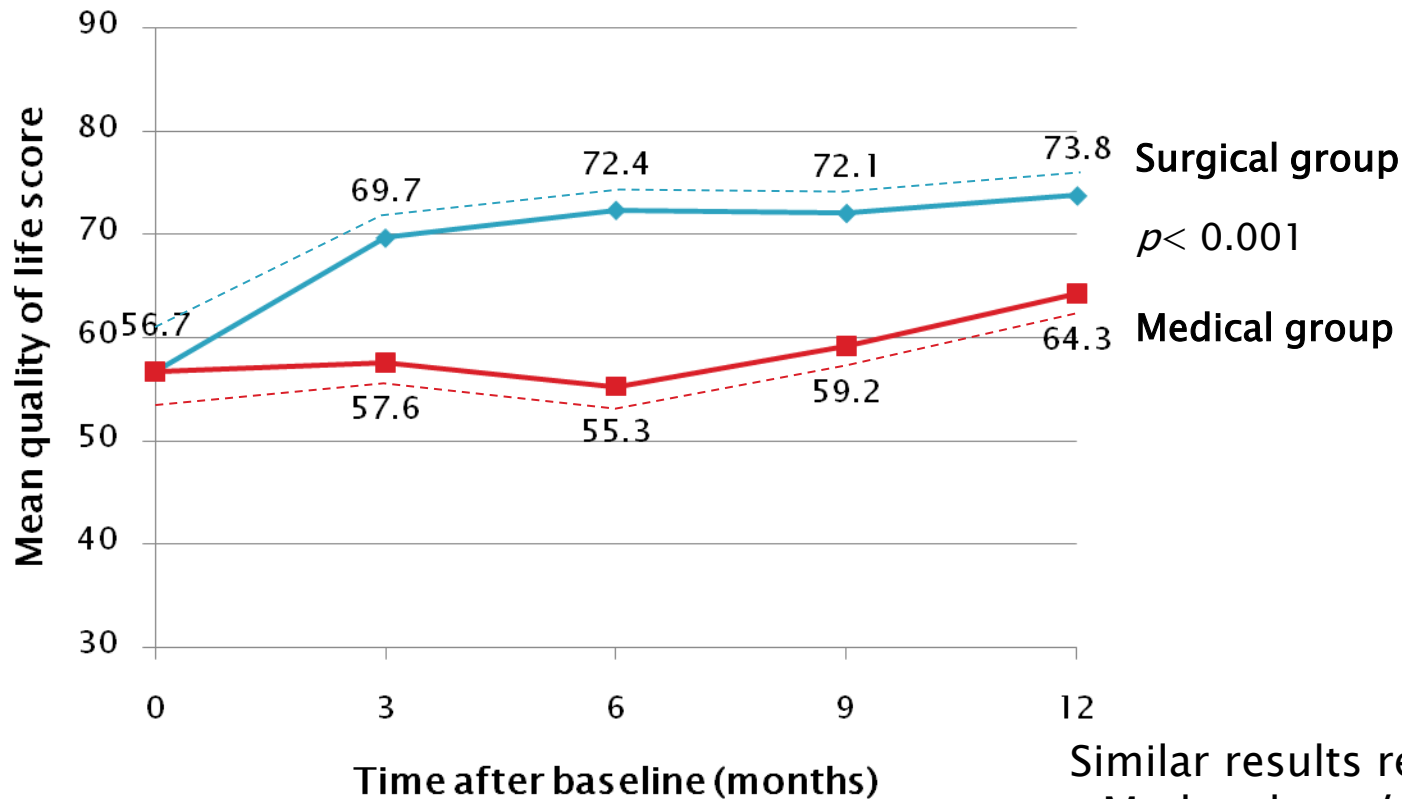
Superiority of surgical treatment in some epilepsies

