

Epilepsy in later life

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Epilepsy is most likely to develop in later life. The burden of this disorder on health-care resources will rise further as the world's population continues to age. Making a secure diagnosis can be challenging because the clinical manifestations of seizures and the differential diagnoses and causes of epilepsy can be different in older individuals compared with younger individuals. Obtaining a reliable account of the events for accurate assessment is particularly important in guiding the appropriate choice and interpretation of investigations to arrive at the correct diagnosis. In older age, unique pharmacokinetic and pharmacodynamic changes occur. The use and selection of antiepileptic drugs is often further complicated by the presence of comorbidities, polypharmacy, and concomitant functional impairment, but there is a paucity of high-level clinical evidence on the effects of these factors as well as on the choice of treatment in the elderly. A comprehensive model of care should combine expertise in the diagnosis and treatment of epilepsy with effective assessment and management of the psychosocial effects to improve the prognosis in this vulnerable and poorly studied group of patients.

Introduction

Falls, faints, and “funny turns” (transient neurological attacks comprising focal, non-focal, or mixed neurological symptoms lasting less than 24 h)¹ are all common reasons for elderly people to present to primary care, emergency departments, and specialist hospital services. Some of these individuals, but by no means all, will have epilepsy, which can be a difficult diagnosis to make with certainty. The likelihood of developing seizures correlates better with biological age than with chronological age. Older people are more likely to have comorbidities, as well as functional and cognitive impairment, than younger individuals, which all require recognition, evaluation, and management.² Additionally, age-associated physiological changes can affect the pharmacokinetics and pharmacodynamics of antiepileptic drugs. The situation is exacerbated by a dearth of good clinical trials investigating 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, geriatricians, neurologists, and cardiologists, and so the necessary expertise for appropriate investigation and management is often diluted across a range of clinical disciplines.³ 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 health-care resources.

In this Review, we focus on people aged 65 years and older who develop late-onset epilepsy rather than patients who have epilepsy throughout their lives. We place particular emphasis on assessing the clinical clues that are essential for making an accurate diagnosis. We review the pharmacology of antiepileptic drug use in old age, highlighting the most common drug–drug interactions. We summarise the double-blind, randomised trials undertaken in the elderly and list the advantages and disadvantages of each antiepileptic drug in this population. We also review the implications of common comorbidities on the management of late-onset epilepsy. Finally, we propose appropriate models of care and

approaches to minimising the effects of epilepsy and its treatment on quality of life in this poorly studied population.

Epidemiology

As the world's population increases and ages, so will the prevalence of epilepsy. Compared with younger individuals, elderly people are more likely to develop seizures, whether provoked by acute illness or without an obvious precipitating cause.⁴ The annual incidence of epilepsy (recurrent unprovoked seizures) rises from 85·9 per 100 000 people in those aged between 65 and 69 years to more than 135 per 100 000 people for those aged older than 80 years compared with an overall incidence of 80·8 per 100 000 people across all age-groups.⁵ Elderly people with epilepsy have 2–3 times greater mortality than the general population.⁶ Additionally, 30% of acute seizures in elderly people present as status epilepticus, which carries a sizeable mortality of about 40%.⁷ Lastly, late-onset seizures are a predictor of subsequent stroke.⁸

Causes

The reported prevalence of specific causes of epilepsy in older people varies depending on the study populations, definitions, investigation strategies, and the presence of underlying pathological changes.^{9–15} In practice, at least in high-income countries, common causes that should be specifically considered in patients with late-onset epilepsy include cerebrovascular disease, primary neurodegenerative disorders associated with cognitive impairment (particularly Alzheimer's disease), intracerebral tumours, and traumatic head injury.¹⁶

Cerebrovascular disease

Stroke is the most important risk factor for the development of subsequent epilepsy in older people and can account for up to 50% of cases in whom a cause can be identified. The risk of epilepsy increases up to 20-fold in the first year after a stroke.¹⁷ Epilepsy is more likely to complicate strokes that involve the cortex, are haemorrhagic, are large, are multiple, or present with acute symptomatic

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seizures.¹⁸ Cerebrovascular disease probably accounts for a proportion of seizures labelled as cryptogenic given the many vascular risk factors in older patients with epilepsy but who have not had previous stroke¹⁹ and the high number of cases of clinically unsuspected stroke identified on brain imaging.²⁰ Indeed, there seems to be a bidirectional association between epilepsy and cerebrovascular disease in older people, with the risk of stroke increased by nearly three-fold in those who develop late-onset seizures.⁸ Therefore, any elderly person developing new-onset seizures should undergo assessment for the presence of cerebrovascular risk factors and be treated accordingly for stroke prevention.

