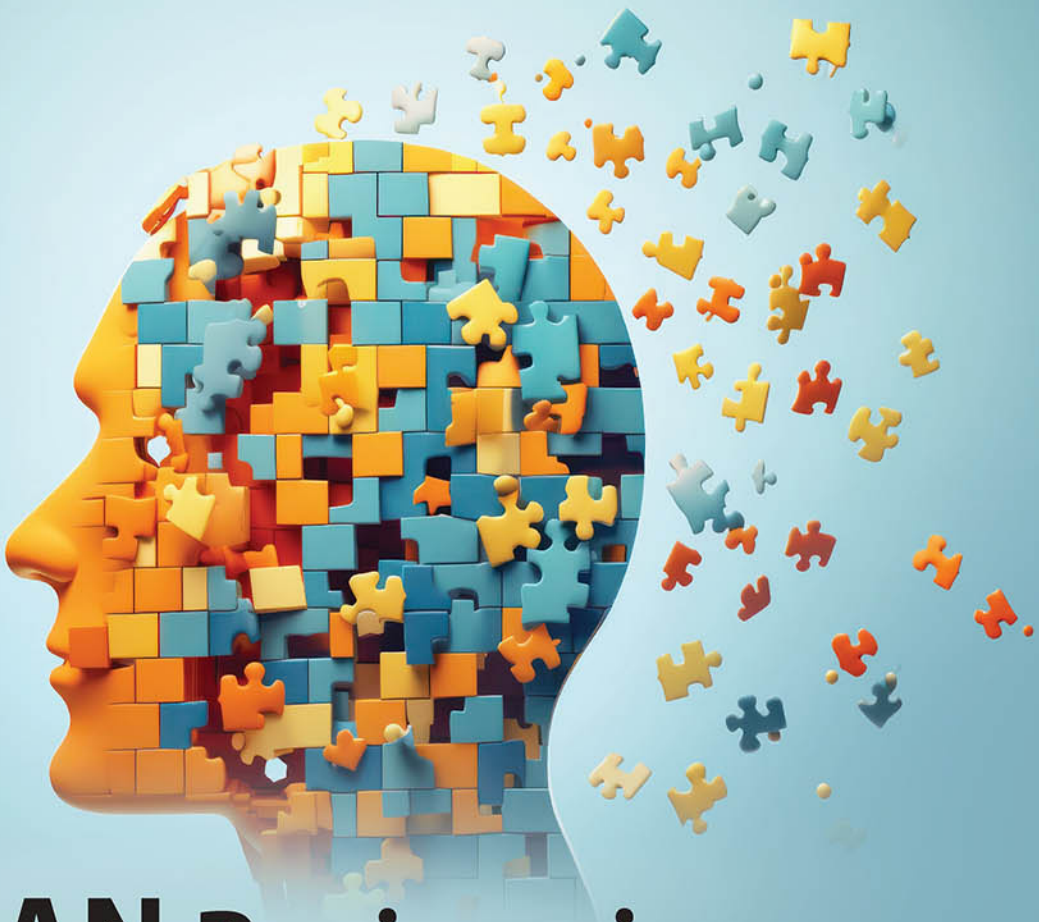

IAN Reviews in Neurology 2024

Dementia

Editors
Sita Jayalakshmi
Sangeeta Ravat

JAYPEE

Contents

CHAPTER 12

Management of Comorbidities of Epilepsy

Bindu Menon, Chandu Premkumar, Praveen Kumar Yadav

ABSTRACT

Comorbidity in persons with epilepsy is very high and diverse. Neurological, psychiatric, cognitive, cardiac, gastrointestinal (GI), somatic, and rheumatological conditions are identified more in persons with epilepsy than in the general population. In the present chapter, we discuss this issue in the context of common epilepsy comorbid conditions: Psychiatric comorbidity, cognitive impairment, attention-deficit hyperactivity disorder, migraine, GI, and endocrine disorders. Current findings, research limitations, and future directions of research efforts are discussed. The treatment of epilepsy requires comprehensive management of these associated conditions to ensure better patient outcomes and a higher quality of life. Optimal management involves multidisciplinary care and the ability to offer personalized treatment.

Keywords: Epilepsy, Comorbidities.

INTRODUCTION

Epilepsy is a chronic neurological disease affecting one in a hundred persons. Comorbidity in persons with epilepsy is very high and diverse. Neurological, psychiatric, cognitive, cardiac, gastrointestinal (GI), somatic and rheumatological conditions are identified more in persons with epilepsy than in the general population. Comorbidities can be a direct link as in patients with stroke. In yet other conditions like psychiatric comorbidities, the relationship could be more complex. Other comorbidities have no relationship as noted in cardiac conditions and could be coincidental. Identifying these comorbidities for comprehensive treatment and improving the quality of life is important.

The goal of epilepsy treatment is often seizure freedom. However, comprehensive care should also involve identifying and managing the comorbidities. Around half of the persons with epilepsy have at least one comorbidity. Larger population-based studies have noted this prevalence to be up to eight times more than the general population. As psychiatric comorbidities are more common, routine screening should be included in the long-term follow-up. The antiseizure medication (ASM) should also be tailored to address the comorbidities. With newer ASMs available, there are fewer pharmacokinetic and pharmacodynamic interactions with better tolerability. Here, we discuss the most common comorbidities of epilepsy in adults.

