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Outcomes in newly diagnosed epilepsy in adolescents and adults: Insights across a generation in Scotland

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ABSTRACT

The outpatient services at the Epilepsy Unit in the Western Infirmary, Glasgow, Scotland was set up in September 1982. From the outset patient data were collected prospectively. A focused approach to patients with newly diagnosed epilepsy was developed and a series of 4 analyses have been undertaken over the intervening years, with results from the latest still being written up for publication. A total of 16 published papers have described patient outcomes over the years, focusing on response to different drug schedules. A number of factors contributing to a poorer prognosis has been identified and follow up data over 30 years has confirmed the lack of overall improvement in prognosis despite the introduction of 14 new AEDs for the common epilepsies in the UK with different mechanisms of action over this time. Patterns of response have confirmed that a majority of patients will go into remission with around 25% of the population appearing to have refractory epilepsy de novo. Since all available options are antiseizure and not antiepilepsy drugs, some patients, who are initially well controlled, are seen to relapse over time and to develop refractory epilepsy. A new approach in identifying and treating epileptogenesis is necessary, if this disappointing scenario is to be reversed with the next generation of antiepileptic drugs.

1. Introduction

> The journey of a thousand miles begins with a single step.
> Lao Tzu 500 BC

My research journey in epilepsy began with a single idea. When I set up my seizure and epilepsy clinics in September 1982, I subsequently collected data from every patient using a "pink folder" system including a standard data collection form and investigative protocol. All subsequent information has been collected prospectively. A dedicated telephone line was made available to patients, families, and their primary care physician to facilitate optimal management. Patient data were included in a computer database and in pink folders which were stored in metal cabinets. The appropriate pink folders accompanied my team to every clinic and were available when patients, relatives and general practitioners phoned the Epilepsy Unit. Over the next 34 years, each new patient was registered in our database and a folder developed for storage. There are currently 8068 pink folders in the system.

One of the first patients referred to my service in 1982 was a 44 year old man reporting more than 10 focal and generalized tonic-clonic seizures each month despite taking high doses of 4 antiepileptic drugs (AEDs). He was markedly ataxic and was helped into the consulting room by his elderly parents. I remember thinking "how did he get into this state" and could I have done better for him? This unfortunate individual was the inspiration for the subsequent outcome work emanating from our newly diagnosed epilepsy programme over the next 35 years!

2. Database

Once the decision was taken to focus our outcome programme on adolescents and adult patients with newly diagnosed epilepsy, a letter was sent to all general practitioners in the West of Scotland offering to review suitable patients reporting a first seizure or with likely untreated epilepsy within a few weeks of referral. A direct line to the Epilepsy Unit office was set up to expedite the review of urgent cases. Around the same time an audit of patients presenting to the casualty department at the Western Infirmary with a first seizure or untreated epilepsy was made and the results published in the *British Medical Journal* [1]. Most of these patients were sent home with no investigations or follow up arranged. Hence, a direct referral arrangement was established with the Epilepsy Unit,

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Table 1
Remission rates (%) in an expanding cohort of newly diagnosed epilepsy.

Recruitment	N	Monotherapy	Polypharmacy	Total
1982–1997 [3]	470	61	3.0	64.0
1982–2001 [6]	780	59	5.4	64.4
1982–2005 [13]	1098	62	6.4	68.4
1982–2012 [17]	1795	55	9.0	64.0

Data taken from Refs. [3,6,13,17].

Table 2
Modern antiepileptic drugs licensed for adjunctive use for adult epilepsy in the United Kingdom and their dates of introduction.

Vigabatrin	1989
Lamotrigine[a]	1991
Gabapentin[a]	1993
Topiramate[a]	1995
Tiagabine	1998
Oxcarbazepine[a]	2000
Levetiracetam[a]	2000
Pregabalin	2005
Zonisamide[a]	2006
Lacosamide	2008
Eslicarbazepine	2009
Retigabine	2011
Perampanel	2012
Brivaracetam	2016

[a] Subsequently licensed for monotherapy in newly diagnosed epilepsy.

which initially bypassed the patient's general practitioner. Lastly, our epilepsy nurse specialists reviewed patients admitted to the emergency and general medical wards with untreated seizures or epilepsy. Appropriate investigations were arranged and rapid referral to our clinic was organised as appropriate. All clinical information available from these patients was included in our database.