Primary neurodegenerative disorder associated with cognitive impairment

Patients with Alzheimer's disease are up to ten times more likely to develop epilepsy than those without

Alzheimer's disease,^{21,22} and dementia and neurodegenerative disorders are estimated to account for 10–20% of all epilepsies in older people.²³ Although data from most studies suggest that epilepsy is more likely to develop in more advanced disease, seizures can occur at any stage of the degenerative process.²³ In a prospective study of 453 patients with mild Alzheimer's disease, 2% had an unprovoked seizure by 5 years of follow-up, an 8-fold increase compared with the general population, with greater risk in younger patients.²⁴ Seizure control does not seem to be more difficult as dementia progresses, although recognition of the occurrence of seizure activity might be more challenging and the long-term effect of epilepsy on cognition or subsequent neurodegeneration is unknown.²⁵

Trauma

Head injury, predominantly due to falls, has a higher occurrence and poorer prognosis in older people than in younger individuals,²⁶ and up to 20% of cases of epilepsy in the elderly can be attributed to trauma.²⁷ Results from a recent study of children and young adults suggested that although the risk of developing epilepsy was highest during the first years after the injury, this risk remained elevated for more than 10 years compared with people without such a history.²⁸ Brain contusion with subdural haematoma, skull fracture, loss of consciousness or amnesia for more than 1 day, and an age of 65 years or older have been identified as risk factors for subsequent epilepsy.²⁹

Tumours

Between 10% and 30% of seizures are associated with tumours, typically gliomas, meningiomas, and brain metastases.^{9,30} Seizures are more commonly seen in association with primary rather than secondary tumours and with low-grade tumours rather than high-grade primary tumours.³¹

Acute symptomatic seizures

Drug treatment, acute metabolic disturbance, and infection can precipitate acute symptomatic seizures, and these problems and perhaps sleep apnoea³² can lower the seizure threshold in patients with established epilepsy. New seizures can also be precipitated by acute stroke or head injury.¹³ Although the risk of the development of epilepsy is increased in any patient with an acute symptomatic seizure, not all will subsequently develop epilepsy.

Presentation and diagnostic evaluation

Epilepsy is both underdiagnosed and overdiagnosed in older patients. About 30% of patients who are ultimately diagnosed with epilepsy do not have this diagnosis considered at first evaluation¹⁴ and some patients, particularly those not referred to a specialist epilepsy service, probably remain undiagnosed.³³ Additionally,

Panel 1: Possible reasons for the misdiagnosis of epilepsy in elderly people

Epilepsy falsely diagnosed

- Inappropriate use of a trial of antiepileptic drug treatment and inadequate follow-up of the result of such treatment
- Poor awareness that myoclonus or other abnormal movements can occur in convulsive syncope
- Incorrect assumption that incontinence during an event occurs only in epilepsy
- Inappropriate reliance on interictal electroencephalographic findings
- Limited, vague, or incomplete history (incomplete history taking, cognitive impairment, no witnesses available)
- Little knowledge of features that distinguish epilepsy from other disorders
- Failure to involve specialist physicians in diagnostic process

Epilepsy falsely excluded or missed

- Under-reporting of events by older patients or their carers³⁴
- Overdiagnosis of simple falls as a cause of recurrent events when patient is uncertain if loss of consciousness occurred
- Overdiagnosis of transient ischaemic attacks, particularly if there is a previous history of transient ischaemic attack or stroke³⁵
- Overdiagnosis of syncope due to high prevalence, false positive rate of findings in ambulatory electrocardiographic monitoring, or provocative cardiovascular tests such as tilt table testing or carotid sinus massage, or failure to identify a link between such findings and symptoms seen in the patient³⁶
- Clinical features of complex partial seizures less likely to be typical in older people³⁷
- Limited, vague, or incomplete history (incomplete history taking, cognitive impairment, no witnesses available)
- Little knowledge of features that distinguish epilepsy from other disorders
- Failure to involve specialist physicians in diagnostic process

some patients seen at such clinics, some of whom will already be on antiepileptic treatment, will have an alternative explanation for their events. The extent of misdiagnosis is, however, unclear and the true prevalence of epilepsy in older people therefore remains difficult to determine with certainty.

Potential reasons for the misdiagnosis of epilepsy in older patients are given in panel 1. Differentiating between epilepsy, syncope, and other common causes of “turns” in the elderly can be challenging and remains highly dependent on the clinical history and a witnessed event. Many publications focus on the clinical features that are useful in establishing or refuting a diagnosis of syncope rather than on making a diagnosis of epilepsy, with little information specifically relating to clinical features presenting in older people. The situation is compounded by the common coexistence of cognitive impairment, which makes obtaining an accurate history from the patient more difficult. Witnessed accounts are said to be less common in older people, who often live alone. Several clinical scenarios, outlined in panel 2, should prompt consideration of the possibility that an older person might have epilepsy.³⁸ When epilepsy is thought possible after any of these events in an elderly person, we suggest the diagnostic steps that are listed in panel 3; key questions for patients and witnesses are given in table 1.

Falls without impairment or loss of consciousness

Figure 1 provides a simple flowchart for approaching the assessment of falls in older people. In practice, the initial diagnostic challenges often involve the determination of whether the event was a simple fall, particularly if it was unwitnessed, and whether there is cognitive impairment or retrograde amnesia compromising recall reliability. If transient impairment or loss of consciousness can be confidently excluded, drop attacks or simple falls are more likely. However, if falls occur frequently and impairment or loss of consciousness cannot be ascertained, the patient should be investigated for possible syncope or epilepsy.

Falls with impairment or loss of consciousness

If transient impairment or loss of consciousness can be confidently established, the primary differential diagnosis lies between syncope and epilepsy. However, given the high occurrence of cardiac diseases in older people, particularly those that affect the conducting system and cardiac outflow such as aortic stenosis, evidence of their presence should not exclude further consideration of possible coexistent epilepsy.

