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Comprehensive Epilepsy Review for Primary Care

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Epilepsy is defined as the propensity to have recurrent seizure attacks. Seizure is a clinical event consisting of sudden and episodic alteration of consciousness, motor behavior, sensory, or cognitive changes with evidence of electrographic abnormality in electroencephalogram (EEG). Epilepsy is by no means a rare disorder. Each year 120,000 new cases of epilepsy are diagnosed. The incidence of new onset epilepsy is 10 to 15 per 100,000 persons. The cumulative lifetime incidence of a single seizure is approximately 10%, while incidence of epilepsy is about 1% up to age 20, and reaches more than 3% over the life span, which means that lifetime incidence of at least one seizure is 3%.[1] The age-specific incidence rates of epilepsy are bimodal. Two peaks of increasing rate are seen in infantile age and elderly, defined as older than 60 years old. The age-specific prevalence rises rapidly in childhood and remains stable from age 15 to 65 years. The prevalence of epilepsy rises to 10 per 1000 among the elderly due to the high incidence of post-stroke seizure.

Etiology

Causes of seizures vary widely. (*See Table 1.*) Genetic abnormalities have been widely discussed in recent studies. It is believed that seizure syndromes and etiologies are largely age-dependent. (*See Table 2.*) Primary generalized seizure is far more common in young patients, and most of them are idiopathic.

In the younger population, epilepsy is more likely to be due to congenital anomaly, cortical dysplasia, bacterial meningitis, inborn errors of metabolism, or idiopathic. Perinatal hypoxic brain injury is also a common cause of seizure. Congenital brain anomaly includes cortical dysplasia, heterotopia, and developmental abnormality due to disorganized neuronal migration process in the early stage of embryonic development. Hereditary cause of seizure is relatively uncommon; however, 10% of young epilepsy patients have a positive family history.

Almost all of the adult onset seizures are complex partial seizure. The majority of them arise from the temporal lobe, and less frequently from the frontal lobe. The most common cause of seizure in the adult population is brain trauma, with motor vehicle, motorcycle, and bicycle accidents as mechanisms for injury. Cerebral vascular ischemia, intracranial hemorrhage, and brain tumors are much greater in the adult age group.

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Arteriovenous malformation (AVM), cavernous hemangioma, and bleeding tumor are highly irritating to the brain cortex and therefore "epileptogenic," while intracranial aneurysm and venous angioma are not of strong epileptogenic inclination. Among tumors, bleeding tumor, metastatic tumor, germinoma, oligodendroglioma, and dysembryoplastic neuroepithelial tumor (DNT) are the most epileptogenic tumors. Seizures related with meningioma and subarachnoid cysts are primarily caused by a pressure effect that causes surrounding tissue irritability. The mass removal may alleviate cortical irritability, and a gradual decrease of seizure activity is sometimes seen.

In developing countries, the most frequent cause of seizures is central nervous system infections, meningitis, and cysticercosis. Alcohol-related seizure is more common in the young adult before age 55. Primary generalized seizures are much less common than in the younger age group. If they occur at all, it is more likely due to metabolic abnormality (hypertension, hyperglycemia, hyponatremia, and so on), or due to drug side effects (metronidazole, theophylline, tricyclics overdose).

Elderly onset epilepsy is most commonly due to stroke (35%), closed head injury (10%), and tumor (10%), while idiopathic or undetermined etiology cases are also prevalent for this population.[2] Any acquired cortical damage could cause seizure. The risk of seizures is 23 times higher than the age-matched population in the first year after a stroke.[3] The clinical condition of epilepsy in the elderly is complicated by coexisting medical problems and, to some extent, influenced by neurodegenerative change. Alzheimer disease rarely causes elderly onset of seizure (3%).[4] The elderly are vulnerable to adverse effects of common anticonvulsants.

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Summary Points

- Most adult onset seizures are partial complex seizures.
- The diagnosis of epilepsy can be confounded by multiple non-epileptic conditions such as syncope, TIAs, and psychogenic seizures.
- Selecting among antiepileptic drugs for epilepsy treatment can be challenging due to their distinctive mechanisms of action, pharmacokinetics, indications, and side-effects.
- Vagus nerve stimulation and surgical options are emerging effective therapies for selected cases of epilepsy.

Diagnosis

Epileptic seizure is a transient paroxysmal event demarcated with a clear onset and end of episode. The signs and symptoms of epileptic seizures are variable among the population but stereotypic in a single patient. The first important step in seizure diagnosis is determining if the paroxysmal events are epileptic seizures or non-epileptic events. The limited duration, stereotypical aura, postictal confusion, and the stereotypical "rubber-stamped" manifestation of sequential ictal events strongly suggest epileptic seizures. Good history-taking and ictal information leads to correct diagnosis.

It is important to differentiate non-epileptic phenomena when diagnosing epileptic seizure. (*See Table 3.*) Syncope is a transient, brief loss of consciousness accompanied by loss of postural tone and caused by a decrease in cerebral perfusion. Syncope frequently can mimic seizure. Transient hypoxia can cause nonspecific jerking. Vasovagal syncope is caused by an accentuated response of normal cardiovascular reflexes. Carotid sinus syncope is caused by accidental stimulation of the carotid sinus, which conversely increases vagal inhibitory outflow by brain stem reflex. The key sign of carotid sinus syncope is that the black-out spell is preceded by neck turning. Orthostatic hypotension due to diabetic neuropathy, Parkinson disease, or alcoholism also may cause syncope. Drug-induced syncope is seen in patients using high-dose tricyclic antidepressants, diuretics, and antihypertensive agents. Trazodone is the most frequent cause of drug-induced syncope in nursing home elderly.[5] Micturition syncope (related to urination) and tussive syncope (related to coughing) are called situational syncope as certain actions induce parasympathetic overflow causing syncope.

Transient ischemic attacks (TIA) cause neurological signs and symptoms of relatively brief duration, sometimes resembling seizures. Conversely, recurrent partial seizure may be misdiagnosed as TIA. Transient global amnesia (TGA) has a sudden onset of prolonged anterograde amnesia typically lasting for hours. However, the duration of epileptic amnesic spells should be much shorter than TGA. It usually lasts for no longer than 5-10 minutes. Panic attacks may mimic partial seizures originating from the amygdala and may be misdiagnosed as seizure, especially if the symptom precedes syncope due to hyperventilation. Some patients with panic attacks may experience symptoms like abdominal discomfort, throat pressure, choking sensation, and even urinary incontinence, and it is confused with partial complex seizure originating from the mesial temporal lobes.[6] Howev-

Table 1. Etiologies of Seizure

- Cerebral ischemic attack
- Intracranial bleeding
- Arteriovenous malformation (AVM)
- Brain tumor
- Brain injury
- Meningitis
- Viral encephalitis (Herpes simplex, etc.)
- Hypoxic brain injury
- Hereditary
- Febrile convulsion
- Idiopathic

er, consciousness should be maintained in panic attack spells. Panic attack spells should last longer (more than 30 minutes) than complex partial seizure spells (minutes).

Psychogenic seizure is non-epileptic behavior paroxysm caused by subconscious psychological reaction to varieties of stress. The condition frequently is seen in those persons who have a history of depression, bipolar disorder, sexual abuse, domestic violence, post-traumatic stress disorder, and mental retardation. Psychogenic attack would not occur out of sleep state and is devoid of postictal confusion. Generalized convulsion without loss of consciousness is most likely psychogenic seizure. Pelvic thrust is a typical behavioral sign suggestive of psychogenic seizure. Ictal transient back arching (opistotonus) never occurs in epileptic seizures.[7] Special attention must be taken with frontal lobe seizures, which are frequently mistaken for psychogenic seizure due to the presentation of complex movement, bizarre vocalization, and partially spared consciousness. Frontal lobe seizure should have stereotypical sequential ictal behavior change, while psychogenic seizure may present with a chaotic sequence. "Each time looks the same" is a key for epileptic seizure, and "each time looks different" is a key for psychogenic seizure. About 25-33% of patients referred to video-EEG study as having intractable seizure disorders are found to have psychogenic seizures, although the population incidence of psychogenic nonepileptic seizures (PNES) may be only 4% that of epilepsy.[8]

Narcolepsy may be either over-diagnosed or misdiagnosed as seizure. Narcolepsy should demonstrate four symptoms: daytime sleep attacks, collapse with emotional outburst (cataplexy), sleep paralysis, and hypnagorgic hallucinations. EEG demonstrates rapid onset REM sleep. When a patient has a history of frequent loss of consciousness, it may be a drop sleep attack instead of seizure attack. It should be kept in mind that patients who have frequent seizure attacks in the frontal lobes during the night may not have sufficient sleep and therefore have excessive daytime sleepiness and drop sleep attacks. Differentiation is critical.