NEUROPSYCHIATRIC COMORBIDITY

Neurological and psychiatric comorbidities are common in people with epilepsy (PWE), affecting around 30–50% of patients.[1] According to population-based studies, the lifetime prevalence of psychiatric comorbidities is 35%, especially mood and anxiety disorders, while migraines are the most common neurological comorbidity, with a reported prevalence of 20–40%.[2,3]

Researchers agree that psychiatric disorders are more common in patients with epilepsy due to the availability of comprehensive epidemiological data on both adults and children with epilepsy.[4] The overall prevalence of active depression in epilepsy was 23.1%. There was an overall risk increase of 2.7 compared with the general population based on a meta-analysis of 14 population-based studies involving >1,000,000 adult participants.[5] A meta-analysis of 27 studies on anxiety disorders and epilepsy, involving >3,000 participants, found a combined prevalence of anxiety disorder at 20.2%. Generalized anxiety disorder was the most common, accounting for 10.2%.[6] In a meta-analysis of 57 studies involving over 40,000 participants, it was found the pooled prevalence of psychosis was 5.6% in unselected individuals, but it increased to 7% in temporal lobe epilepsy, and the pooled odds ratio for risk of psychosis among PWE compared with controls was 7.8.[7]

About 12% of PWE also experience psychogenic nonepileptic seizures (PNES) according to a meta-analysis. Additionally, 22% of those with PNES also have epilepsy.[8] Even though there is a strong emphasis on developmental disorders, data from pediatric epilepsy patients indicated no significant variances. According to a population-based study of 85 children and adolescents aged 5–15 years with active epilepsy, approximately 33% of the patients had attention deficit hyperactivity disorder (ADHD), 21% had autism spectrum disorder, 7% had depression, and 13% had anxiety.[9] The relationship between epilepsy and psychiatric disorders is complex, arising from a combination of psychosocial and biological factors. Epilepsy continues to be a highly stigmatized condition, leading to discrimination and marginalization.[10]

Patients with epilepsy often experience low self-esteem, social withdrawal, isolation, and distress due to challenges in social interaction, the unpredictability of seizures, and the potential for social embarrassment. Several biological factors contribute to the increased occurrence of psychiatric disorders in these individuals. Neuroimaging studies have found network abnormalities, particularly in the limbic structures, in patients with epilepsy and co-occurring depression.[10]

Various data from prospective observational studies have suggested that there is a bidirectional relationship between epilepsy and psychiatric disorders. Early death in individuals with epilepsy is associated with psychiatric comorbidities. Various factors, such as an increased risk of substance or alcohol abuse, a higher likelihood of injury, and elevated suicide rates can be possible causes.[10] There is a five-fold increased risk of sudden unexpected death in epilepsy (SUDEP) in female patients compared with those without such comorbidities as per the data from a nationwide population-based study.[11]

In primary and secondary care settings, screening tools are available for nearly all major psychiatric conditions in the general population. These tools are cost-effective as they are brief, standardized against the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria, and require fewer resources than a full clinical interview.[10]

The primary aim of any psychiatric intervention should always be to fully alleviate symptoms. However, there is

limited current evidence on how to address psychiatric comorbidities in epilepsy. Nonetheless, there is no reason to believe that guidelines for treating psychiatric disorders on an international level may not apply to epilepsy. It is reasonable to follow psychiatric standards of care while taking into account the specific needs of individuals with epilepsy. This involves understanding the interactions between psychotropic drugs and ASMs, as well as the risk of seizures.[10]

There is a lack of literature about treatment options for individuals with epilepsy and psychiatric comorbidities. Studies have shown that selective serotonin reuptake inhibitors (SSRIs) and newer antidepressants can be used in PWE. Sertraline and citalopram are commonly used as first-line antidepressants for anxiety.[10] Different ASMs such as lamotrigine (LTG) and valproate (VPA) have various effects on mood. LTG has antidepressant effects, while VPA can lead to aggression. Certain antidepressants have been associated with an increased risk of seizures. ASMs such as phenytoin (PHT) and carbamazepine (CBZ) which induce enzymes, can lower the levels of antidepressants, while VPA and newer ASMs do not have the same effect. The connection between ASMs and suicide is not definitive. It is important to monitor side effects such as weight gain (with VPA and CBZ) and hyponatremia (with serotonin and norepinephrine reuptake inhibitors) in combination with CBZ, oxcarbazepine (OXC), and eslicarbazepine (ESL). Caution should be exercised with ASMs that have negative psychotropic effects such as benzodiazepines (BDZ), topiramate (TPM), and levetiracetam (LEV), while others such as LTG, lacosamide (LCM), pregabalin (PGB), and gabapentin are beneficial.[12]

COGNITIVE IMPAIRMENT

Patients with epilepsy often experience cognitive comorbidities that can impact their psychosocial functioning, education, career, emotional and social abilities, as well as overall well-being.[13]

