Epilessie farmacoresistenti

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LA RICHIESTA DI COMPETENZA NEUROLOGICA NEL PROSSIOM FUTURO

ROMA 13- 14 APRILE

10 domande
o
concetti da sapere

1. Come si definisce la FR?

- **"…FAILURE OF ADEQUATE TRIALS OF TWO TOLERATED, APPROPRIATELY CHOSEN AND USED ANTIEPILEPTIC DRUG SCHEDULES TO ACHIEVE SUSTAINED SEIZURE FREEDOM…"**
  - (Kwan, P. et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia, 2009)

Epilepsia, 51(6):1069–1077, 2010
doi: 10.1111/j.1528-1167.2009.02397.x

SPECIAL REPORT

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

*[1]Patrick Kwan, †Alexis Arzimanoglou, ‡Anne T. Berg, §Martin J. Brodie, ¶W. Allen Hauser, #[2]Gary Mathern, **Solomon L. Moshé, ††Emilio Perucca, ‡‡Samuel Wiebe, and §§[2]Jacqueline French

"Sustained seizure freedom": cosa significa?

- ✓ At least one year (minimum time consistently associated with meaningful improve of QoLi) without seizure or ...
- ✓ Three times the longest interval (95% confidence of therapeutic effect) between seizures in the year before the last seizure
- ✓ Whichever the longest !

“Adequate trials” with two “appropriately chosen” AEDs: cosa significa?

- ‘‘Adequate’’ trial: intervention adequate in strength/dosage for a sufficient length of time.
- ‘‘Appropriate’’ trial: correct intervention for the patient’s epilepsy and seizure type.
- An ‘‘appropriate’’ intervention should have previously been shown to be effective, preferably in RCT.

2. E' veramente una epilessia FR?

- Farmaci antiepilettici Sodio-bloccanti possono rendere una Epilessia Idiopatica generalizzata "intrattabile"

Worsening of Seizures by Oxcarbazepine in Juvenile Idiopathic Generalized Epilepsies

*Philippe Gelisse, †Pierre Genton, *Callixte Kuate, *Aurélie Pesenti, *Michel Baldy-Moulinier, and *Arielle Crespel

