The prognosis of epilepsy

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For patients with seizures, prognosis means the probability of further seizures after a single unprovoked seizure or the likelihood of achieving seizure freedom or terminal remission after a pattern of recurring seizures has been established[1]. It is now accepted that up to 70% of people with epilepsy will enter remission, usually in the early years of the condition[2]. However, in discussing the prognosis of epilepsy, various aspects need to be considered: the likelihood of recurrence following a single seizure, the impact of early versus late treatment, the probability of relapse after prolonged remission, the probability of seizure freedom following epilepsy surgery or relapse following antiepileptic medication withdrawal.

Recurrence after a single unprovoked seizure

Prospective studies of single seizures are difficult, as many events go unrecognised or are unwitnessed and patients do not usually present to medical attention unless the seizure is convulsive. The overall risk of recurrence following a single seizure has been reported to be 27−71%. A meta-analysis found that the average risk of seizure recurrence was 40% in prospective studies and 52% in retrospective studies[3]. The time interval between the seizure and inclusion in the follow-up influences recurrence, as many patients have a recurrence within weeks of the first seizure and are therefore classified as having epilepsy. This artificially lowers the estimated recurrence rate following a single seizure if there is a long delay between the initial seizure and recruitment into a recurrence study[4]. The risk of subsequent seizures decreases with time, with up to 80% of recurrences occurring within two years of the initial seizure[3].

In the community-based study National General Practice Study of Epilepsy (NGPSE), 67% of those with a single seizure had a recurrence within 12 months and 78% within 36 months[5] which, while high, is within the reported range. In a prospective study of children with a first unprovoked seizure, 45% had a second seizure with the median time to recurrence being 6.2 months. The cumulative risk of a second seizure was 22% (six months), 29% (one year), 37% (two years), 43% (five years) and 46% (ten years)[6]. Another prospective study of adults with a single seizure found a recurrence rate of 58% at 750 days' follow-up. No further recurrences were recorded thereafter during a median follow-up of 10.3 years, underlying the impression that the risk of seizure recurrence highest in the first 1−2 years following the seizure[7].

Recurrence after a second seizure

The risk of recurrent seizures following a second seizure was investigated in a predominantly adult population[8]. The risk of a further seizure was 32% at three months, 41% at six months, 57% at one year and 74% at four years. Of those who did not have a

Table 1. Long-term prognosis studies in epilepsy.

Country	Number	Follow-up (years)	Proportion 5YR TR (%)	Proportion 5YR TR off AEDs (%)	Study design
USA[12]	N = 457	20	70%	50%	Historic incident cohort
Japan[13]	N = 1868	10	58.3%	N/A	Retrospective multi-institutional study
UK[14]	N = 194	12	64%	40%	Retrospective (P)
Japan[15]	N = 730	10-15	79.1%	N/A	Retrospective (P)
Japan[16]	N = 143	18.9	62.8%	54.7%	Retrospective (P)
Sweden[11]	N = 107	10	64%	17.5%	Prospective (All >17 years)
Finland[17]	N = 144	40	67%	58%	Prospective (P)
Holland[18]	N = 413	14.8	70.9%	61.9%	Prospective (P)

P=Paediatric study; 5YR TR=5-year terminal remission rate

recurrence after the second seizure within the first four years of follow-up, none had a relapse in the subsequent three years. The majority of those with a third seizure had a further seizure, with 31% of people who already had three seizures going on to have a fourth seizure at three months, 48% at six months, 61% at one year and 78% at three years. As with single seizures, the risk of further seizures is highest immediately after the last one. Similarly for children, the risk of a third seizure was 57% at one year, 63% at two years and 72% at five years after having a second seizure[6].

Short- and medium-term prognosis

In a prospective study of children with newly diagnosed epilepsy followed up from the time of diagnosis, 74% had achieved a period of remission (≥2 years' seizure freedom), of whom 24% had a further seizure. In those who had a relapse, approximately 50% occurred when an antiepileptic drug (AED) was being withdrawn or had been stopped[9]. In the NGPSE after nine years, 86% had achieved a remission of three years and 68% a remission of five years. The proportion in terminal remission by nine years was 68% for three years and 54% for five years[10]. In a study of patients aged ≥17 with newly diagnosed epilepsy, at ten years' follow-up the cumulative remission rates were 68% (one year), 64% (three years) and 58% (five years)[11].