Generally, patients with epilepsy frequently report difficulties with attention, executive functioning, and memory. Up to 70% of untreated patients found these issues before the onset of seizures or early in the diagnostic process.[14] These findings suggest shared mechanisms underlying cognitive and behavioral impairments, as well as seizures in individuals with epilepsy, known as essential comorbidities. Seizure activity in epilepsy can temporarily lead to cognitive impairment. Cognitive impairment may be due to interictal spikes, the adverse effects of ASMs, and can be made worse by mood and behavioral issues. In the DSM-5, having an intellectual disability is generally defined as having a full-scale intelligence quotient (IQ) of ≤65–75, indicating cognitive functioning that is significantly below the population average of 100.[10]

Psychiatric and behavioral issues are 2.5 times more common in children with epilepsy than in their healthy peers. This can be challenging in persons with moderate-to-severe intellectual disabilities due to behavioral issues such as aggression or self-injurious behaviors.[10]

Notable developmental delays, intellectual disabilities, and severe, drug-resistant epilepsy occur in many childhood epilepsy syndromes.[15] These conditions are often referred to as developmental epileptic encephalopathies and include syndromes such as Lennox–Gastaut syndrome and Landau–Kleffner syndrome.

Dementia is an increasingly important cognitive comorbidity of epilepsy. Dementia and epilepsy have a bidirectional relationship, with an increased risk of seizures among those with dementia and an increased risk of dementia for those with epilepsy. To emphasize the importance of understanding cognitive comorbidities in epilepsy, individuals with epilepsy and intellectual

disabilities are at a greater risk of developing dementia compared to those with epilepsy but without intellectual disabilities.[16]

For the diagnosis of cognitive comorbidity and the identification of patients who require more detailed neuropsychological assessment, cognitive screening measures such as the montreal cognitive assessment (MoCA) or mini-mental state examination (MMSE) can be useful.

A formal neuropsychological assessment is a collaborative and holistic process that takes into account biological, neurodevelopmental, psychological, and broader social factors. It is essential for accurately diagnosing cognitive deficits.[10]

Only a few studies have looked at how well medications or neuromodulatory interventions improve cognition, even though a lot of research on cognitive issues in epilepsy is available. Noninvasive neuromodulation for epilepsy is attractive because it could potentially reduce seizure frequency and interictal epileptiform discharge frequency, but there is still limited data on its effects on cognition.[17]

Compared to other types of dementia, epilepsy in Alzheimer's disease (AD) may respond better to ASMs as per a few studies. A thorough discussion with patients and their families and careful weighing of the risks and benefits of undergoing surgery is required, when surgical treatment is considered for epilepsy.[10]

An increasing body of research indicates that modified therapeutic approaches, such as cognitive behavioral therapy (CBT), can be effective in treating anxiety and depression in patients with cognitive impairments.[18] The relationship between AD and epilepsy is not well understood. Preclinical models of AD are important for studying the connections between AD and epilepsy and for developing new ASMs. Limited research exists on ASMs in preclinical models of late-onset epilepsy, and more high-quality randomized controlled trials (RCTs) are needed to determine the therapeutic efficacy of ASMs in AD. Future research should focus on AD patients with subclinical epileptiform activity and utilize tools like video electroencephalogram (EEG) to identify those who might benefit from ASMs.[19]

SLEEP DISORDERS

In persons with epilepsy, sleep disorders are around twice as common compared to healthy controls, and about one-third of PWE report a disturbance in their sleep.[20] Insomnia is common in PWE, with an estimated prevalence of up to 50%.[20] About 10–35% of individuals with epilepsy also experience comorbid obstructive sleep apnea (OSA), and a significantly higher incidence of OSA in those with refractory seizures.[21] With a possible prevalence of up to 89%, OSA seems to be more prevalent in older patients and late-onset epilepsy.[21] In elderly patients, OSA is likely to promote seizure occurrence.[21]

An increased prevalence of OSA in epilepsy is linked to several factors, such as a higher incidence of metabolic syndrome. This is influenced by reduced physical activity and weight-gaining ASMs like VPA.[22] In 28–57% of patients, vagal nerve stimulation (VNS) can also trigger or worsen OSA possibly by inducing adduction of the left vocal cord.[22]

In PWE, excessive daytime sleepiness affects 11–34% of individuals, and 13% experience restless leg syndrome (RLS).[23]

All of these disorders are approximately twice as common in PWE, than in the control group, with odds ratios ranging from 1.7 for insomnia to 4.7 for RLS in epilepsy patients compared to controls.[24,25]

The PWE often experience changes in their sleep patterns, not only because of seizures during the night. Those with juvenile

myoclonic epilepsy (JME) tend to have lower sleep efficiency, less non-rapid eye movement (REM) sleep, reduced time in REM sleep, and increased wakefulness compared to those without epilepsy.[21]

A lack of sleep at night could raise the likelihood of experiencing seizures during the day and night. Mental health issues and difficulties with thinking for PWE result from a cycle of seizures and sleep problems which ultimately reduce their overall quality of life.[21]