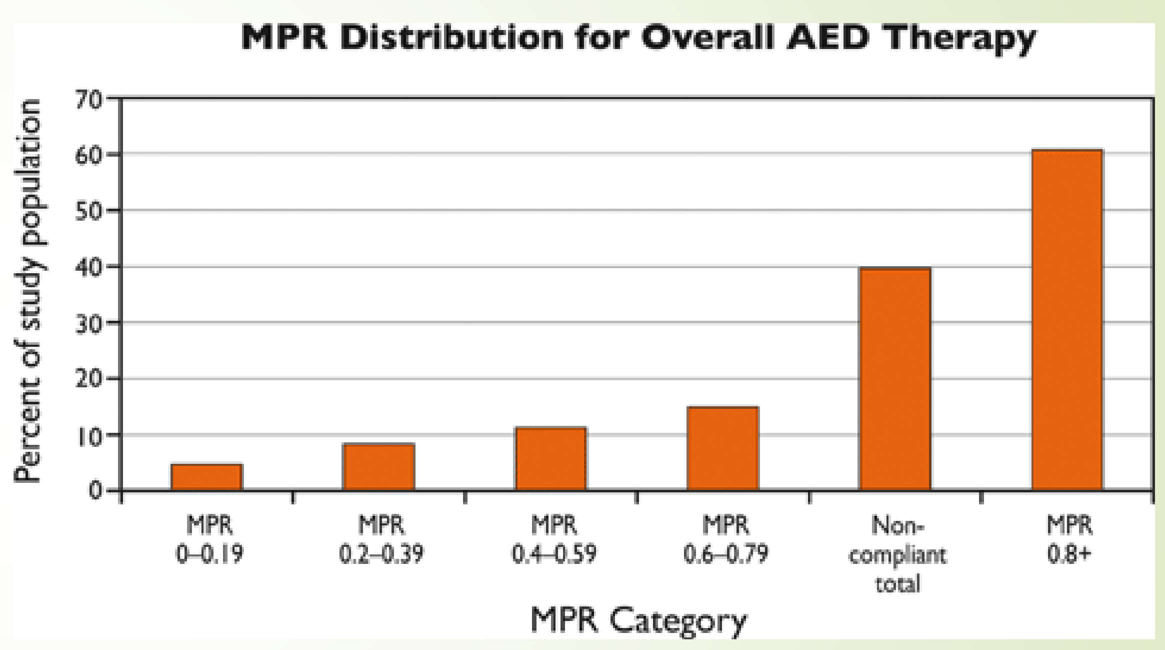
Epilepsia 2003

Focal seizure symptoms in idiopathic generalized epilepsies

Neurology 2015

2. E' veramente una epilessia FR?

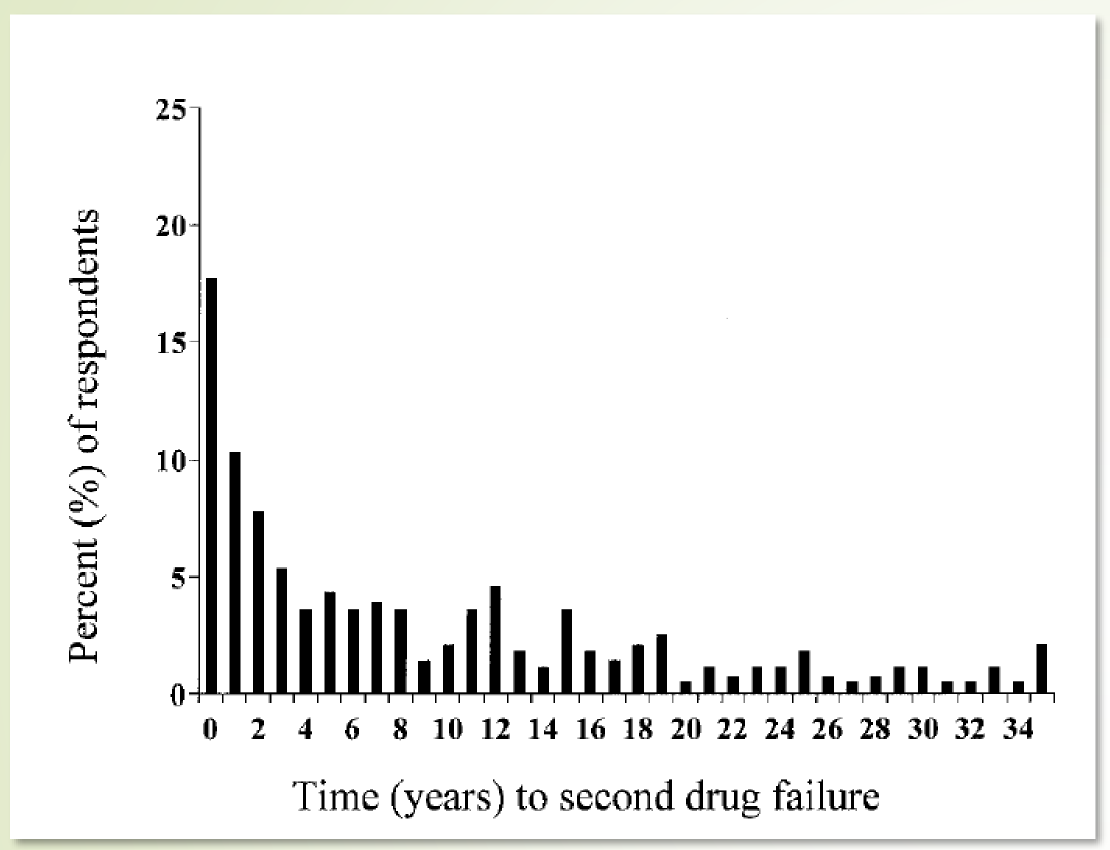
- I pazienti non complianti hanno un rischio del 50% di accessi in PS



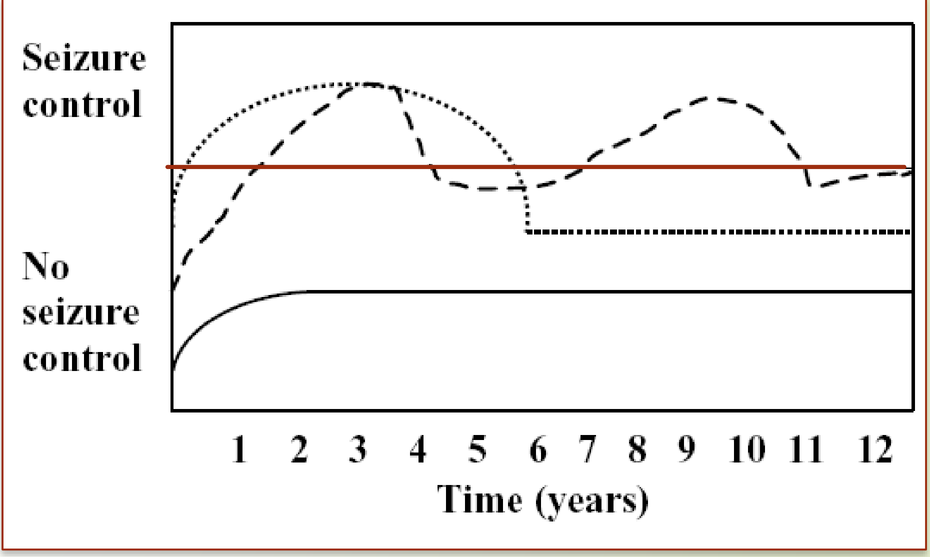
Davis et al. Epilepsia 2007

3. Quando e perché una epilessia diventa FR?

- **"Costituzionale"**: presente ancora prima della prima crisi o prima dell'inizio della terapia (Kwan & Brodie, 2000)
- **Progressiva**: si sviluppa nel tempo, anche dopo significativi periodi di remissione (Berg et al., 2003)
- **Intermittente** ("remitting and relapsing"): periodi di epilessia attiva interrotti da fasi di remissione (Goodridge & Shorvon, 1983; French et al, 2004)



