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Diagnosing refractory epilepsy: response to sequential treatment schedules

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Diagnosing refractory epilepsy would facilitate referral for specialist pharmacological review and early consideration of epilepsy surgery. An outcomes study was undertaken in an unselected cohort of newly diagnosed patients to determine the number of antiepileptic drug (AED) regimens needed to be failed before the epilepsy could be designated as pharmacoresistant. Between July 1982 and May 2001, 780 adolescents and adults prescribed their first AED at the Western Infirmary in Glasgow, Scotland provided longitudinal data suitable for analysis. Overall, 504 (64.6%) patients became seizure free for at least 12 months. Of these, 462 (59.2%) remained in remission, while 42 (5.4%) relapsed and subsequently developed refractory epilepsy. The relapse rate peaked at 10.4% after 8 years of follow-up. The other 276 (35.4%) patients were uncontrolled from the outset. Prognosis appeared better in seniors (85% remission, $P < 0.001$) and adolescents (65% remission, $P < 0.01$) than in the remainder of the population (55% remission). Overall response rates with the first, second and third treatment schedules were 50.4, 10.7 and 2.7%, respectively, with only 0.8% patients responding optimally to further drug trials. Patients not tolerating at least one AED schedule did better than those failing because of lack of efficacy. These data suggest that suitable patients failing two AED regimens should be referred for epilepsy surgery. Those who do not attain long-term seizure freedom with the first three treatment schedules are likely to have refractory epilepsy.

Introduction

Over 30% of people with epilepsy never achieve remission with antiepileptic drug (AED) therapy [1–4]. These individuals suffer the physical, psychological and societal consequences of intractable seizures with a heavy drug burden and an increased mortality [5]. Refractory epilepsy, in addition, represents a significant drain on health care resources [6]. Some of these patients could benefit from non-pharmacological treatment modalities, especially epilepsy surgery [7]. Indeed, resective surgery in refractory temporal lobe epilepsy has been shown in a randomized study, to provide substantially better outcomes than continued manipulation of AED therapy [8]. Many patients with remediable syndromes suffer seizures for >20 years before opting for surgery [9]. Defining a situation where the epilepsy is likely to be pharmacoresistant will help in the early identification of those patients to be referred for further evaluation to an epilepsy service. We analysed outcomes in patients with newly diagnosed epilepsy followed up at a single centre over a 20-year period with the objective of correlating response to sequential drug schedules with prognosis. This analysis is a follow-up of our preliminary observations in a smaller cohort published in 2000 [4].

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Patients and methods

Individuals presenting with a suspected seizure disorder were referred to the Epilepsy Unit in the Western Infirmary in Glasgow (Scotland, UK) by general practitioners, accident and emergency physicians and other clinicians. A structured protocol was used to collect clinical information and detailed histories were obtained from patients and relatives regarding suspected seizures.

Investigations including electroencephalography (EEG) and brain imaging were carried out routinely [10]. Seizure types and epilepsy syndromes were classified at the time of analysis according to the criteria of the International League Against Epilepsy [11,12]. Seizure disorders were divided broadly into idiopathic generalized (presumed genetic), symptomatic (cause identified) and cryptogenic (cause not identified) epilepsies. Eleven patients with idiopathic focal epilepsies (six benign epilepsy with centrotemporal spikes, four benign occipital epilepsy, one benign partial epilepsy of childhood) were included in the cryptogenic group. Symptomatic and cryptogenic epilepsies were combined

as localization-related (focal) epilepsies for some analyses [13]. When a diagnosis of epilepsy was made, patients were prescribed their first AED. Research notes were maintained for each patient in the Epilepsy Unit. Hospital review was carried out at 4–6 weekly intervals. Serum AED concentrations were measured as necessary to guide dosage changes and monitor compliance.