Best and worst scenario in different studies



QoL and refractory epilepsy

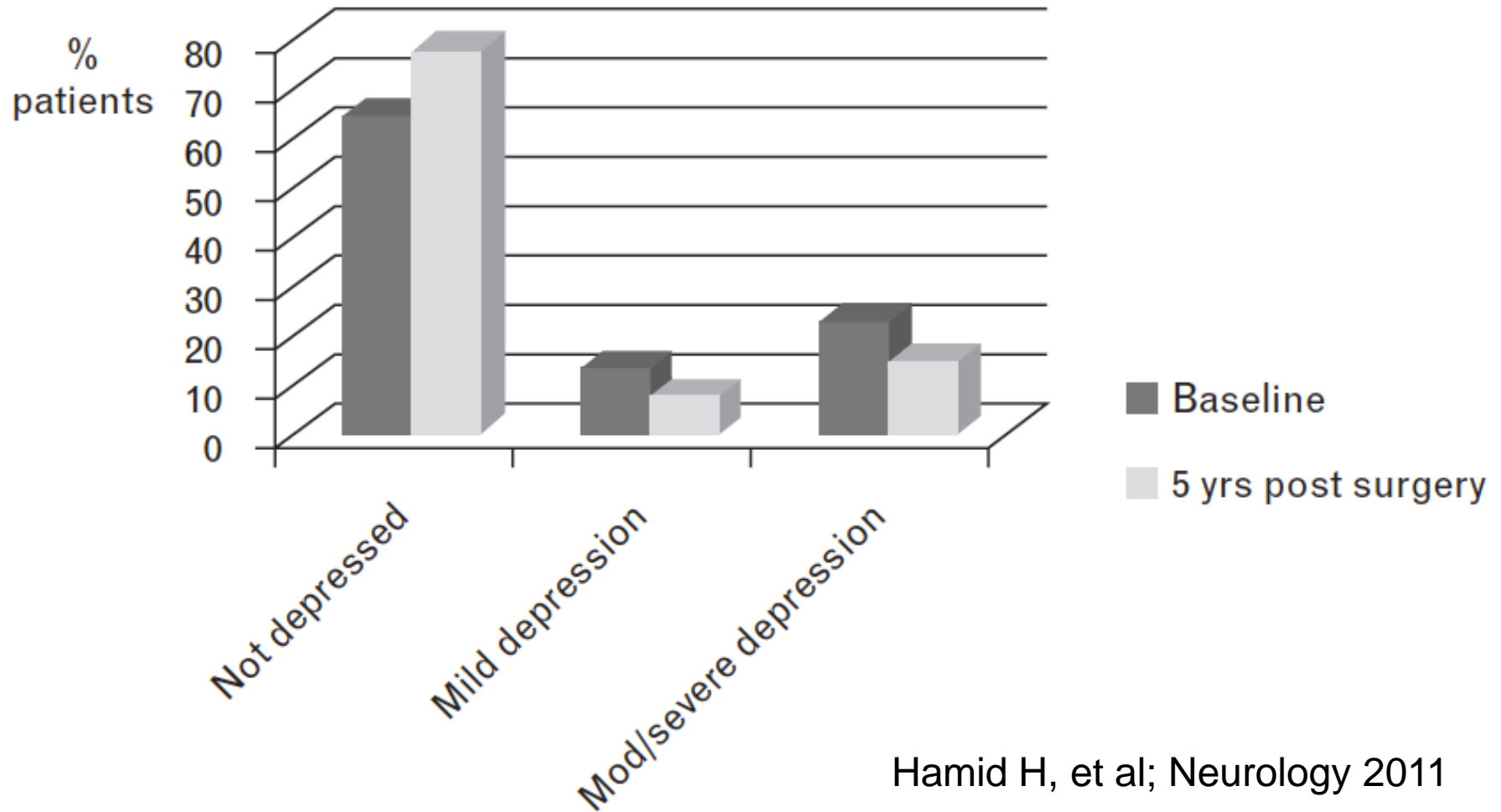
Results of QOLIE-89: 40 patients treated with anterior temporal lobectomy vs 40 treated medically.



Wiebe et al; NEJM 2001

Similar results reported by:
▶ Markand *et al. Epilepsia* 2000
▶ Lowe *et al. Epilepsia* 2004
▶ and others

Depression after surgery



Hamid H, et al; Neurology 2011

Risk factors for SUDEP

- ▶ GTC seizures and their frequency^{1,7,9}
- ▶ Duration of epilepsy^{2,7,9} and early onset⁸
- ▶ Absence of treatment and poor compliance^{11,12}
- ▶ Polytherapy^{2,3,9}
- ▶ Intellectual disability^{4,9}
- ▶ Seizures during sleep^{5,10}
- ▶ Sudden atonic fall during CP seizure⁶
- ▶ Carbamazepine therapy⁷

After successful epilepsy surgery death rates are similar to general population¹³

