Management of epilepsy in elderly

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Abstrak

Manajemen epilepsi pada lanjut usia memerlukan pemahaman tentang ciri-ciri khas menyangkut aspek biokimiawi dan farmakologi. Keputusan manajemen harus berdasar atas klasifikasi serangan atau sindrom epilepsi, pemeriksaan neurologis menyeluruh untuk mencari faktor etiologi, dan penilaian tentang status kesehatan dan kehidupannya. Penyakit lain yang menyertai misalnya gangguan jiwa, metabolik, jantung dan gangguan saraf lainnya memerlukan perhatian, perencanaan dan instruksi spesifik. Dibandingkan dengan golongan anak, golongan lanjut usia mempunyai berbagai masalah yang sangat berbeda. Masalah-masalah tersebut antara lain penyebab epilepsi yang beraneka ragam, diferensial diagnosis yang lebih bervariasi, penyakit lain yang tidak berhubungan dengan epilepsi, perbedaan farmakokinetik dan farmakodinamik, dan efek psikososial. ***(Med J Indones 2003; 12: 40-7)***

Abstract

Management of epilepsy in elderly requires understanding the unique biochemical and pharmacological characteristics of these patients. Management decisions must be based on accurate classification of seizures or epilepsy syndromes, a thorough neurological assessment to define etiology, and a comprehensive assessment of the patient's health and living situation. Concomitant illnesses such as neurological, psychiatric, metabolic, or cardiac disorders will require individualization of plans and instructions. Specific problems of treatment of epilepsy in the elderly compared to childhood patients are as follows: distinctive range of causes of epilepsy, distinctive differential diagnosis, concurrent pathologies unrelated to epilepsy, pharmacokinetic and pharmacodynamic differences, and distinctive psychosocial effects. ***(Med J Indones 2003; 12: 40-7)***

Keywords: epilepsy, elderly, management, concomitant illness, pharmacokinetic

Epilepsy is a relatively common disorder among older people, with the incidence increasing significantly with the age. Worldwide, epilepsy is a major cause of disability in the elderly and, in the context of an aging population, it is of increasing importance as a public health issue.[1] Epileptic seizures are the third most frequently neurological condition identified in the elderly, after cerebrovascular disease and dementias.[2] The incidence of epilepsy has a distinctly U-shaped distribution, in which children less than 5 years and people over 60 years of age have the higher risk of epilepsy. After the age of 60 the incidence of epilepsy increases rapidly, with the peak at the 80-year-old.[3,4]

The high frequency of seizures and epilepsy in the elderly is primarily related to the greater risk of other medical diseases in this age group. The conditions such as stroke, brain tumor, or head injury have a peak incidence in the oldest age of group. The importance of seizures in the elderly was founded in a British study, that showed that almost 25% of newly identified seizures were founded at the ages 60 and over. Meanwhile, in population studies, stroke is the most commonly identified cause of epilepsy in adult older than 35 years.[3,5]

The most common etiology in elderly patients with the symptom of seizures is stroke. The incidence of cerebrovascular disease increases with age and it contributes to the sharp rise of prevalence of epilepsy after age of 65 years. The other causes of seizures in the elderly include tumor, degenerative disorders, head trauma, toxic or metabolic factors and drug-induced seizures.[6,7,8,9]

There is a different distribution of seizure types and epilepsy syndromes in the elderly compared to the younger patients. Primary generalized epilepsy is rarely diagnosed in the elderly and the majority of

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seizures are partial, either simple, complex or secondarily generalized.[9,10,11] This conditions is a reflection of the underlying causes in the population. In the elderly complex partial seizures are probably more common than appreciated with clinical features different to the more typical mesial temporal lobe complex partial seizures seen in younger patients.[12]

The spectrum of epilepsy and seizures type in elderly differs from those of the younger ones. Establishing the diagnosis of epilepsy in the elderly poses particular difficulties. There are multiple medications available for the management of seizures, some of them were just introduced in the last decade. However, most of them have not been systematically studied in elderly. Age-related changes in metabolism, physiology, and pathology will influence the pharmacokinetics of these medications, and these should be taken into consideration when treating elderly patients with antiepileptic drugs.[1] This paper reviews diagnostic assessment and general principles of treatment of epilepsy in the elderly, as will as the assessment of efficacy and toxicity of anti-epileptic drug (AED).