A total of 890 patients were diagnosed with epilepsy and prescribed their first AED between July 1982 and May 2001. None had previously received an AED for any indication. A total of 110 patients (12%) were excluded from analysis because of lack of sufficient follow-up information. Their demographic and clinical parameters did not differ significantly from those who continued in the study. Outcomes were known for the remaining 780 (88%) patients. Of these, 405 (52%) were male and 375 (48%) female. The median age at onset of epilepsy was 29 years (range 1–93) and at diagnosis was 31 years (range 9–93). Overall, 222 patients had an idiopathic generalized epilepsy, whilst 244 had symptomatic syndromes and 314 had cryptogenic epilepsy. Patients suffered a median of four seizures (range 1 to >100) before starting treatment. Median duration of follow-up was 79 months (range 24–252). Patients were followed up until 1 May 2003, when all had received treatment for at least 2 years. A total of 93 patients died during the study period (median age 63 years, range 18–96). Mortality will be discussed in detail in a separate publication.

Monotherapy was employed initially in all patients. Treatment schedules were modified as necessary based on clinical response and drug tolerability. Patients were asked to maintain seizure diaries. Those developing idiosyncratic reactions, such as rash, or experiencing intolerable side effects, such as sedation, at low AED doses, were deemed to have failed treatment because of adverse effects. Patients who continued to experience seizures despite tolerating high doses of medication were designated as treatment failures because of lack of efficacy. Patients not tolerating their first AED were prescribed an alternative. Those failing treatment because of lack of efficacy either had the original drug substituted or were offered combination therapy. The extent of seizure control was assessed at the time of the patient's last clinic visit.

Data were collected by review of case notes and seizure diaries. Response to treatment was defined as achievement of 12-month seizure freedom on an unchanged treatment schedule. This is the minimum period of seizure control required to regain driving privileges in the UK and was, therefore, deemed a clinically relevant and easily measured outcome measure. Remission was defined as having no further seizures after responding to treatment. Relapse occurred in responders in whom initial control was lost and whose epilepsy subsequently became pharmacoresistant. Patients were regarded as uncontrolled if they had never been seizure-free for any 12-month period. Categorical data were analysed using the chi-square test and the Bonferroni method was used to correct for multiple comparisons. Life table analysis using the actuarial method was employed to calculate time to achieving remission. The risk of relapse was quantified using Kaplan–Meier analysis. All statistical tests were two-tailed.

Results

Overall, 504 (64.6%) patients became seizure free for at least 12 months, 399 (79%) of whom remained in remission until the end of follow-up (Fig. 1). The remaining 105 (21%) initial responders reported further seizures after being free of attacks for 12 months or more. Seizure freedom was regained in 63, in whom the epilepsy subsequently remained controlled. The other 42 patients (5.4% of the total population) developed refractory epilepsy and so fulfilled the criterion for

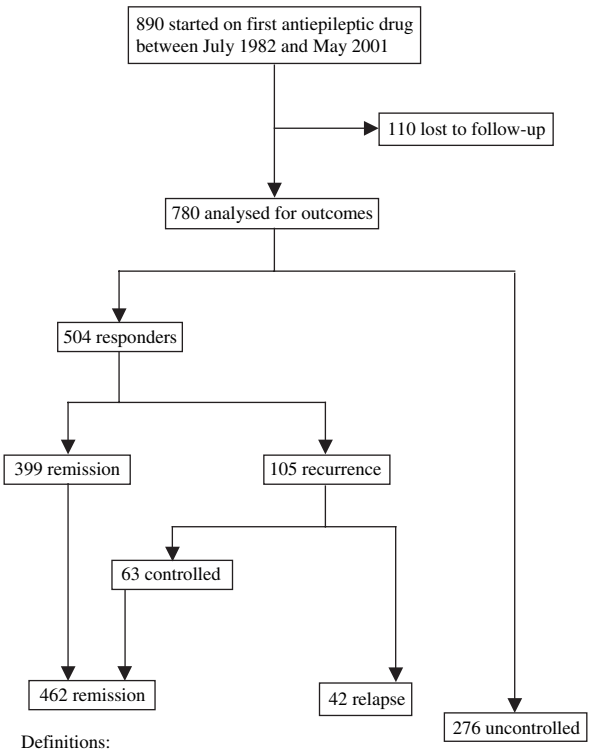

Figure 1 Profile of patient population.

relapse. The remaining 276 patients (35.4%) never obtained adequate control of seizures for any 12-month period from the outset.