Seizures in older people are sometimes atypical. Auras are less commonly reported, and symptoms and signs can be non-specific. Automatisms can be less frequent, and postictal confusion can be more prolonged, lasting up to days.^{14,39,40}

The presence of abnormal movements in the form of myoclonic jerking during syncope can result in over-

Panel 2: Clinical clues to the diagnosis of epilepsy in elderly people

- Confusion, behavioural change, or unresponsiveness not associated with loss of postural control
- Loss or impairment of consciousness
- Twitching, involuntary movement, or sensory disturbance of a limb, limbs, or face without loss of consciousness
- Recurrent episodes of troublesome sleep disturbance
- Frequent falls about which the patient has no recollection

Panel 3: Suggested diagnostic steps when epilepsy is suspected in an elderly patient

1 Consider whether cognitive impairment is present

This factor is important, as cognitive impairment might compromise history taking, have implications for the investigation and selection of treatment, and, if unrecognised, confound subsequent assessment of the adverse events of treatment. Simple screening with a standardised tool such as the mini-mental state examination is recommended.

2 Establish whether any events have been witnessed

If so, take a detailed history from the witness as soon as possible after the event. If an event or events have been unwitnessed and the diagnosis is unclear, educate those who might witness future attacks on the key clinical features to note³⁸ (table 1). If the patient is in a residential care setting, appropriately trained staff should be asked specifically to take the pulse at the time of an event.

3 Establish the form of the event

Generally, event history might be dominated by the patient falling down with or without loss of consciousness or by abnormal behaviour, confusion, or focal neurological features. Overlap might be present in some cases. If recurrent events take different forms, consider the possibility of more than one cause. Epilepsy is often stereotyped with a specific semiology being seen in an individual patient. Episodes are unlikely to be ictal when dizziness is the dominant clinical feature with or without an associated fall or when true vertigo is followed by a fall without loss of consciousness. A clear picture should include details of what happened before, during, and after the event.

diagnosis of epilepsy and, less commonly, syncope might precipitate generalised seizure activity, causing diagnostic uncertainty.⁴¹ A summary of clinical features that might aid in the differentiation between seizures and syncope is provided in table 2.^{39,42} A scoring system based on common clinical features has been proposed to distinguish syncope from seizures with a high degree of accuracy.⁴²

In addition to obtaining a careful history, further investigation via physical examination, focusing particularly on the cardiovascular and nervous systems,

Ask the patient	Ask the witness
What were you doing at the time?	What was the patient doing at the time?
Did you get any warning?	Did you notice or did the patient complain of anything before the event happened?
Did you "black out"? If so, for how long?	Did they lose consciousness, have altered responsiveness, or seem unaware of your presence? If so, for how long did this last?
What happened afterwards?	Were they still or did they jerk, twitch, or move?
Do you take any medications and have any been changed recently?	What happened after the event?
Was there a witness?	Did anyone try to take the pulse?

Adapted from "Epilepsy in later life—a good practice guide",³⁸ with permission from Epilepsy Scotland.

Table 1: Key questions for elderly patients and witnesses when assessing a suspected epileptic seizure

and 12-lead electrocardiogram (ECG) are mandatory. In many cases, a clear diagnosis can be rapidly made. In some patients, further investigations will be required. The aim of these additional examinations should be to either confirm or exclude a positive diagnosis of epilepsy, or make or exclude a positive diagnosis of an alternative cause for the events, particularly syncope.

Confirming or excluding epilepsy

The interictal electroencephalogram (EEG) is of limited diagnostic value in older people owing to the high occurrence of non-specific abnormalities. EEG should not be used as a diagnostic test in patients with clinical histories that are uncertain or more suggestive of syncope. In a series of elderly patients with possible epilepsy, McBride and colleagues⁴³ detected interictal epileptiform discharges in 26% of patients with non-epileptic events and in 75% of those with epilepsy by use of video-EEG recording. Therefore, the interictal EEG has a low sensitivity and specificity in this age-group and should not be used to prove or disprove the diagnosis of epilepsy.

Patients with definite epilepsy or recurrent events of uncertain aetiology should undergo brain scanning to detect structural epileptogenic pathological changes. MRI is usually the preferred modality in this setting.⁴⁴ In elderly people, brain imaging will frequently indicate evidence of small vessel or white matter changes, previously unrecognised cerebral infarction, or other unsuspected structural abnormalities such as a meningioma. The presence of such abnormalities does not necessarily prove that an event was an epileptic seizure.

Videotelemetry is not widely available, but can be particularly useful if recurrent atypical events occur or when their frequency is high.⁴⁵ In such situations, this investigation can lead to a rapid differentiation between epileptic and non-epileptic events.⁴³

Confirming or excluding syncope

Most of the key cardiovascular investigations used in evaluating a possible diagnosis of syncope are associated with a high degree of false positives in older patients.⁴⁶

For example, detection of asymptomatic arrhythmias or other abnormalities on the ECG or echocardiogram, as well as positive responses to provocative tests such as carotid sinus massage and tilt table testing, are not uncommon. Finding abnormal test results, therefore, does not necessarily prove the diagnosis of syncope or exclude the diagnosis of epilepsy. False-negative results can also occur, particularly in time-limited ambulatory ECG recording. If syncope seems likely from the clinical event history, but initial 24–48 h ambulatory ECG monitoring does not capture an event, more prolonged recording should be undertaken, perhaps with implantable loop recording. All positive test results must be correlated with the history and their significance depends on whether or not the patient's typical symptom complex occurred or was reproduced during the test. When there is a difficult or unclear history, a firm diagnosis of syncope should not be made unless a recorded arrhythmia is shown to be associated with the patient's symptoms or an episode precipitated by a provocative test such as tilting accurately replicates the patient's event or events.