OVERVIEW

Several studies have shown a linear increase of the incidence of epilepsy after age of 60 years.[13] The incidence of epilepsy and unprovoked seizures is highest in patients older than 75 years, followed by less than 1 year old infants.[3] Similar pattern of epilepsy in the elderly have been also reported from the United Kingdom and France.[13]

The high incidence of seizure disorders in the elderly correlates to the increased incidence of the other conditions resulting in static or progressive ence-phalopathy and cerebrovascular disease. Stroke is the commonest etiology of seizure disorders in olderly. Degenerative diseases, systemic metabolic disturbances, neoplasm, trauma, and toxic encephalopathy are also important etiology of seizure in elderly.[3]

Management of seizure in elderly should be based on accurate classification of seizures or epilepsy syndromes, thorough neurological assessment to define etiology, and comprehensive assessment of the patient's health and living situation. The health status of the patient and other medications used by the patient will influence the selection of AED.[14] Moreover, appropriate management requires rapid investigation, accurate diagnosis, effective treatment, sympathetic education, and assured support. The emerge of seizures in elderly places an increasing burden on health-care facilities and costs.[13]

Delay in diagnosis of epileptic seizures in the elderly is not uncommon. In the elderly, where dementia is common, and memory function is declining, obtaining a clear history of the seizure-like event from the patient can be very difficult. This condition increases the need for alloanamnesis. Partial seizures may be misdiagnosed as non-specific confusional states. Non-convulsive status epilepticus may simply be interpreted as acute behavioral changes, dementia or delirium.[1,15]

Management of epilepsy in the elderly is a challenge. The elderly may have concomitant disease that usually requires obligatory polypharmacy with drug interactions. In the elderly there are changes in body physiology that alter drug absorption, protein binding, metabolism, and drug elimination. Administration of medication to the elderly patient is complicated by complex and specific pharmacokinetics and sensitivity to drug that result in narrowing of the useful therapeutic range of the drug.[13]

The elderly patients with declining intellectual function, motor impairment, or altered sensory function are especially susceptible to dose-related central nervous system side effects of AED. Decline in mental function may be accentuated by drug-induced delirium or intensification of underlying dementia. Drug-induced delirium is a common problem in the elderly.[16]

DIAGNOSTIC ASSESSMENT

Anamnesis

Careful history taking and a thorough neurologic examination are important in establishing the clinical diagnosis of epilepsy. The diagnosis of epilepsy is generally made after a person has got had two or more seizures. Irrespective of the patients' age, investigations in patients with seizure are geared to (1) confirm or support the clinical diagnosis of an underlying epileptic syndrome and the particular subtype and (2) identify the underlying cause. Seizures in the elderly may occur in the setting of acute systemic or neurologic insults, where the underlying cause, such as stroke, hypoxic-ischemic

insults, or severe metabolic derangements, is readily recognized.[1,17]

A detailed description of seizures i.e. time of onset, duration, events before and after, is necessary for accurate diagnosis and optimal treatment. This is especially important in elderly people, as seizures can be confused to other behavioral disorders, including those caused by drugs such as delirium, cardiac arrhythmias, syncope, transient ischemic attacks, transient global amnesia, vertigo, hypoglycemia, nonketotic hyperosmolar states, and drug-induced dystonia.[18]

Syncope may be caused by blood pressure changes or impairment of the vascular reflexes linked to posture. Acute confusional states can be ictal, postictal or caused by non-convulsive status, but it is frequently misdiagnosed as manifestations of functional psychiatric illness, dementia or vascular disease. The discrimination of these events from epilepsy can pose a challenge.[18,19]

Laboratory tests

Investigations of first seizure in the elderly should include serum electrolytes and glucose, electrocardiogram, and electroencephalogram (EEG). Care must be taken when interpreting EEG result, so that normal age-related changes are not interpreted as the cause of seizures or a reflection of seizure activity. On rare occasions, video EEG monitoring may be needed to clarify the diagnosis.[1,20]