A total of 462 (59.2%) patients achieved remission, 5% of whom subsequently managed to come off AED therapy. Patients with idiopathic generalized epilepsies had higher remission rates (66%) than those with cryptogenic (57%, $P = 0.041$) or symptomatic (56%, $P = 0.035$) epilepsies. When analysed by age at the start of treatment, a bimodal distribution was apparent for localization-related epilepsy and all epilepsies (Fig. 2), with the greatest likelihood of remission occurring in the youngest and oldest patients (Table 1). Number of pre-treatment seizures ($P = 0.024$), but not duration of epilepsy, predicted outcome (Fig. 3). Higher number of seizures in the 3 months prior to starting treatment were highly associated ($P < 0.001$) with uncontrolled epilepsy (Fig. 3).

Table 1 Pharmacological outcomes in newly diagnosed epilepsy by age at starting treatment

Patient groups	Age (years)	*n*	Remission (%)	Relapse (%)	Uncontrolled (%)
Adolescent	< 20	170	65*	12	23
Adult	20–64	520	53	4	43
Elderly	> 64	90	85**	1	14

*Adolescent versus adult $P < 0.01$; **elderly versus adolescent and adult $P < 0.001$.

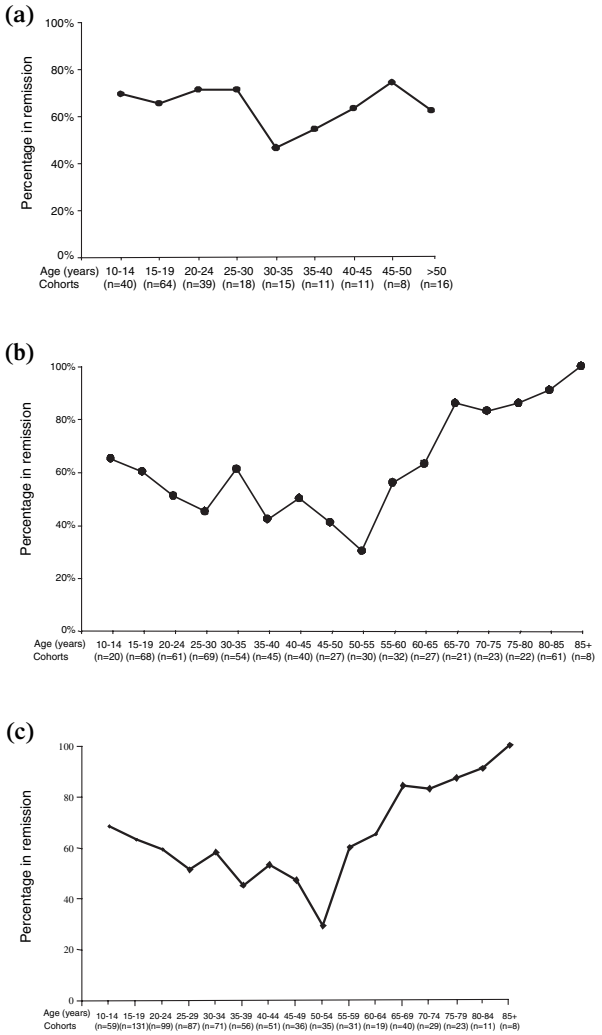

Figure 2 Remission rates according to age at starting treatment for (a) idiopathic epilepsies, (b) localization-related epilepsies and (c) all epilepsies.

