Peculiarity of Epilepsy in Elderly People: A Review

Particularités de l'Epilepsie chez les sujets agés : Revue

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ABSTRACT

BACKGROUND: **Incidence of epilepsy in elderly patients is higher than in any other group. The diagnosis of epilepsy in old age is particularly challenging and is often overlooked or missed. Selection of appropriate antiepileptic drugs (AEDs) for this group of patient also requires more attention than younger patients.**

OBJECTIVE: **To summarise the clinical presentation, aetiology, diagnosis, treatment, and neuropsychiatric complications of epilepsy in old age.**

METHODS: **Systematic review of existing literature on epilepsy in the elderly was carried out using original articles, review articles, meta-analysis, case reports, standard neurology text and the Cochrane library data.**

RESULTS: **Stroke and neurodegenerative disorders account for most causes of epilepsy in older patients. Simple partial and complex seizures are common modes of clinical manifestation. Post-ictal confusion and memory lapses are particularly prolonged in the elderly. The presence of other co-morbidities, age-related changes in pharmacokinetics and possible risk of drug-drug interaction needs to be considered before commencement of medication. Older AEDs like phenobarbitone and phenytoin should be avoided in the elderly because of their pharmacological profiles. Although newer AEDs have better tolerability, there is no evidence that they are advantageous over the older ones in terms of seizure control and should be used as add-on pills. The older AEDs have the advantages of being cheaper and being readily available in developing countries.**

CONCLUSION: **The goal of epilepsy management in the elderly goes beyond attainment of seizure control but should include improvement in quality of life. AEDs should be introduced cautiously based on patient's frailty and starting with lower dosage.   WAJM 2010; 29(6): 365–372.**

Keyword: **Elderly, seizure, epilepsy, diagnosis, review.**

RÉSUMÉ

CONTEXTE : L'incidence de l'épilepsie chez les patients âgés est plus élevée que dans les autres tranches d'âge. Le diagnostic de l'épilepsie chez ces sujets est un vrai défi, et souvent évoqué par excès, ou pris par défaut. La sélection des médicaments anti-épileptiques (MAE) appropriés pour ce groupe demande encore plus d'attention que pour les sujets plus jeunes.

OBJECTIFS: Passer en revue la présentation clinique, les étiologies, le diagnostic, le traitement, et les complications neuropsychiatriques de l'épilepsie chez les sujets âgés.

METHODES : Une revue systématique de la littérature disponible sur l'épilepsie du sujet âgé a été effectuée à partir d'articles, revues, méta-analyses, cas cliniques, livres de Neurologie, et des données de la Bibliothèque Cochrane.

RESULTATS : Les Accidents vasculaires cérébraux et les troubles neurovégétatifs sont à l'origine de la plupart des cas d'épilepsie. Les crises convulsives simples partielles , ou complexes sont des manifestations cliniques courantes. La confusion postcritique et la perte de mémoire sont particulièrement prolongées chez le sujet âgé. La présence d'autres co-morbidités, les modifications pharmacocinétiques liées à l'âge, et les possibles risques d'interactions médicamenteuses doivent être pris en compte avant l'instauration d'un traitement. Les anciens MAE comme le Phenobarbital la Phenytoine devraient être évitées à cause de leur profil pharmacologique. Bien que les MAE plus récents présentent une meilleure tolérance, il n'y a pas de preuve évidente de leur avantage sur les anciens en terme de contrôle des convulsions, et devraient ainsi être utilisés en supplément. Les MAE ont l'avantage d'être moins chers et disponibles dans les pays en voie de developpement.

CONCLUSION : Le but de la prise en charge de l'épilepsie du sujet âgé va au-delà du contrôle des convulsions, et devrait inclure l'amélioration de la qualité de vie. Les MAE doivent être prescrits avec une prudence basée sur la fragilité du patient et en démarrant avec de petites doses. WAJM 2010; 29(6): 365–372.

