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Review Article

Treatment for epilepsy in later life

Martin J Brodie

Clinical and Research Director, Epilepsy Unit, Western Infirmary, Glasgow, Scotland, UK

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Summary

Old age is now the commonest time to develop epilepsy, often as a consequence of underlying cerebrovascular or neurodegenerative disease. Age-related physiological changes can affect the pharmacokinetics and pharmacodynamics of antiepileptic drugs. Only three double-blind, head-to-head, randomised, controlled trials have been undertaken in this patient population and so pharmacological treatment tends to be empirical, often based on what antiepileptic drug not to chose for an individual patient. The available evidence has tended to favour lamotrigine, and perhaps gabapentin, over carbamazepine, based on better tolerability rather than superior efficacy for newly diagnosed epilepsy in this population. Preliminary data with levetiracetam suggest that this drug will also be useful in older people as a consequence of its favourable side-effect profile and lack of idiosyncratic reactions and drug interactions. Despite the dearth of high quality trial evidence, published outcome data hint at a good prognosis with a single antiepileptic drug for the majority of elderly people with epilepsy. A few patients will require low dose combination therapy. Epilepsy surgery is also an occasional option in this population. As life expectancy rises, so will the likelihood of presenting with seizures in later life placing an increasing burden on healthcare resources.

Correspondence: Professor Martin J Brodie Epilepsy Unit, Western Infirmary, Glasgow G11 6NT, Scotland, UK
Tel +44-141-211-2534 Fax +44-141-211-2072 Email: mjb2k@clinmed.gla.ac.uk

Introduction

"And in the end, it's not the years in your life that count. It's the life in your years"

Abraham Lincoln, 1809-65

Abraham Lincoln did not live long enough to confirm the truth of his widely quoted aphorism. Never has this observation been more relevant than in the present day with many more people living long and healthy lives. One adverse consequence of this, however, is that old age is now the commonest time in life to develop epilepsy in high income societies [1].

Falls, faints and funny turns are all common reasons for older people to present to primary care, emergency departments and specialist hospital services. Some, but by no means all, will have epilepsy, which can be a difficult diagnosis to make with certainty [2]. The likelihood of developing seizures correlates better with biological than chronological age. Older people have a high prevalence of comorbidities, as well as of functional and cognitive impairment, all of which require recognition, evaluation and management [3]. In addition, age-related physiological changes can affect the pharmacokinetics and pharmacodynamics of antiepileptic drugs. The situation is compounded by a dearth of good clinical trials exploring the choice of treatment for this increasingly common problem.

Because of the range of possible differential diagnoses, older people can be reviewed by general physicians and geriatricians as well as by neurologists and cardiologists, and so the necessary expertise for appropriate investigation and management is often diluted across a range of clinical disciplines [4]. With the continuing ageing of the world's population, the number of older people with epilepsy is set to rise further, placing an increasing burden on healthcare resources.

Pharmacology of old age

Age-related changes in the function and composition of the human body require adjustments of drug selection and dosage for older individuals [5]. The differences in the pharmacokinetics and pharmacodynamics of drugs depend on the physical status of the patient, the presence or absence of relevant comorbidities, and the influence of concomitant medicines [6]. In general terms, absorption, protein binding and hepatic drug metabolism are well preserved into old age, except in the frail and malnourished. Renal function progressively declines with age and attention needs to be taken to tailoring the doses of drugs that are excreted unchanged by the kidneys in line with creatinine clearance.

The pharmacodynamics of drug use in the elderly provides a more complex series of challenges [7]. The brain is an especially sensitive pharmacological target in older people. One of the characteristics of the ageing process is a progressive decline in counter-regulatory (homoeostatic) mechanisms. Thus, the rate and intensity of adverse effects tend to be higher supporting the premise of "start low and go slow" in prescribing successfully for this population [8]. In addition, some drugs can lower the seizure threshold [9]. Antidepressants, antipsychotics and antibiotics are most commonly implicated in this scenario.