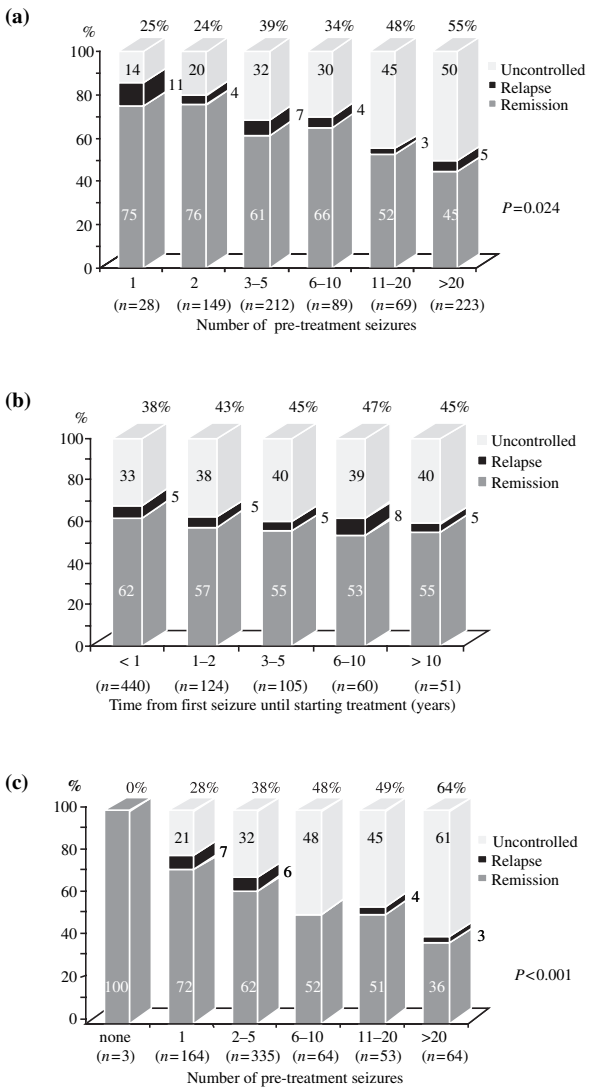

Figure 3 Outcomes by (a) number of pre-treatment seizures, (b) duration of epilepsy prior to starting treatment and (c) seizure numbers in the 3 months before starting treatment. Numbers within bars represent percentages. Percentages on top of bars represent patients with refractory epilepsy (uncontrolled and relapsed).

The majority of patients who responded to treatment did so early with 93% becoming seizure free for at least 12 months within 3 years of initiation of therapy. Indeed, 245 patients (31.4% of the whole cohort) suffered no further seizures after starting treatment. Remission was achieved in 88 and 94% of cases who reported no seizures during the first 3 and 24 months of treatment respectively. The median time to relapse was 25 months (range 12–97). Sixty-nine percent of relapses occurred within 3 years of initial response. Kaplan–Meier plot of time to relapse showed a rate of 4.2% at 2 years rising to a maximum of 10.4% after 8 years of follow-up (Fig. 4). There were no further relapses after a further median observation period of 38 months (range 1–144).

Of the 504 patients responding to treatment, 462 (92%) did so on monotherapy usually with the first ($n = 393$) or second ($n = 57$) AED. Only 12 patients became seizure free with subsequent monotherapies. Forty patients responded to duotherapy. Combinations of three and four drugs produced seizure freedom in just one patient each. Thus, just 8% of responders (5.4% of total population) were controlled with more than one AED. Overall response rates for the first, second or third treatment schedules as proportion of the population were 50.4, 10.7 and 2.3%, respectively, with just six (0.8%) patients responding to further drug trials (Table 2). This pattern was maintained when idiopathic generalized and localization-related (focal) epilepsy cohorts were analysed separately. Similar slightly lower values were found for remission rates

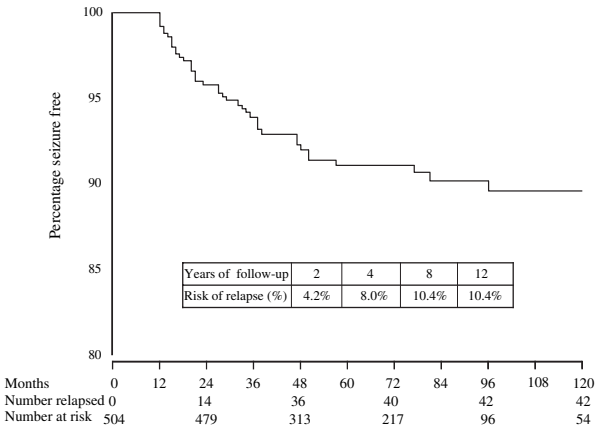

Figure 4 Kaplan–Meier plot of time to relapse.