Mots-clés: Vieillesse, convulsion, épilepsie, diagnostic, revue

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INTRODUCTION

Epilepsy is a brain disorder that is characterized by a persistent predisposition to generate unprovoked seizures.[1] The elderly are a unique subset of the population and are the fastest growing segment in most countries. Age 65 years and above has been arbitrarily taken as the cut-off for defining the elderly, however there is no definite medical evidence that showed drastic change in health status by this age. This age is viewed as the interface between older adults and geriatric age and has been used in several studies.[2]

Presence of multiple disorders is the rule rather than exception in the elderly and one of these is epilepsy. Earlier views showed that epilepsy was most common in children;[1] however, recent epidemiologic studies have shown that the incidence of acute symptomatic seizures, epilepsy and status epilepsy is highest in the elderly.[3,4] Management of new onset epilepsy is particularly challenging in older patients because aetiology and mode of seizure presentation differ greatly from children and younger adults.[4] Eyewitness account that is essential for diagnosis is usually not available which makes misdiagnosis of epilepsy very common in the elderly.[3,4]

The World Health organization (WHO) has projected that by the year 2050, elderly people will account for 20% of the total world population,[5] of which, majority will be residing in the developing countries.[6] Thus the burden of epilepsy is likely to increase and will undoubtedly pose a greater challenge for epilepsy-care worldwide, especially in resource-scarce countries. In Nigeria, the 1991 census figure estimated that individuals 60 years and above constituted 5.7% of the entire population.[7] In one study they accounted for 11% of medical admissions into a tertiary hospital.[8] Presently in most developing countries the available social and health services are inadequate to cater for the need of this peculiar age group. Unfortunately, the extended family structure that fulfills this role in the community is gradually and inadvertently being eroded.

Since seizures are a major health problem in the elderly greater considera-tion should be given to as how to make the diagnosis easier with provision of increased education for physicians. This review focuses on the peculiarities of seizure and epilepsy in elderly people.

Epidemiology of Epilepsy in the Elderly

Epilepsy is the third most common neurological disorder after stroke and dementia in geriatric patients.[5] Systematic reviews and meta-analysis have shown that the incidence of new-onset seizure in individuals 65 years and over is 136 per 100,000[9–11] while after 80 years of age it is greater than 150 per 100,000.[11] The Veterans Affairs Cooperative prospective Study found that the incidence of epilepsy in elderly patients is six to ten times higher than in younger adults and that the recurrence rate is more than 90% if left untreated.[12] Incidence of status epilepsy in the elderly varies from 22 to 86 per 100,000[13] with mortality rate of close to 50%.[13] Status epilepsy is the mode of presentation in about 40% of elderly patients brought to hospitals in Europe and USA with new-onset seizure.[2,5,13] The prevalence rate of active epilepsy in individuals between age 65 to 75 years is about 1.5%, while after 80 years it rises to 3.5%.[12,14]

Information on incidence and prevalence of epilepsy in the elderly is particularly scarce in Africa and little is known about the magnitude of epilepsy in older people in sub-Saharan Africa. Plausible reasons for this might be due to the fact the often-bizarre symptoms are discountenanced by patients, relatives or doctors. An earlier WHO-sponsored neuroepidemiological study in Nigeria carried out three decades ago showed that the prevalence of active epilepsy in persons 55 years and above was 4.8 per 1000 individuals.[14]

AETIOLOGY OF EPILEPSY IN THE ELDERLY

An underlying aetiological agent is found in about 60% of newly diagnosed elderly epileptics,[9] while in the remaining this might be unrevealing.[9,10,15] The most frequently reported factor for newly diagnosed epilepsy in the elderly is cerebrovascular disease followed by neurodegenerative diseases.[10,16]

Cerebrovascular Accidents

Strokes account for close to 50% of acute symptomatic seizures in geriatric patients.[16,17] Both ischaemic and haemor-rhagic strokes can predispose to development of epilepsy.[18] Epileptic seizure that occurs within the first seven days of ictus is referred to as "early seizure", while the late form will occur after seven days.[19] Even asymptomatic cerebral infarct is a risk factor for epilepsy in the elderly.[19] Independent predictors of post-stroke seizures from several prospective studies include haemorrhagic stroke, subdural haematoma, rebleeding, late-onset seizures, African-American background and epileptiform discharges on electroencephalogram (EEG).[19,20] Electroencephalographic features that have been associated with increased risk of post-stroke epilepsy include frontal intermittent rhythmic delta activity (FIRDA), periodic lateralized epileptic discharges (PLEDs), and diffuse slowing.[20] Prophylactic use of antiseizure drugs has been variously suggested, but a recent publication of the Cochrane data base did not find enough evidence to justify routine use of antiepileptic medication for epilepsy prevention after stroke.[21]