Identifying seizure type is the first step of the treatment of epilepsy.[9] Seizure classification prompts recognition of seizure symptoms and guides the treatment plan. Seizure disorders have been classified according to the description of seizure attack (semiology), age of onset, EEG findings, and concomitant neurological dysfunction according to the traditional guidelines by the International League Against Epilepsy (ILAE) since 1981. With advances in video-EEG recordings and neuro-imaging studies, the seizure classification has been further enriched to represent clinical reality.[10]

The first 1981 ILAE classification consisted of two major factors: clinical symptoms and EEG findings. In the updated 1989 ILAE, the classification included concepts of syndromes with more specific clinical manifestations and the age of onset. However, seizure types and syndrome classification could be frequently altered by new findings with advancement of neuroimaging techniques and genetic studies. An increasing number of epilepsy cases would not fit into rigorous categories. At this point, the author recommends primary physicians stay with the 1981 ILAE classification and use the 1989 ILAE to determine the category of symptoms.

In accordance with the 1981 ILAE classification, the first step is to define if the seizure activity is generalized or partial. Generalized epilepsy has abnormal seizure activity in bilateral hemispheres upon onset. Partial epilepsy is characterized by localized seizure onset. The term "focal seizure" refers to a seizure that is from a pathological lesion, while "partial" refers to the fact that the part of the cerebral cortex is affected by electroencephalographic finding. The two words "focal" and "partial" are used interchangeably, but the former word is of pathology background and the latter is associated with EEG activity. It has been proposed to use the term "localization-related epilepsy" to integrate the two terms.

Simple partial (localization-related) seizures are localized onset in origin and do not impair consciousness. Any partial seizure that affects consciousness is, by definition, complex partial (localization-related) seizure. An aura is a first seizure manifestation consisting of subjective ictal phenomena that the patient may experience at the onset of a spell. Seizures should be either symptomatic or idiopathic from an etiological standpoint. Symptomatic implies that the seizure is caused by a known reason such as stroke, infection, traumatic damage, or other non-specific cortical lesions. Idiopathic means essentially no attributable underlying abnormalities explain the seizure.

The most practical way to classify seizures in the primary care clinic is to determine if a seizure semiology and EEG findings suggests generalized or localization-related seizure and to search for focal lesion by CT or MRI. The physician may then review the patient's clinical picture to determine if it fits any specific epileptic syndrome. The two-axis approach for simple categorization is useful in busy primary clinics as it will promptly determine the treatment orientation and the basic choice of anticonvulsants.

Both absence seizure and complex partial seizure are characterized by loss of consciousness. It is not uncommon that complex partial seizure spells are inadvertently misnamed as "petit mal" seizure. To avoid confusion, the word "petit mal" should not be used. Absence seizure is typically short (several seconds) in duration with abrupt onset and termination. The ictal EEG demonstrates generalized 3 Hz spike and wave discharge patterns. Complex partial seizure is typically longer (a few minutes), may be preceded by aura sensation, and is followed by post-ictal confusion. EEG may demonstrate temporal slowing or sharp epileptiform discharges.

In contrast, brief spells of memory lapse may be partial com-

Table 2. Seizure Etiology and Syndrome in Different Age Groups

AGE OF ONSET	ETIOLOGY	SYNDROME
Neonate	• Cortical dysplasia • Metabolic abnormality	• Symptomatic neonatal seizure • Otawara syndrome • Benign familial convulsion
1-2 years	• Hypoxia • Intracranial bleeding • Cortical dysplasia • Chromosomal abnormality • Meningitis	• West syndrome • Severe infantile myoclonus • Symptomatic complex partial seizure • Paroxysmal infantile benign myoclonus
3-9 years	• Hypoxia • Cortical dysplasia • Meningitis • Encephalitis • Head injury	• Myoclonus-Astasis seizure • Lennox-Gastaut syndrome • Continuous spike and wave in sleep syndrome • Myoclonic absence seizure • Rolandic seizure • Absence seizure
10-19 years	• Head injury • Meningoencephalitis	• Temporal lobe seizure • Progressive myoclonus • Juvenile absence • Juvenile myoclonic epilepsy • Grand mal seizure at arousal • Reading epilepsy
Adult	• Stroke • Head injury • Tumor	• Complex partial seizure

plex seizure, particularly in the elderly. Abrupt abnormal behavior or episodic mental status changes can be epileptic phenomena. Sometimes patients are able to tell the attacks are coming by sensing aura, i.e. noxious smell, stomach upset, dissociating sensation, déjà vu, or vague and warm skin sensations. Information of aura is very important as it may help localization of the seizure focus. Aura may not be felt in primary generalized seizure and some complex partial seizures if seizure propagation is quick.

Generalized seizures are characterized by bilateral hemispheric onset. The distinction between partial seizure and generalized seizure affects the treatment plan because some of the medications working for one may not work for the other or they may make the seizures worse. For example, carbamazepine and oxcarbazepine are good anti-epilepsy drugs for partial seizures, but they may aggravate primary generalized seizures, including 3 Hz spike-wave absence seizures and juvenile myoclonic epilepsy. Ethosuximide is of no use for partial seizure.

Generally, seizure severity and frequency would be aggravated by fatigue, sleep deprivation, and dehydration. (*See Table 4.*) Emotional stress is not a cause of seizure, but it may aggravate seizure frequency. Hyperventilation may lower seizure threshold. There is no direct dietary aggravation except alcohol. Alcohol ingestion not only decreases the seizure threshold by affecting GABA-mediated inhibitory mechanism of seizure activity but also facilitates dehydration. Heat and increased core body temperature decreases seizure threshold. Blinking light stimulation could induce some of the occipital seizures and primary generalized seizures. Concomitant drugs may aggravate seizure. Theophylline, tramadol, bupropion, thorazine, and antiemetics may precipitate seizure attacks in patients who have a history of epileptic syndrome.

The First Seizure. It is estimated that 40-50% of patients presenting with an unprovoked first seizure in adulthood will go on to develop to epilepsy.[11] Approximately one-third of children and adults with seizure disorders initially present a picture of "a single, isolated episode of seizure attack." As defined by the ILAE, a first unprovoked seizure is a seizure occurring in a person older than 1 month of age with no prior history of unprovoked seizures.[12] The definition excludes neonatal seizures or febrile seizures. A seizure flurry occurring within 24 hours with return to baseline between seizures is considered to represent a first seizure by the ILAE guidelines. The recurrence rate after a single seizure is reported to vary between approximately 30% and 50%. Designing prospective studies of the first seizure is problematic. It is very difficult to confirm that a self-reported first seizure actually was the first one and that a subtle partial seizure did not occur at some time prior to the reported "first seizure." Despite these difficulties, many studies report 50% of recurrences occur within 6 months of the initial seizure.

