2023 GW Epilepsy Board Review & Best Practices

Epilepsy Comorbidities

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Disclosures

None

Outline

- Psychiatric comorbidities
- Medical complications
- Mortality/SUDEP
- Sleep
- Migraine

Psychiatric Comorbidities

Epilepsy and Psychiatric Comorbidities

Table 1. Prevalence of current psychiatric disorders in epilepsy population compared to general population.

Psychiatric disorder	Epilepsy patients	General population
Mood disorders	24-74%	3.3% Dysthymia 5-17% Major depression
Anxiety disorders	10-25%	5-7% GAD 1-4% Panic disorder
Psychosis	2-7%	1-3% Schizophrenia
Attention deficit with hyperactivity	12-37%	4-12%

GAD: generalized anxiety disorder.

Araújo Filho, G. M. de, & Caboclo, L. O. S. F. (n.d.). *Anxiety and mood disorders in psychogenic nonepileptic seizures*. Journal of Epilepsy and Clinical Neurophysiology.

Epilepsy and mood disorders
Depression

- The most frequent psychiatric comorbidity in epilepsy
- Causes:
  - Biological
  - Psychosocial: Stigma, social limitations (driving license loss etc.), social embarrassment, poor self-esteem, social withdrawal, isolation, and demoralization
- Although common, but remains underdiagnosed

Epilepsy and mood disorders
Depression

- <u>Some studies suggest:</u>

- Depression is an important prognostic marker, associated with:

➢ Associated with poor quality of life

Boylan LS, Flint LA, Labovitz DL, Jackson SC, Starner K, Devinsky O. Depression but not seizure frequency predicts quality of life in treatment-resistant epilepsy. Neurology 2004;62:258–61.

➢ Anti-seizure drug resistance

NogueiraHitirisN,MohanrajR,NorrieJ,SillsGJ,BrodieMJ.PredictorsofpharmacoresistantepilepsyEpilepsy Res 2007;75(2-3):192–6
MH,YasudaCL,CoanAC,KannerAM,CendesF.Concurrentmoodandanxietydisorders are associated with pharmacoresistant seizures in patients with MTLE. Epilepsia 2017;58(7):1268–76.

➢ Increased seizure severity

Cramer JA, Blum D, Reed M, Fanning K. The influence of comorbid depression on seizure severity. Epilepsia 2003;44:1578–84.

➢ Increased side effects of ASMs

Mula M, von Oertzen TJ, Cock HR, Lozsadi DA, Agrawal N. Clinical correlates of memory complaints during AED treatment. Acta Neurol Scand 2016;134(5):368–73.

Epilepsy and mood disorders
Depression

- <u>Some studies suggest:</u>

- Depression is an important prognostic marker, associated with:

➢ Increased risk of accident and injuries

Gur-Ozmen S, Mula M, Agrawal N, Cock HR, Lozsadi D, von Oertzen TJ. The effect of depression and side effects of antiepileptic drugs on injuries in patients with epilepsy. Eur J Neurol 2017;24 (9):1135–9.

➢ Poor outcome after surgery

Kanner AM, Byrne R, Chicharro A, Wuu J, Frey M. A lifetime psychiatric history predicts a worse seizure outcome following temporal lobectomy. Neurology 2009;72(9):793–9.

➢ Increased mortality

Fazel S, Wolf A, La˚ngstro€m N, Newton CR, Lichtenstein P. Premature mortality in epilepsy and the role of psychiatric comorbidity: a total population study. Lancet 2013;382(9905):1646–54.

Epilepsy and mood disorders
Depression- Epidemiology

- <u>Adults:</u>
- Increased prevalence
- Between 17% and 22%
- Up to 55% in patients with drug-resistant epilepsy

- <u>Children:</u>
- A large US survey showed depression in 8% of children with current epilepsy, 7% of children with a previous history of seizures, and 2% of controls

Epilepsy and mood disorders
Periictal mood symptoms

Table 2 Mood symptoms in relationship to seizures

Peri-ictal depression	Pre-ictal	Dysphoric moods or insomnia up to 24 h before a convulsion (reported by up to 30% of patients with TLE but still controversial)
	Ictal	Rare (less than 1% of patients with focal seizures). No lateralizing or localizing value identified
	Postictal	Up to 18% of patients (data from monitoring unit) Consider also postictal mood worsening in patients with interictal depression
Para-ictal depression	Forced normalization	Rare but reported (prevalence unknown)
Interictal depression	Comorbid DSM-5 mood disorders	Major depressive disorder Persistent depressive disorder
	Other clinical entities	Interictal dysphoric disorder

DMS, Diagnostic and Statistical Manual of Mental Disorders; *TLE*, temporal lobe epilepsy.

Epilepsy and mood disorders
Depression and ASMs

- Depressive symptoms during ASMs treatment has been linked mainly with GABAergic drugs (eg.: tiagabine, topiramate, vigabatrin etc.)