Table 3 Percentage chance of remission with sequential regimens in patients with newly diagnosed epilepsy ($n = 780$) failing treatment because of lack of efficacy or adverse effects

	Lack of efficacy	Adverse effects	All causes
First drug	21	42	26
Second schedule	8	17	11
Third schedule	4	14	9

(Table 2). Patients who did not tolerate at least one drug or regimen because of poor tolerability tended to have better outcomes than those failing treatment because of lack of efficacy (Table 3). Response rates in patients exposed to a second or third monotherapy or AED combination are illustrated in Table 4.

Discussion

Most people with newly diagnosed epilepsy responded to treatment with their first AED or second regimen. Indeed, 31.4% of our population never had another seizure after taking the first dose of medication. A large number of seizures before starting treatment was a poor prognostic indicator, an observation that has been made previously [14,15]. However, duration of epilepsy was not a significant prognostic factor. High seizure density within 3 months of diagnosis and treatment initiation was predictive of subsequent poor control. In addition, patients who remained seizure free during the first 3 months of treatment achieved remission in 88% of cases, with the figure rising to just 94% after 2 years of seizure freedom. In more than a third of the patients, seizures were inherently pharmacoresistant and these individuals appeared to have refractory epilepsy *de novo*. Thus, response to the first AED is a powerful predictor of prognosis [4,16,17].

Only 5% of the patients subsequently developed refractory epilepsy after having been seizure free for 12 months or more. The relapse rate peaked at just over 10% after 8 years of follow-up. This scenario has been recognized retrospectively in patients with refractory epilepsy undergoing work up for epilepsy surgery [18], but the extent has not been documented in newly diagnosed epilepsy. Interestingly, outcomes in senior citizens with localization-related seizures were better than those in younger patients. This observation requires corroboration, but may be important because

Type of epilepsy	*n*	First drug	Second schedule	Third schedule	Other schedules
Idiopathic generalized	222	58.1 (53.3)	11.2 (9.9)	2.7 (2.3)	0.5 (0.5)
Localization-related	558	47.3 (43.2)	10.6 (10.2)	2.7 (2.3)	0.9 (0.9)
All epilepsies	780	50.4 (46)	10.7 (10.1)	2.7 (2.3)	0.8 (0.8)

Table 2 Overall response (remission) rates (%) with sequential treatment schedules in newly diagnosed epilepsy

Table 4 Response rates (%) for second and third treatment schedules in patients receiving alternative monotherapies or antiepileptic drug combinations

	Second schedule			Third schedule		
Type of epilepsy	Monotherapy	Combination	Total	Monotherapy	Combination	Total
Idiopathic generalized	44	48	45	33	44	35
Localization-related	31	31	31	23	21	23

old age is now the commonest time in life to develop epilepsy [19]. Adolescents too appeared to have a better prognosis, although they reported the highest relapse rate. The higher rate (49%) of idiopathic generalized epilepsy in this population contributed to the overall better outcome.

Overall remission rates with the first, second and third treatment schedules in relation to the total population were 46, 10.1 and 2.3%, respectively, with only 0.8% patients responding optimally to further drug trials. Patients failing at least one schedule because of poor tolerability tended to do better than those in whom lack of response was the reason for continuing seizures. Response to alternative monotherapies or AED combinations differed little. This analysis was undertaken in adolescents and adults. A number of similar studies have been carried out on prognosis in children [16,20,21]. Combining data across the complete age range is essential to obtain a clear overall picture of the development of refractory epilepsy.