The herbal remedy, ginkgo biloba, can also precipitate seizures in older people [10].

The cognitive decline that commonly parallels the ageing process can exacerbate the situation with some elderly individuals becoming confused and forgetful about their prescribed medications. A policy of screening older people with suspected or proven epilepsy for cognitive impairment can be recommended, given the implications of the findings for diagnosis, treatment, and support of the patient and carers. Comorbidities and associated polypharmacy are frequent accompaniments of ageing and can complicate the diagnosis and treatment of epilepsy.

Drug interactions

Polypharmacy is the rule rather then the exception in older people, particularly when seizures are a consequence of cerebrovascular disease or neurodegenerative disorders. Treatment adherence typically declines, and the risk of drug-drug interactions increases, as the number of prescribed drugs rises. All older patients with epilepsy, therefore require careful review of their entire drug prescription by physicians competent to decide on the appropriateness and dosage of each drug.

Enzyme induction can be a particular problem for this patient population, since broad spectrum inducers such as phenobarbital, primidone (metabolised to phenobarbital), phenytoin and carbamazepine will increase the metabolism of a range of commonly prescribed drugs, including warfarin, cytotoxics, statins, cardiac antiarrhythmias, antihypertensives, corticosteroids and other immunosuppressants [11].

The effects of enzyme induction on endogenous substances, such as vitamin D and male sex hormones, can also have clinical implications by producing osteoporosis [12] and sexual dysfunction [13]. Fracture risk is increased due to the effects of chronic antiepileptic drug use on bone loss, seizures per se and drug-induced gait instability [12]. Bone density should be measured and preservation strategies put in place when epilepsy is diagnosed and treatment begun in an older person [14].

Drugs that can inhibit hepatic metabolic processes and thereby increase the circulating concentrations of antiepileptic and other drugs include sodium valproate, cimetidine, erythromycin, isoniazid, verapamil and diltiazem [15]. The primary targets for clinically relevant inhibitory interactions are carbamazepine, phenytoin and phenobarbital.

Important pharmacodynamic interactions producing hyponatraemia can occur when carbamazepine and oxcarbazepine are prescribed for patients established on a thiazide or other diuretics, or vice versa [16]. Sedation is more likely when an antiepileptic drug is introduced in patients already taking psychoactive agents such as benzodiazepines, antidepressants and antipsychotics. Similarly, care must be taken in prescribing carbamazepine and phenytoin in patients with defects in cardiac conduction.

Double-blind trials

Only three randomised, double-blind, comparative clinical trials have been undertaken in

older people with newly diagnosed epilepsy [17-19]. For the many reasons outlined by Ramsay and his colleagues, these are particularly difficult to recruit for and to complete [20]. However, it is essential that like is compared with like in this drug-sensitive population. Thus, equivalent titration schedules and maintenance doses of appropriate formulations need to be chosen for each arm of such a comparative trial.

In the first published study, lamotrigine was shown to be as effective as and much better tolerated than carbamazepine [17]. However, this difference was almost completely negated by substituting a controlled-release for the standard formulation of carbamazepine using an identical study design with similar treatment schedules [19]. Both of these were flexible dosing studies that targeted identical low daily maintenance doses of both drugs (carbamazepine 400 mg versus lamotrigine 100 mg). The major difference between the studies was in the median carbamazepine concentration, which was 6.9 mg/L with standard carbamazepine compared with 5.1 mg/L when a controlled-release formulation was employed. The median lamotrigine levels were almost identical (2.2 versus 2.3 mg/L) across the two studies.

In the Veterans administration study, lamotrigine, gabapentin and carbamazepine were compared using a randomised, double-blind design [18]. Seizure control was similar among the treatment groups. Carbamazepine was significantly less well tolerated than the other two drugs, which was perhaps not surprising given the lowish targeted maintenance daily doses of lamotrigine (150 mg) and gabapentin (1500 mg) compared to that of carbamazepine (600 mg daily). In addition and probably more importantly, a standard and not a controlled-release formulation of carbamazepine was employed in this trial producing higher peak concentrations. Discontinuation rates due to adverse events were 12% with lamotrigine, 22% with gabapentin and 31% with carbamazepine. These dosing issues explain the retention rates favouring lamotrigine and gabapentin over carbamazepine which was the primary end-point for the study.