- Other drugs with different mechanism of action eg.: Levetiracetam

Epilepsy and mood disorders
Depression and ASMs

Forced normalization phenomenon

The sudden improvement or even normalization of EEGs in people with intractable epilepsy who then develop psychiatric symptoms, very often a psychotic episode, but depressed mood has also been reported

Epilepsy and mood disorders
Depression and ASMs

- 8% of patients with drug-resistant epilepsy develop treatment-emergent psychiatric adverse events regardless of the mechanism of action of the individual ASM
- The rapidity of the titration rate of an ASM:

- A study on TPM
- History of depression is associated with a 3.5-times increased risk of developing depression as a treatment-emergent adverse event
- But, rapid titration schedule on top of a previous history of depression is associated with a 23-fold increased risk

Epilepsy and mood disorders
Depression after epilepsy surgery

- Most studies agree that depressive symptoms can be identified in about 10%–30% of patients at three months after epilepsy surgery

- Patients with a preexisting depressive disorder are at increased risk developing psychiatric complications

- Further studies are needed

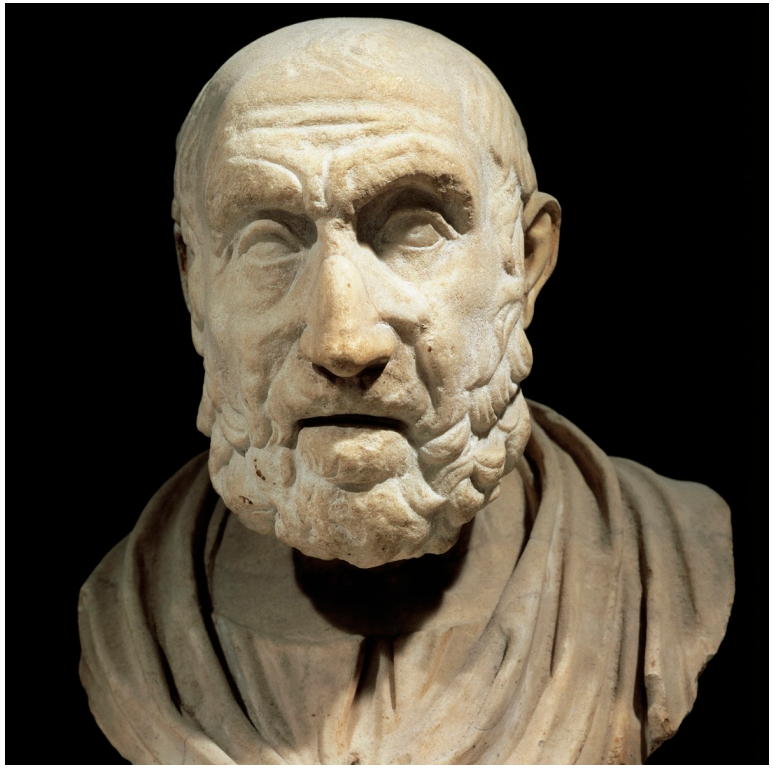
Epilepsy and mood disorders
Suicide in epilepsy

- 3x higher than the general population
- Some authors have suggested a link with temporal lobe epilepsy, but others found no association with epilepsy-related variables
- The issue of suicide in epilepsy has been linked with ASMs as potentially responsible for such an increased risk
- No robust data supporting a causal role for ASMs
- Clinicians should always consider treatment-emergent psychiatric adverse events during ASM treatment

Epilepsy and mood disorders

Depression-Epilepsy Bidirectional relationship

“melancholics ordinarily become epileptics, and epileptics, melancholics: what determines the preference is the direction the malady takes; if it bears upon the body, epilepsy, if upon the intelligence, melancholy”



Hippocrates

Epilepsy and mood disorders
Depression-Epilepsy Bidirectional relationship

- A bidirectional relation between depressive disorders and epilepsy has been suggested by several population-based studies and is supported by experimental studies

- Potential mechanisms include a hyperactive hypothalamic–pituitary–adrenal (HPA) axis

- Disturbances in serotonergic, noradrenergic, (GABA)ergic and glutamatergic neurotransmitter systems

Epilepsy and mood disorders
Treatment

- New compound antidepressants (SSRIs for example)

Anxiety

- 10–25%, majority GAD
- Likely is the result of the unpredictable nature of seizures and a perceived “loss of control”

Epilepsy and psychosis
POE (psychosis of epilepsy)

Can be divided into 5 groups:

1. Preictal
2. Ictal
3. Postictal
4. Interictal psychoses: not directly related to the ictal discharge, but where involvement of the limbic system structures by abnormal electrical activity and/or the lesion causing the fits
5. Psychosis brought on by treatment of epilepsy (medication, surgery, following the forced normalization theory)

Epilepsy and psychosis
Epidemiology

- A long history of uncontrolled seizures can lead to a chronic psychotic state in more than 5% of patients
- Postictal psychosis (PIP) occurs in 2–7.8% of epilepsy patients and is defined by hallucinations, delusions, and/or gross abnormalities of behavior or affect up to seven days after a seizure
- Psychosis following epilepsy surgery (de novo): Rates vary from <1–28.5%, with a mean of 7% among literature reports documenting this outcome, biasing towards an increased rate