The main reasons for referring a patient with refractory epilepsy to a specialist centre are to confirm the diagnosis, to classify seizures and syndromes, to optimize AED therapy, and, if appropriate, to consider work up for epilepsy surgery. Up to 30% of patients with presumed 'refractory epilepsy' have psychogenic seizures [22–24]. In-patient EEG monitoring has a high yield in changing diagnosis and management [25]. Accurate classification of seizures and syndromes is essential to ensure appropriate choice of treatment. In a recent study, 48% of patients with idiopathic generalized epilepsy were treated inappropriately with phenytoin or carbamazepine [26]. Temporal lobe epilepsy with hippocampal atrophy is the commonest cause of refractory localization-related epilepsy. Anterior temporal lobectomy can abolish disabling seizures in more than 60% of patients with this syndrome [8]. Despite this, many patients continue to suffer intractable epilepsy for >20 years before being referred for surgery [9]. Other lesions, such as malformation of cortical development [27] and tuberous sclerosis [28], may also be amenable to a surgical approach. Brain stimulation techniques can also produce good outcomes in selected patients with pharmacoresistant epilepsy [29].

All patients diagnosed with epilepsy and started on AED therapy were included in this analysis, irrespective of underlying pathology, occasional lapses in adherence to treatment, and the presence of adverse lifestyle factors such as occasional recreational drug usage or high alcohol consumption. These results, therefore, reflect 'real-life' outcomes. Overall, epilepsy in 56% of patients remitted with the first AED or second regimen. In addition, more than a third never had a prolonged period of optimum control and could be designated as inherently pharmacoresistant. Thus, more than 90% of this patient population either had a good response to their first or second treatment schedule or had refractory epilepsy *de novo*. There are a number of possible explanations for this intriguing observation [30], including differences in brain expression of drug efflux transporter proteins [31].

Conclusions

The prognosis for the majority of people with newly diagnosed epilepsy, whether good or bad, becomes apparent within a few years of starting treatment. Around 10% of patients who initially respond to treatment relapse later and remain uncontrolled. Outcomes can be broadly predicted from seizure densities immediately before starting treatment and response to the first AED or second regimen. The elderly, and to a lesser extent teenagers, are more likely to have good outcomes than the remainder of the population. Patients who do not attain long-term seizure freedom with the first two AED schedules are unlikely ever to have a useful period of remission. These patients should be referred to an epilepsy service for further evaluation including videotelemetry for confirmation of seizure and syndrome classifications, optimization of pharmacotherapy, and consideration of other therapeutic options, particularly epilepsy surgery. Failure of three AED regimens provides a working diagnosis of refractory epilepsy.

References

1. Annegers JF, Hauser WA, Elveback LR. Remission of seizures in and relapse in patients with epilepsy. *Epilepsia* 1979; **20:** 729–737.
2. Cockerell OC, Johnson AL, Sander JW, Hart YM, Shorvon SD. Remission of epilepsy: results from the National General Practice Study of Epilepsy. *Lancet* 1995; **346:** 140–144.