The study findings imply that gamma-aminobutyric acid (GABA) enhancers (specifically tiagabine), calcium-channel blockers (like CBZ), synaptic vesicle protein 2A (SV2A) ligands (like LEV), and broad-spectrum ASMs did not have an impact on slow wave sleep (SWS), REM sleep, or sleep efficiency.[26] The impact of ASMs on sleep remains poorly investigated in PWE till date.[27]

When sleep disorders are suspected, diagnostic tests such as actigraphy, home sleep testing, and polysomnography (PSG) are generally recommended by clinical practice guidelines. These recommendations apply to both people with stable epilepsy and those without epilepsy. Individuals with nonstable forms of epilepsy should undergo inpatient or ambulatory video-PSG with extended EEG coverage. This is considered appropriate for diagnosing sleep-disordered breathing (SDB) and other comorbid sleep disorders, as well as for identifying unreported nocturnal epileptic seizures that may contribute to sleep disruption.[21] First-generation ASM, including barbiturates, BDZ, PHT, and phenobarbital (PB), have been found to decrease the duration of REM and SWS. These medications have the potential to impact the quality and duration of sleep due to their effects on REM and SWS patterns. BDZ, LTG, LEV, gabapentin, and PGB are known to increase sleep efficiency. Cannabidiol (CBD) can control drop attacks, and cannabis may have therapeutic benefits for sleep but can also negatively impact sleep after withdrawal. Continuous positive airway pressure (CPAP) therapy is an effective method for treating OSA and improving oxygen saturation levels during sleep.[28]

MIGRAINE

Migraine and epilepsy are neurological disorders that share similar paroxysmal clinical manifestations, yet migraine is a more prevalent episodic neurological disorder. The prevalence of migraine in populations of individuals with epilepsy is estimated at 8–24%.[29-31]

The co-occurrence of epilepsy in people with migraine ranges from 1 to 17% with a median prevalence of 5.9%, significantly higher than the general population being 0.5–1%. Epilepsy being a complex disorder than migraine is often accompanied by a range of co-occurring comorbidities. Epilepsy not only carries its challenges but also poses a risk for developing comorbid conditions such as depression, anxiety, dementia, migraine, heart disease, and peptic ulcer disease, with a prevalence up to eight times higher than the general population.

Migraine is thought to be triggered by a phenomenon known as cortical spreading depression (CSD), which involves a wave of cellular hyperexcitability and depolarization in the brain. In contrast, epilepsy results from abnormal hypersynchronous electrical activity within specific brain circuits.[32-34] Glutamate, the primary excitatory neurotransmitter in the brain plays a central role in the pathophysiology of both migraine and epilepsy. In epilepsy, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor-mediated neuronal excitability leads to seizures. In migraine on the other hand, it is thought to induce migraine attacks by activating N-methyl-D-aspartate (NMDA)

receptors, which causes hyperexcitability in the trigeminovascular system and the dura mater.[35]

There is a strong genetical association between epilepsy and familial hemiplegic migraine (FHM), of these *CACNA1*, *ATP1A2*, *SCN1A*, and *PRRT2* are the four genes involved in genetic mutation. A common genetic thread links epilepsy, FHM, and a specific mutation in the *CACNA1* gene. This mutation can be found in patients with either epilepsy or FHM alone, as well as in those with both conditions existing concurrently as comorbidities.[36]

The ASM exerts antimigraine activity by attenuating neurogenic inflammation in the trigeminal vascular system by preventing the release of calcitonin gene-related peptide (CGRP), and other vasoactive peptides and blocking CSD and preventing central sensitization, which are responsible for triggers of migraine. ASMs that are approved for migraine prophylaxis and epilepsy are sodium VPA/divalproex sodium maximum of 500–1,000 mg/day and TPM maximum of 100 mg/day with low titration.[37-39]

While not conventionally used as migraine prophylaxis ASMs such as LTG, zonisamide, gabapentin, PGB, CBZ, and LEV, are effective in the management of migraine with aura, particularly when conventional migraine prophylactics fail.

Women with childbearing potential are recommended to avoid VPA and CBZ which is highly potential to cause major congenital malformation and neurodevelopmental disorders.

GASTROINTESTINAL SYSTEM

The GI system communicates to the Brain via vagus nerve fibers and the gut-brain axis.[40] This network is maintained by gut microbiota and neurotransmitter substances such as serotonin, immune-mediated release of cytokines, interleukin-1β, and tumor necrosis factor alpha (TNF-α) via afferent neuronal messages from the enteric nervous system (ENS).[40,41] Approximately 0.7–9.1% of patients with celiac disease and irritable bowel syndrome (IBS) are known to cause epilepsy.[42,43] Immune-mediated mechanism, vitamin B12 and thiamine deficiency are implicated in the pathogenesis of epileptic seizures in immune-mediated GI disorders.[44] ASMs have no major role in GI-induced epilepsy mainly for celiac and IBS. Many drugs have been avoided mainly due to their side effect profile such as abdominal cramps, nausea, vomiting, weight loss, and hepatotoxicity in drugs such as valproic acid, ethosuximide, TPM, and felbamate.[44-47] The mainstay of treatment in these conditions is immunomodulatory drugs. The ketogenic and gluten-free diet has been beneficial for curing celiac disease.[48]