Confusional states

Prolonged confusion might be a feature of the ictal or post-ictal phases in older patients with epilepsy. Abrupt and transient confusion should always prompt consideration of atypical complex partial seizures. Such confusional states can be particularly difficult to recognise in patients with pre-existing dementia, in whom fluctuations in consciousness might be regarded as part of the primary disease process.²³ Patients with delirium can have myoclonus or asterixis, causing further diagnostic difficulty. To make matters worse, delirium and seizure activity can coexist and share the same causative factors.

Non-convulsive status epilepticus poses a particular diagnostic challenge in older people and should be considered as a cause of unexplained coma⁴⁷ or confusional state even when there is no past history of epilepsy.⁴⁸ Because of the lack of overt motor features, diagnosis is often delayed, although an alteration in mental state is the hallmark feature.⁴⁹ A high degree of suspicion and an early EEG is required for prompt recognition of non-convulsive status epilepticus.⁴⁸

Memory symptoms or hallucinations

Several disorders with paroxysmal loss of consciousness or other episodic neurological symptoms can be confused with epilepsy.⁵⁰ For example, transient global amnesia is characterised by abrupt-onset anterograde amnesia usually lasting 1–12 h with repetitive questioning in the absence of clouding of consciousness or other neurological signs or symptoms.⁵¹ This type of amnesia usually occurs as an isolated event and recurrence is uncommon.⁵² Transient global amnesia should be distinguished from complex partial seizures, during

which consciousness is impaired, and from transient epileptic amnesia, which usually lasts less than 1 h and frequently recurs.⁵³

Migraine with visual auras can be confused with occipital seizures. This is particularly the case when, during the process of ageing, a migraine attack loses the headache element, so that only (visual) aura symptoms remain.⁵⁴ Migraine and epilepsy are increasingly recognised as being genetically interrelated.⁵⁵ The two disorders often coexist,⁵⁶ although new-onset migraine in an elderly person is uncommon.⁵⁴

Focal neurological symptoms

Misinterpretation of focal neurological symptoms can lead to misdiagnosis of epilepsy for cerebrovascular events, and vice versa. In general, symptoms associated with transient ischaemic attacks involve loss of function. Knowledge of the duration of focal symptoms might be helpful, with a shorter duration (less than 5 min) being more suggestive of epilepsy than transient ischaemic attack.⁵⁷ Additionally, loss of consciousness is an uncommon feature of a transient ischaemic attack. A diagnosis of transient ischaemic attack that has been based on an episode of change in awareness or positive focal neurological symptoms should, therefore, be regarded with caution.

Sleep disorders

Rapid eye movement sleep behaviour disorder is a type of parasomnia that usually presents in men older than 60 years of age and that features kicking, shouting, or swearing during vivid dreams.⁵⁸ This sleep disorder might be difficult to distinguish from nocturnal frontal lobe seizures, which arise exclusively out of sleep and feature violent movements, vocalisation, and automatisms. However, episodes of this sleep disorder tend to occur in isolation in the second half of sleep, whereas nocturnal frontal lobe seizures usually begin in childhood and often cluster in the first 30 min of (stage 2) sleep. Periodic leg movements and restless leg syndrome are other parasomnias that are common in old age and that need to be considered in the differential diagnosis of nocturnal motor events.⁵⁹ A sleep study with concurrent video-EEG monitoring might be required to distinguish epileptic seizures from sleep disorders.

Treatment

Pharmacology in old age

Age-associated changes in the function and composition of the human body require adjustments in drug selection and dosage for older individuals.⁶⁰ 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 effect of concomitant medicines.⁶¹ Generally, absorption, protein binding, and hepatic drug metabolism are not altered in old age, except in those who are frail or malnourished.

Renal function progressively declines with age and care must be taken when tailoring the doses of drugs that are excreted unchanged by the kidneys in line with impairment in creatinine clearance (which affects drug elimination rates). Thus, lower doses need to be used in patients with moderate to severe renal failure.

The pharmacodynamics of drug use in the elderly provides a more complex series of challenges.⁶² The brain is a particularly sensitive pharmacological target in old age. One of the characteristics of the ageing process is a progressive decline in counter-regulatory (homeostatic) mechanisms. Thus, the rate and intensity of adverse events tend to be higher in the elderly, supporting the essential premise of “start low and go slow” in prescribing successfully for these patients.⁶³ Some drugs can lower the seizure threshold,⁶⁴ particularly antidepressants, antipsychotics, and

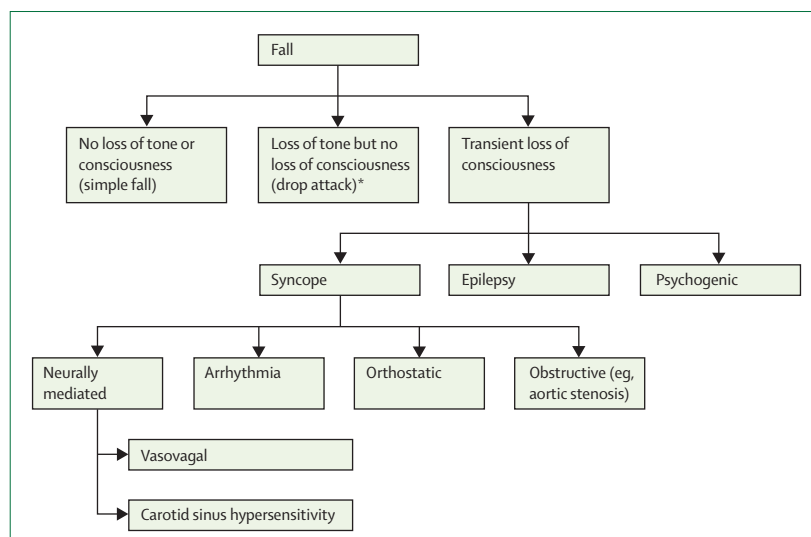


Figure 1: A flowchart approach to the assessment of falls in older people

*Drop attacks might be caused by atonic seizures, vertebrobasilar transient ischaemic attacks, or vestibular pathology; if recognised, these attacks should be assessed to exclude each of these pathologies.