Neurodegenerative Diseases

Alzheimer's disease (AD) and other neurodegenerative disorders are associated with increased risk of epilepsy in old people.[22] About two percent of all epilepsy in old age are due to AD[14] and between 10–17% of patients diagnosed with Alzheimer will develop epilepsy after five to 10 years of disease onset.[14,23] Established risk factors for seizure recurrence in AD include younger age of onset of dementia and advanced stage of the disease.[23]

Brain Tumours

Tumours of the brain are common causes of acute symptomatic seizures and epilepsy in elderly people[24] with close to 30–50% presenting with seizure as the initial clinical feature. Both primary and secondary tumours could manifest with seizure, however the former is more likely. Seizures are most common with low grade astrocytoma, less common with anaplastic astrocytomas and least common in glioblastoma.[25]

Head Injury

Head traumas with diffuse axonal injury and cortical contusions with or

without intracranial haematoma can also predispose to epilepsy development.[26,27] Brain injuries are often followed by a latent period of time before the appearance of recurrent seizure. During the latent period morphologic and biochemical changes that occur in the brain include neuronal necrosis, apoptosis, synaptogenesis, changes in gene expression, and axonal sprouting.[27] Epileptogenesis refers to the transformation of a normal neuronal network into one, which is chronically hyperexcitable and could develop spontaneous seizures. It takes variable length of time for this to develop from a few weeks to 20 years after the initial brain insult.[28] Brain contusions and subdural haematoma are very strong risk factors for development of late seizures.[27,29]

Other causes of Epilepsy in the Elderly

Metabolic causes and electrolyte imbalance are other clinically important causes of acute seizures in the elderly[1,5,30]. The main ones are hypo- and hyper-natraemia, hypocalcaemia, and hypo-magnesaemia. Hypo- and hyperglycaemia along with uraemia, hypothyroidism, and hepatic encephalopathy are common in the aged.[30]

Infections of the central nervous system can also present with acute seizures in the geriatric people with or without fever. Some frequently prescribed drugs in the elderly can lower seizure threshold and so predispose to develop-ment of acute seizures. Examples of such drugs are theophylline, antipsychotics, antibiotics, levodopa, thiazides, and herbal remedies like ginkgo biloba.[10,30,31] Alcohol abuse can also precipitate acute seizures in older people.[31]

MECHANISM OF SEIZURE GENERATION

Partial seizure, the most common form in elderly, begins in discrete region of the cortex before spreading to surrounding neurones.[32] Seizure generation consists of two phases; namely initiation and spreading phases. The initiation phase is made up of two events that occur simultaneously within an aggregate of neurones; high-frequency bursts of action potentials, and hypersynchroniza-tion. The event is preceded by sudden influx of calcium ions

into aggregate of neurones. This results in long-lasting depolarization of neuronal membrane and subsequent burst of neuronal activity.[1] Opening of voltage-dependent sodium channel follows with generation of repetitive action potentials. The synchronized burst activity from such group of neurones is what produces the spike discharge seen on EEG. Normally the spread of the burst activity is prevented by hyperpolarization and inhibition of surrounding neurones. Seizure results because the repetitive discharge and activation of sufficient number of neurones leads to recruitment of surrounding ones through mechanisms such as:

a. increased extracellular K^+ that blunts off the hyperpolarization and inhibition of surrounding neurones;
b. accumulation of Ca^{2+} in pre-synaptic neurones that leads to increased neurotransmitter release; and
c. the Ca^{2+}-mediated depolarization results in N-methyl-D-aspartate (NMDA) release. NMDA is a subtype of excitatory amino acid receptor.

When sufficient numbers of neurones are recruited through the above mechanisms, there is subsequent propagation of seizure activity into contiguous areas. Seizure propagation to adjacent areas and distant cortex involves pathways such as local cortical connections and long commissural neurones e.g. corpus callosum.