Certain factors increase the risk of seizure recurrence after the first unprovoked seizure. A remote symptomatic first seizure renders a higher recurrence risk than idiopathic or cryptogenic first seizure for both adults and children. The EEG is an important predictor of recurrence. Studies of recurrent risk after the first seizure in childhood demonstrated that the presence of an abnormal EEG renders higher recurrence risk than normal EEG.[13] Epileptiform abnormality furthermore may increase the future recurrent risk. For children, if the first seizure occurs in sleep state, the recurrent risk seems higher for undetermined reasons.[14]

A recently issued practice parameter by the Quality Standards Subcommittees of the American Academy of Neurology and the American Epilepsy Society recommends considering a routine EEG (abnormal 23%), neuro-imaging study with computed tomography (CT) or magnetic resonance imaging (MRI), routine laboratory tests including blood count, electrolytes, blood sugar, toxicology screen, and lumbar puncture depending on specific clinical circumstances, based on the history and physical examination after a first unprovoked seizure.[15]

Antiepileptic drug treatment for the first seizure is a matter of debate. Traditionally, the first single isolated episode of seizure is not treated with antiepileptic drugs. The decisions to treat first

Table 3. Conditions Mimicking Epileptic Syndrome

- Cardiogenic syncope
- Complicated migraine
- Recurrent TIA
- Transient global amnesia
- Orthostatic hypotension
- Psychogenic seizure
- Panic attack
- Metabolic encephalopathy

Table 4. Seizure Aggravating Factors

- Sleep deprivation
- Dehydration
- Increased core body temperature
- Alcohol ingestion
- Stress
- Noncompliance
- Drugs (antipsychotics, antiemetics, tricyclics, tramadol)

seizures were sometimes arbitrary if not empirical. The main argument to start antiepileptic drug treatment for the first seizure is seizure prophylaxis if EEG is abnormal and MRI showed, for example, a definite hemorrhagic lesion or an evidence of oligodendroglioma. The risk of seizure recurrence is also significantly higher in patients with histories of remote cerebral injuries, such as stroke, cerebral contusion, abscess, etc. The risk of epilepsy is higher in elderly patients who have had their first complex partial seizure. Convulsive status epilepticus (seizure lasting more than 15 minutes) could be the first unprovoked seizure. Status epilepticus is more frequent in the younger population than the elderly. The risk of status epilepticus in the population of the first seizure is low, but recurrence is limited to those who have had it before. Therefore, initiating antiepileptic drug treatment after the first unprovoked status epilepticus is definitely recommended.

In the more recent Multicenter Trial for Early Epilepsy and Single Seizures (MESS), immediate treatment after a first unprovoked seizure reduced the risk of recurrence from 50% to 25%, but did not provide a measurable beneficial effect on long-term outcome.[16] The effect of treating a first seizure reduced the chance of seizure recurrence at 2 years, but the recurrence rate between treated and nontreated first seizure was the same by 4 years. The results suggest that antiepileptic drug therapy is effective in reducing the risk of recurrent seizure but does not alter the underlying epileptogenic pathology, and therefore no change in the long-term prognosis is appreciated. Currently, our recommendation is to wait conservatively for a second seizure before initiating treatment unless the patients had status epilepticus or definite evidence of strong epileptogenic lesions. A practice parameter from the American Academy of Neurology recommends that treatment with antiepileptic drugs is not indicated for the prevention of the development of epilepsy, and treatment with antiepileptic drugs may be considered in circumstances where the benefits of reducing the risk of a second seizure outweigh the risk of pharmacological and psychosocial adverse effects.[17] Risks of adverse antiepileptic drug reaction are inevitable. Approximately 15% of patients terminate antiepileptic drug use due to acute adverse and idiosyncratic reactions. Physicians should discuss if it is worth undertaking the risk of acute or chronic adverse effects of antiepileptic drug for a single first seizure. In the MESS trial, injuries occurred more frequently in the patients treated immediately with antiepileptic drugs than in the deferred group, suggesting that treatment with antiepileptic drugs does not protect patients from injuries.

Lastly, it is important to emphasize that the first "obvious" generalized tonic clonic (GTC) seizure is not necessarily the first seizure, as GTC seizures frequently are preceded for months by absence seizure or partial seizure.[18] Only careful history-taking may detect the predictive episodes that would easily escape recognition otherwise. If a patient has already experienced such heralding episodes, "the first seizure" is indeed not the first, and treatment should be initiated promptly.

Utilization of EEG in Treatment of Seizures

EEG is the gold standard to diagnose epilepsy, with the next being good history-taking. The important elements of seizure diagnosis include: age of onset, description of seizure attack, and EEG findings. The EEG provides three vital pieces of information: confirmation of presence of abnormal electrical activity; type of electrical abnormality; and the location of the abnormal activity. A normal EEG does not necessarily rule out seizure because the EEG may be normal in between seizure attacks (interictal period), and frontal lobe seizure activities easily escape detection by routine scalp EEG. In approximately 50% of epileptic patients, a single EEG study may be normal.[19] Sometimes, a few isolated sharp discharges may be reported in a temporal lobe while the patient had no history of seizure. Isolated sharp epileptiform discharges may be seen in up to 15% of healthy control patients.[19] The yield of epileptiform discharges over age 40 after the first seizure is only 7%.[20] Unequivocal epileptic abnormality directs seizure treatment, but EEG is not always conclusive.

EEG may be repeated in situations where reported incidental abnormalities confuse the diagnosis. On the other hand, EEG definitely should be repeated if EEG findings are normal while epilepsy remains a clinical concern. In approximately 10% of patients who have true epileptic seizures, multiple EEGs may be reported as normal. Epileptiform discharges originating from the primary motor cortex may not be detected by a routine EEG because the inter-electrode distance may be too large in the standard international scalp system to pick up activities originating from pin-pointed foci on the narrow motor strip. Likewise, epileptiform discharges from insular cortex, involution cortex in the sylvian fissure, mesial frontal supplementary cortex, and from the hippocampus/amygdala may not readily be detected by routine scalp EEGs. Special recording techniques will be utilized in these situations to increase yield of EEG recordings. Prolonged sleep state EEG may increase the yield of epileptiform discharge by 20%; however, clinical usefulness of sleep-deprived EEG is controversial. Sleep-deprived EEG is reported as either being helpful

or as having no significant benefit. In my experience, sleep-deprived EEG is more useful in the context of prolonged EEG recordings rather than the routine EEG recording setting because longer recording duration increases yield of abnormalities by more chance of discovering interictal discharges. Twenty-four-hour outpatient ambulatory EEG monitoring can be utilized to demonstrate epileptiform discharges in suspicious cases in which routine EEG showed no evidence of seizure. They are more helpful than simply repeating a routine EEG.

EEG recordings may be performed with extra electrodes. Double-density scalp electrodes may be useful to search for seizure focus in the frontal neocortex. Upon judgment by epileptology specialists, sphenoidal electrodes may be placed to capture discharges from mesial temporal lobe structures. Nasopharyngeal electrodes have been almost abandoned because of the discomfort and low signal-to-noise ratio. Modern EEG recording techniques have improved the detection rate of epileptic phenomena. If available, a continuous video-EEG monitoring study should be recommended for intractable seizure and potential psychogenic seizure to expedite the definitive diagnosis rather than repeating routine scalp EEGs. A video/EEG monitoring study is invaluable in evaluation of questionable seizure cases in which the patients remain intractable despite therapy, particularly in the setting of normal EEGs.

Selection of Antiepileptic Drug

There are 16 antiepileptic drugs commonly available in the United States. The goal in epilepsy treatment is complete freedom from seizures without adverse effects of medications. The availability of many antiepileptic drugs with different mechanisms and different pharmacokinetics makes the selection more challenging. The evidence for efficacy is not equal for all antiepileptic drugs. There is no evidence of differential efficacy among antiepileptic drugs against specific partial seizure types. An antiepileptic drug effective against complex partial seizure is likely effective to simple partial seizures and partial complex seizures with secondarily generalization. The first-generation antiepileptic drugs are often believed to have FDA-approved indications, but there were not actual approvals. The FDA granted indications based on the established benefit while they have stayed on the market for a long time. Any new antiepileptic drug must be compared with carbamazepine (CBZ), the archetype first-generation antiepileptic drug, to prove superiority for monotherapy indications. New antiepileptic drugs have demonstrated non-inferior efficacy or benefit of adjunctive therapy, but not many antiepileptic drugs have proven monotherapy superiority due to ethical difficulties in designing such a drug study.

The most modern principle of the pharmacological treatment of seizure is to start with monotherapy with a broad-spectrum antiepileptic drug covering multiple seizure types.[21] Carbamazepine, phenytoin, phenobarbital, and valproate are all effective in reducing the frequency of partial seizures. For tonic-clonic seizures, valproate, phenytoin, and carbamazepine are generally effective. Among the newer generation antiepileptic drugs, oxcarbazepine and topiramate are FDA-approved as monotherapy in treatment of partial seizure disorders.[22] However, lamotrigine, zonisamide, levetiracetam, and gabapentin frequently are considered for the same purpose.[23] Lamotrigine, while not FDA approved as initial therapy, is approved for monotherapy. It is approved for conversion to monotherapy from other medications.