Long-term prognosis

Few studies have looked at the long-term prognosis of people with epilepsy and most are retrospective and in paediatric cohorts (Table 1). In the Rochester study[12], 65% had achieved a five-year period of remission at ten-year follow-up and 76% at 20 years. At ten years after diagnosis 61% were in terminal remission with 70% in terminal remission at 20 years. Of

those in remission, 20% continued on AEDs while 50% had successfully discontinued medication and remained seizure-free for ≥5 years. In a cohort of children with active epilepsy followed up for 12 years 64% were in terminal remission (defined as ≥3 years seizure free) after 12 years[14].

In a study of children followed up for an average 37 years, 67% were in terminal remission, on or off medication. Early remission, defined as remission occurring within the first year of treatment, was achieved by 31%, and the remission continued to terminal remission in half of these. Remission without relapse occurred in 50% with a mean delay of nine years. A total of 14% entered remission but subsequently relapsed with further remission, indicating a relapse-remitting pattern, while 19% continued with seizures from the onset[17]. Of children followed up for a median of 40 years, 93% had one or more periods of remission (one year), emphasising the overall excellent prognosis of childhood epilepsy[19].

For those with chronic epilepsy, up to one-third will have a relapsing remitting pattern with at least one period of significant seizure freedom[20].

Prognostic factors

Many studies have looked at possible predictors of seizure prognosis, including age of onset, gender, aetiology, seizure type, EEG patterns, number of seizures prior to treatment and early response to treatment[21]. In patients presenting with a first-ever seizure, the presence of multiple discrete seizures within 24 hours is not associated with a worse prognosis than those with a single seizure[22]. Remote symptomatic epilepsy, the presence of a neurological birth deficit and learning disability are consistently shown to be associated with a poorer prognosis. In one study the three-year remission rate was 89% for those with idiopathic epilepsy and normal examination compared to only 49% in those with a neurological deficit or learning disability[13]. The number of seizures in the first six months after onset has been found to be a strong determinant of the probability of subsequent remission, with 95% of those with two seizures in the first six months achieving a five-year remission compared with only 24% of those with more than ten seizures[23].

Seizure type has been an inconsistent prognostic factor with some studies indicating that those with partial seizures have a poorer prognosis[12] while other studies have demonstrated a poorer prognosis for those with generalised onset seizures[24]. People with multiple seizure types, as is typical in the childhood encephalopathies, appear to have a poorer prognosis[25]. A significant reduction or complete cessation of seizures within three months of initiating treatment has been shown to be a strong predictor of subsequent remission[26]. The probability of seizure remission decreases significantly with each successive treatment failure. Only 11% of patients who discontinued the first appropriate AED due to lack of efficacy became seizure free on a second AED and only 4% on a third medication or on polypharmacy[27].

Children who experience clusters of seizures during treatment are much more likely to have refractory epilepsy than children without clusters and are less likely to achieve five-year terminal remission[28]. Children who continued to have weekly seizures during the first year of treatment had an eight-fold increase in the risk of developing intractable epilepsy and a two-fold increase in the risk of never achieving one-year terminal remission[19].

The impact of aetiology on prognosis

When comparing prognosis by aetiology, patients with idiopathic generalised epilepsy appear to have a better prognosis than patients with symptomatic or cryptogenic partial epilepsy. In one study 82% of people with idiopathic generalised seizures achieved one-year seizure

freedom compared to only 35% with symptomatic partial epilepsy and 45% with cryptogenic partial epilepsy[28]. Temporal lobe epilepsy (TLE) is associated with a poorer prognosis than extra-temporal lobe epilepsy[29,30].

For patients with a single identified lesion, TLE with hippocampal sclerosis (HS) had a particularly bad prognosis (11% seizure free) compared with other aetiologies (24% with cortical dysplasia seizure free). Patients with HS and another identified pathology (dual pathology) had the worst prognosis (3% seizure free)[29]. In another study no difference in prognosis between those with symptomatic and cryptogenic partial epilepsy was found[30]. Comparing patients by aetiology, they found that mesial TLE had the worst prognosis compared to rates for other aetiologies[30].