Epilepsy is a clinical diagnosis. There must be a clinical description of episodes that compatible with epilepsy. Epilepsy cannot be diagnosed from EEG alone. EEG plays only a supporting role to the clinical impression. The value of the EEG in the diagnosis of epilepsy depends on when the EEG is done and the clinical pattern of the event under question. In the elderly, there are a variety of EEG changes which complicates the diagnosis. Such changes are easily mistaken as epileptogenic patterns.[19,21]

Brief runs of temporal slow activity, especially on the left, becomes increasingly evident after the age of 50 years and should be considered as a normal variant. Small sharp spikes during sleep and drowsiness also increase in frequency in elderly. Runs of temporo-parietal activity can occur in individuals over 50 years old. This pattern is known as the subclinical rhythmic electrographic discharges in adults (SREDA) pattern, and is not associated with epilepsy. Cerebrovascular disease produces focal and bilateral temporal changes which are also commonly mistaken as epilepsy, and are not predictive of overt epileptic seizures.[19,21]

Etiology

In establishing the diagnosis of epilepsy in the elderly, the identification of causative factors is imperative. Cerebrovascular disease accounts for 30 to 50% of the cases. Approximately 7% of ischemic and 15% of hemorrhagic cortical strokes are complicated by acute or early seizures (within 2 weeks of stroke onset).[6,7,19] Evidence of cerebrovascular disease can be found in about 15% of those with apparently idiopathic late-onset epilepsy.[22,23]

Head injury and encephalitis have relative or absolute peaks in incidence in the elderly. Systemic metabolic disorders such as uremia, hyponatremia, and hypoglycemia, are also frequent in this group.[19,22,24] Some studies suggest that approximately 16% of Alzheimer's patients will go on to develop seizures. Despite extensive investigations including neuroimaging, no any cause can be identified in a significant proportion of elderly patients.[10,11]

Subdural hematoma is another under diagnosed cause of epilepsy in the elderly. Seizures also commonly occur in cerebral aneurysm, ruptured or unruptured. Meanwhile, cerebral tumors account for between 5 and 15% of all late onset epilepsies. The tumors are most commonly metastatic or gliomas. A few is meningioma which is potentially operable.[19]

CT scans provide sufficient information on the patients with acute provoked seizures, to allow identification of lesions that might need urgent neurosurgical management, such as large masses or hemorrhages. In almost every other instances, MRI of the brain is preferable. MRI may be contraindicated for the patients who uses cardiac pacemakers, suffer from claustrophobia, or have non-MRI compatible clips on cerebral aneurysms.[17]

In conclusion, the comprehensive diagnostic assessment of epilepsy in the elderly should be done appropriately. The comprehensive approach will result in accurate diagnosis, precise classification of seizure type, accurate identification of the underlying disease e.g., cerebral lesions and/or systemic disorders, and recognition of non-epileptic conditions that will not be treated by using AED.

GENERAL PRINCIPLES OF THERAPY

Although the elderly represent heterogeneous population, they must be considered to consist of the healthy elderly and the elderly with multiple medical problems. A drug of choice appropriate for one patient may not be appropriate for the other. Even in the healthy elderly, there will be a decline functions of the various organ systems, leading to lower hepatic and renal clearance of AEDs and possible increase in sensitivity of the central nervous system to side effects.[25]

In addition, cost of AEDs for most of people will be an important factor. These issues are greatly complicated for those with multiple medical problems. In addition, the health of the patient may change from time to time, so a choice appropriate at one time may not be appropriate later. The physician must be aware of the benefits and shortcomings of AEDs, the state of finance and physical health of the patient.[25]

Managing drug therapy in elderly with epilepsy requires special attention to age-related alterations in both the pharmacokinetic disposition and pharmaco-dynamic effects of AED therapy. Pharmacokinetic parameters such as protein binding, distribution, and elimination change with age, may complicate dosing and monitoring of AEDs in elderly patients. Generally, the elderly are more sensitive to the pharmacodynamic effects of many medications, especially those affecting the central nervous system.[14]