CLINICAL MANIFESTATION OF SEIZURES IN THE ELDERLY

These are summarised in Table 1.

Focal seizures with or without secondary generalization are the most common mode of presentation in the elderly and they occur in close to 70% of them.[4,5,9] In contrast to younger patients, seizure focus in the elderly is extra-temporal and mostly in the frontal lobe.[10] This explains why the clinical presentation differs from those in the younger adult. Simple partial seizure presenting with motor and/or sensory features is the usual mode of manifestation. Close to one-third of elderly patients with epilepsy present with complex partial seizures.[12] Auras may present as dizziness and asthenia[31] while complex partial seizures

manifest as altered mentation, periods of starring, unresponsiveness or blackout spells. Post-ictal state could present as confusion or paresis that lasts from few hours to days or weeks, and may be confused with dementing illnesses.[1,31] Secondary generalization is less common than in the younger age group.[5,10] Orofacial automatisms, hand rubbing, tapping and stroking, and wandering and removal of clothing are also ways by which seizures could manifest in later life[1]. Since those symptoms may not be considered as seizures they are often overlooked by the family and attending clinicians, especially if they are short-lived. Primary generalized tonic-clinic seizures, the common mode of presenta-tion, in the younger age, is less common in the geriatric age.[5] It remains unclear whether the generalized tonic-clonic seizure seen in a few elderly patients is a late manifestation of idiopathic generalized epilepsy that occurs in adolescents and young adults.[4,10]

Table 1: Common Clinical Manifesta-tions of Seizure in the Elderly

Altered level of consciousness
Confusion
Unresponsive starring
Blackout or spells
Periods of inattention
Orofacial automatism
Wandering
Episodes of memory lapses

DIAGNOSIS OF EPILEPSY IN THE ELDERLY

The diagnosis of epilepsy is clinical and often made after occurrence of two or more unprovoked seizures.[10] In the elderly this can be entertained in the presence of common aetiological factors. Detailed history should consider all medications the patient might be using including prescribed and over counter medications. In the elderly use of interictal EEG has low specificity and sensitivity and should not be used solely to establish or refute the diagnosis of epilepsy.[1] Of all neuroradiologic facilities, brain magnetic resonance imaging is the most preferred, but if not available brain computerised tomography scan could still be of help.[32] These are indicated in elderly patients

with definite epilepsy or in recurrent events of uncertain aetiology and are helpful in verifying the presence of structural brain lesion.

Laboratory workup including serum chemistry is essential along with cerebrospinal fluid analysis, if central nervous system (CNS) infection or cancer is suspected. Screening for toxic substances may be necessary where alcohol and drug abuse or withdrawal is suspected.[1]

DIFFERENTIAL DIAGNOSES OF EPILEPSY IN THE ELDERLY

Convulsive syncope is the most common cause of non-epileptic seizures and a very important differential diagnosis of epileptic seizure.[1,22,32] It should be considered in seizures that occur in later life in the absence of stroke, tumour, or neurodegenerative disease. Seizure resulting from syncope is posture related and is due to sudden drop in oxygen and blood supply to the brain. The most common differential diagnosis of seizures in the elderly are as shown in Table 2:[1,30]

Table 2: Differential Diagnoses of Epilepsy in the Elderly

System	Disorders Mimicking Seizure
Cardiovascular	Vasovagal syncope
	Orthostatic hypotension
	Cardiac arrhythmias
	Structural heart disease
	Carotid sinus syndrome
Endocrine/Metabolic	
	Hypoglycaemia
	Hyponatraemia
	Hypokalaemia
	Hypomagnesaemia
Neurological	Transient ischaemic attack
	Transient global amnesia
	Migraine
	Narcolepsy
	Restless legs syndrome
Psychological	Non-epileptic psychogenic seizures.
Sleep disorders	Obstructive sleep apnoea
	Hypnic jerks
	Rapid eye movement sleep disorders

ANTIEPILEPTIC THERAPY IN THE ELDERLY
Choice of Therapy

The standard practice is that antiseizure therapy is indicated after two or more unprovoked seizures in children and young adults.[33] On the contrary, single seizure may be treated in the elderly, especially if there is a history of a previous stroke or structural brain lesion on neuroimaging.[32] Old age is an important risk factor for seizure recurrence and the impact of repeated seizure in this age is enormous.[33] The choice of an AED in the old age depends strongly on seizure type and patient's biology (frailty) rather than the chronologic age.[32,33] The guiding principle for AED usage for seizure control in older people is to "start slow" and "go slow". Thus, AEDs should be commenced at a low dose and thereafter slowly titrated to avoid toxicity until the seizure is well controlled with modest dosage.