The impact of medication on prognosis

In the Western world most patients are commenced on AED after two unprovoked seizures, implying that prognostic studies from Western countries are essentially those of treated epilepsy. Evidence from studies from resource-poor countries where a significant treatment gap exists suggests that many patients may enter spontaneous remission with no AED[31].

Indeed the response to AEDs in patients with chronic long-standing epilepsy is comparable to that of patients with new-onset seizures[31,32]. Such evidence contradicts the belief that epilepsy is a chronic progressive condition unless early treatment is commenced[33]. It has been suggested that patients with epilepsy can be subdivided into prognostic groups based on their aetiology and epileptic syndrome. This important concept implies that the need and response to antiepileptic treatment in epilepsy is determined by the different prognostic groups[1,2].

Early versus late treatment

Two studies have assessed the impact of medication on the risk of seizure recurrence. In the FIRST study, patients with first unprovoked generalised seizures were randomised to either immediate treatment (treated group) or to treatment only after a further seizure (untreated group). While immediate treatment reduced the risk of early relapse, it did not affect the long-term prognosis, with comparable five-year remission rates in the two groups[34].

In the MESS study patients with a single seizure or early epilepsy (all types) were randomised to receive immediate or deferred treatment. Patients in the immediate treatment group had increased time to first and second seizure and first generalised seizure, in addition to having a reduced time interval to two-year remission. At five years' follow-up, however, 76% in the immediate group compared to 77% in the deferred group had achieved 3−5 years' seizure freedom[35].

In conclusion, immediate treatment delays the early recurrence of seizures but does not affect the medium- or long-term prognosis.

Prognosis following AED withdrawal

In the largest randomised controlled trial of continued treatment vs drug withdrawal in 1013 patients in remission (two or more years seizure free), at two years post-randomisation 41% of those who had discontinued medication had had a recurrence of seizures compared to 22% of those who stayed on medication. The difference in relapse rates between the two groups was maximal at nine months, with the rate of relapse higher in the discontinuation group up to two years' follow-up, but by 2−4 years the risk of relapse was higher in those continuing treatment[36]. Patients who experienced a relapse were followed up, and by three years 95%

had a further one-year remission and by five years 90% had had a further two-year remission period, indicating that the long-term prognosis was similar in both groups[37].

A further analysis of the data from the MRC AED withdrawal study using regression modelling has recently been reported[38]. The recurrence risk within the first 12 months following AED withdrawal was 30% (95% CI 25–35) while the risk of recurrence within the next 12 months three months after AED withdrawal was 15% (95% CI 10–19). For those who had a seizure recurrence, three months after recommencing treatment the risk of seizure recurrence within the next six months was 18% (95% CI 10–27) and 26% (95% CI 17–35) within 12 months[38].

An analysis of 14 AED withdrawal studies found that the recurrence rate following AED discontinuation ranged from 12−66% (mean 34%) and reinstatement of treatment was successful in obtaining further remission in, on average, 80% with no significant differences between age groups. A second remission may, however, take many years to achieve, while in an average of 19% the reintroduction of the medication did not control the seizures as before. Up to 23% of those discontinuing treatment go on to develop intractable epilepsy. Risk factors for subsequent poor treatment outcome were symptomatic partial epilepsy and cognitive deficits[39].

Despite the risk of seizure recurrence, patients may choose to discontinue treatment because of the impact of continuing antiepileptic medication on quality of life. In one study[40], the effect of AED withdrawal on quality of life was assessed. At one year seizure recurrence had occurred in 15% of the withdrawal group compared with 7% in the non-withdrawal group. The proportion of patients having completely normal neuropsychological findings increased from 11% to 28% in the withdrawal group while decreasing from 11% to 9% in the non-withdrawal group. No differences in quality of life were observed between the two groups. At 41 months' follow-up, predictors of continued seizure freedom following treatment withdrawal were prior use of carbamazepine (approximately three-fold increase in likelihood of remaining seizure free compared with patients on any other drug) and a normal neurological examination[40].