Phenobarbital (PNB) is the most potent, least expensive, and the most widely available antiepileptic drug on the market in the world. The World Health Organization recommends its use as first-line for partial and generalized tonic-clonic seizures in developing countries.[24] PNB is a GABA inhibitory receptor enhancer, prolonging the chloride channel opening, and blocking the sodium channel.[25] Although PNB has been most widely used since 1948, drowsiness sometimes may be intolerable. If PNB is selected for therapy, it is recommended to be used within the recommended therapeutic range to minimize the sedative effect. To minimize the sedative effect, the starting dose should be low (60 mg a day). PNB is rapidly and completely absorbed following oral doses and is eliminated very slowly. The elimination half-life is as long as 130 hours. Fifty-five percent of PNB is bound to plasma proteins and is widely distributed throughout the body. PNB is a strong hepatic enzyme inducer, and its use necessitates adjustment of other concomitant drugs that are metabolized by the liver. It is not an uncommon occurrence that discontinuation of PNB in a patient receiving multiple antiepileptic drugs paradoxically seems to improve seizure control by decreasing hepatic induction. In fact, PNB causes paradoxical seizure aggravation in supratherapeutic levels. Other side effects associated with PNB are porphyria, osteomalacia, and aggressive behavior changes. PNB is prone to cause withdrawal seizure after its abrupt discontinuation.

Phenytoin (PHT, Dilantin) was the most popular antiepileptic drug until recently. It is a sodium channel blocker. It is inexpensive and easy to start, but may be difficult in maintaining the optimal steady therapeutic level in serum due to Michaelis-Menten's nonlinear pharmacokinetics, which means that the metabolism of the drug saturates. The result is that a small-dose increment in the middle therapeutic level may cause a dramatic increase of the serum drug level to cause overdosage. A starting dose of 5 mg per kilogram body weight raises the plasma concentration within the target range of 10-20 micrograms per milliliter in most patients. Gastrointestinal absorption is also saturated. For example, doses of 20 mg/kg given as a single bolus may result in lower concentrations than four equally spaced doses of 5 mg/kg. Side effects of PHT include ataxia, nausea, diplopia, hirsuitism, folate deficiency, osteomalacia, and gingival hyperplasia. Institutionalized patients are more affected by the side effects due to prolonged exposure. Gingival hyperplasia may be preventable by regular gum brushing. Ninety percent of PHT is protein bound in serum, and protein bound PHT is pharmacologically inactive. Only free PHT has an active anticonvulsant effect. One unit of free PHT is equivalent to 10 units of total PHT level. Therefore, free PHT level 3.0 is equivalent to total PHT level 30, and a patient may have signs of toxicity. PHT toxicity is aggravated by hypoalbuminemia, liver failure, malnutrition, and alcoholism.[26]

Carbamazepine (CBZ, Tegretol) is the least sedating agent among the first-generation antiepileptic drugs. CBZ acts by inhibiting repetitive action potentials by blocking voltage-dependent sodium channels. It has linear pharmacokinetics and is easy to titrate. It

has been regarded as a "gold standard antiepileptic drug" among first-generation drugs since the VA cooperative studies demonstrated better tolerability than other first-generation antiepileptic drugs. Traditionally CBZ was the best choice for treatment of complex partial seizure of any age group. The starting dose should be as small as 200 mg to 300 mg per day. Elimination half-life varies in the range between 8-20 hours. Hepatic induction may occur so that serum CBZ level will abruptly drop in 3-5 weeks after initiation. Maintenance doses of CBZ have to be increased according with the spontaneous drop of the serum concentration. CBZ is less tolerated in the elderly due to GI upset, nausea, and vomiting. 10, 11-epoxide is a problematic toxic metabolite of CBZ. Serious skin hypersensitive reactions have been associated with a polymorphism in the tissue necrosis factor alpha promoter gene and, therefore, may have a family history of skin reaction. Dizziness and diplopia are common side effects in supratherapeutic range. Agranulocytosis and aplastic anemia occurred in very rare incidence (2/500,000). CBZ may aggravate absence seizure, juvenile myoclonic epilepsy, and hereditary seizure disorders relating sodium channel mutation (for example: Dravet syndrome).[27]

PNB, PHT, and CBZ are strong hepatic enzyme inducers. They induce hepatic catabolism of coumadin, digoxin, oral contraceptives, and many oncology chemotherapy agents. The dose adjustment may be necessary if patients are using any of the medications.

Primidone (PMD, Mysoline) is a phenobarbital analog and was used frequently because it was believed to be less sedating than PNB. However, it turned out to be the least tolerable antiepileptic drug among the first-generation antiepileptic drugs in the comparative study[28] and thus lost popularity. PMD is still a useful drug in treatment of essential tremor.

Valproic acid (VPA, Depakote) is a potent broad-spectrum AED. The compound is fat soluble and works by proposed multiple mechanism including GABA reuptake inhibition, reducing sustained, repetitive, high-frequency firing by blocking voltage-sensitive sodium channels, or by activating calcium-dependent potassium conductance. It is very effective in treating partial and generalized seizure. VPA is known for hair loss, weight gain, tremor, reversible thrombocytopenia, and rare liver failure. VPA may be preferably replaced by lamotrigine (LMT). Unlike PNB or CBZ, VPA is an inhibitor of hepatic catabolic enzyme. Concomitant use of VPA and LMT will significantly increase the elimination half life of LMT. VPA is also effective for all type of generalized seizure. VPA has a proven teratogenic effect to the fetus, and is not recommended in women with childbearing potential.[29] VPA should be avoided for infants younger than 1 year old for risk of liver failure and pancreatitis. The starting dose is 250 mg bid of Depakote, 500 mg per day if using the slow-releasing form (Depakote ER). The slow-releasing form is preferred to maintain the stable therapeutic concentration.

Ethosuximide (ETX, Zarontin) is used for patients with uncomplicated absence seizures. It blocks low threshold, transient, voltage-dependent calcium channels in thalamic neurons.[30] The starting dose is 500 mg daily, and the dose should be titrated slowly up to 2000 mg. The common side effects of ethosuximide include GI upset, ataxia, and lethargy. The severity of the side effects is not dose dependent.

Oxcarbazepine (OXC, Trileptal) is a structural analogue of CBZ and is better tolerated than CBZ because it is less toxic, has less hepatic enzyme induction, and has fewer drug interactions. This drug is a designed prodrug that undergoes presystemic reduction to 10, 11-dehidro-10-hydroxy-carbamazepine which is known as the monohydroxylated derivative (MHD). MHD is the active form of OXC. The metabolic pathway totally bypasses formation of 10, 11-epoxide, unlike CBZ metabolism. Unlike CBZ, OXC does not induce its own metabolism. OXC significantly reduces the bioavailability of oral contraceptives. Concomitant use of verapamil may decrease MHD bioavailability. Side effects of OXC are similar to but less than CBZ. Somnolence, headache, ataxia, nausea, and diplopia were frequently reported. It should be noted that OXC has a higher incidence of hyponatremia than CBZ. OXC has no role for treatment of primary generalized seizure.

Lamotrigine (LMT, Lamictal) is equally as effective as CBZ and covers both partial and generalized seizure disorders. Unlike CBZ or PHT, LMT selectively blocks the slow, inactivated state of sodium channels, which inhibits the release of glutamate. LMT also inhibits the calcium channel. Because of the multi-pharmacological actions, LMT is an effective broad-spectrum AED for partial, absence, and some myoclonic seizures. It is approved for use in Lennox-Gastaut syndrome and bipolar disorder. Absorption from the GI tract is rapid and complete. The bioavailability achieves up to 98%. The elimination half-life is about 22 hours. The common side effects in LMT monotherapy include ataxia, dizziness, rhinitis, and headache. LMT has less effect on higher cognitive function. LMT does not reduce bone density with long-term use. The only, but rare, serious side effect is a hypersensitivity reaction presenting as skin rash. A high introductory dose of LMT may increase the risk of Steven-Johnson syndrome. It is always wise to start LMT from the small dose, i.e., 25 mg bid. If a patient has been already on VPA, as the half-life of LMT will be extremely prolonged and potentially increase the risk of skin rash, the smallest initial dose (i.e., 25 mg a day) and slower titration is recommended.[31]

Tiagabine (TGB, Gabitril) is a selective inhibitor of the GABA reuptake process in glial cells. The mechanism is indirect enhancement of GABA receptor functions. TGB is indicated for simple partial seizures and complex partial seizures and is not indicated for absence seizure or other primary generalized seizures. The elimination half-life is about 7 hours. The common side effects are dizziness, fatigue, generalized weakness, tremor, confusion, and depression. Tiagabine rarely causes paradoxical aggravation of seizure resulting in nonconvulsive status epilepticus in patients with epilepsy.