FIBROMYALGIA

Fibromyalgia is a chronic pain disorder, causing pain and tenderness throughout the body as well as fatigue and insomnia, affecting 2% of the population. Among patients with fibromyalgia, 11% had epileptic seizures, 74% had psychogenic nonepileptic events, and 15% had psychological nonepileptic events.[49] PNES is most seen in association with fibromyalgia and self-limiting seizures. The mechanism postulated is the discomfort produced in chronic pain which causes psychological distress and PNES.[50] ASMs that are approved for fibromyalgia and chronic low backache are gabapentin and PGB with less side effect profile.[51] Other ASMs including CBZ, clobazam, PHT, and VPA have no or insufficient evidence of effect.[50-51]

ENDOCRINE DISORDERS

Thyroid hormones play an essential role in the maintenance of central nervous system

development, myelination, and physiological functions. Thyroid hormones are necessary to maintain mitochondrial brain function, modulate the development and function of GABAergic interneurons, and regulate the brain's antioxidant properties.[52]

Epilepsy is one of the most common neurological disorders affecting people of all ages, and the pathogenesis behind thyroid hormone functions and epilepsy share similar mechanisms.[53] Epilepsy is caused by the failure in regulation of excitatory neurotransmitter (glutamate) and inhibitory (GABA) amino acids in the brain, along with oxidative stress and mitochondrial dysfunction.[54]

Polytherapy specifically CBZ, OXC, PHT, VPA, and PB treatment has been shown to reduce thyroid hormones and lead to hypothyroidism and its related disease-related complications.[55]

REPRODUCTIVE ENDOCRINE DISORDER INCLUDING POLYCYSTIC OVARY SYNDROME

Epilepsy is associated with reproductive endocrine disorders like polycystic ovary syndrome (PCOS), isolated components of this syndrome such as polycystic ovaries, hypothalamic amenorrhea, and hyperprolactinemia. The mechanism behind endocrine disorders and epilepsy postulated are the direct effect of ASMs, enzyme-inducing agents such as CBZ and PHT on endocrine control centers in the brain mainly the hypothalamic-pituitary-adrenal axis.[56] Patients on VPA should be cautious of PCOS and weight gain, there can be menstrual disturbance, fertility issues, hirsutism, and galactorrhea in patients on VPA.[56]

If women with PCOS and reproductive endocrine disorders are found, antiepileptic drug treatment should be reviewed to ensure whether the drug is accurate for a particular seizure type.[56]

CARDIOVASCULAR SYSTEM

Cardiovascular diseases cause a major risk of mortality in patients with epilepsy.[57] Cardiovascular risk factors such as obesity, diabetes, hypertension, and hyperlipidemia have a direct association with epilepsy and are considered the major cause of death in PWE.[58,59]

The incidence ratio of heart disease to stroke in epilepsy is (3.54–4.9) for heart disease and (4.19–5.84.) for stroke respectively.[60] Among cardiovascular disorders incidence of myocardial infarction (MI) is around 2.34–10.1 and mortality due to MI is higher as compared to the general population.[61] Older ASMs such as PHT, PB, and CBZ are hepatic enzyme inducers associated with vascular risks. Fosphenytoin is safer when compared to PHT with a lower incidence of hypotension and lesser tissue side effects. VPA and LTG are generally well tolerated. The newer ASM, LCM has cardiac effects with rapid intravenous dosing and is associated with first-degree atrioventricular (AV) block in less than one-fourth of the patients.[62]

HYPERTENSION AND DIABETES

Hypertension and diabetes are some of the vascular risk factors for late-onset epilepsy. Patients with preexisting cardiovascular disorders, arrhythmias, and heart failures are at high risk of SUDEP. Heart rate variability during seizures is the reason underlying SUDEP; reduced heart rate variability is associated with risk of cardiac mortality from arrhythmias and sudden cardiac death.[63,64]

During prolonged seizures especially during generalized tonic-clonic seizures (GTCS), the vagus nerve acts to reduce

heart rate via sinoatrial (SA) and AV node by protecting the heart from hypoxia, ischemia, and stress.

Mechanisms underlying the association between epilepsy and cardiovascular disease include the adverse effects of enzyme-inducing ASMs on cholesterol, lipid metabolism, and obesity, lifestyle habits such as increased smoking and decreased physical activity in persons with epilepsy. Chronic epilepsy itself has adverse effects on the heart.

CONCLUSION

The treatment of epilepsy requires comprehensive management of the associated conditions to ensure better patient outcomes and a higher quality of life. Optimal management involves multidisciplinary care and the ability to offer personalized treatment. Both pharmacological and nonpharmacological treatments need to be considered. Patient education is essential to ensure treatment adherence.