Berg et al. Neurology 2003



D. Schmidt & W. Lőscher, 2005

4. E' possibile predirre la FR?

- Elevata frequenza di crisi all'esordio
- Crisi ad esordio precoce
- Presenza di lesioni strutturali
- Stato epilettico

Aicardi and Shorvon, 1997;

Regesta and Tanganelli, 1999

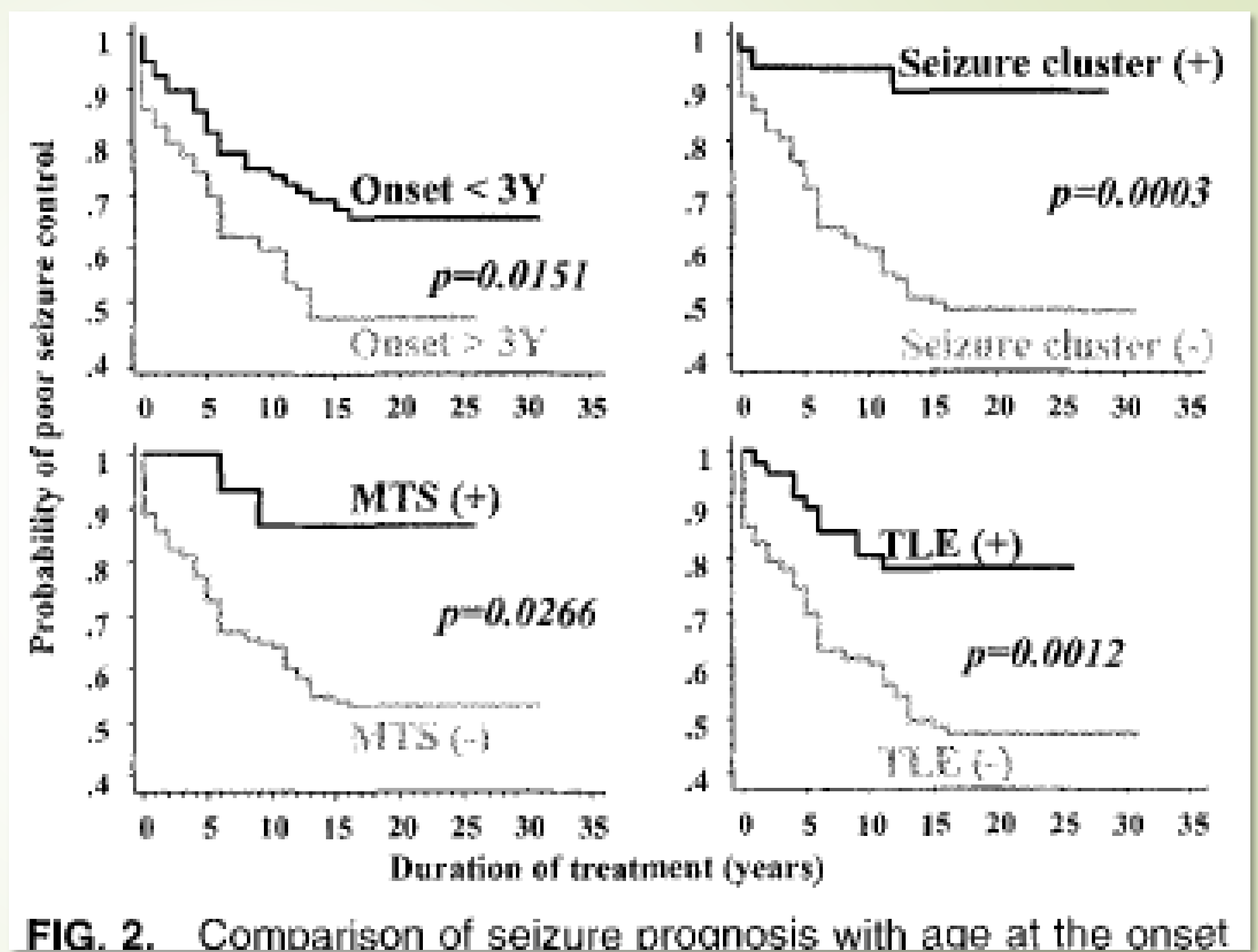


FIG. 2. Comparison of seizure prognosis with age at the onset

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La diagnosi sindromica

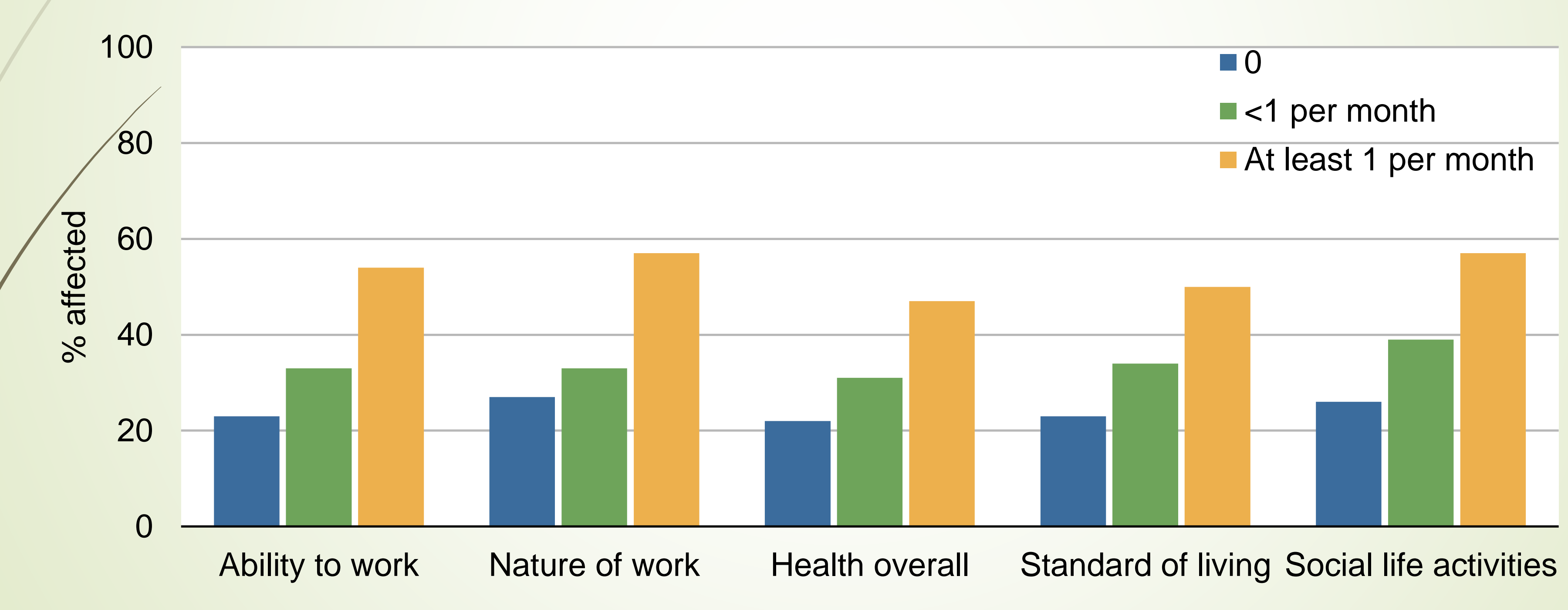
- Rappresenta il fattore prognostico più importante
- Tuttavia non sempre è possibile definire la diagnosi iniziale
- Attenzione quindi agli indicatori "parziali"

Proportion in Remission
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Idiopathic seizures (n=68)
Cryptogenic seizures (n=54)
Remote symptomatic seizures (n=123)
0 5 10 15 20 25 30 35 40 45
Years after the Onset of Epilepsy

Sillampa et al. 1998

5. Che cosa comporta la FR per il paziente?

Qualità della vita



Baker et al. 1998

La qualità della vita migliora solo se si raggiunge un completo controllo delle crisi