Topiramate (TPM, Topamax) is broad spectrum multi-mechanism antiepileptic drug.[32] It is not only a voltage-dependent sodium channel blocker, but also a blocker of glutamate receptor of AMPA type, calcium channel blocker, and weak inhibitor of CNS carbonic anhydrase. TPM is effective in treating partial seizure, primary generalized tonic-clonic seizures, atonic, and myoclonic seizures.[33] Because 90% of TPM is absorbed from the GI tract, high-fat meals may decrease the rate of absorption. The elimination half-life is about 19 to 23 hours. The patients who have renal insufficiency

have a decreased clearance of TPM, necessitating up to 50% of dose reduction. Common adverse effects include burning/tingling sensation of fingertips, paresthesia, and weight loss. Word-finding difficulty (dysnomia) may be encountered if the dose is typically above 300 mg/day, but sensitive patients may have this in less than 50 mg/day doses. Kidney stone formation may be aggravated in patients who have a previous history of it. TPM is contraindicated in patients with open-angle glaucoma. Although the package insert instructs initial dose of 50 mg a day with 50 mg/week dosage increments, lower initial doses of 25 mg a day with 25 mg/week dosage increase are better tolerated in any age group. Patients may be more compliant with the medication regimen using the slower titration dosing plan. "Start small and increase slowly" is a helpful general principle in the outpatient clinic.

Zonisamide (ZNS, Zonegran) is a multi-mechanism broad spectrum anticonvulsant developed in Japan and has become the most popular broad coverage antiepileptic drug in the Pacific countries. The mechanism includes voltage-dependent sodium channel blocking, voltage-dependent T-type calcium channel blocking, and inhibiting the release of excitatory neurotransmitter amino-acids. Japanese studies demonstrated evidence of non-inferior efficacy in comparison to carbamazepine.[34,35] Although not approved in the United States, monotherapy use is frequently tried in Japan and Europe. ZNS is useful for treatment of partial seizures and generalized seizures including absence seizures and JME. There was no reported teratogenic effect of zonisamide in pregnant women with epilepsy. ZNS has been increasingly acknowledged as a safe and effective agent in monotherapy as well as adjunctive therapy.[36] About 70% of ZNS is metabolized in the liver, and 30% is eliminated in urine without being metabolized. The elimination half-life is very long, up to 65 hours, which enables once-per-day dose regimen. The most common side effects reported by patients are GI upset, headache, and weight reduction. Kidney stone is a rare side effect. Oligohidrosis (decreased sweating) may occur in the pediatric age group. The medication is also useful for treatment of trigeminal neuralgia (TN) and reflex sympathetic dystrophy (RSD).[37] The starting dose is 100 mg once pera day. Some patients may do well with 50 mg per day. The maximum dose is 300-400 mg per day.

Levetiracetam (LEV, Keppra) has been increasing in popularity among the newer generation antiepileptic drugs. It has a completely unique mechanism of action: it affects modulators of GABA; it has a specific binding site in CNS (synaptic protein SV2A); and it impedes the process of chronic kindling of epileptic activity, which may recruit more epileptogenic neurons and enlarge seizure irritable zone. There are no known drug interactions or hepatic enzyme induction. LEV is more effective for chronic seizure than for acute symptomatic seizure.[38,39] The elimination half-life is about 7 hours. LEV was recently found equivalent to controlled-release CBZ in a large trial that earned LEV approval by the European Medicines Agency for initial therapy of partial seizures. It is also helpful for photosensitive epilepsy, juvenile myoclonic epilepsy, post-hypoxic myoclonus, and Lance-Adams syndrome. Common side effects include somnolence, lethargy, dizziness, headache, and behavioral changes, including irritability, aggressiveness, and emotional lability.[40] Smaller doses may be effective for myoclonus starting at 250 mg twice per day. The dose may be increased slowly up to 3000 mg per day in two divided doses.

Gabapentin (GPN, Neurontin) is a GABA analogue and was originally designed to act on GABA receptors by mimicking GABA molecules, but instead has been found to block the calcium channel. It exerts a mild to moderate anticonvulsive effect against partial seizures but was proven inferior to CBZ in partial seizure. GPN monotherapy is not beneficial for intractable partial complex seizures. It has decreased in popularity in seizure treatment but is used more for neuropathic pain. It is still a valuable agent because it is not metabolized by hepatic enzymes, is exclusively excreted through the kidney, and is less price-prohibiting than pregabalin and levetriacetam. The real value of GPN is absence of significant drug interaction. Common side effects are weight gain and gait ataxia, particularly in adults. Starting dose is 300 mg twice per day, and may be titrated to 900-1200 mg per day. The dose can be safely escalated up to 3600-4000 mg per day. The elderly may be more susceptible to ataxia in higher doses.

Felbamate (FBM, Felbatol) is a glutamate blocker of NMDA type. FBM is a very potent anticonvulsant. It is the most effective for treatment of Lennox-Gastaut syndrome. Adverse effects of FBM include anorexia, weight reduction, and, at times, psychotic reaction in persons with frontal lobe seizures. FBM is also known for hepatic failure and bone marrow suppression. FBM treatment is rarely initiated in the primary care clinic. It is important to be vigilant of progressive medical side effects and periodically check CBC and electrolytes. Practice advisory is useful for further detail.[41]

Pregabalin (PGB, Lyrica) is similar to gabapentin in the way it does not act on GABA receptors, but binds presynaptically to the alpha-2-delta subunit of the voltage gated calcium channel. It does not block the calcium ions but it modulates the influx in excited neurons. It only acts in the brain and spinal cord and does not affect calcium channels of any other part of the body. PGB is significantly more potent than GPN, but has a favorable side effect profile. The most frequently reported side effects are dizziness, somnolence, and weight gain. The starting dose is 50 mg per day, and target dose is 300 mg per day in two divided doses.

Overall, the selection of the most appropriate anticonvulsant relies upon understanding the different stages of the human life cycle and varying physiology. Younger patients may better tolerate a hepatic enzyme inducer, and the elderly tolerate it less. Older patients may be more susceptible to sedating side effects, while younger patients may worry more about cognitive side effects. From the primary care standpoint, the best antiepileptic drug choices for a patient are wide-spectrum, low-toxicity agents that start from a low dose and increase slowly. Phenytoin was traditionally a first agent to start for seizure treatment. Valproic acid and/or carbamazepine were the second-line agents. Now, lamotrigine, topiramate, zonisamide, and levetiracetam are more frequently used as the first agents. Topiramate and valproic acid may be used preferably if there is concomitant migraine syndrome. Topiramate, zonisamide, and felbamate may cause weight reduction, while valproic acid, gabapentin, and pregabalin cause weight gain. Valproic acid is avoided in epileptic women with child-bearing capability.

The choice of the anticonvulsant is affected by the altered state of physiology and vulnerability to various adverse effects. Newer generation drugs generally are less sedating and less influenced by hepatic enzyme. If patients fail to obtain adequate seizure control (more than one per 6 months) despite the first medication, neurology consultation is always beneficial for their care.