A summary of top line outcomes in the 4 major analyses undertaken over the past 20 years is shown in Table 1. Seizure freedom was defined as having no seizures for at least the previous year. Each series of analyses will now be described in detail. Modern AEDs licensed for adjunctive use and as monotherapy in the UK for adolescents and adults during the time of all 4 analyses are listed in Table 2. Most of the analyses used the older classification of seizures and syndromes published in 1989 by the International League against Epilepsy (ILAE) [2]. The final analysis of 1795 newly diagnosed patients is ongoing and the paper has not yet been submitted for publication.

3. First analyses

The first set of analyses was undertaken in 1999 focusing on 470 previously untreated patients with newly diagnosed epilepsy (median age 29 years, range 9–93 years). The first outcome paper was published in the *New England Journal of Medicine* in 2000 and has now been cited more than 3000 times [3]. The headline results are outlined in Table 1. Most of the patients were originally referred by their primary care physicians with just 8% coming from the hospital accident and emergency department. Response to first, second or third AED schedule were 50%, 13% and 1% respectively. Only 3% of this patient population became seizure free on polypharmacy. Interestingly, among patients who did not respond to the first AED, the percentage who subsequently became seizure free was much smaller when failure was a consequence of lack of efficacy (11%) than due to poor tolerability (41%) or an idiosyncratic drug reaction (55%).

There was a significant linear trend in the proportion of patients with uncontrolled epilepsy relative to an increasing number of pre-treatment seizures ($p < 0.001$). Among the patients with inadequate seizure control on the first well tolerated AED, those who received a second monotherapy (n = 35; 17%) had similar seizure free rates to the those treated with duotherapy (n = 42; 26%) [4]. More of the latter patients became fully controlled when the combination involved a sodium channel blocker with a drug possessing multiple mechanisms of action (30%) compared with other combinations (7%, $p = 0.05$). Most of the patients attaining complete control of their seizures with their first AED did so at modest or moderate dosing [5]. The commonest daily dosage ranges were 400–600 mg for carbamazepine, 600–1000 mg for sodium valproate and 125–200 mg lamotrigine. Most withdrawals due to poor tolerability also occurred at or below these dose levels (carbamazepine 98%, sodium valproate 100%, lamotrigine 75%).

4. Second analyses

The second set of analyses involving 780 patients was undertaken in 2003 [6]. Overall, 64.4% of this population remained seizure free, with 5.4% controlled on 2 or more AEDs. Response rates with the first, second and third treatment schedule were 50.4%, 10.7% and 2.5%, respectively, with only 0.8% patients becoming seizure free with subsequent AED trials. The prognosis was marginally better in patients with idiopathic (n = 222, 66% seizure free) than cryptogenic (n = 314, 57% seizure free) or symptomatic (n = 244, 56% seizure free) epilepsies. Outcomes versus total pre-treatment seizure numbers, duration of epilepsy prior to starting treatment, and seizures reported in the 3 months before starting treatment are illustrated in Fig. 1. This last observation demonstrated a significant association with increasing seizure density ($p < 0.001$). This relationship was also observed with seizure numbers 6 and 12 months before the diagnosis of epilepsy was made and treatment started. Interestingly, total seizure numbers prior to treatment initiation did not predict outcome [6].

Prognosis appeared better in patients 65 years of age and above (85% remission, $p < 0.001$) and in adolescents (65% remission, $p < 0.01$), compared to the remainder of the population (55% remission) [6]. As before, seizure freedom was achieved with modest or moderate doses of the most commonly used AEDs in the majority of patients (Fig. 2) [7]. In patients failing initial monotherapy, subsequent response to a combination of 2 AEDs (27%) was no different from that with alternative monotherapy (32%).

Outcomes in the 558 patients with newly diagnosed focal epilepsies varied according to the underlying pathology (Table 3) [8]. Many patients in each category, including some with mesial temporal lobe epilepsy, had no further seizures after starting AED therapy. Patients with post-traumatic epilepsy had the worst outcomes (35% seizure free), while those with underlying cerebral atrophy (71% seizure free) or cerebrovascular disease (70% seizure free) did best. Remission rates in patients with cortical dysplasis (60%), hippocampal atrophy (50%) and primary brain tumours (52%) appeared little different from those with other focal epilepsies.

Of 118 patients with genetic generalized epilepsies, 64% achieved remission [9]. The seizure free rate with sodium valproate was superior to that with lamotrigine (66% versus 45%, $p = 0.073$), particularly in patients with juvenile myoclonic epilepsy (75% versus 39%, $p = 0.014$). Interestingly, a history of febrile convulsions was associated with a reduced likelihood of remission ($p = 0.032$) in this analysis.

In a separate analysis including all 780 newly diagnosed patients, a number of factors were predictive of pharmacoresistant

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