	Syncope more likely	Epilepsy more likely
Before	<ul style="list-style-type: none"> Events occur exclusively in the upright position Events occur consistently in association with micturition, coughing, or defaecation The prodrome is dominated by dizziness, nausea and vomiting, or sweating Events precipitated by emotional stimuli (eg, pain, fear) 	<ul style="list-style-type: none"> Aura (eg, smell) Events occur in various positions, postures, or circumstances Events occur exclusively during sleep
During	<ul style="list-style-type: none"> Facial pallor Myoclonic jerking A reliable witness history describes a “fall down, lie still” event 	<ul style="list-style-type: none"> Turn of the head at onset of lateralised movements, or chewing or lip smacking Tonic-clonic movements Events follow a similar pattern on each occasion (stereotyped)
After	<ul style="list-style-type: none"> Nausea and vomiting Confusion or amnesia that lasts less than 1 h 	<ul style="list-style-type: none"> Facial cyanosis, suffusion, bitten lateral tongue, or headache and myalgia suggest generalised seizure Confusion or amnesia that lasts more than 1 h

Adapted from “Epilepsy in later life—a good practice guide”,³⁸ with permission from Epilepsy Scotland.

Table 2: Clinical features that might aid differentiation of syncope and epilepsy in elderly people

antibiotics. The herbal remedy ginkgo biloba can also precipitate seizures in older people.⁶⁵

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. This problem is compounded by the high rate of polypharmacy in this population.¹⁴ 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.

Comorbidities and drug–drug interactions

Comorbidities and associated polypharmacy are frequent accompaniments of ageing and can complicate the diagnosis and treatment of epilepsy. Some clinical implications of common comorbid conditions are listed in table 3. Cognitive impairment is increasingly common and merits particular attention. In one study, almost a third of older patients with epilepsy, who had not been known to have cognitive dysfunction at presentation, were found to have impaired cognition on subsequent testing.¹⁴ A policy of screening older people with suspected or proven epilepsy for cognitive impairment can be justified, given the implications of the findings for diagnosis, treatment, and support of the patient and carers.

Polypharmacy is the rule rather than the exception in older people, particularly when seizures are a consequence of cerebrovascular disease. In one study of older patients with epilepsy, a quarter were taking 15 or more prescribed medications (with a mean of seven drugs).¹⁴ Treatment adherence typically declines and the risk of drug–drug interactions increases as the number of prescribed drugs rises.

Enzyme induction can be a particular problem for these patients as broad-spectrum inducers, such as phenobarbital, primidone (metabolised to phenobarbital),

phenytoin, and carbamazepine, increase the metabolism of many commonly prescribed drugs, including warfarin, cytotoxics, statins, cardiac antiarrhythmias, anti-hypertensives, corticosteroids, and other immunosuppressants.⁶⁶ Switching to a drug that does not cause enzyme induction can be problematic as the concentrations of all concomitant drugs metabolised by the relevant liver enzymes will rise, leading to an increased risk of toxicity.

The effects of enzyme induction on endogenous substances, such as vitamin D and male sex hormones, can also have long-term clinical implications by causing osteoporosis⁶⁷ and sexual dysfunction.⁶⁸ In one study, fracture risk was slightly increased (odds ratio 1.21; 95% CI 1.14–1.28 for any fracture) owing to the effects of long-term antiepileptic drug use on bone loss, seizures, and drug-induced gait instability.⁶⁷ Bone density should be measured and preservation strategies put in place when epilepsy is diagnosed and treatment begun.⁶⁹

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.⁷⁰

Important pharmacodynamic interactions that cause hyponatraemia can occur when carbamazepine and oxcarbazepine are prescribed for patients established on a thiazide or other diuretic drugs, or vice versa.⁷¹ The risk of clinically significant hyponatraemia (<125 mmol/L) is greater with oxcarbazepine than with carbamazepine.⁷² Unpleasant sedation is more likely when an antiepileptic drug is introduced in patients already taking psychoactive drugs, such as benzodiazepines, antidepressants, and antipsychotics. Similarly, care must be taken in prescribing carbamazepine and phenytoin in patients with defects in cardiac conduction.

Randomised and other clinical trials

Only three randomised, double-blind, comparative clinical trials have been undertaken in older people with newly diagnosed epilepsy.^{73–75} For the many reasons outlined by Ramsay and colleagues,¹⁴ these trials are particularly difficult to recruit for and to complete. However, like must be compared with like in this drug-sensitive population and so titration schedules and maintenance doses must be equivalent for each antiepileptic drug.