Other pharmacological studies

There are a number of published studies reporting the use of other antiepileptic drugs in elderly patients. Open trials are available in support of lamotrigine [20], oxcarbazepine [21], and levetiracetam [22-25] in this population. A randomised comparison of low (50 mg/day) versus high (200 mg/day) dose topiramate in older people with partial onset seizures not surprisingly favoured the former regimen [26] and supported the results from a previous open study [27]. Overall, there is a trend away from using older antiepileptic drugs in this population, but this does not yet represent a substantial change in clinical practice [28].

Therapeutic strategies

The goal of management should be the maintenance of a normal lifestyle with complete control of seizures without (or with

minimal) side effects. Time needs to be taken to explain the diagnosis and, if relevant, the likely underlying cause of the epilepsy and the reason for treatment. The support and understanding of the patient's family and other caregivers is an essential component to a successful outcome. The word "epilepsy" has a particularly derogative connotation for some older people and may be better avoided in managing sensitive patients.

All elderly people reporting more than one well documented or witnessed unprovoked event should be offered antiepileptic drug treatment. Whether this should be started after a single seizure depends on the clinical circumstances and the patient's attitude. If the semiology of the seizure is consistent with the results of investigations, particularly focal abnormalities on brain imaging, it would be reasonable to add in a small dose of an antiepileptic drug to the other medications that the patient is likely to be taking for their coexistent cerebrovascular or degenerative brain disease.

The decision whether or not to start antiepileptic drug treatment should be made after ample discussion with the patient and family about the risks and benefits of both courses of action. Most older patients will have localisation-related epilepsy, although on rare occasions a primary generalised epilepsy syndrome will be diagnosed [29]. Pseudoseizures can also present in this population [30] and so accurate classification of the epilepsy is essential [31]. Trials of drug treatment when the diagnosis is unclear should be avoided whenever possible.

Older people are more likely than younger populations to develop idiosyncratic skin reactions with antiepileptic drugs, particularly following the introduction of phenobarbital, phenytoin, carbamazepine, lamotrigine, oxcarbazepine and zonisamide [32]. These can be life-threatening and so a history of a previous allergic reaction may be a good reason for avoiding an antiepileptic drug capable of producing a skin rash since cross reactivity is a common phenomenon in old age [33].

Drug choices

In addition to the established antiepileptic drugs phenobarbital, phenytoin, carbamazepine and sodium valproate, the newer agents lamotrigine, gabapentin, oxcarbazepine, topiramate and levetiracetam are all variously licensed in different countries for the initial treatment of newly diagnosed epilepsy. Their advantages and disadvantages for use in older people are summarised in Table 1. Also included in the table are the other available AEDs, which can be used as adjunctive therapy. There are no recognised differences in efficacy among all the AEDs for this indication [34-35]. Accordingly, choice will depend on the side-effect profile and the potential for drug interactions [36]. The best randomised trial evidence supports the use of lamotrigine as first-line treatment in older people [17-19]. Gabapentin is a possible alternative [18]. Levetiracetam may be an acceptable choice for some patients, since it appears to be well tolerated and devoid of interaction potential [22-25]. Slow titration to an initial maintenance of lamotrigine 50 mg