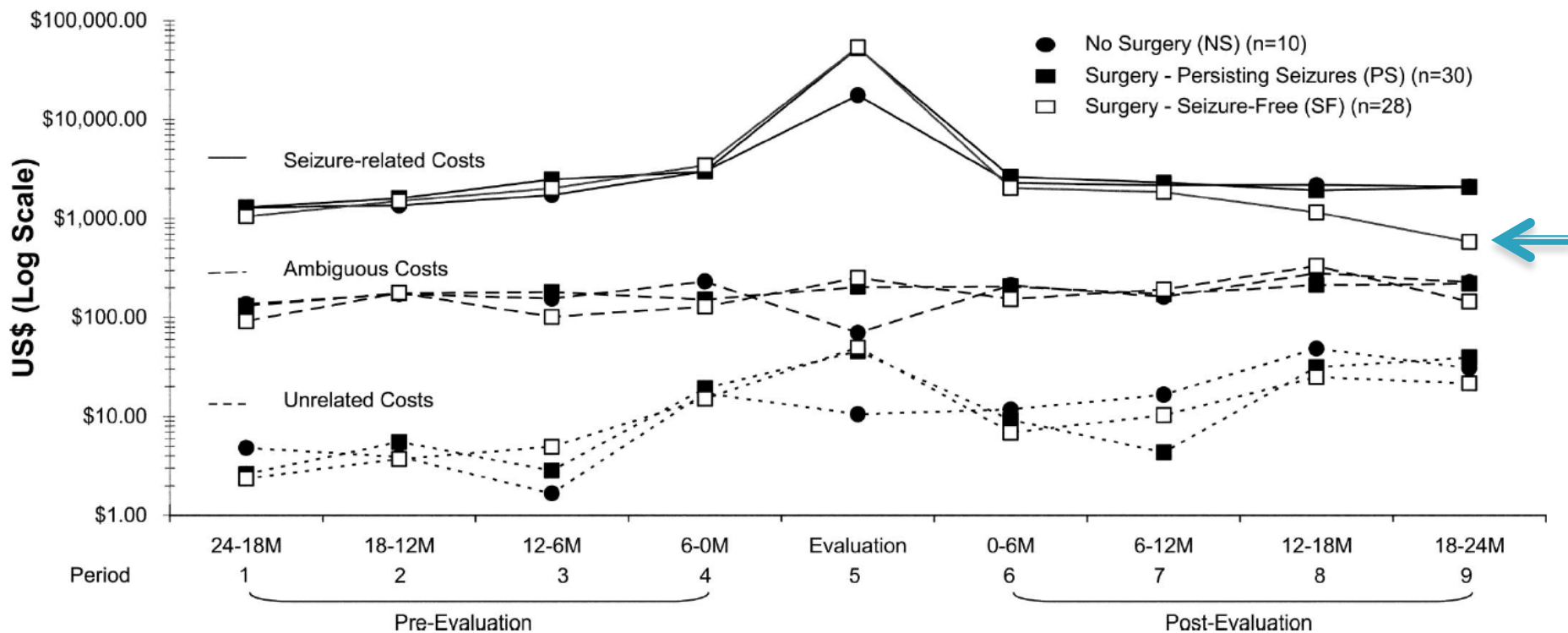
1. Timmings et al. Seizure 1993
2. Nilsson et al. Lancet 1999
3. Beran et al. Seizure 2004
4. Jick et al. Pharmacoepidemiol Drug Safety 2004

5. Opeskin et al. Epilepsia 1999
6. Rocamora et al. Epilepsia 2003
7. Langan et al. Neurology 2005
8. Hitiris et al. Epilepsy Behav 2007
9. Walczak et al. Neurology 2001

10. Kloster et al. J Neurol Neurosurg Psych 1999
11. George and Davis. J Forensic Sci 1998
12. Williams et al. J Neurol Neurosurg Psych 2003
13. Sperling et al. Epilepsia 2005

Health care cost decline after successful epilepsy surgery

Geometric Mean Costs by Period, Seizure-Relatedness & Group



Decline in seizure related cost from \$2,068 – 2,094 to \$582 in seizure free patients

ILAE Consensus.

Definition refractory epilepsy

Failure of adequate trials of **two** tolerated and appropriately chosen and used AEDs (whether as monotherapies or in combination) to achieve sustained seizure freedom.

Kwan P, Arzimanoglou A, Berg AT, et al.

Definition of drug resistant epilepsy.

Consensus proposal by the ad hoc Task Force of the ILAE

Commission on Therapeutic Strategies. *Epilepsia* 2009

Definition of refractory epilepsy

For many years different definitions have been very close in the concept of refractory epilepsy

- ▶ Persistence of seizures after **1 year**¹
- ▶ Seizures of sufficient frequency and severity after **2 years**²
- ▶ Persistence after highest tolerated dose of AED³
- ▶ Persistence after use of potentially effective AEDs⁴
- ▶ 2 monotherapies and 1 combination⁵
- ▶ **1 year** or 2–3 AEDs⁶

1. Leppik, 1992
2. Jallon, 1997
3. Wolf, 1994
4. Burgeois, 2001
5. Sánchez, 2002
6. Arzimanoglou and Ryvlin, 2008

Lost in translation

Current situation: Duration of Epilepsy Prior to Surgical Evaluation

<u>Author</u>	<u>Area</u>	<u>Epilepsy Duration</u>
Halasz	Hungary	15 years
Kumlien	Sweden	15.3 years
Gil-Nagel	Madrid	19 years
Wiebe	Toronto	22 years