In one study, lamotrigine was as effective as and much better tolerated than carbamazepine.⁷³ However, this difference was almost completely negated by substituting a controlled-release formulation for the standard formulation of carbamazepine using an identical study design.⁷⁵ Both of these studies had a flexible dosing design that involved identical low daily maintenance doses of both drugs (carbamazepine 400 mg vs lamotrigine 100 mg). The major difference between the studies was the median carbamazepine concentration, which was 6.9 mg/L with

	Implication	Action
Dementia	Treatment adherence might be compromised Seizure frequency might be difficult to monitor Patient education might not be possible	Consider routine screening in all older patients with new or suspected epilepsy Assess indication for drug treatment of dementia Review supervision of medication intake Provide appropriate carer training
Stroke	Risk of first or further stroke increased	Address vascular risk factors
Osteoporosis	Some antiepileptic drugs (eg, phenytoin, carbamazepine) increase rate of bone loss Possible increased risk of bone injury during events	Consider pharmacological bone protection
Chronic renal disease	Altered elimination of some antiepileptic drugs	Review antiepileptic drug use
Diabetes mellitus	Hypoglycaemia might lower seizure threshold	Review control and monitoring of plasma glucose
Frailty	General physical function impaired	Assess mobility (eg, rise from the floor unassisted after an event) Review need for safety alarm

Table 3: Common comorbidities and their clinical implications in elderly patients with epilepsy

the standard carbamazepine formulation compared with 5.1 mg/L when a controlled-release formulation was used. The median lamotrigine concentrations were almost identical (2.2 vs 2.3 mg/L) across the two studies.

In the Veterans administration study,⁷⁴ lamotrigine, gabapentin, and carbamazepine were compared using a randomised, double-blind design. Seizure control was similar among the treatment groups. Carbamazepine was significantly less well tolerated than the other two drugs. The relative maintenance doses of lamotrigine and gabapentin were lower than that of carbamazepine, but the use of a standard rather than a sustained-release formulation was probably the main reason for the differences in tolerability among the drugs. Discontinuation rates due to adverse events were 12% with lamotrigine, 22% with gabapentin, and 31% with carbamazepine. These dosing schedules explain the retention rates (figure 2) in favour of lamotrigine and gabapentin, which was the primary endpoint for the study.⁷⁴

There are surprisingly few published data reporting the use of other antiepileptic drugs in elderly patients. Open studies are available in support of lamotrigine,⁷⁶ oxcarbazepine,⁷⁷ and levetiracetam⁷⁸⁻⁸¹ in this population. A randomised comparison of low-dose (50 mg/day) versus high-dose (200 mg/day) topiramate in older people with partial-onset seizures favoured the low-dose regimen⁸² and supported the results from a previous open study.⁸³ Overall, there is a trend away from the use of older antiepileptic drugs in this population, but this pattern does not yet represent a substantial change in clinical practice.⁸⁴

Drug choices and 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 and the need 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" can have derogative connotations for some older people and might be better avoided if the patient seems particularly sensitive about the diagnosis.

All elderly people who report more than one well documented or witnessed unprovoked event should be offered antiepileptic drug treatment. Whether this approach should be started after a single seizure depends on the clinical circumstances and the patient's attitude. Old age was found to be a significant predictor of seizure recurrence by the FIRST Seizure Trial Group.⁸⁵ Thus, if the semiology of the seizure is consistent with the results of investigations, particularly focal abnormalities on brain imaging, addition of a small dose of an antiepileptic drug to the other medications that the patient might be taking for a coexistent disorder such as cerebrovascular or degenerative brain disease would be reasonable.

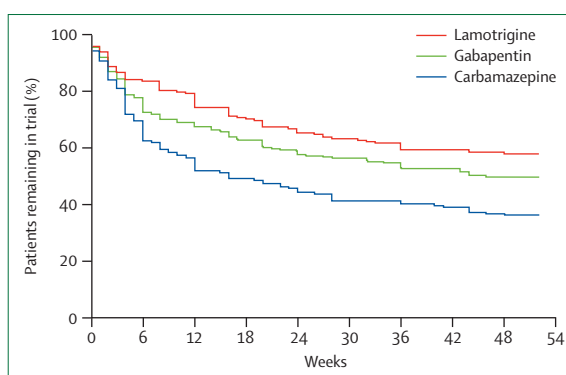


Figure 2: Percentage of patients remaining in the Veterans administration study over time (52 weeks)

In paired group comparisons, elderly patients randomly assigned to receive monotherapy with carbamazepine (n=197) were less likely to remain on treatment than were those who were randomly assigned to receive gabapentin (n=194; p=0.008) or lamotrigine (n=199; p<0.0001). Reproduced from Rowan and colleagues,⁷⁴ with permission from Lippincott Williams & Wilkins.

Limiting the loss of a driving licence to just 1 year (in the UK) for an older person might be another reason for choosing to start treatment after a single witnessed seizure. There is no indication for the long-term prophylactic use of antiepileptic drugs in elderly patients who have a severe traumatic head injury⁸⁶ or who have been diagnosed with a cerebral neoplasm.⁸⁷

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 a primary generalised epilepsy syndrome will be diagnosed on rare occasions.⁸⁸ Pseudoseizures can also present in this population⁸⁹ and so accurate classification of the epilepsy is essential.⁹⁰ 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 with phenobarbital, phenytoin, carbamazepine, lamotrigine, oxcarbazepine, and zonisamide.⁹¹ These adverse events can be life threatening; therefore, history of a previous allergic reaction might be a good reason to avoid an antiepileptic drug that can produce a skin rash as cross-reactivity is a common event in old age.⁹²