Elderly Seizure Issues

Seizures in the elderly are often favorably managed with the use of antiepileptic drug therapy, although the treatment outcome is often affected by compliance in the elderly. If complicated with memory difficulty, elderly patients may have difficulty in maintaining round-the-clock ingestion of antiepileptic drugs at multiple times in a day, particularly when a patient lives alone or family support is poor. In such situations, a once-a-day regimen is preferred to maintain compliance. Compliance may be ensured by occasional checks of blood levels if seizure control deteriorates. The compliance of antiepileptic drug use may be monitored by using a seizure calendar and a pill box. Drug absorption from GI tract becomes less reliable in the elderly. A delayed release form of fat-soluble valproic acid may be a reasonable choice if a once-a-day phenytoin regimen is not reliable due to erratic absorption. Zonisamide has sufficiently long half-life so that it may be used once a day. Serum drug level checks are not mandatory in the newer generation antiepileptic drugs because once the drug shows effectiveness, the dose may be slowly increased to the point that patients have maximum benefit or have side effects. The prognosis of seizure control appears better in the elderly than in younger populations if treated appropriately with rapid assessment and effective drug selection.[42] The susceptibility to side effects increases in the elderly. Elderly patients also have polypharmacy issues. Hepatic enzyme induction of phenytoin, phenobarbital, and carbamazepine are often problematic as it may reduce efficacy of concomitant medications like coumadin and digoxin. The first-generation antiepileptic drugs are more likely to cause drug interactions. Carbamazepine may be less tolerable in some elderly due to fatigue and increasing incidence of GI side effects. Gabapentin is a good antiepileptic drug because it does not interact with liver enzyme and is preferred in polypharmacy patients. However, the dose should be reduced if renal insufficiency is a comorbidity, and it may increase the risk of unsteadiness and ataxia even in the usual dose that younger patients could tolerate. New generation antiepileptic drugs are generally better tolerated in elderly. Nevertheless, "start small and increase slowly" should be kept in mind.

Driving Issues

Most states prohibit patients from driving motor vehicles for six months after a recurrence of seizure attack in which consciousness was lost. The patients may be allowed to drive again if they experience a seizure-free period of at least 6 months with contingent use of current anticonvulsants in the United States. The obligatory seizure-free period is determined to be one year in the United Kingdom and two years in Japan. In some states, loss of consciousness may cause temporary suspension of driving privileges regardless of its cause. Patients should comply with the local state law. Driving is allowed if a patient does not lose consciousness in partial seizures or if a patient has only nocturnal seizure out of sleep. Even after the seizure-free period, physicians should advise patients not to drive when excessively tired, sleep-deprived, or driving long distances. Alcohol ingestion is absolutely contraindicated to ensure the maximum protection from seizure recurrence.[43]

Intractable Seizure

In 30-40% of patients with epilepsy, seizure will persist despite maximum dosing with multiple antiepileptic drugs. Intractable seizure generally is defined as frequent seizure recurring more than once a month despite multiple trials of a maximized dose of antiepileptic drugs. Nevertheless, a few factors must be excluded before the diagnosis of drug-resistant intractable seizure is concluded. First, the diagnosis should be reassessed. As mentioned previously, 30% of patients with intractable seizures in a university-based epilepsy program actually have psychogenic seizures.[44] All other possible non-epileptic seizure disorders should be filtered out, including migraine variants, syncope, paroxysmal movement disorders, and others.

The second issue is incorrect antiepileptic drug selection. Exacerbation of absence seizure and juvenile myoclonic epilepsy by carbamazepine is a good example. Rarely, myoclonic seizure may be aggravated by lamotrigene. Topiramate and levetiracetam may aggravate partial seizures in a small percentage of patients for an undetermined reason. A supratherapeutic dose of barbiturate may aggravate seizures. Concomitant proconvulsive prescriptions (for example, tramadol, antiemetics, bupropion, tricyclics) should be minimized to avoid iatrogenic intractable seizures. Even with eliminating all of these possible seizure aggravating factors, up to 15-25% of patients remain refractory to antiepileptic drugs. If a patient failed with one medication, a second agent may be tried. However, the likelihood of successful seizure control is smaller in the second agent, and the third, and so on.[45]

According to Morrell, chronic uncontrolled seizure focus may extend the epileptogenic activity, which recruits more neurons to participate in its activity by chronic bombardments of interictal signals by axonal transmissions. The process is called the secondary epileptogenesis. The secondary epileptogenesis is believed to be more prominent in AVM and metastatic tumors. If the chronic seizure duration is sufficiently long, it would start making another seizure focus at the symmetrical point on the contralateral hemisphere; that is called "a mirror focus."[46] Although the phenomenon is better demonstrated in animal models than in human epilepsy, it is speculated that same process will occur in the chronic temporal lobe epilepsy, and the seizure process eventually becomes bilateral, independent, and more resistant to pharmacological intervention. Chronic seizures also affect brain function by the development of short-term memory problems and depression. AVM lesions may generate highly epileptogenic foci as leakage of blood from pathologic tissue makes a hemosiderin deposit in the surrounding cortical tissue, which may induce peroxidation degenerative process that becomes more irritable and causes strong epileptogenesis.[47]

The expectation of seizure remission varies according to the

type of seizure. For example, the majority of patients with primary generalized epilepsies are expected to achieve seizure freedom with medication, while partial seizure patients may achieve only 30-70% freedom from seizures by antiepileptic drug manipulation. Refractory epilepsy could be identified in 12-18 months. Medically intractable seizure may be an indication for epilepsy surgery.

Vagus Nerve Stimulation

Vagus nerve stimulation (VNS) therapy is an established method for treating patients with refractory seizures that has been used since 1988. The long-term efficacy of vagus nerve stimulation was studied. With average treatment time of 20 months, 40% of patients with partial seizures and 62% of patients with Lennox-Gastaut syndrome had more than 50% seizure reduction.[48] Side effects were mild. VNS is a safe and effective treatment for refractory epilepsy. The efficacy of VNS has been accepted for pharmacologically refractory partial seizures in which surgical treatment may not be feasible. One VNS study for generalized seizure patients demonstrated greater than 50% reduction in seizure frequency and reduced antiepileptic drug regimen in 36% of idiopathic generalized epilepsy cases that were medically intractable.[49] VNS seems to be a broad-spectrum treatment for epilepsy. Improvement is not immediate but increases over 18-24 months of treatment. Side effects are mainly stimulation-related and reversible laryngeal discomforts that tend to decrease over time. No idiosyncratic side-effects have been reported in 12 years of experience, and VNS does not interact with antiepileptic drugs. VNS does not have cognitive and systemic side effects.[50] VNS is a viable treatment option for low-IQ patients with pharmacoresistant epilepsy who are living in long-term care facilities. One study for institutionalized patients demonstrated seizure reduction of antiepileptic medications from 3.3 per subject at baseline to an average of 2.3 per subject after 2 years with improvement in cognitive functions and quality of life.[51] The effectiveness of VNS is maintained during prolonged stimulation, and overall seizure control continues to improve with time.[52]

Surgical Options

Surgical options for epilepsy have become an important consideration in the past two decades. Presurgical evaluation using video-EEG monitoring studies in epilepsy monitoring units, and functional neuroimaging studies such as PET and SPECT scans may help determine if patients are surgical candidates. Patients with a clearly defined seizure focus by EEG and localization that correlates clearly with visible structural abnormalities (tumor, dysplasia, vascular anomaly, etc.) have shown favorable outcomes by appropriate resective surgical procedures. If there is no visible lesion in the cerebral cortex by MRI study, the cause of the seizure is most likely due to low-grade cortical dysplasia[53] and the post-surgical outcome is mildly less favorable than those with an MRI-visible lesion. To maximize seizure reduction in such non-visible lesion cases, the seizure foci and irritable cortical area have to be clearly defined by intracranial EEG electrodes and PET/SPECT scan to ascertain the localization of a surgically treatable portion. With identifiable lesions, favorable outcome of epilepsy surgery is greater in temporal lobe epilepsy (seizure free 70-80%) than extra-temporal lobe epilepsy (seizure free 50-60%).[54,55] It must be emphasized, however, that non-lesional epilepsy cases have lower seizure-free rates and, moreover, any seizure surgery does not guarantee seizure-free state, even in the most straightforward temporal lobe cases. Surgical treatment is a consideration for intractable seizure patients to improve the quality of life by reducing seizure occurrence. For this population, it is not a realistic goal to make them 100% seizure free and free of medications. Most patients remain on some antiepileptic drug but perhaps lesser amounts to maintain reasonable seizure control.

There was a randomized, controlled prospective trial of surgery for temporal lobe epilepsy.[56] Eighty patients were randomly assigned to mesial temporal lobectomy or to continue antiepileptic drug therapy for one year. At one year, 58% of patients who underwent surgery were seizure free, while only 8% of the patients who stayed with medication treatment were seizure free ($p < 0.001$). The study suggested that timely surgical interventions might be a desirable option for those patients with intractable temporal lobe epilepsy who do not respond to antiepileptic drug therapy. Although epilepsy surgery does not guarantee patients to be seizure free, it may offer significant possibility of symptomatic palliation and improve patients' quality of life. Surgical options should be considered as a proactive choice rather than a last resort. Timely identification of potential candidates for surgery should be discussed with available neurologists and epileptologists[57] for available updated options.