Drug therapy is the mainstay of epilepsy management for patients of all ages. The primary goal in epilepsy management is the complete control of seizures using a treatment regiment with minimal or no adverse effects. In most patients, treatment with a single AED is sufficient to meet this goal. The initial choice of therapy should be based on the patient's epilepsy syndrome, seizure type, adverse effect considerations, concomitant medical conditions, and the likelihood that the patient will be able to adhere to the regimen such as the cost, dosing frequency, and other relevant factors. If the first agent, after it titrated to the maximal tolerated dose and did not adequately control seizures or caused unacceptable adverse effects, then another agent should be tried as monotherapy. Most practitioners recommend sequential trials of two to three agents as monotherapy before considering AED polytherapy.[12]

SELECTION OF AED

The choice of AED is driven by some considerations, including proven efficacy for the particular seizure type, tolerability, personal experience of the physician, and especially how comfortable the physician and the patient feel using a specific agent. In the treatment of epilepsy in the elderly, several additional factors have to be considered.[26]

The physiologic changes due to the aging process influence on the decision of AED administration. These include the need for lower dose, monitoring total and unbound drug levels, and increased alertness to subtle side effects. In selecting AED for elderly patients, the physician needs to be aware of the pharamacokinetic properties of the drugs, such as absorption and distribution, hepatic elimination profile, protein binding, and neurological side effects.[19,25,27] Since the elderly is predisposed to problems associated with polypharmacy e.g., non-adherence, drug interactions, AED monotherapy is preferred and often can provide a good seizure control.[28]

In the elderly, the pharmacokinetic change and affect drug handling and the relationship between dose and serum level can be very different compare to that of younger adults. For many drugs, age is an important variable in a wide range of pharmacokinetic parameters. Compliance on the medication can be poor as a result of memory lapses, failing intellect or confusion. In this situation, drug administration should be supervised. The adverse effects of the AEDs in the elderly may take unfamiliar forms such as confusion, general ill health, affective change or uncharacteristic motor or behavioral disturbances. The therapeutic ranges defined in younger age groups do not necessarily appropriate to elderly patients, who are generally more susceptible to drug side-effects at lower serum levels than in younger patients.[19]

Treatment of the elderly with AED, as with many other medications, is complicated by the drug interactions in multiple drug therapy. When clinicians prescribe drugs for the elderly, they must consider the concomitant disorders and individual variability.[25]

ASSESSMENT OF EFFICACY AND TOXICITY OF AED

The provision of safe and effective drug therapy to elderly requires an understanding of the unique age-

related changes in the pharmacokinetics and pharmacodynamics of AEDs.[14] Assessment of AED treatment efficacy and toxicity in elderly patients is challenging because of the following circumstances: (a) seizures are sometimes difficult to observe, (b) signs and symptoms of toxicity can be attributed to other causes i.e., Alzheimer' disease, stroke, or co-medications, and (c) the patient may not be able to accurately self-report their problems. These circumstances require the physician to devote extra attention when he assesses the evaluation of the elderly treated with AED.[27,29]

Evaluation potential causes of lack of efficacy

The potential causes for lack of efficacy consist of two main factors i.e., "fast metabolizers" and noncompliance. In a large population of AED serum concentrations after a fixed dose should be a bell-shape curve. The vast majority of patients will show drug levels within the target range (mean ± 2 SD) expected from a dosage based on body weight. Patients with AED serum levels more than 2 SD below the mean for a fixed dose can be considered genetically "fast metabolizers". These fast AED metabolizers require significantly higher doses to achieve the same serum concentrations to get desired therapeutic effect.[29]

Many patients requiring therapy for prolonged period of time tend not to take their medications as prescribed.[28] Patient with a chronic disease, that does not cause pain or other unusual discomfort such as epilepsy or hypertension, may easily neglect to take their medicine. The end result of such noncompliance is exacerbation of the existing disorder in the future. Noncompliance has been, and still is, one of the most common causes for failure of AED therapy.[30,31]

Therapeutic drug monitoring (TDM) can assist in identifying compliance problems. TDM will allows identification of "fast metabolizers" individuals i.e., lack of seizure control, no side effects, and low serum concentrations in the context of good compliance, and ensures that their medication regimens can be appropriately adjusted to fit their own metabolic patterns. Without TDM, a prolonged period of trial-and-error therapy is required to achieve the appropriate dosage regimen, and unnecessarily subjecting the patient to a time interval during which the disease process is uncontrolled.[29]