REFERENCES

1. Gaitatzis A, Carroll K, Majeed A, W Sander J. The epidemiology of the comorbidity of epilepsy in the general population. Epilepsia. 2004;45(12): 1613-22.
2. Tellez-Zenteno JF, Patten SB, Jetté N, Williams J, Wiebe S. Psychiatric comorbidity in epilepsy: a population-based analysis. Epilepsia. 2007; 48(12):2336-44.
3. Hesdorffer DC, Lúdvígsson P, Hauser WA, Olafsson E, Kjartansson O. Co-occurrence of major depression or suicide attempt with migraine with aura and risk for unprovoked seizure. Epilepsy Res. 2007;75(2-3):220-3.
4. Salpekar JA, Mula M. Common psychiatric comorbidities in epilepsy: How big of a problem is it? Epilepsy Behav. 2019;98(Pt B):293-7.
5. Fiest KM, Dykeman J, Patten SB, Wiebe S, Kaplan GG, Maxwell CJ, et al. Depression in epilepsy: a systematic review and meta-analysis. Neurology. 2013;80(6):590-9.
6. Scott AJ, Sharpe L, Hunt C, Gandy M. Anxiety and depressive disorders in people with epilepsy: A meta-analysis. Epilepsia. 2017;58(6):973-82.
7. Clancy MJ, Clarke MC, Connor DJ, Cannon M, Cotter DR. The prevalence of psychosis in epilepsy; a systematic review and meta-analysis. BMC Psychiatry. 2014;75:14.
8. Kutlubaev MA, Xu Y, Hackett ML, Stone J. Dual diagnosis of epilepsy and psychogenic nonepileptic seizures: Systematic review and meta-analysis of frequency, correlates, and outcomes. Epilepsy Behav. 2018;89:70-8.
9. Reilly C, Atkinson P, Das KB, Chin RF, Aylett SE, Burch V, et al. Neurobehavioral comorbidities in children with active epilepsy: a population-based study. Pediatrics. 2014;133(6):e1586-93.
10. Mula M, Coleman H, Wilson SJ. Neuropsychiatric and cognitive comorbidities in epilepsy. Continuum (Minneap Minn). 2022;28(2):457-82.
11. Sveinsson O, Andersson T, Carlsson S, Tomson T. The incidence of SUDEP: A nationwide population-based cohort study. Neurology. 2017;89(2):170-7.
12. Trimble MR, Mula M. Antiepileptic drug interactions in patients requiring psychiatric drug treatment. In: Majkowski J, Bourgeois BFD, Patsalos PN, Mattson RH, Lam E, Routledge PA, et al. (Eds). Antiepileptic Drugs. Cambridge: Cambridge University Press; 2005. pp. 350-68.
13. Quintas R, Raggi A, Giovannetti AM, Pagani M, Sabariego C, Cieza A, et al. Psychosocial difficulties in people with epilepsy: a systematic review of literature from 2005 until 2010. Epilepsy Behav. 2012;25(1):60-7.
14. Witt JA, Helmstaedter C. Cognition in epilepsy: current clinical issues of interest. Curr Opin Neurol. 2017;30(2):174-9.
15. Kaga M, Inagaki M, Ohta R. Epidemiological study of Landau-Kleffner syndrome (LKS) in Japan. Brain Dev. 2014;36(4):284-6.
16. Robertson J, Hatton C, Emerson E, Baines S. Prevalence of epilepsy among people with intellectual disabilities: A systematic review. Seizure. 2015;29:46-62.
17. Jacobs CS, Willment KC, Sarkis RA. Non-invasive Cognitive Enhancement in Epilepsy. Front Neurol. 2019;10:167.
18. Ponsford J, Lee NK, Wong D, McKay A, Haines K, Downing M, et al. Factors associated with