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Physician CME Questions

21. Which factor is the most predictive of seizure recurrence in the first unprovoked seizure?
    A. Positive family history
    B. Abnormal EEG
    C. Alcohol abuse
    D. Abnormal CT

22. All of the these drugs could cause weight reduction *except*:
    A. topiramate.
    B. zonisamide.
    C. pregabalin.
    D. felbamate.

23. How likely is it that a single routine EEG of a chronic epilepsy patient is normal?
    A. 100%
    B. 75%
    C. 50%
    D. 25%

24. Which factor does *not* make seizure symptoms worse?
    A. Lack of sleep
    B. Emotional stress
    C. Alcohol ingestion
    D. Too much salt in diet

CME Answer Key: 21. B; 22. C; 23. C; 24. D

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PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert*, *Clinical Oncology Alert*, *Critical Care Alert*, *Infectious Disease Alert*, *Internal Medicine Alert*, *Neurology Alert*, *OB/GYN Clinical Alert*, *Primary Care Reports*, *Travel Medicine Advisor*.

Safety of Inhaled Anticholinergics for COPD Scrutinized

In the Issue: Ongoing safety review of tiotropium; raloxifene reduces the risk of endometrial cancer; one-day treatment with famciclovir may be as effective as 3-day treatment with valacyclovir; new Clinical Practice Guideline from the American College of Physicians regarding pharmacologic treatment for low bone density and osteoporosis; FDA Actions.

THE SAFETY OF INHALED ANTICHOLINERGICS FOR the treatment of chronic obstructive pulmonary disease (COPD) has come under scrutiny in recent months. In July, the FDA issued an "Early Communication" about an ongoing safety review of tiotropium (Spiriva®) the most widely used agent for the treatment of COPD. The review is focused on a possible increased risk of stroke and is based on a pooled analysis of 29 trials which showed the risk of stroke at 8 patients per 1000 treated with tiotropium versus 6 patients per 1000 treated with placebo.

Now two new studies suggest that inhaled anticholinergics (ipratropium [Atrovent®] and tiotropium) increase the risk for all-cause mortality and cardiovascular disease in patients with COPD. In a large meta-analysis (*JAMA* 2008;300: 1439-1450), researchers reviewed 17 trials involving nearly 15,000 patients with COPD who were randomized to an inhaled anticholinergic or control. The primary outcome was a composite of cardiovascular death, MI, or stroke. The secondary outcome was all-cause mortality. The primary outcome occurred in 1.8% of patients receiving inhaled anticholinergics and 1.2% of patients receiving control therapy (RR 1.58, 95% CI, 1.21-2.06; $P < 0.001$). Inhaled anticholinergics significantly increased risk of MI, cardiovascular death, and all-cause mortality (RR 1.26). When the analysis was restricted to long-term trials, the risk was even greater for cardiovascular death, MI, or stroke (RR 1.73). The number needed to harm for MI was 174 per year, while the number needed to harm for cardiovascular death was 40 per year. The authors concluded that inhaled anticholinergics are associated with a significantly increased risk of cardiovascular death, MI, or stroke among patients with COPD.

In a second nested, case-control study (*Ann Intern Med* 2008;149:380-390), the National Veterans Affairs databases were used to review all-cause mortality, respiratory and cardiovascular deaths, and exposure to COPD medications including inhaled corticosteroids, ipratropium, long-acting beta agonists, and theophylline in the 6 months preceding death. The adjusted odds ratios for all-cause mortality were 0.80 for inhaled chronic steroids, 1.11 for ipratropium, 0.92 for long-acting beta agonists, and 1.05 for theophylline. Ipratropium was associated with increased cardiovascular deaths (OR 1.34), whereas inhaled corticosteroids were associated

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5468. E-mail: paula.cousins@ahcmedia.com.

with reduced risk for cardiovascular death (OR 0.80). The authors conclude that there is a possible association between ipratropium and elevated risk for all-cause and cardiovascular death and that further studies are needed. They also suggest that the risk of ipratropium may be somewhat mitigated by concomitant use of inhaled corticosteroids, but caution should be exercised if ipratropium is used alone in patients with recently diagnosed COPD.

Raloxifene reduces endometrial cancer risk

It is well known that raloxifene reduces the risk of breast cancer; now there is evidence that the drug reduces the risk of endometrial cancer as well. Raloxifene (Evista®) is a selective estrogen receptor modulator (SERM) that is indicated for treatment and prevention of osteoporosis and for breast cancer prevention. Researchers from the University of Pennsylvania compared endometrial cancer rates in women on raloxifene, tamoxifen, and non-users of SERMs in a case-control study of 547 women with endometrial cancer and 1410 controls. After adjustment for other risk factors the odds of endometrial cancer among raloxifene users was 50% that of non-users (OR = 0.50; 95% CI, 0.29-0.85), whereas tamoxifen users had 3 times the odds of developing endometrial cancer compared to raloxifene users (OR = 3.0; 95% CI, 1.3-6.9). Among raloxifene users who developed endometrial cancer, the tumors had a more favorable histologic profile and were predominantly stage I and low grade. The authors conclude that raloxifene users have significantly lower risk of developing endometrial cancer compared with tamoxifen users and SERM non-users, perhaps even suggesting a role for raloxifene and prevention of endometrial cancer (*J Clin Oncol* 2008; 26:4151-4159).

One-day famciclovir = three-day valacyclovir

For patients with recurrent genital herpes outbreaks, one-day treatment with famciclovir may be as effective as 3-day treatment with valacyclovir, according to a new study. In a double-blind parallel group study, 1179 adults with a history of recurrent genital herpes were randomized to receive either famciclovir 1000 mg twice daily for one day vs valacyclovir 500 mg twice daily for 3 days. Patients initiated treatment within 6 hours after a recurrence. Approximately one-third of patients in each group aborted genital herpes outbreaks altogether, but for those who went on to develop lesions, median time to healing was 4.25 days for famciclovir vs 4.08 days for valacyclovir. Time to healing was the same in both groups and the incidence of adverse affects was 23.2% for famciclovir vs 22.3% for valacyclovir. The study demonstrates that a single day of famciclovir (1000 mg twice daily) is equivalent to 3 days of valacyclovir (*Clin Infect Dis* 2008;47:651-658). Other regimens for treatment of recurrent HSV episodes include acyclovir 800 mg 3 times daily for two days or 400 mg three times daily for 3-5 days, famciclovir 125 mg twice a day for 3-5 days, or valacyclovir 500 mg twice daily for 3 days. Both acyclovir and famciclovir are available generically, but acyclovir is considerably less expensive; however, the convenience of a one-day treatment with famciclovir may be worth the extra cost for many patients.

New practice guideline for osteoporosis

The American College of Physicians has issued a Clinical Practice Guideline regarding the pharmacologic treatment of patients with low bone density or osteoporosis (*Ann Intern Med* 2008; 149:404-415). The expert committee recommends that clinicians offer pharmacologic treatment to men and women who have known osteoporosis and to those who have experienced fragility fractures. They also recommend that pharmacologic treatment should be considered for men and women who are at risk of developing osteoporosis and that the choice of pharmacologic treatment should be based on assessment of risk and benefits in individual patients. The guideline reviews different treatment modalities including bisphosphonates, calcitonin, estrogen, teriparatide, SERMs, testosterone, and calcium plus vitamin D. Left unanswered are the questions of duration of treatment with bisphosphonates and the optimal dose of calcium and vitamin D.

FDA actions

The FDA has issued warning letters to Ranbaxy Laboratories Ltd. of India in an Import Alert for the company's generic drugs produced in two Indian plants. The warning letters identify concerns about deviations from U.S. current Good Manufacturing Practice requirements at Ranbaxy's manufacturing facilities and the Import Alert allows officials to detain at the rest border any active pharmaceutical ingredients manufactured at Ranbaxy facilities. Ranbaxy manufacturers more than 30 generic drugs including commonly used antibiotics, antihypertensives, and antivirals. ■

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Cognitive Impairment Progression Blunted by Exercise

Source: Lautenschlager NT, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: A randomized trial. *JAMA* 2008; 300:1027-1037.