In addition to the established antiepileptic drugs (phenobarbital, phenytoin, carbamazepine, and sodium valproate), the newer drugs (lamotrigine, gabapentin, oxcarbazepine, topiramate, and levetiracetam) are all variously licensed in different countries for the treatment of newly diagnosed epilepsy. Their advantages and disadvantages for use in older people are summarised in table 4. There are no recognised differences in efficacy among all the available drugs for the treatment of newly diagnosed epilepsy.^{93,94} Choice will accordingly depend on the side-effect profile and

	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 induction Hyponatraemia Bone loss
Sodium valproate	Gold standard for generalised seizures Broad spectrum Rapid titration Few interactions Relatively cheap	Tremor Weight gain Enzyme inhibition Parkinsonism Bone loss
Modern		
Lamotrigine	Broad spectrum Good tolerability Few interactions Studied in elderly	Slow titration Dose-associated 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. Adapted from Brodie and Kwan,² with permission from the BMJ Publishing Group.

Table 4: Advantages and disadvantages of antiepileptic drugs in the elderly

the potential for drug interactions.⁹⁵ The best randomised trial evidence supports the use of lamotrigine as first-line treatment in older people.⁷³⁻⁷⁵ Levetiracetam might be a suitable alternative for some patients, as this drug seems to be well tolerated and devoid of interaction

potential.⁷⁷⁻⁸⁰ Slow titration to an initial maintenance of lamotrigine 50 mg twice daily or levetiracetam 500 mg twice daily would be a reasonable starting point as seizures will be controlled with modest dosing in most older people.⁹⁶

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.⁹⁵ The diagnosis of neurotoxicity (eg, dizziness, unsteadiness, tremor), commonly associated with antiepileptic drug therapy, can be problematic in the context of concomitant cerebrovascular disease or dementia in a patient established on a range of other medicines. If an antiepileptic drug is suspected to have caused neurotoxicity, a small decrease in dosage might clarify the situation. These neurological symptoms can present at low doses in older people. A few patients will respond to low-dose combination therapy.⁹⁷ Surgical treatment for refractory epilepsy can also be an option for a few older people if the underlying pathological substrate is appropriate.⁹⁸

According to the few published statistics on this matter, elderly patients with epilepsy seem to have better outcomes with pharmacological treatment than younger patients with epilepsy.^{3,96,99} Treatment is usually lifelong as any causative factors provoking the development of epilepsy in old age are not likely to remit over the next few years of seizure freedom.

Lifestyle factors

There are few studies in the elderly, but the data from all indicate that the adverse consequences of a diagnosis of epilepsy are at least as important in this population as those occurring in younger people.¹⁰⁰⁻¹⁰² In later life, the effect on occupation is less frequently important, but the social and functional effects are diverse. The occurrence of any event that causes falls, confusion, or amnesia (including seizures) might 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 might limit the ability of the patient and their spouse to retain their independence, and provoke further isolation for those who are already living alone. Many older people associate epilepsy with negative images of intellectual disability and poor seizure control that dominated their formative years, and so might be reluctant to share the problem with friends or accept the diagnosis of epilepsy. Data from studies of elderly people with epilepsy suggest decreased mental status, a higher prevalence of depression and anxiety, and poorer sleep compared with peers of a similar age who do not have epilepsy.¹⁰³ Some of these features are likely to be a consequence of comorbidities relevant to the development of epilepsy. All of these factors translate into a poorer quality of life.¹⁰⁴

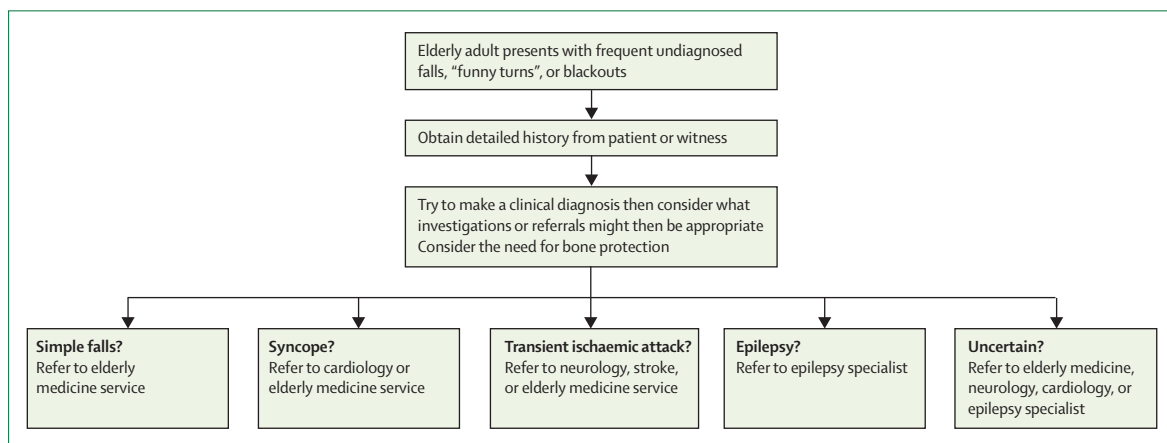


Figure 3: Model pathway for primary-care diagnosis of epilepsy in elderly people

It is important to remember that a clear clinical diagnosis can be very difficult to make. If one suspected condition is excluded and events continue, reconsider the history and make a referral for an alternative specialist opinion. The need for referral or investigation will depend on patient preference, frequency of events, effect of events on quality of life or function for the patient, and extent of suspicion of identifying a remediable cause. Investigations are most useful to confirm a diagnosis made first from the clinical history or when there is diagnostic doubt; they are more likely to confirm other causes of symptoms than prove epilepsy, and false-positive investigation results are more common in elderly people. Adapted from "Epilepsy in later life—a good practice guide",³⁸ with permission from Epilepsy Scotland.