3. Mattson JH, Cramer JA, Collins JF. Prognosis for total control of complex partial and secondary generalised tonic-clonic seizures. *Neurology* 1996; **47:** 68–76.
4. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *New England Journal of Medicine* 2000; **342:** 314–319.
5. Kwan P, Brodie MJ. Refractory epilepsy: a progressive, intractable but preventable condition? *Seizure* 2002; **11:** 77–84.
6. Devinsky O. Patients with refractory seizures. *New England Journal of Medicine* 1999; **40:** 1565–1570.
7. Engel J, Wiebe S, French J, *et al*. Practice parameter: temporal lobe and localized neocortical resections for epilepsy: Report of the Quality Standards Subcommittee of the American Academy of Neurology in Association with the American Epilepsy Society and the American Association of Neurological Surgeons. *Neurology* 2003; **60:** 538–547.
8. Wiebe S, Blume WT, Girvin JP, Eliasziw M for the Effectiveness and Efficacy of Surgery for Temporal Lobe Epilepsy Study Group. A randomised, controlled trial of surgery for temporal lobe epilepsy. *New England Journal of Medicine* 2001; **345:** 311–318.
9. Trevathan E, Gilliam F. Lost years. Delayed referral for surgically treatable epilepsy. *Neurology* 2003; **61:** 432–433.
10. Brodie MJ, French JA. Management of epilepsy in adolescents and adults. *Lancet* 2000; **356:** 323–329.
11. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsy and epileptic seizures. *Epilepsia* 1981; **22:** 489–501.
12. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsy and epileptic syndromes. *Epilepsia* 1989; **30:** 389–399.
13. Wolf P. International classification of the epilepsies. In: Engel J, Pedley TA, eds. *A Comprehensive Textbook*. Philadephia, PA: Lippincott Raven, 1997: 773–777.
14. 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.
15. Sillanpää M. Remission of seizure and predictors of intractability in long-term follow-up. *Epilepsia* 1993; **34:** 930–936.
16. Sillanpää M, Jalava M, Kaleva O, Shinnar S. Long-term prognosis of seizures with onset in childhood. *New England Journal of Medicine* 1998; **338:** 1715–1722.
17. Dlugos DJ, Sammel MD, Strom BL, Farrar JT. Response to first drug trial predicts outcome in childhood temporal lobe epilepsy. *Neurology* 2001; **57:** 2259–2264.
18. Berg AT, Langfitt J, Shinnar S, *et al*. How long does it take for partial epilepsy to become intractable? *Neurology* 2003; **60:** 186–190.
19. Stephen LJ, Brodie MJ. Epilepsy in elderly people. *Lancet* 2000; **355:** 1441–1446.
20. Berg AT, Shinnar S, Levy SR, Testa FM, Smith-Rapeport S, Beckerman B. Early development of intractable epilepsy in children: a prospective study. *Neurology* 2001; **56:** 1445–1452.
21. Arts WFM, Brouwer OF, Peters ACB, *et al*. Course and prognosis of childhood epilepsy: 5 year follow up of the Dutch study of epilepsy in childhood. *Brain* 2004; **127:** 1774–1784.
22. Francis P, Baker GA. Non-epileptic attack disorder (NEAD): a comprehensive review. *Seizure* 1999; **8:** 53–61.
23. Smith D, Defalla BA, Chadwick DW. The misdiagnosis of epilepsy and the management of refractory epilepsy in a specialist clinic. *The Quarterly Journal of Medicine* 1999; **92:** 15–23.
24. Benbadis SR, Hauser WA. An estimate of the prevalence of psychogenic non-epileptic seizures. *Seizure* 2000; **9:** 280–281.
25. Ghougassian DF, D'Souza W, Cook MJ, O'Brien TJ. Evaluating the utility of inpatient video-EEG monitoring. *Epilepsia* 2004; **45:** 928–932.
26. Benbadis SR IV, Tatum WO, Gieron M. Idiopathic generalized epilepsy and choice of antiepileptic drugs. *Neurology* 2003; **61:** 1793–1795.
27. Sisodiya SM. Surgery for malformations of cortical development causing epilepsy. *Brain* 2000; **123:** 1075–1091.
28. Jarrar RG, Buchhalter JR, Raffel C. Long-term outcome of epilepsy surgery in patients with tuberous sclerosis. *Neurology* 2004; **62:** 479–481.
29. Theodore WH, Fisher RS. Brain stimulation for epilepsy. *Lancet Neurology* 2004; **3:** 111–118.
30. Elger CE. Pharmacoresistance: modern concept and basic data derived from human brain tissue. *Epilepsia* 2003; **44**(Suppl. 5)**:** 9–15.
31. Kwan P, Brodie MJ. Potential role of drug transporters in the pathogenesis of medically intractable epilepsy. *Epilepsia* 2005; **46:** 225–235.