Conventionally, antiepileptic drugs are divided into old drugs and new drugs, according to whether or not they were available before the 1990s. There is presently no evidence that new drugs are more effective for seizure control in the elderly, although they might be better tolerated, than old drugs.[34] Established older AEDS include carbamazepine, phenobarbitone, phenytoin and sodium valproate.[32,34] Some of the approved newer AEDs in the USA and Europe are lamotrigine, topiramate, tiagabine, levetiracetam, gabapentin, and oxcarbazepine.[32,36] Two recent randomized double blind studies showed that newer AEDS have efficacy that are comparable with the older ones and have added advantages of better tolerability in elderly patients.[37,38]

CLINICAL PHARMACOLOGY OF AEDs IN THE ELDERLY

Ageing is associated with alterations in pharmacodynamics and pharmacokinetics of AED metabolism.[32] Reduction in serum albumin level is common by age 65 years[37] and this may be worsened by medical disorders like malnutrition, rheumatoid arthritis, and chronic renal failure, which are common in the elderly.[3] These might result in decrease in drug binding, increased

concentration of free unbound drugs and metabolites with resultant prolongation of half-life of AEDs. Impairment in liver metabolism of drugs is also common with advancing age. The phase I metabolism which consists of oxidation, reduction, and hydroxylation is affected more than phase II of glucuronidation, acetylation, and sulfation of drugs.[33]

Other age-related physiological changes that could affect metabolism of AEDs include decrease in ratio of body water to fat, reduction in creatinine clearance and rate of drug absorption from the gastrointestinal tract.[1,33] These physiological changes increase the chance of an elderly patient to develop side effects to AED. Older people are also prone to forgetfulness, complex multi-drug regimens and reduced drug purchasing power cost which could affect drug adherence.

MECHANISM OF ACTION OF AEDS

Antiepileptic drugs act by blocking the initiation or spread of seizures through a variety of mechanisms that modify the activity of ion channels or neuro-transmitters. In most instances the actions of AEDs are multiple and include the following:[1]

1. Inhibition of sodium ion channel and sodium dependent action potentials in a frequency-dependent manner (e.g. phenytoin, carbamazepine, lamotrigine, topiramate, zonisamide).
2. Inhibition of voltage-gated calcium ion channels (e.g. phenytoin).
3. Decrease in glutamate release (e.g. lamotrigine).
4. Potentiation of GABAs receptor function (e.g. benzodiazepines and barbiturates).
5. Increase in availability of GABA neurotransmitters (e.g. valproic acid, gabapentin, tiagabine).

Presently, there is no AED that can act to prevent seizure generation (epileptogenesis) which develops after structural brain injury such as stroke, trauma and infection.[28,39] Future development of such AED will prevent the formation of seizure focus after CNS injury, the most common aetiologic factor for epilepsy in the aged. The properties of the commonly prescribed assents are summarised in Table 4.

Table 3: Properties of Anti-epilepsy Drugs[30,33]