Prognosis following epilepsy surgery

Only two randomised controlled trials have compared the outcomes of patients with temporal lobe epilepsy randomised to either surgery or continued medical treatment[41,42], the latter study being of somewhat limited value due to difficulty recruiting suitable patients for inclusion in the study[42]. In the earlier study, 80 patients with temporal lobe epilepsy were randomised to have either epilepsy surgery or continued medical treatment for one year. A total of 90% of patients in the surgery group underwent surgery with 64% free from seizures impairing consciousness (42% completely seizure free) compared to 8% (3% completely seizure free overall) in the medical group at one year. Quality of life was also improved in patients after surgery compared to patients in the medical group ($P < 0.001$)[41].

In a recent review of controlled studies (total 2734 patients, all but one study non-randomised) 44% of patients in the surgical group (mainly temporal lobe surgery) were seizure free compared to 12% with medical treatment only. Moreover surgical patients were four times more likely to be able to discontinue medication compared to non-surgical patients[43].

In the long-term follow-up of 615 adults who underwent epilepsy surgery (497 anterior temporal resections, 40 temporal lesionectomies, 40 extratemporal lesionectomies, 20 extra-temporal resections, 11 hemispherectomies, and seven palliative procedures [corpus callosotomy, subpial transection]), patients who had extra-temporal resections were more likely to have seizure recurrence than were those who had anterior temporal resections

(hazard ratio [HR] 2.0, 1.1-3.6; $P = 0.02$). The longer a person remains seizure free the less likely they would relapse, while conversely the longer seizures persisted post-operatively the less likely seizure remission would be achieved[44].

In summary, in appropriately selected patients, surgery is four times more likely to render patients seizure-free than medical treatment alone.

Prognosis in those with intractable epilepsy

Studies suggest that failure to control seizures with the first or second AED implies that the probability of subsequent seizure control with further AEDs is slim[27]. This can lead to clinical nihilism when dealing with such patients in clinic. A recent series of papers suggests, however, that such a view is overly pessimistic. In a retrospective analysis of the effect of 265 medication changes in 155 patients with uncontrolled epilepsy of at least five years' duration, 16% of all patients were rendered seizure free (12 months or more) following a drug introduction while a further 21% had a significant reduction of seizure frequency. Overall 28% of the cohort was rendered seizure free by medical changes[45].

In another study a group of 246 patients with refractory epilepsy was followed for three years. Excluding those who became seizure free because of surgery, 26 (11%) became seizure free (six months' terminal remission) as a result of medication change (addition of a new AED or dose change). No single AED was associated with a statistically significant probability of inducing seizure freedom. Patients with mental retardation were statistically less likely to achieve a remission. Overall approximately 5% per year became seizure free, highlighting the fact that, irrespective of the number of AEDs previously tried, there is still a possibility of inducing meaningful seizure remission in this population[46].

The probability of seizure relapse following remission was retrospectively studied in a cohort of 186 patients with intractable epilepsy who were followed for a median of 3.8 years. Overall 20 patients achieved a remission of ≥12 months with a 4% probability of remission per year. Of these, five subsequently suffered a relapse with the estimated cumulative probability of relapse 33% at two years and 44% at three years. No clear predictors of remission or subsequent relapse were identified[47].

In summary, approximately 4−5% a year of those with refractory epilepsy will achieve a remission of 12 months on medication, although more long-term follow-up demonstrates that approximately one-half will subsequently relapse[48].

Conclusions

The overall prognosis for people with newly diagnosed epilepsy is good, with 60−70% becoming seizure-free, many of whom doing so in the early course of the condition. The probability of obtaining seizure freedom is particularly high in those with idiopathic generalised epilepsy and normal neurological examination. For those who continue to have seizures despite multiple appropriate AED treatments, in appropriate candidates epilepsy surgery is four times more likely to render seizure freedom than continued medical treatment alone. Despite this, medical changes will achieve a remission of 12 months in 4−5% a year of those with seemingly intractable epilepsy.

References

1. SANDER JW. Some aspects of prognosis in the epilepsies: a review. *Epilepsia* 1993;34:1007-16.
2. KWAN P, SANDER JW. The natural history of epilepsy: an epidemiological view. *J Neurol Neurosurg Psychiatry* 2004;75:1376-81.