T-score change in QOLIE-89

8
6
4
2
0
-2
-4
-6
-8

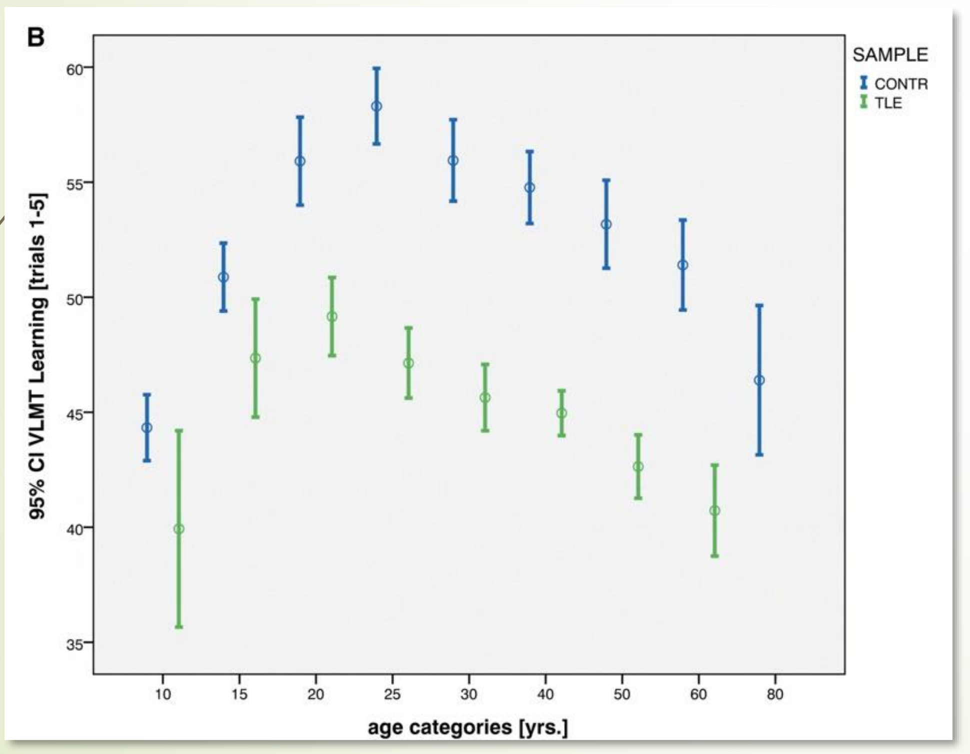
0-50% | 50-74% | 75-99% | 100%

Seizure reduction

After Birbeck et al. Epilepsia 2002

6. L'epilessia FR si associa a deficit cognitivi e aumento del rischio di SUDEP

Memory and cognition in TLE



Helmstaedter et al. Brain 2009

SUDEP

- 1 in 500-1000 per year overall risk
- 1 in 200 per year refractory epilepsy
- 1 in 100 per year surgical assessment

7. Come possiamo trattarla con i farmaci?

brivaracetam
perampanel
phenytoin
carbamazepine
valproate
clobazam
lamotrigine
gabapentin
topiramate
tiagabine
oxcarbazepine
levetiracetam
pregabalin
zonisamide
lacosamide

No. of combinations

1 drug	15
2 drugs	105
3 drugs	455

1+2+3 = 575

3 months per combination
= 192 years

7. Come possiamo trattarla con i farmaci?

Multiple modes of action
Topiramate
Valproate
Zonisamide

GABAergic drugs
Clobazam
Phenobaritone
Primidone
Tiagabine
Vigabatrin

Glutamatergic drugs
Perampanel
Felbamate

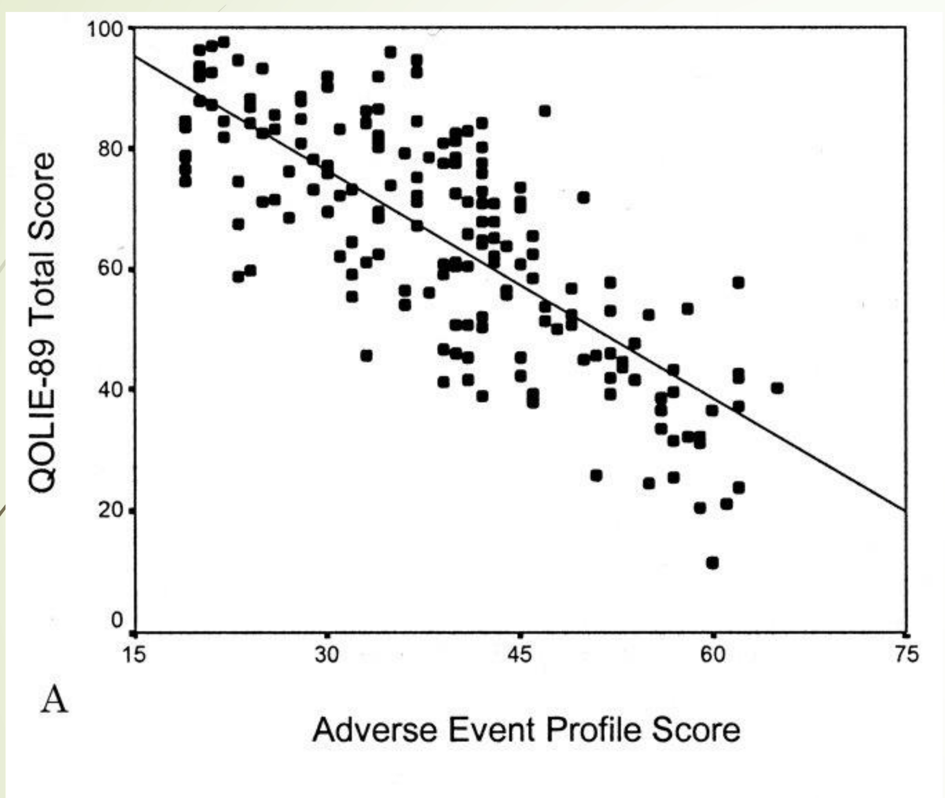
Sodium channel blockers
Carbamazepine
Lacosamide
Lamotigine
Oxcarbazepine
Phenytoin