Drug	Indication	Metabolism/ Route of Excretion	Adverse effects
Carbamazepine	Focal & generalize seizures monotherapy	Extensive protein binding; hepatic & renal metabolism	Diplopia, visual blurring, skin rash, sedation, ataxia abnormal liver function tests, hyponatremia myelosuppression
Gabapentine	Focal seizures adjunctive	Renal excretion dosage may be reduced by 30–50% in elderly.	Somnolence, dizziness, ataxia, headache, tremor, diplopia, nystagmus, rhinitis, nausea and vomiting
Lamotrigene	Focal & generalized seizure, adjunctive, monotherapy	Hepatic	Rash, Steven-Johnson, bulluos erythema, headache, nausea, dizziness, diplopia, tremor, hallucination, psychosis
Levetiracetam	Focal seizures	Renal	Drowsiness, behavioral Abnormalities
Oxcarbazepine	Focal seizures adjunctive, monotherapy	Hepatic	Nausea and vomiting, rash, dizziness, somnolence, hyponatremia
Phenobarbitone	Focal & generalized seizures, monotherapy	Hepatic metabolism long $t(1/2)$; renal excretion	Nystagmus, ataxia, confusion, irritability, impotence, depression,
Phenytoin	Focal, generalized seizures,	Extensive protein binding; hepatic & renal excretion monotherapy	Sedation, ataxia, hepatitis, renal failure, confusion, gingival hypertrophy, osteomalacia, bloody dyscrasis, facial coarsening, neuropathy, cardiac arrhythmias, QT-prolongation, hypotension
Topiramate	Focal seizures	Liver & renal metabolism <10% protein bound	Weight loss, renal stone, cognitive impairment
Valproate	Focal, generalized	Protein binding; hepatic metabolism; renal metabolism	Postural tremor, liver failure weight gain, hair loss, pancreatitis, hepatitis, thrombopenia, pancytopenia, weight increase.

Phenytoin Sodium

Phenytoin (PHT) was first introduced in 1938 by Merritt and Putman.[39] In the United States of America, PHT is the single most prescribed AED in general clinical practice and in old people's home.[2,32] It is one of the most commonly used AEDs for treating secondarily generalized tonic-clonic seizures and SE. Phenytoin is useful for geriatric patients since it is suitable for localisation-related seizures, but has a narrow therapeutic range and complex pharmacokinetics.[1,40] About 95% of the drug is metabolized in the liver while the rest is excreted unchanged in the urine.[32]

A prospective study on pharmacokinetics of PHT in elderly, middle-aged and younger adults with epilepsy, noted a decrease in PHT metabolism with age.[37] Drug saturation can occur readily in the elderly even at lower daily dose of 3 mg/kg rather than the 5 mg/kg per day used in younger adults.[34,41] Therefore, smaller maintenance doses are needed to attain desired serum concentrations while small dose increments ($\leq$ 10%) are recommended during dose adjustments. One Cochrane data base review found no significant difference in clinical profiles between PHT and OXC.[34]

Carbamazepine

Carbamazepine (CBZ) is well established to be effective for localization-related epilepsies and suitable for elderly epileptics.[35] There is a fall in the drug clearance with ageing and so lower doses are required in the elderly.[35] Hyponatraemia is a frequent side effect of this drug, especially if there is polydipsia, prolonged use of diuretics or salt-restriction.[32] Other complications of long-term usage of CBZ include neutropenia, aplastic anaemia, hepatotoxicity, and cardiac dysrrhythmia. The risk of drug-drug interactions is high when CBZ is used along with medications that inhibit the cytochrome P450 isoenzyme (CYP 3A4) that metabolises CBZ. Examples of such drugs include erythromycin, fluoxetine, ketoconazole, propoxyphene and cimetidine.[1,32] Evidence from several multicentre studies shows that use of CBZ in the elderly is associated with greater side effects than lamotrigine and gabapentine although there is no difference in their clinical profile.[35,36]

Phenobarbitone

Phenobarbitone (PB) is the least expensive of all established AEDs and is still widely used in resource poor countries. Phenobarbitone is useful for generalized and localization-related epilepsies.[37] PB along with CBZ and phenytoin are inducers of hepatic monocyclooxygenases.[32,33] Metabolism of some commonly used drugs in the elderly like warfarin, cardiac antiarrhythmic drugs, and steroids is increased by these inducers. They also affect vitamin D metabolism and so elderly patients placed on such drugs should be given calcium supplement.[33] Phenobarbitone is metabolized by hydroxylation in liver while a small proportion of it is excreted unchanged in the urine,. Renal excretion of PB depends on rate of urine flow and acidity.[36] Pronounced cognitive and sedative side effects of PB make it unsuitable for use in the elderly.[36,37] Phenobarbitone can also cause depression, mood disorders or suicidal ideation in the elderly.[35,41] A Cochrane data base review showed that PB is more likely to be withdrawn by patients than CBZ due to its greater side effects.[42]