CLINICAL TRIALS OF PHARMACOTHERAPY to prevent progression of cognitive decline in those with mild cognitive impairment (MCI) have been disappointing; neither cholinesterase inhibitors (donepezil, rivastigmine, galantamine), vitamin E, nor COX-2 inhibitors has demonstrated any clinically meaningful benefit in placebo-controlled MCI trials.

Observational data are consistent that regular physical activity, even if started late in life, is associated with reduced risk of dementia. Whether exercise might prevent progression in persons with MCI was the subject of this first randomized trial to address the issue.

Subjects (n = 170) with MCI between the ages of 50-77 (mean age, 68.6 years) were randomized to receive either 50-min sessions of moderate-intensity exercise (e.g., brisk walking, ballroom dancing, and swimming) three times weekly vs control (general education about health, including physical activity, diet, alcohol, and stress management). All educational materials were also provided to the intervention group. All participants (control and intervention) wore a pedometer and provided diaries of daily total number of steps. Physical activity and cognitive function were assessed at 6, 12, and 18 months after randomization.

At each assessment point, cognitive scores for the intervention group were better than the control group. The intervention group averaged approximately 6000 more steps/week than the control group. Exercise, averaging as little as 21 min/day, reduces cognitive decline in persons with MCI. ■

Incidentalomas in the Knee

Source: Englund M, et al. Incidental meniscal findings on knee MRI in middle-aged and elderly persons. *N Engl J Med* 2008;359:1108-1115.

ONE OF THE PRIMARY THINGS THAT has stood in the way of definitive diagnosis of acute low back pain is the extraordinarily high rate of false-positive findings seen on plain films, CT, or MRI. Indeed some studies suggest that as many as half of healthy, asymptomatic individuals studied by MRI of the lumbar spine have findings consistent with disk pathology.

Little is known about the frequency of incidental findings seen upon MRI of the knee, since studies generally investigate symptomatic individuals; subsequent radiographic findings, if they correlate with symptomatology, have been taken to support a causal relationship.

Englund et al performed an MRI of the right knee in 991 randomly selected adult subjects ages 50-90 in Massachusetts. Excluded subjects included those with rheumatoid arthritis, knee replacement, terminal illness, or non-ambulatory status.

The incidence of meniscal tears seen ranged from 19% in the youngest women (ages 50-59) to 56% in senior men (ages 70-90). Among the group with radiographic changes of osteoarthritis, the frequency of meniscal tears in symptomatic and asymptomatic individuals was similar (63% vs 60%, respectively). Overall, the majority of persons (60%) with meniscus tears confirmed by MRI had no symptoms referable to the knee.

It appears that as with back MRI, incidental findings of pathology are frequent, and call into question an ironclad attribution of knee symptoms to positive findings on MRI. ■

Hormone Replacement and Skin Health in Menopausal Women

Source: Phillips TJ, et al. Does hormone therapy improve age-related skin changes in postmenopausal women? *J Am Acad Dermatol* 2008;59:397-404.

AS LITTLE AS A DECADE AGO, MENOpausal status alone was the ticket of admission to advocate hormone replacement therapy (HRT). The "story line" went that HRT prevented cognitive decline, improved symptoms, enhanced cardiovascular health, and preserved cutaneous health, i.e., reduced age-related wrinkles, dryness, and laxity. Unfortunately, HRT has failed to live up to numerous of its hopeful claims.

To study the effects of HRT on menopausal women's skin, 485 subjects were randomly assigned to placebo or two different HRT doses in double-blind fashion. Dermatologists evaluated skin wrinkling, laxity, and texture (as did the patients) over a 48-week interval. The mean age of the women was 54 years.

At study end, there were no statistically significant differences in any primary endpoint of the trial. When the data were analyzed for impact of baseline levels of estradiol, race, or age, no meaningful differences were found. During the trial, all study groups enjoyed some skin improvements attributable to daily application of moisturizing cream and sunscreen, but HRT added nothing to this. Claims that HRT provides reduced risk of age-related skin changes are not supported by this trial. ■

Reconfirmation of the Death of Homocysteine

Source: Ebbing M, et al. Mortality and cardiovascular events in patients treated with homocysteine-lowering B vitamins after coronary angiography: A randomized controlled trial. *JAMA* 2008;300:795-804.

HOMOCYSTEINE (HCYS) HAS ALL THE trappings of a first-rate cardiovascular risk factor: as strong an association with CVD endpoints as cholesterol, ease of identification, and simplicity of modulation. Trouble is, trials to date have been unable to show that reductions of homocysteine provide meaningful benefits to patients. Indeed, one recent commentary following a large double-blind intervention-

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al trial of HCYS for cardiovascular endpoints began with "The homocysteine hypothesis is dead … ."

Apparently as undaunted as Mark Twain ("The reports of my death are greatly exaggerated …"), Ebbing et al tested HCYS reduction through B vitamins after coronary angiography. The primary endpoint of the study was all-cause mortality, non-fatal stroke and MI, and hospitalization for unstable angina (composite).

The trial (n = 3096) was designed to follow patients for 4 years, but was stopped at 38 months due to information from another trial that had reported a possible negative effect of B vitamin intervention. B vitamins did reduce HCYS by approximately 30%, but failed to have any impact (positive or negative) upon endpoints. The HCYS hypothesis is still dead. ■

Pramlintide as a Weight-Loss Adjunct

Source: Smith SR, et al. Sustained weight loss following 12-month pramlintide treatment as an adjunct to lifestyle intervention in obesity. *Diabetes Care* 2008;3:1816-1823.

SOMETHING THAT NEITHER MOTHER NOR medical school taught us was that more than one hormone is secreted from the beta cells of the pancreas in response to rising glucose. In conjunction with insulin, the hormone amylin is released. Pramlintide is a synthetic form of amylin. The physiologic effects of amylin include slowed gastric emptying (thereby slowing the rate of glucose delivery to the intestine), suppression of glucagon, and centrally mediated satiety. For addressing obesity, there is great conceptual appeal to an agent that improves satiety.

Smith et al performed a double-blind, placebo-controlled trial of various doses of subcutaneous pramlintide (bid to tid) in obese, nondiabetic subjects, who were also receiving intensive lifestyle (diet/exercise) intervention. The initial 4-month double-blind phase was followed by a 4-month single-blind extension (for those who completed the initial phase without protocol violation).

Weight loss was dose-proportional: At 360 µg twice daily the placebo-corrected weight loss was 3.3 kg at month 4 and 7.2 kg at month 12. No safety concerns were seen. Nausea, which is also the most common adverse event seen in diabetic subjects, was mostly mild to moderate, and improved over time. Nausea is not the mechanism of action, since weight reduction was similar in those who did and did not experience nausea. These initial data are encouraging that pramlintide may find a role in enhancing weight loss when used in conjunction with lifestyle intervention. ■

Undiagnosed Diabetes in Obese Americans

Source: Wee CC, et al. Obesity and undiagnosed diabetes in the U.S. *Diabetes Care* 2008;31:1813-1815.

NO CLINICIAN IS SURPRISED TO SEE that diabetes often goes undiagnosed. Patients can persist with modest symptoms, or even asymptomatically, for protracted periods during the early stages of type 2 diabetes. The fact that literally half of type 2 diabetics have one or more of the traditional complications of diabetes (neuropathy, nephropathy, retinopathy, dermopathy) at the time of clinical diagnosis attests to the fact that diagnosis lags substantially behind disease onset.

Most type 2 diabetics are obese, and obesity provides an environment that promotes insulin resistance, a cardinal dysfunction in early diabetes and pre-diabetes. Hence, scrutiny of obese subjects provides a window of observation into a population felt to be at greater risk for developing diabetes. On the one hand, the clinician might think that the presence of obesity would prompt greater vigilance for diabetes; on the other hand, there is evidence that compared to the non-obese, obese individuals experience delays in receiving preventive care.

From the 1999-2004 NHANES data, it was determined that 9.8% of the population had diabetes (defined as FBG > 126 mg/dL). Slightly more than one-fourth (28.1%) of persons with FBG > 126 mg/dL had not been diagnosed with diabetes. When parsed into BMI categories, normal weight individuals were actually less likely to have undiagnosed diabetes than overweight or obese persons (22.2% vs 32.5% vs 27.4%, respectively). Because more than one-half of undiagnosed diabetes is seen in overweight and obese individuals, enhanced vigilance is appropriate. ■