response to adapted cognitive behavioral therapy for anxiety and depression following traumatic brain injury. J Head Trauma Rehabil. 2020;35(2):117-26.
19. del Pozo A, Lehmann L, Knox KM, Barker-Haliski M. Can old animals reveal new targets? The aging and degenerating brain as a new precision medicine opportunity for epilepsy. Front Neurol. 2022;13:833624.
20. van Golde EG, Gutter T, de Weerd AW. Sleep disturbances in people with epilepsy; prevalence, impact and treatment. Sleep Med Rev. 2011;15(6):357-68.
21. Nobili L, Beniczky S, Eriksson SH, Romigi A, Ryvlin P, Toledo M, et al. Expert Opinion: Managing sleep disturbances in people with epilepsy. Epilepsy Behav. 2021;124:108341.
22. Söylemez E, Öztürk O, Baslo SA, Balçık ZE, Ataklı D. Metabolic syndrome and obstructive sleep apnea syndrome among patients with epilepsy on monotherapy. Epilepsy Behav. 2020;111:107296.
23. Lowe CJ, Safati A, Hall PA. The neurocognitive consequences of sleep restriction: A meta-analytic review. Neurosci Biobehav Rev. 2017;80:586-604.
24. Gammino M, Zummo L, Bue AL, Urso L, Terruso V, Marrone O, et al. Excessive daytime sleepiness and sleep disorders in a population of patients with epilepsy: a case-control study. J Epilepsy Res. 2016;6(2):79-86.
25. Lin Z, Si Q, Xiaoyi Z. Obstructive sleep apnoea in patients with epilepsy: a meta-analysis. Sleep Breath. 2017;21(2):263-70.
26. Yeh WC, Lu SR, Wu MN, Lee KW, Chien CF, Fong YO, et al. The impact of antiseizure medications on polysomnographic parameters: a systematic review and meta-analysis. Sleep Med. 2021;81:319-26.
27. Romigi A, Cappellano S, Caccamo M, Testa F, Centonze D. The impact of antiseizure medications on polysomnographic parameters: a systematic review and meta-analysis. Sleep Med. 2021;88:290.
28. Choi S, Huang BC, Gamaldo CE. Therapeutic uses of cannabis on sleep disorders and related conditions. J Clin Neurophysiol. 2020;37(1):39-49.
29. Toldo I, Perissinotto E, Menegazzo F, Boniver C, Sartori S, Salviati L, et al. Comorbidity between headache and epilepsy in a pediatric headache center. J Headache Pain. 2010;11:235-40.
30. Ottman R, Lipton RB. Comorbidity of migraine and epilepsy. Neurology. 1994;44:2105-10.
31. Haut SR, Bigal ME, Lipton RB. Chronic disorders with episodic manifestations: focus on epilepsy and migraine. Lancet Neurol. 2006;5(2):148-57.
32. Trevelyan AJ, Sussillo D, Yuste R. Feedforward inhibition contributes to the control of epileptiform propagation speed. J Neurosci. 2007;27(13):3383-7.
33. Yamaguchi S, Donevan SD, Rogawski MA. Anticonvulsant activity of AMPA/kainate antagonists: comparison of GYKI 52466 and NBOX in maximal electroshock and chemoconvulsant seizure models. Epilepsy Res. 1993;15(3):179-84.
34. Pietrobon D, Moskowitz MA. Chaos and commotion in the wake of cortical spreading depression and spreading depolarizations. Nat Rev Neurosci. 2014;15(6):379-93.
35. Jasper HH, Ward A, Pope A. In: Noebels JL, Avoli M, Rogawski MA, Olsen RW, Delgado-Escueta AV (Eds). Jasper's Basic Mechanisms of Epilepsies, 4th Edition. Bethesda (MD): National Center for Biotechnology Information (US); 2012.
36. Rogawski MA. Migraine and epilepsy-shared mechanisms within the family of episodic disorders. In: Noebels JL, Avoli M, Rogawski MA, Olsen RW, Delgado-Escueta AV, (Eds). Jasper's Basic Mechanisms of the Epilepsies. Bethesda, MD: National Center for Biotechnology Information (US); 2012.
37. Calabresi P, Galletti F, Rossi C, Sarchielli P, Cupini LM. Antiepileptic drugs in migraine: From clinical aspects to cellular mechanisms. Trends Pharmacol Sci. 2007;28(4):188-95.
38. Frank F, Ulmer H, Sidoroff V, Broessner G. CGRP-antibodies, topiramate and botulinum toxin type A in episodic and chronic migraine: A systematic review and meta-analysis. Cephalalgia. 2021;41(11-12):1222-39.
39. Zobdeh F, Kraiem A, Attwood MM, Chubarev VN, Tarasov VV, Schiöth HB, et al. Pharmacological treatment of migraine: Drug classes, mechanisms of action, clinical trials and new treatments. Br J Pharmacol. 2021;178(23):4588-607.
40. Mittal R, Debs LH, Patel AP, Nguyen D, Patel K, Hamed G, et al. Neurotransmitters: The critical modulators regulating gut-brain axis: HHS public access. J Cell Physiol. 2017;232(9):2359-72.
41. Pfeiffer RF. Gastroenterology and neurology. Continuum: Lifelong Learning in Neurology. 2017;23(3):744-61.
42. Işikay S, Kocamaz H. Prevalence of celiac disease in children with idiopathic epilepsy in Southeast Turkey. Pediatr Neurol. 2014;50(5):479-81.
43. Djuric Z, Nagorni A, Jocic-Jakubi B, Dimic M, Novak M, Milicevic R, et al. Celiac disease prevalence in epileptic children from Serbia. Turk J Pediatr. 2012;54(3):247.