3. BERG AT, SHINNAR S. The risk of seizure recurrence following a first unprovoked seizure: a quantitative review. *Neurology* 1991;41:965-72.
4. HOPKINS A, GARMAN A, CLARKE C. The first seizure in adult life. Value of clinical features, electroencephalography, and computerised tomographic scanning in prediction of seizure recurrence. *Lancet* 1988;i:721-6.
5. HART YM, SANDER JW, JOHNSON AL et al. National General Practice Study of Epilepsy: recurrence after a first seizure. *Lancet* 1990;336:1271-4.
6. SHINNAR S, BERG AT, O'DELL C et al. Predictors of multiple seizures in a cohort of children prospectively followed from the time of their first unprovoked seizure. *Ann Neurol* 2000;48:140-7.
7. LINDSTEN H, STENLUND H, FORSGREN L. Seizure recurrence in adults after a newly diagnosed unprovoked epileptic seizure. *Acta Neurol Scand* 2001;104:202-7.
8. HAUSER WA, RICH SS, LEE JR et al. Risk of recurrent seizures after two unprovoked seizures. *N Engl J Med* 1998;338:429-34.
9. BERG AT, SHINNAR S, LEVY SR et al. Two-year remission and subsequent relapse in children with newly diagnosed epilepsy. *Epilepsia* 2001;42:1553-62.
10. COCKERELL OC, JOHNSON AL, SANDER JW et al. Prognosis of epilepsy: a review and further analysis of the first nine years of the British National General Practice Study of Epilepsy, a prospective population-based study. *Epilepsia* 1997;38:31-46.
11. LINDSTEN H, STENLUND H, FORSGREN L. Remission of seizures in a population-based adult cohort with a newly diagnosed unprovoked epileptic seizure. *Epilepsia* 2001;42: 1025-1030.
12. ANNEGERS JF, HAUSER WA, ELVEBACK LR. Remission of seizures and relapse in patients with epilepsy. *Epilepsia* 1979;20:729-37.
13. OKUMA T, KUMASHIRO H. Natural history and prognosis of epilepsy: report of a multi-institutional study in Japan. The group for the study of prognosis of epilepsy in Japan. *Epilepsia* 1981; 22: 35-53.
14. BRORSON LO, WRANNE L. Long-term prognosis in childhood epilepsy: survival and seizure prognosis. *Epilepsia* 1987;28:324-30.
15. OKA E, YAMATOGI Y, OHTSUKA Y et al. Clinical course and prognosis of childhood epilepsy. *Acta Paediatr Jpn* 1989; 31: 259-66.
16. WAKAMOTO H, NAGAO H, HAYASHI M et al. Long-term medical, educational, and social prognoses of childhood-onset epilepsy: a population-based study in a rural district of Japan. *Brain Dev* 2000; 22: 246-55.
17. SILLANPAA M, SCHMIDT D. Natural history of treated childhood-onset epilepsy: prospective, long-term population-based study. *Brain* 2006;129:617-24.
18. GEERTS A, ARTS WF, STROINK H et al. Course and outcome of childhood epilepsy: a 15-year follow-up of the Dutch Study of Epilepsy in Childhood. *Epilepsia* 2010; 51: 1189-97.
19. SILLANPAA M, SCHMIDT D. Early seizure frequency and aetiology predict long-term medical outcome in childhood-onset epilepsy. *Brain* 2009;132:989-998.
20. NELIGAN A, BELL GS, SANDER JW et al. How refractory is refractory epilepsy? Patterns of relapse and remission in people with refractory epilepsy? *Epilepsy Res* 2011;96:225-30.
21 SANDER JW. The epidemiology of epilepsy revisited. *Curr Opin Neurol* 2003;16:165-70.
22 KHO LK, LAWN ND, DUNNE JW et al. First seizure presentation: do multiple seizures within 24 hours predict recurrence? *Neurology* 2006;67:1047-9.
23 MACDONALD BK, JOHNSON AL, GOODRIDGE DM et al. Factors predicting prognosis of epilepsy after presentation with seizures. *Ann Neurol* 2000;48:833-41.
24 SHAFER SQ, HAUSER WA, ANNEGERS JF et al. EEG and other early predictors of epilepsy remission: a community study. *Epilepsia* 1988;29:590-600.
25 Collaborative Group for the Study of Epilepsy. Prognosis of epilepsy in newly referred patients: a multicenter prospective study of the effects of monotherapy on the long-term course of epilepsy. *Epilepsia* 1992;33:45-51.
26. SILLANPAA M, JALAVA M, KALEVA O et al. Long-term prognosis of seizures with onset in childhood. *N Engl J Med* 1998;338:1715-22.
27. KWAN P, BRODIE MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000;342:314-9.
28. SILLANPAA M, SCHMIDT D. Seizure clustering during drug treatment affects seizure outcome and mortality of childhood-onset epilepsy. *Brain* 2008;131:938-44.
29. SEMAH F, PICOT MC, ADAM C et al. Is the underlying cause of epilepsy a major prognostic factor for recurrence? *Neurology* 1998;51:1256-62.
30. STEPHEN LJ, KWAN P, BRODIE MJ. Does the cause of localisation-related epilepsy influence the response to antiepileptic drug treatment? *Epilepsia* 2001;42:357-62.
31. PLACENCIA M, SANDER JW, ROMAN M et al. The characteristics of epilepsy in a largely untreated population in rural Ecuador. *J Neurol Neurosurg Psychiatry* 1994;57:320-5.
32. FEKSI AT, KAAMUGISHA J, SANDER JW et al. Comprehensive primary health care antiepileptic drug treatment programme in rural and semi-urban Kenya. ICBERG (International Community-based Epilepsy Research Group). *Lancet* 1991;337:406-9.
33. REYNOLDS EH. Early treatment and prognosis of epilepsy. *Epilepsia* 1987;28:97-106.
34. LEONE MA, SOLARI A, BEGHI E. Treatment of the first tonic-clonic seizure does not affect long-term remission of epilepsy. *Neurology* 2006;67:2227-9.
35. MARSON A, JACOBY A, JOHNSON A et al. Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial. *Lancet* 2005;365:2007-13.
36. MRC Antiepileptic Drug Withdrawal Study Group. Randomised study of antiepilpetic drug withdrawal in patients in remission. *Lancet* 1991;337:1175-80.
37. CHADWICK D, TAYLOR J, JOHNSON T. Outcomes after seizure recurrence in people with well-controlled epilepsy and the factors that influence it. The MRC Antiepileptic Drug Withdrawal Group. *Epilepsia* 996;37:1043-50.