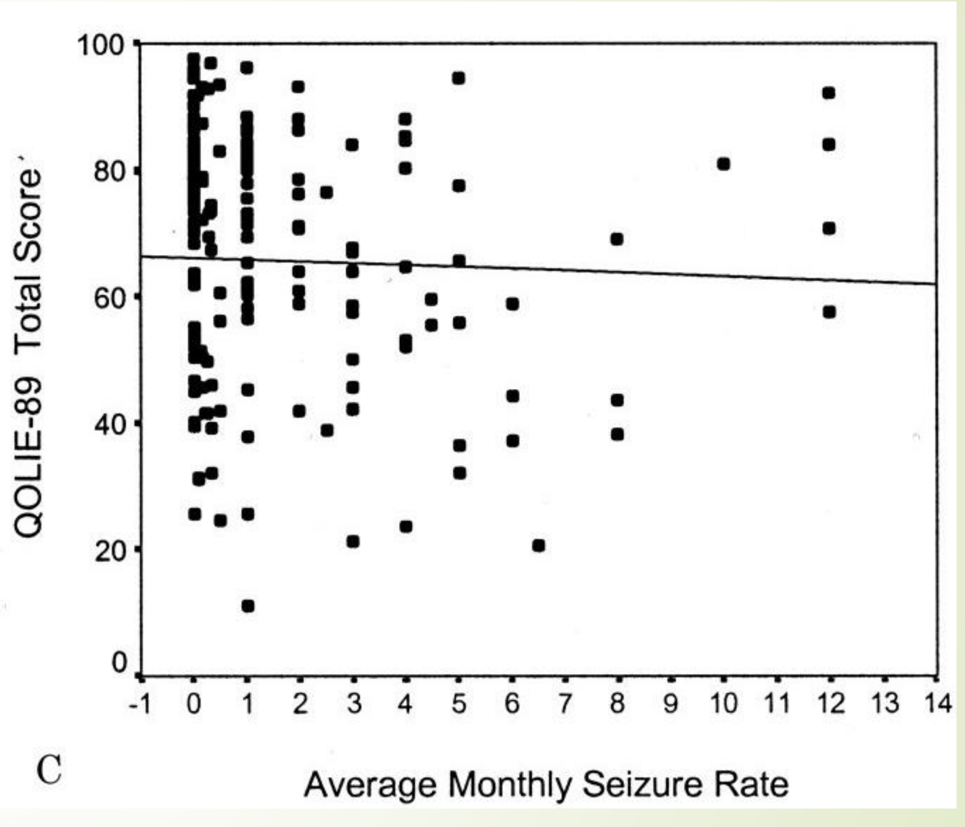
Vesicular protein SV2a
Levetiracetam
Brivaracetam

Presynaptic calcium channel
Gabapentin
Pregabalin

Potassium channel
Retigabine

Ma ricordatevi sempre:





Gilliam et al. Neurology 2002

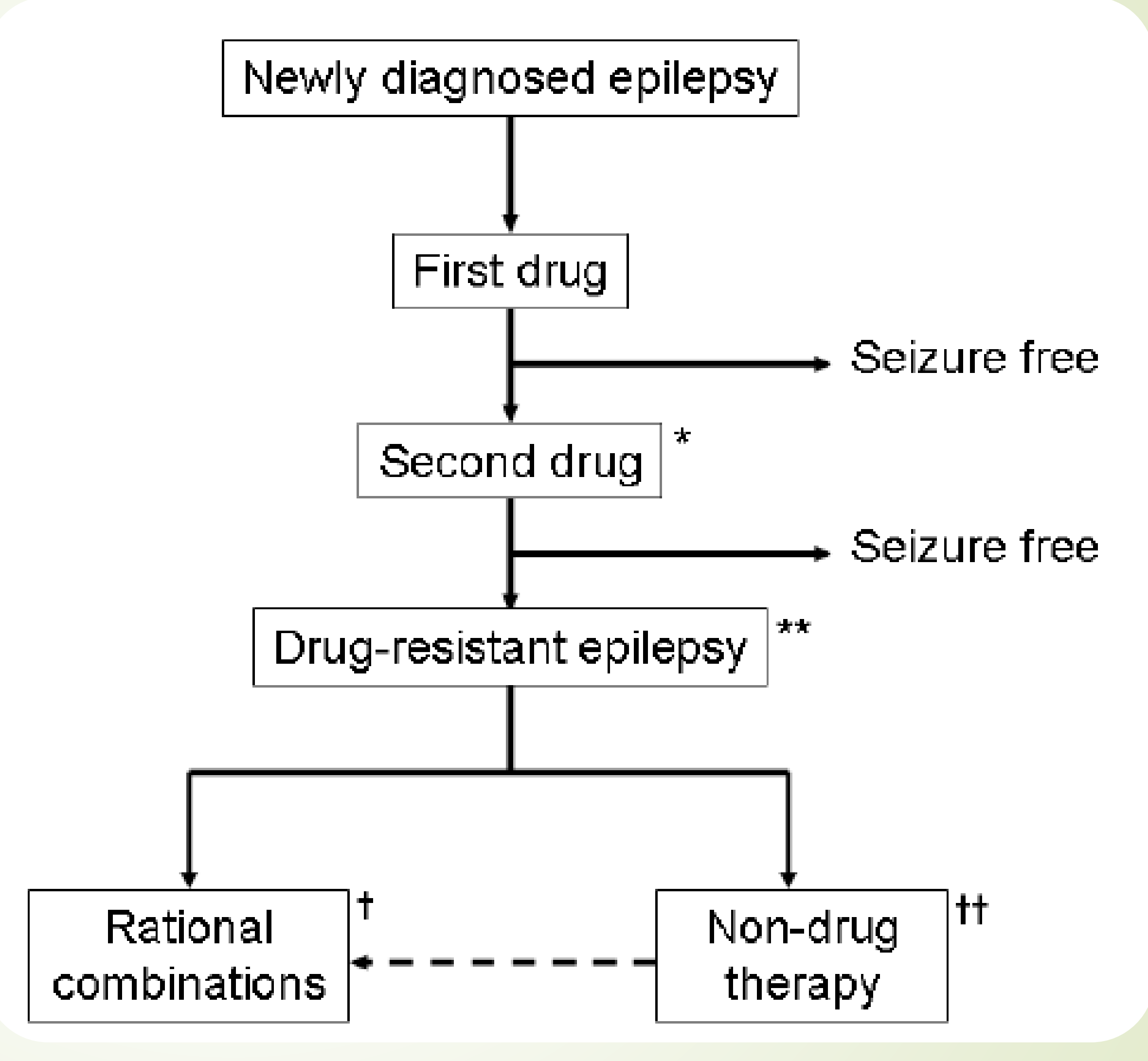
8. La legge del tentativo successivo

- 47% response to first drug (chance 47%)
- 13% response to second drug (chance 25%)
- 4% response to third drug (chance 10%)

95% Confidence Interva
95% Confidence Interva
% Patients
100
80
60
40
20
0
1 (470)
2 (190)
3 (65)
4 or More (25)
Antiepileptic Drug Regimens