No definition has ever said that we should wait very long
However, clinicians often wait **20 years** before referring
patients for epilepsy surgery^{1,2}

1. Berg et al. Neurology 2003
2. Benbadis et al. Seizure 2003

Attitude of neurologists to epilepsy surgery

- ▶ 1. Survey to 69 hospitals and 14 neurology clinics treating patients with epilepsy, excluding those performing surgery. Physicians considerations:
 - No experience: 38%
 - Reduces seizure frequency: 61%
 - Improves QOL: 53%
 - Cost effective: 92%

- ▶ 2. Referrals for epilepsy surgery evaluation obtained from computerized nationwide database:
 - 88 candidates to surgery
 - 40 referred
 - 15 considered but not referred
 - 33 not considered

1. Kulien E and Mattson P; Seizure 2010
2. de Flon et al; Eur J Neurol 2010

Variability in access to epilepsy surgery

- ▶ Comparing 1998 to 2009 there were no changes in epilepsy surgery in USA despite^{1,2}
 - Increase in access to video-EEG monitoring
 - Published guidelines by AAN
- ▶ Higher rate of utilization in²:
 - White people
 - Patients with private insurance

1. Englot DJ, et al; *Neurology* 2012

2. Schiltz NK, et al; *Epilepsy Research* 2013

Available resources

Atlas of Epilepsy Care Around the World

ILAE and WHO, 2005

- ▶ 11% countries do not have epilepsy specialists
- ▶ 33.3% countries do not have access to epilepsy surgery
- ▶ Medical specialists involved in epilepsy (per 100,000 pop)
 - Adult neurologists 0.33
 - Pediatric neurologists 0.14
 - Neurosurgeons 0.04
- ▶ Training in epileptology available in 31.8% countries
- ▶ Professional organization in epilepsy available in 91.1% countries

Survey. European Epilepsy Monitoring Association

- ▶ 231 centers identified. Questionnaire returned: 47 centers of 16 countries
- ▶ Video-EEG and intracranial recordings performed in all of them
- ▶ All covered by NHS, in different modalities:
 - Covered within the hospital budget
 - Flat fee per patient (differences within the same country)
 - Fee per day of monitoring (differences within the same country)
 - Only one lifetime evaluation per patient allowed in one country
- ▶ Limited or no coverage by private insurance companies in 7 patients:
 - No coverage of electrodes
 - No coverage of intracranial studies

Survey of Central Europe Epilepsy Experts Working Group. J Jedrzejczak et al; Seizure 2013

- ▶ Questionnaire sent to 10 experts: Bulgaria, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Slovakia and Slovenia.
- ▶ No epilepsy surgery centers in 3 countries, 2 of these reimbursed patients operated in other countries.
- ▶ Waiting time from presurgical evaluation to time of surgery:
 - Less than 6 months in 7 countries
 - 2–3 years in 2 countries
 - Surgery not available in 1 country
- ▶ Surgeries per million inhabitants/year: 0.95 to 7.60

Conclusions

- ▶ Epilepsy surgery can improve seizure control, quality of life comorbidity and morbidity in patients with refractory epilepsy
- ▶ Inequalities in access to epilepsy surgery occur within the same country and between different countries
- ▶ Future actions (?):
 - Identify these areas of inequality
 - Homogenize access and quality of surgical evaluation and surgery
 - Improve referrals of patients
 - Demand coverage by private insurances
 - Establish European standard and survey

Comparative epidemiology

- ▶ **HIV worldwide** UNAIDS 2011, pg: 1-10
 - 32 million HIV infection
 - 1.8 deaths in 2012, down from 2.2 in 2005
 - 516 deaths in the UK in 2008 Health Protection Agency: HIV in the United Kingdom, 2010 report
- ▶ **HIV worldwide** UNAIDS 2011, pg: 1-10

Burden of refractory epilepsy

LINCE Study: Health and non-health care resources use in the management of adult outpatients with drug-resistant epilepsy

- ▶ 762 patients, multicentre, epilepsy clinics in Spain
- ▶ Significant increase in the cost (€):
 - Yearly total: 6,838 (2,000 for controlled epilepsy)
 - Health care: 4,977
 - Indirect: 1,618
- ▶ Higher cost in patients with more severe seizures

Neurologist's views on epilepsy surgery and refractory epilepsy

- ▶ Survey mailed to 415 US neurologists. 84 (20%) responses
- ▶ Definition of refractoriness:

Proportion of responders (%)	Number of monotherapy trials		Proportion of responders (%)	Number of polytherapy trials
14	2	+	9	0
52	3		15	1
14	4		77	2
19	All approved AEDs		15	VNS

- ▶ Other findings:
 - 55% responders considered surgery if Sz frequency >1 in 3 months
 - 11% did not discuss epilepsy surgery with their patients