Table 4: Factors Concerning AEDs Prescription in the Elderly

- Presence of co-morbid conditions
- Use of several medications
- Slower drug metabolism
- Decreased protein binding and associated increase in free unbound drugs
- Decreased in creatinine clearance and reduced rate of renal excretions of drugs
- Side effects of medication very common
- Start low and go slowly with drug increase
- Compliance is often an issue due to forgetfulness and cost

Valproic Acid

Valproate (VPA) is a broad spectrum AED and is preferred for idiopathic generalised epilepsy in old age.[33] The drug is likewise effective for partial seizures and has a slightly better cognitive and behavioural profile than the other old AEDs.[41] Valproate is 80–90% protein bound and is metabolized in the liver through glucuronidation, b-oxidation and v-oxidation. Valproate does not induce hepatic enzymes but it is associated with reduction in bone mineral density through reduction in osteoblastic function.[35,36,43] Its other important side effects in the elderly include dose-dependent tremor and reversible parkinsonism.

Ageing affects the amount of VPA that is bound to albumin and half-life of the drug is prolonged to twice the value in younger adults.[34] Therefore the desired clinical response may be achieved with a lower dose than usual. Valproate should be avoided in elderly patients with chronic liver disease and bone marrow disorder.[34,41]

Gabapentin

Gabapentin (GBP) is best suited for localization-related epilepsies in the older people.[33,44] There is no risk of drug-drug interaction with use of GBP because it is excreted mainly in the kidney. Elderly patients with likelihood of reduced renal function need to have reduced dosage with regular monitoring of drug level at the initial phase drug commencement. The drawback against GBP prescription in old age is its short half-life, the need for frequent dosage, and issue of cost being a high priced medication.

Lamotrigine

Lamotrigine (LTG) is effective for both focal and generalized epilepsies. Its antiseizure profile is similar to carbamazepine and levetiracetam.[38] A recent multi-centre prospective study found LTG a suitable alternative in elderly patients who can no longer tolerate the older AEDs.[45] In the study, elderly patients who had LTG either as add-on medication or monotherapy had a better clinical profile outcome with significantly fewer side effects compared to patients on older AEDs.[40,45]

Lamotrigine is primarily metabolized in the liver by glucuronida-tion and ageing has no effects on its clearance from the body. The dose of LTG needs to be adjusted in the presence liver disease and based on patient's response rather than drug serum level.[37] The usefulness of lamotrigine in neuralgic pain makes it appropriate for elderly epileptics with chronic pain.[44]

Levetiracetam

Levetiracetam (LVT) is well tolerated in the aged and is preferred for partial-onset seizures.[32] Its extreme water solubility allows for rapid and complete absorption after oral administration. Levetiracetam is not metabolized by the liver and it lacks protein binding (<10%), which makes it free of drug-drug interactions and less likely to displace highly protein-bound drugs.[33]

Evidence from recent prospective studies shows that LVT is well tolerated in the elderly with epilepsy and does not worsen cognitive function in those with concomitant Alzheimer's disease.[37]

Tiagabine

Tiagabine (TGB) is effective for localization-related epilepsies and has an efficacy profile appropriate for the elderly. It is primarily metabolized in the liver by CYP 3A4.[1,32] Administration of drugs that affect CYP 3A4 substrates will also affect the metabolism of TGB, giving it a drug interaction profile similar to CBZ. There may be a reduction in its clearance with advancing age. A major feature of TGB is its potency. The effective doses are 20–60 mg/day, and effective concentrations are 100–300ng/ml or 100-fold lower than the other AEDs.[30,40] There are limited studies on the use of TGB in the elderly.