Evaluation potential causes of drug toxicity

There are four important factors relating to the drug of toxicity i.e. altered drug utilization as a consequence of physiologic conditions, "slow metabolizers", altered drug utilization due to pathologic conditions, and drug-drug interactions. Geriatric patients often exhibit reduced rates of drug elimination and therefore require reduced drug dosages. It is possible for geriatric patients to have a total drug plasma concentrations within the optimal therapeutic range, with elevated free drug concentrations that can produce adverse side effects.[29,32] The clinical signs of drug intoxication in the elderly often present clinically as lethargy and confusion, and TDM is useful for distinguishing drug-induced confusion from organic deterioration.[29]

The vast majority of patients exhibit drug levels within the target of drug serum range (mean ± 2 SD) expected from a dosage based on body weight. Patients with AED levels more than 2 SD above the mean for a fixed dose can be considered as genetically "slow metabolizers". These slow AED metabolizers require significant lower doses to achieve the same serum concentrations and therapeutic effect. Patients who are slow drug metabolizers will be intoxicated and experience side effects if they get standard therapeutic doses of the drugs. Therefore, optimal drug levels should be maintained in these patients with dosages below the standard regimen.[29]

TDM allows identification of individuals who are slow metabolizers i.e., frequent side effects with high serum concentrations in the context of good compliance, and ensures that their medication regimens can be appropriately adjusted to fit their individual metabolic pattern. Without TDM, a prolonged period of trial-and-error therapy can occur before the appropriate dosage regimen is reached and the patient is proned to high risk of AED side effects.[29]

Acute or chronic uremia can dramatically decrease the elimination of a drug that is primarily dependent on urinary excretion, and renal failure can alter the protein-binding to albumin of many drugs. In both situations, the ratio of free drug to total drug may increase to the point at which free drug concentrations are high enough to produce a clinically evident toxic drug response, even though the total serum drug concentrations are within optimal therapeutic range.[29,33]

Hepatic disease can extensively alter the therapeutic response by impairing a patient's ability to metabolize the drugs. Most drugs depend on liver detoxification for conversion the drugs to water-soluble products, which are easily eliminated from the body. Therefore, a precipitous increase in parent drug concentrations can occur as the unmetabolized drug, which normally would have been eliminated from the system, accumulates.[33]

Drug-drug interactions in the elderly should be also considered appropriately. Ideally, patients would achieve the best quality of life without seizures or side effects on AED monotherapy. Unfortunately, AED polypharmacy is still frequently needed to treat severe epilepsy. As a number of AEDs used concomitantly increases, the risk of the patient to get side effects also increases. In a patient receiving AED polypharmacy and suffering from side effects, TDM can assess which AED is most likely to have caused the problem.[34]

Many older AEDs such as phenobarbital, primidone, phenytoin, and carbamazepin are inducers of hepatic microsomal P450 enzymes and valproic acid is an inhibitor.[33] Newer AEDs do not affects hepatic microsomal P450 enzymes, but some e.g., lamotrigine, topiramate, oxcarbazepine, and zonisamide, undergo significantly increased metabolism when combined with enzyme-inducing older AEDs.[29]

Those new AEDs are introduced predominantly as adjunctive therapy in patients receiving enzyme inducers. Therefore, if seizure control without side effects is achieved, attempts to wean the original enzyme-inducing older AEDs can result in de-induction of hepatic microsomal P450 enzymes. This process usually takes 3-6 weeks and can result in an insidious rise in the serum concentration of the newer AED with the slow appearance of toxicity. Before a patient is weaned from an enzyme-inducing AED, the serum concentrations of the remaining AEDs should be determined and then repeated 3-6 weeks after to identify changes that might lead to overt or covert toxicity.[29,33]

Evaluation the potential causes for loss of efficacy

TDM plays an important role in helping the clinician to assess whether breakthrough seizures can be due to altered or changing AED pharmacokinetics resulting from a physiologic condition, a pathologic condition, a change in formulation, or a drug-drug interaction. The potential causes for loss of efficacy are altered drug utilization as a consequence of physiological conditions, altered drug utilization as a consequence of pathological conditions, change in formulation, as well as drug-drug interaction.[29]