38. BONNETT LJ, SHUKRALLA A, TUDUR-SMITH C et al. Seizure recurrence after antiepileptic drug withdrawal and the implications for driving: further results from the MRC Antiepileptic Drug Withdrawal Study and a systematic review. *J Neurol Neurosurg Psychiatry* 2011; 82: 1328-33.
39. SCHMIDT D, LOSCHER W. Uncontrolled epilepsy following discontinuation of antiepileptic drugs in seizure-free patients: a review of current clinical experience. *Acta Neurol Scand* 2005;111:291-300.
40. LOSSIUS MI, HESSEN E, MOWINCKEL P et al. Consequences of antiepileptic drug withdrawal: a randomized, double-blind study (Akershus Study). *Epilepsia* 2008;49:455-63.
41. WIEBE S, BLUME WT, GIRVIN JP et al. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N Engl J Med* 2001;345:311-8.
42. ENGEL J JR, McDERMOTT MP, WIEBE S et al. Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomised trial. *JAMA* 2012;307:922-30.
43. SCHMIDT D, STAVEM K. Long-term seizure outcome of surgery versus no surgery for drug-resistant partial epilepsy: a review of controlled studies. *Epilepsia* 2009;50:1301-9.
44. De TISI J, BELL GS, PEACOCK JL et al. The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. *Lancet* 2011;378:1388-95.
45. LUCIANO AL, SHORVON SD. Results of treatment changes in patients with apparently drug-resistant chronic epilepsy. *Ann Neurol* 2007;62:375-81.
46. CALLAGHAN BC, ANAND K, HESDORFFER D et al. Likelihood of seizure remission in an adult population with refractory epilepsy. *Ann Neurol* 2007;62:382-9.
47. CHOI H, HEIMAN G, PANDIS D et al. Seizure remission and relapse in adults with intractable epilepsy: a cohort study. *Epilepsia* 2008;49:1440-5.
48. NELIGAN A, BELL GS, ELSAYED M et al. Treatment changes in a cohort of people with apparently drug-resistant epilepsy: an extended follow-up. *J Neurol Neurosurg Psychiatry* 2012;83:810-3.