Table 1. Advantages and disadvantages of antiepileptic drugs in the elderly

Antiepileptic drugs	Advantages	Disadvantages
ESTABLISHED		
Phenobarbital	Broad spectrum Once daily Cheapest	Sedation Cognitive impairment Behavioural problems Enzyme induction Bone loss
Phenytoin	Once daily No titration Cheap	Sedation Allergic reactions Saturation kinetics Enzyme induction Bone loss
Carbamazepine	"Gold standard" for partial seizures Studied in elderly Relatively cheap	Neurotoxicity Allergic reactions Enzyme inducer Hyponatraemia Bone loss
Sodium valproate	"Gold standard" for generalised seizures Broad spectrum Rapid titration Few interactions Relatively cheap	Tremor Weight gain Enzyme inhibitor Parkinsonism Bone loss
MODERN		
Lamotrigine	Broad spectrum Good tolerability Few interactions Studied in elderly	Slow titration Dose-related rash Insomnia
Gabapentin *	No allergic reactions No interactions Studied in elderly	Sedation Dizziness Weight gain Thrice daily dosing
Topiramate	Broad spectrum Weight loss in obesity	Slow titration Cognitive impairment Renal stones
Oxcarbazepine	Good tolerability	Neurotoxicity Allergic rash Selective enzyme induction Hyponatraemia
Tiagabine *	Few allergic reactions Few interactions Broad spectrum	Dizziness Few data in elderly Thrice daily dosing
Levetiracetam	No allergic reactions No interactions Fast titration	Sedation Behavioural problems
Pregabalin *	No allergic reactions No interactions	Dizziness Weight gain Few data in elderly
Zonisamide *	Broad spectrum Once daily Weight loss in obesity No interactions	Slow titration Allergic rash Sedation Renal stones Behavioural problems Few data in elderly

* Licensed for adjunctive use only in the UK

twice daily, gabapentin 400 mg three times daily or levetiracetam 500 mg twice daily would be a reasonable starting point, since seizures will control on modest dosing in most older people [37].

If the first drug is not well tolerated, another should be rapidly substituted. If seizures continue despite increasing dosage, a drug with a different mechanism of action should be tried [36]. A few patients will respond to low dose combination therapy [38]. Surgical treatment for refractory epilepsy can also be an option for a few older people if the underlying pathological substrate is appropriate, although outcomes tend to be less good than in younger populations [39]. Pharmacological response to AEDs in old age appears to be better than in the general population according to the few published studies exploring this issue [4, 37, 40]. Treatment is usually lifelong given that any aetiological factors provoking the development of epilepsy in this age group are not likely to remit over the next few years of seizure freedom.

Lifestyle issues

Studies in the elderly are limited, but agree that the adverse consequences of the diagnosis of epilepsy are at least as important in this population as those occurring in younger people [41-43]. In later life, occupational impact is less frequently significant, but the social and functional effects are diverse. The occurrence of any event that causes falls, confusion or amnesia, including seizures, may erode confidence and contribute to social isolation if the individual becomes frightened of leaving the house alone or embarrassed about the prospect of an event happening in the presence of others. Driving restrictions may limit the ability of the patient and their spouse to retain their independence, and provoke further isolation for those individuals who are living alone. Many older people associate epilepsy with negative images of intellectual disability and poor seizure control that dominated their formative years, and so may be reluctant to share the problem with friends or accept the diagnosis [44]. Studies in elderly people with epilepsy suggest decreased mental status, a higher prevalence of depression and anxiety, and poorer sleep compared with age-mates without epilepsy [45]. Some of these features are likely to be a consequence of comorbidities relevant to the development of epilepsy. All these observations translate into poorer quality of life [46].

Conclusions

The development of epilepsy is common in later life. Prognosis in terms of seizure control may be better than in younger populations. The choice of antiepileptic drugs should focus on avoidance of side effects and adverse drug interactions, with the best available data supporting the use of lamotrigine, gabapentin and possibly levetiracetam. The objective should be complete control of seizures with enhanced quality of life using a modest dose of a single antiepileptic drug. Optimal management requires rapid assessment, accurate diagnosis, effective treatment, focused education, and sympathetic support for the increasing group of older people with epilepsy who often have

important co-morbidities and may already be taking a number of other medicines. A multidisciplinary approach will minimise the effects of epilepsy and its treatment on quality of life in this poorly studied but increasingly numerically important population.

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