For any AED, the range of plasma concentrations that are clinically effective remains fairly constant across the range spectrum. However, the dosage of AED needed by the patient to achieve this plasma concentration can vary dramatically by age. Furthermore, changes in AED protein binding, volume of distribution, metabolism, and clearance during pregnancy may be associated with dramatic decrease in serum AED concentration and exacerbation of seizures in pregnant women with epilepsy.[35]

Pathologic conditions can alter drug utilization. Patients receiving long-term drug therapy may become acutely ill and require additional therapeutic agents. The illness itself may results in changes in drug utilization, with subsequent decreases in AED serum concentration and the occurrence of breakthrough seizures. Concomitant medications may lead to hepatic microsomal P450 enzyme induction that could, in turn, lead to lower AED serum concentrations and breakthrough seizures. TDM can help to assess whether AED concentrations are being altered by the pathologic process or by the treatment.[29,36]

Various formulations of the same AED may have different pharmacokinetic characteristics, including variation in bioavailability and peak concentrations. Changing a patient from intravenous to oral formulations or from brand name to generic can result in breakthrough seizures if the pharmacokinetic differences are greater than the patients tolerance. After a change to the alternative formulation, TDM can shows the changes in serum concentrations that might explain the later breakthrough seizures.[37]

Drug-drug interactions should be considered appropriately if polypharmacy regimen is administered to patients. Valproic acid is an inhibitor of hepatic microsomal P450 enzymes and significantly affects lamotrigine's pharmacokinetics. Concomitant use of valproic acid and lamotrigine will results in an artificially elevated lamotrigine serum concentration compared to lamotrigine used in monotherapy.[38]

CONCLUSION

Epilepsy in the elderly is a significant health problem. The management of epilepsy in the elderly requires understanding of various underlying diseases, concomitant diseases related to drug-drug interactions and appreciation of common seizure types as well. Diagnostic assessment, general principles of therapy, selection of AED and assessment of the efficacy and toxicity of AEDs are important issues in the management of epilepsy in the elderly.

Managing drug therapy in elderly individuals with epilepsy requires special attention to age-related alterations in both the pharmacokinetic disposition and pharmacodynamic effects of AED therapy since the pharmacokinetic parameters such as protein binding, distribution, and elimination change with age. These changes may complicate the dosing and monitoring of AEDs in elderly patients.