Models of care

The early involvement of specialist physicians with an interest in epilepsy should improve diagnostic accuracy. Primary care or general physicians should be encouraged to refer patients with "turns" to such specialist services early, and specialists should refer among themselves, for example, between neurovascular and syncope services in cases of diagnostic doubt or in the face of several negative investigations. Local specialist availability will determine referral patterns and various care pathways have been suggested.^{46,105} Figure 3 outlines one such pathway specifically for older people presenting with unexplained events in primary care.³⁸

Given the increasing prevalence of many chronic diseases, older patients often have at least one other comorbidity that affects their management. Epilepsy, therefore, might not necessarily cause the greatest functional effect or symptomatic problem. Investigation and treatment should always be considered in the context of the patient's overall health status. Additionally, some patients will have unidentified or unaddressed functional and support needs at the time of their presentation with "turns" or definite epilepsy. The management of older people with proven or suspected epilepsy should focus on (i) identification of relevant comorbid disorders, including cognitive impairment; (ii) identification, assessment, and management of functional impairment; (iii) identification, assessment, and support of social or psychological problems, including the needs of carers; and (iv) for those with proven epilepsy, ongoing review of all medications and their potential interaction with planned or current antiepileptic drug therapy.

Given the complexity of need, a multispecialty, multiprofessional approach to care would seem most appropriate. Epilepsy specialists and physicians who

specialise in elderly medicine can each contribute substantially to the care of patients with both suspected and proven epilepsy, but there are few examples of joint or shared services, training, or interest and experience in the UK. Additionally, little formal evaluation of any specific approach can be found elsewhere. The traditional outpatient clinic model will address the needs of many older people with epilepsy, but those with functional impairment and a need for multidisciplinary assessment and rehabilitation might be better managed in a day hospital or domiciliary setting. Outreach and domiciliary support, particularly that delivered by epilepsy nurse specialists, have a part to play in the education of patients and carers. Further work is required to define the best means to manage the various needs of this vulnerable population as the number of elderly people with epilepsy increases over the coming decades.

Conclusions

Despite the rising prevalence and potentially profound physical and psychosocial effects of new-onset epilepsy in elderly people, this disorder has received surprisingly little research focus. There is increasing consensus that future treatment strategies should move beyond symptomatic relief (seizure control) to achieving cure and prevention for those at risk. In line with this goal, the European scientific community has recently identified a number of research priorities.¹⁰⁶ Aspects that are particularly pertinent to the elderly population include preventing the development of epilepsy after brain trauma, translating genetic knowledge to optimise care of patients, reducing the life-burden of seizures, and improving treatment and prognosis.

Although results from epidemiological studies have shown that epilepsy arising in old age has different causes

Search strategy and selection criteria

References for this Review were identified through searches of PubMed, Embase, and the Cochrane Collaboration with the search terms "epilepsy", "seizures", "elderly" "aged", and "anticonvulsants" from 1995 until July, 2009. We then handsearched these papers for earlier publications, focusing on those that specifically included elderly patients and covered clinically relevant topics. Only papers published in English were reviewed.

from that occurring in younger adults, our ability to distinguish at-risk patients with various brain insults based on clinical factors alone remains weak. Identification of genetic or other biomarkers that reliably predict the epileptogenic process would facilitate a more targeted approach in developing preventive strategies. Data from recent studies have improved our understanding of the psychosocial effects of the diagnosis of epilepsy in the elderly. This knowledge should encourage research in developing appropriate care delivery models and lessening the life-compromising burden of the disorder.

Given the unique pharmacokinetic and pharmacodynamic changes in old age, greater effort should be devoted to including elderly people in the drug development process using novel methodological strategies that overcome the logistic barriers in undertaking clinical trials in this age-group. Additionally, research is needed to better understand the chronic adverse events of antiepileptic drugs that are particularly relevant to this age-group, including those that affect bone¹⁰⁷ and vascular health.¹⁰⁸

Old age has become the most common time in life to develop epilepsy in high-income societies. Because of the often atypical presentation, concomitant cognitive impairment, and non-specific abnormalities in routine investigations, establishing a correct diagnosis can be particularly challenging. A multispecialty, multi-professional strategy can help to facilitate rapid diagnosis and ensure a comprehensive approach in ameliorating the physical as well as the psychosocial effects of the diagnosis of epilepsy on elderly patients and their families.

Contributors

All authors contributed equally to the literature search, preparation of the tables and figures, and the writing of this Review. MJB coordinated preparation of this paper.

Conflicts of interest

MJB is a consultant for Pfizer, UCB Pharma, Eisai, GlaxoSmithKline, Valeant, Johnson & Johnson, Schwarz Pharma, Sierra Neuropharmaceuticals, Ikano Therapeutics, and Medtronic. He has received research grants from Pfizer, UCB Pharma, and Eisai within the past 3 years. PK has received contracted research grants from Eisai, Johnson & Johnson, Pfizer, and UCB Pharma within the past 3 years. ATE has no conflicts of interest.

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