Kwan et al. NEJM 2000

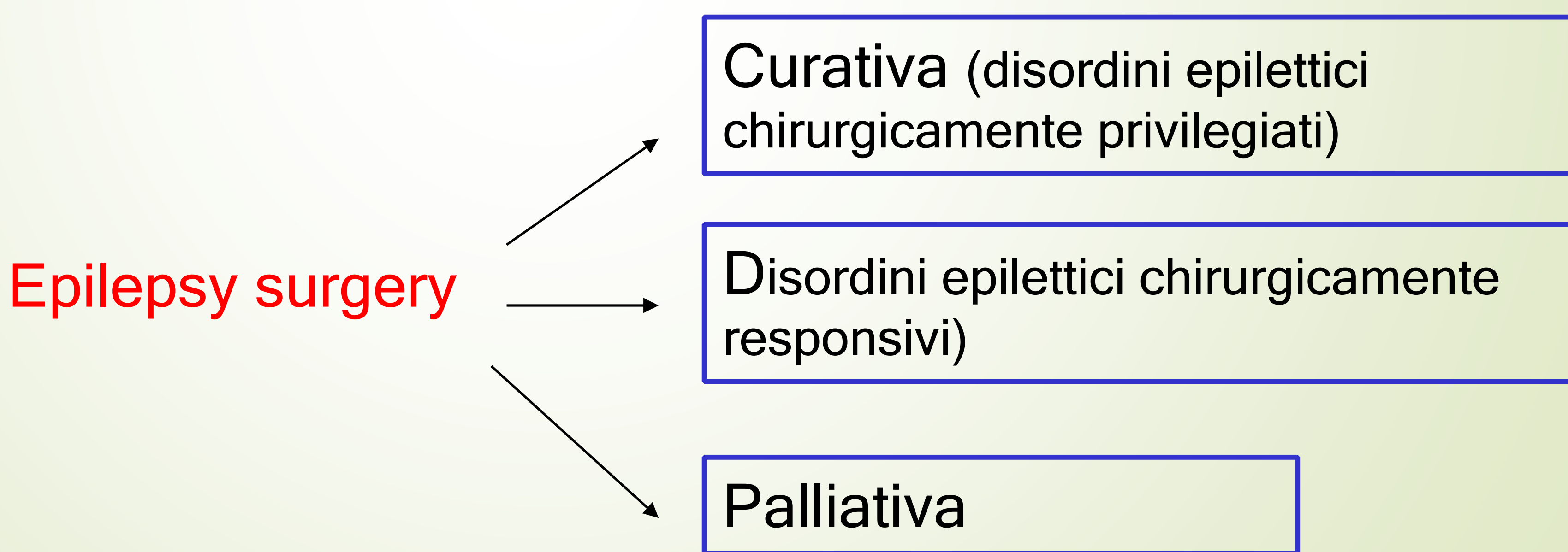
9. Principi di trattamento



Kwan et al. 2011

10. La chirurgia dell' epilessia

La chirurgia viene ancora considerata come l'ultima spiaggia terapeutica. Una errata opinione che ha causato, e causa, dei ritardi spesso inaccettabili nell'esecuzione di una procedura che in casi selezionati può fornire risultati eccellenti.



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Journal of Medicine

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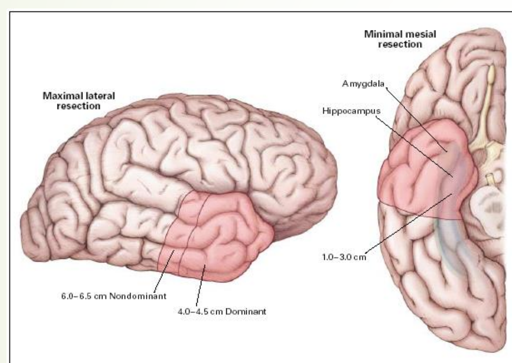
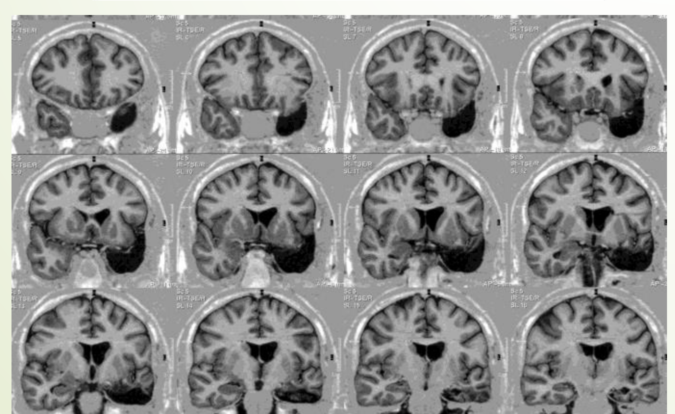
VOLUME 345 AUGUST 2, 2001 NUMBER 5

A RANDOMIZED, CONTROLLED TRIAL OF SURGERY FOR TEMPORAL-LOBE EPILEPSY

SAMUEL WIEBE, M.D., WARREN T. BLUME, M.D., JOHN P. GIRVIN, M.D., PH.D., AND MICHAEL ELIASZIW, PH.D., FOR THE EFFECTIVENESS AND EFFICIENCY OF SURGERY FOR TEMPORAL LOBE EPILEPSY STUDY GROUP*





A
Percentage without Seizures Impairing Awareness
100
80
60
40
20
0
0 2 4 6 8 10 12
Surgical group (n=40)
58%
Medical group (n=40)
8%

B
Percentage without Any Seizures
100
80
60
40
20
0
0 2 4 6 8 10 12
Months
Surgical group (n=40)
38%
Medical group (n=40)
3%

Early Surgical Therapy for Drug-Resistant Temporal Lobe Epilepsy

A Randomized Trial

JAMA, March 7, 2012—Vol 307, No. 9

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for the Early Randomized Surgical Epilepsy Trial (ERSET) Study Group

Results Zero of 23 participants in the medical group and 11 of 15 in the surgical group were seizure free during year 2 of follow-up (odds ratio=∞; 95% CI, 11.8 to ∞; $P < .001$). In an intention-to-treat analysis, the mean improvement in QOLIE-89 overall T-score was higher in the surgical group than in the medical group but this difference was not statistically significant (12.6 vs 4.0 points; treatment effect=8.5; 95% CI, −1.0 to 18.1; $P = .08$). When data obtained after surgery from participants in the medical group were excluded, the effect of surgery on QOL was significant (12.8 vs 2.8 points; treatment effect=9.9; 95% CI, 2.2 to 17.7; $P = .01$). Memory decline (assessed using the Rey Auditory Verbal Learning Test) occurred in 4 participants (36%) after surgery, consistent with rates seen in the literature; but the sample was too small to permit definitive conclusions about treatment group differences in cognitive outcomes. Adverse events included a transient neurologic deficit attributed to a magnetic resonance imaging–identified postoperative stroke in a participant who had surgery and 3 cases of status epilepticus in the medical group.

Conclusions Among patients with newly intractable disabling MTLE, resective surgery plus AED treatment resulted in a lower probability of seizures during year 2 of follow-up than continued AED treatment alone. Given the premature termination of the trial, the results should be interpreted with appropriate caution.