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REFERENCES

1. Kilpatrick CJ, Lowe AJ. Management of epilepsy in older people. J Phar Pract Res 2002;32:110-4.
2. Kramer G. Epilepsy in the elderly: some clinical and pharmacotherapeutic aspects. Epilepsia 2001;42(Suppl. 3):55-9.
3. Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked in Rochester Minnesota: 1935-1984. Epilepsia 1993;34:453-68.
4. Van Cot AC. Epilepsy and EEG in the elderly. Epilepsia 2002;43(Suppl 3):94-102.
5. Sander JWA, Hart YM, Johnson AL, Shorvon SD. National general practice study of epilepsy: newly diagnosed epileptic seizures in a general population. Lancet 1990;336: 1267-71.
6. Kilpatrick CJ, Davis SM, Tress BM, Rossiter SC, Hopper JL, Vandendriesen ML. Epileptic seizures in acute stroke. Arch Neurol 1990;47:57-60.
7. Kilpatrick CJ, Davis SM, Hopper JL, Rossiter SC. Early seizures after acute stroke: risk of late seizures. Arch Neurol 1992;49:509-11.
8. Romanelli MF, Morris JC, Ashkin K, Coben LA. Advanced Alzheimer's disease is a risk factor for late-onset seizures. Arch Neurol 1990;47:157-60.
9. Hauser WA. Seizure disorders: the changes with age. Epilepsia 1992;33(Suppl. 4): S6-S14.
10. Thomas RJ. Seizures and epilepsy in the elderly. Arch Intern Med 1997;157:605-17.
11. Scheuer MI, Cohen J. Seizures and epilepsy in the elderly. Neurol Clin 1993;11:787-804.
12. DeToledo JC. Changing presentation of seizures with aging: clinical and etiological factors. Gerontology 1999;45: 29-35.
13. Stephen LJ, Brodie MJ. Epilepsy in elderly people. Lancet 2000; 355(9213):1441-6.
14. Bourdet SV, Gidal BE, Alldredge BK. Pharmacologic management of epilepsy in the elderly. J Am Pharm Assoc 2001;41(3):421-36.
15. Tallis R. Epilepsy in old age. Lancet 1990; 336(8710): 295-6
16. Romanelli MF, Morris JC, Askin K, Coben LA. Advanced Alzheimer's disease is a risk factor for late-onset seizures. Arch Neurol 1990;47:847-50.
17. Drury I. Diagnostic assessment of seizures in the elderly. In: Willmore LJ, editor. Epilepsy in the elderly: current concepts in understanding and treatment. American Epilepsy Society; 2000. p.17-28.
18. Tinuper P. The altered presentation of seizures in elderly patients. In: Rowan AJ, Ramsay RE, editors. Seizures and epilepsy in elderly patients. Boston: Butterworth-Heinemann; 1997. p.123-30
19. Shorvon S. Handbook of Epilepsy Treatment. London: Blackwell Science, 2000.
20. Sirven JI. Epilepsy in older adults: causes, consequences and treatment. J Am Geriat Soc 1998;46:1291-301
21. Manford M. Assessment and investigation of possible epileptic seizures. J Neurol Neurosurg Psychiatry 2001; 70(Suppl 2):ii3-ii8.
22. So EL, Annegers JF, Hauser WA, Whisnant JP, O'Brien PC. Population based study of the risk factors of epileptic seizures following cerebral infarction. Neurology 1996;46: 350-5.
23. Silverman IE, Restrepo L, Mathews GC. Poststroke Seizures. Arch Neurol 2002; 59:195-201.
24. Annegers JF, Hauser WA, Coan SP, Rocca WA. A population based study of seizures after traumatic brain injuries. N Engl J Med 1998;338:20-4.
25. Leppik IE. Treatment of epilepsy in the elderly. Epil Curr 2001;1(2):46-7.
26. Brodie MJ, French JA. Management of epilepsy in adolescent and adults. Lancet 2000;356:323-9.
27. Leppik IE. Choosing antiepileptic drugs for the elderly. In: Willmore LJ, editor. Epilepsy in the elderly: current concepts in understanding and treatment. American Epilepsy Society; 2000. p. 65-71.
28. Lackner TE. Strategies for optimizing antiepileptic drug therapy in elderly people. Pharmacotherapy 2002; 22(3):329-64.
29. Glauser TA, Pippenger CE. Controversies in blood-level monitoring: reeximaning its role in the treatment of epilepsy. Epilepsia 2000;41(Suppl 8):S6-S15.
30. Mattson RH, Cramer JA, Collins JF. Aspects of compliance: taking drugs and keeping clinic appointments. Epil Res 1988;1(Suppl):111-7.
31. Devinsky O. Patients with refractory seizures. N Engl J Med 1999;340:168-70.
32. Willmore LJ. Management of epilepsy in the elderly. Epilepsia 1996;37:S23-33.

33. Asconape JJ, Penry JK. Use of antiepileptic drugs in the presence of liver and kidney disease: a review. Epilepsia 1982;23:S65-S79.
34. Brodie MJ, Dichter MA. Antiepileptic drugs. N Engl J Med 1996;334:168-75.
35. Yerby MS, Friel PN, McCormick K. Antiepileptic drug disposition during pregnancy. Neurology 1992;42:12-6.
36. Chadwick DS. The management of epilepsy. J Neurol Neurosurg Psychiatry 2001; 70 (Suppl 2): ii15-ii21.
37. Johannessen SI. General principles: laboratory monitoring of antiepileptic drugs. In Levy R, Mattson R, Meldrum B, editors. Antiepileptic drugs. 4th ed. New York: Raven Press; 1995. p179-87.
38. McKee PJW, Brodie MJ. Lamotrigine. In: Shorvon SD, Dreifuss F, Fish D, Thomas D, editors. The treatment of epilepsy. London: Blackwell Science; 1996. p. 438-45.