Topiramate

Topiramate (TPM) is an anti-convulsant that is useful for focal and generalized epilepsies[30] and is suitable for epilepsy control in the elderly.[35] Topiramate is minimally bound to plasma proteins (20%) and has a half-life of about 21 hours.[36] Close to 20% of the drug is metabolized in the liver while about 40% is excreted unchanged via the kidney. The enzymes involved in the drug's metabolism have not been identified; however, the cytochrome P450 system is suspected to be involved. It is suspected that TPM excretion is likely to decrease with age which may result in higher than expected serum concentrations at doses that are used in younger adults.[40] Often reported side effects of TPM are weight loss, nausea, behavioral and cognitive impairment. Elevation of liver enzymes has been documented with TPM usage.[36]

Oxcarbazepine

Oxcarbazepine (OXC) has similar chemical properties to its parent compound CBZ.[36] It is useful for focal and generalized epilepsies. The spectrum of action of OXC is similar to CBZ, but it is a less potent enzyme inducer with relatively less prominent interaction with other AEDs.[30,36] Two randomized double-blind trials on OXC monotherapy showed that OXC is as effective as CBZ, VPA and PHT and superior to placebo, and had superior tolerability when compared to the older antiepileptics.[46,47] It is primarily metabolized in the liver to 10-hydroxcarbazepine its active metabolite which is further metabolized by glucuronidation and then excreted by the kidneys. One study that compared metabolism of OXC in healthy young males with elderly males and those of healthy young with elderly females showed that OXC has a significantly higher maximum concentration and lower elimination rate in the elderly.[48] One key advantage of OXC is the less enzyme induction than many other AEDs including CBZ have leading to its fewer drug interactions.[34] The most common chronic effect of OXC is hyponatraemia, which is usually mild, asymptomatic and of no clinical significance. The hypo-natremia is likely to be possibly due to a marked antidiuretic effect, and consump-

tion of large fluid volumes (including large quantities of beer) should be discouraged.[36] Elderly patients on OXC need a regular serum sodium monitoring. One particular indication for OXC is as an alternative to patients who develop a CBZ induced rash. Common side effects necessitating OXC withdrawal from comparative monotherapy trials are diarrhea, dizziness, visual impairment, rash, alopecia and headaches.[36] The dose of OXC may need to be lowered in moderate to severe renal failure.

NEUROPSYCHIATRIC DISORDERS IN THE ELDERLY PATIENTS WITH EPILEPSY

Psychiatric illnesses are common co-morbid conditions associated with epilepsy in the elderly.[49] The causes and consequences of the disorder are yet unclear. The occurrence of psychiatric illness with epilepsy is associated with poorer quality of life and functions irrespective of the seizure control.[11] Neuropsychiatric comorbidities in particular result in fatalism and indifference toward therapy. Cognitive decline which may complicate strokes, degenerative disorders or brain tumours, could lead to difficulties in complying with the prescribed medication regimen.

Depression and anxiety are particularly very common in patients with epilepsy with frequencies of 30% and 10–25% respectively.[50,51] In geriatric patients, depression is probably the most common psychiatric illness and the aetiology is multifactorial.[51] The most frequently reported causes are social and occupational disability, limbic system dysfunction and genetic susceptibility. Although, patients with epilepsy tend to have poorer socioeconomic indices, occurrence of depression has greater negative impact than the illness *per se*.[51] Selective serotonine receptor inhibitors are the drug of choice for treating depression in elderly patients with epilepsy because of their favorable safety profile.[51]

COMPLICATIONS OF EPILEPSY IN THE ELDERLY

Myriad of complications has been reported to follow epilepsy in geriatric patients.[32] These vary from structural to psychological derangements.[1,32,33] Some of these are subdural haematoma, intracerebral bleeding, and prolonged post-ictal fugue that could persist for days or weeks. Psychological consequences include fear of socialization, increasing isolation, decrease in mobility and depression. Mortality is two to three times higher than in the younger adults.[32] Other clinically important complications are those resulting from AEDs therapy like problems with libido, potency, and orgasm, which are more rampant with drugs like phenobarbitone, phenytoin and carbamazepine.

CONCLUSION

Despite the high prevalence of epileptic seizures in the elderly, they are often overlooked or misdiagnosed. The differences in aetiology, outcome and responses to drug between younger adult and elderly make extrapolation of standardized treatment of young adult into geriatric patient difficult. Single seizures may be treated in the aged, especially in the presence of history of stroke, dementing illnesses or brain injury. The goal of epilepsy management goes beyond attainment of seizure controls but should include psychosocial considera-tion because the effect of repeated seizures in the elderly is often worse than in the younger age group. AEDs should be introduced cautiously starting with low dosage and taking into consideration risk for drug-drug interaction.

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