44. Casella G, Tontini GE, Bassotti G, Pastorelli L, Villanacci V, Spina L, et al. Neurological disorders and inflammatory bowel diseases. World J Gastroenterol. 2014;20(27):8764-82.
45. Powell-Jackson PR, Tredger JM, Williams R. Hepatotoxicity to sodium valproate: A review. Gut. 1984;25(6):673-81.
46. Dreifuss FE, Langer DH. Side effects of valproate. Am J Med. 1988;84(1A):34-41
47. O'Neil MG, Perdun CS, Wilson MB, McGown ST, Patel S. Felbamate-associated fatal acute hepatic necrosis. Neurology. 1996;46(5):1457-9.
48. Pratesi R, Modelli IC, Martins RC, Almeida PL, Gandolfi L. Celiac disease and epilepsy: Favorable outcome in a child with difficult to control seizures. Acta Neurologica Scandinavica. 2003;108(4): 290-3.
49. Tatum WO, Langston ME, Acton EK. Fibromyalgia and seizures. Epileptic Disord. 2016;18(2):148-54.
50. Benbadis SR. A spell in the epilepsy clinic and a history of "chronic pain" or "fibromyalgia" independently predict a diagnosis of psychogenic seizures. Epilepsy Behav. 2005;6:264-5.
51. Wiffen PJ, Derry S, Moore RA, Aldington D, Cole P, Rice AS, et al. Antiepileptic drugs for neuropathic pain and fibromyalgia–an overview of cocrane reviews. Cochrane Database Syst Rev. 2013;2013(11):CD010567.
52. Tamijani SMS, Karimi B, Amini E, Golpich M, Dargahi L, Ali RA, et al. Thyroid hormones: possible roles in epilepsy pathology. Seizure. 2015;31: 155-64.
53. Veliskova J, Desantis KA. Sex and hormonal influences on seizures and epilepsy. Horm Behav. 2013;63(2):267-77.
54. Chang SJ, Yu BC. Mitochondrial matters of the brain: mitochondrial dysfunction and Oxidative status in epilepsy. J Bioenerg Biomembr. 2010;42(6):457-9.
55. Lai EC, Yang YH, Lin SJ, Hsieh CY. Use of anti-epileptic drug and risk of hypothyroidism. Pharmacoepidemiol Drug Saf. 2013;22(10): 1071-9.
56. Isojärvi JI. Reproductive dysfunction in women with epilepsy. Neurology. 2003;61(6 Suppl 2): S27-34.
57. Gaertner ML, Mintzer S, DeGiorgio CM. Increased cardiovascular risk in epilepsy. Front Neurol. 2024;15:1339276.
58. DeGiorgio CM, Curtis A, Carapetian A, Hovsepian D, Krishnadasan A, Markovic D. Why are epilepsy mortality rates rising in the United States? A population-based multiple cause-of-death study. BMJ Open. 2020;10(8):e035767.
59. DeGiorgio CM, Curtis AT, Hertling D, Kerr WT, Markovic D. Changes in epilepsy causes of death: a US population study. Acta Neurol Scand. 2021;144(5):478-85.
60. Chen Z, Liew D, Kwan P. Excess mortality and hospitalized morbidity in newly treated epilepsy patients. Neurology. 2016;87:718-25.
61. Janszky I, Hallqvist J, Tomson T, Ahlbom A, Mukamal KJ, Ahnve S. Increased risk and worse prognosis of myocardial infarction in patients with prior hospitalization for epilepsy–the Stockholm Heart Epidemiology Program. Brain. 2009;132:2798-804.
62. Lu Y-T, Lin C-H, Ho C-J, Hsu C-W, Tsai M-H. Evaluation of Cardiovascular Concerns of Intravenous Lacosamide Therapy in Epilepsy Patients. Front Neurol. 2022;13:891368.
63. Galinier M, Pathak A, Fourcade J, Androdias C, Curnier D, Varnous S, et al. Depressed low frequency power of heart rate variability as an independent predictor of sudden death in chronic heart failure. Eur Heart J. 2000;21:475-82.
64. Shah SA, Kambur T, Chan C, Herrington DM, Liu K, Shah SJ. Relation of short-term heart rate variability to incident heart failure (from the Multi-Ethnic Study of Atherosclerosis). Am J Cardiol. 2013;112:533-40.

IAN Reviews in Neurology 2024
Dementia

Salient Features

- Comprehensive update about Dementia from Indian Academy of Neurology
- The compilation of 22 chapters by eminent Neurologists working in the field of Cognitive Neurology provides insights into human cognition, dementia evaluation, biomarkers, and recent advances in the management of dementia, including rehabilitation and role of gadgets

Sita Jayalakshmi MD DM FIAN is a Senior Consultant and In-Charge of Comprehensive Epilepsy Surgery Program, Department of Neurology at Krishna Institute of Medical Sciences, Secunderabad, Telangana, India. She is the current CME Convenor of Indian Academy of Neurology and Treasurer of Indian Epilepsy Society. She has more than 150 publications in peer reviewed journals. She is on the editorial board of Annals of Indian Academy of Neurology and Neurology India. She has received the 2023 AB Baker Teacher Recognition Award by the American Academy of Neurology.

Sangeeta Ravat MD DM is the Professor and Head, Department of Neurology, and Dean, Seth GS Medical College and KEM Hospital, Mumbai, Maharashtra, India. She is the Chief Epileptologist at Comprehensive Epilepsy Care Centre at KEM Hospital and Global Hospital. She did her Epilepsy Fellowship at Melbourne, Australia in 1998. She was the past President of Maharashtra Association of Neurologists and Vice President of Indian Epilepsy Association, Bombay Chapter. She is the President Elect of Indian Academy of Neurology. She has more than 70 publications in indexed journals.

Printed in India

Available at all medical bookstores or buy online at www.ejaypee.com

JAYPEE BROTHERS
Medical Publishers (P) Ltd.
EMCA House, 23/23-B, Ansari Road, Daryaganj, New Delhi - 110 002, INDIA
www.jaypeebrothers.com

Join us on facebook.com/JaypeeMedicalPublishers
Follow us on instagram.com/JaypeeMedicalPublishers

Shelving Recommendation
NEUROLOGY

ISBN 978-93-5696-887-5