(Nadkarni et al., "Psychosis in Epilepsy Patients")

Epilepsy and psychosis
Chronic interictal psychosis

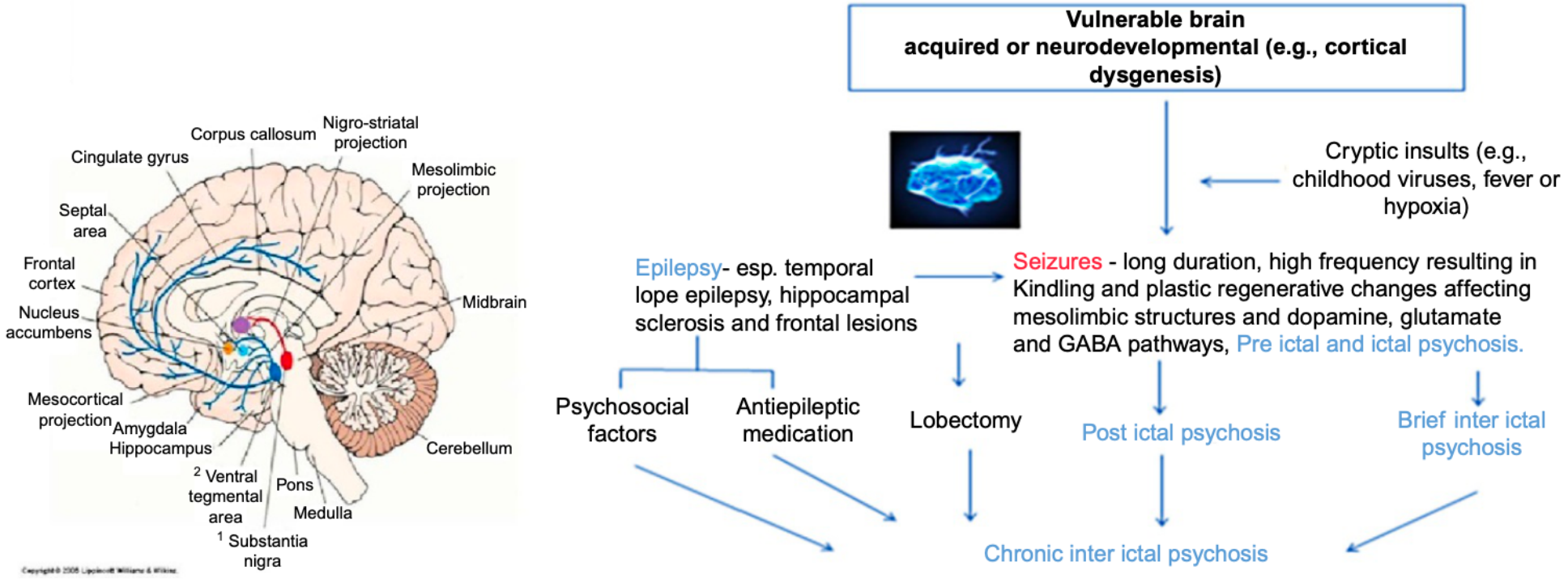


Fig. 2 Pathophysiology of chronic interictal psychosis [18].

Sachdev P. Schizophrenia-like psychosis and epilepsy: the status of the association. Am J Psychiatry 1998;155:3.

Table 2 Summary of different groups of psychosis of epilepsy [32]

Psychosis of epilepsy	Feature	Treatment of psychosis
Preictal	EEG important; prodromal symptoms days to hours leading up to a seizure	Psychosis normally resolves without treatment. Aim to control seizures
Ictal	EEG important; often involves a type of nonconvulsive status epilepticus Brief hours-days	If extends beyond days likely to be ictal behavior Psychosis normally resolves without treatment. Aim to control seizures
Postictal	Psychiatric symptoms normally occur within 7 days after a seizure or seizure cluster; after a lucid interval of hours to 1 week Insomnia, aggression, and self-harm are features	Often resolves without treatment, but psychosis can be shortened and normally responds well to antipsychotic treatment, e.g., risperidone, quetiapine, or olanzapine
Interictal (brief/chronic)	Can occur at any time with no relationship to the timing of seizures Common with longstanding complex partial seizures (e.g., temporal lobe epilepsy)	Normally responds well to treatment, e.g., risperidone, quetiapine, or olanzapine. Clozapine has also been effective if other APDs have failed and not exacerbated epilepsy ECT was found to be effective and has emerging anticonvulsive properties
Epileptic treatment	Psychosis may be the expression of adverse effects of AEDs or surgery. But discontinuation of an AED with mood-stabilizing properties can also trigger mania or psychoses Temporal lobectomy is followed by psychosis in a small percent of patients	Medication-induced psychosis by AEDs is more likely in treatment resistant epilepsy Psychosis has been controlled and surgery carried out successfully, responding well to antipsychotic drugs

Medical complications

Bone Health in epilepsy

- An approximately twofold risk of fracture in people with epilepsy
- Around two-thirds of the increased risk is likely due to the effects of AEDs on bone metabolism
- Newer AEDs, such as lamotrigine and levetiracetam, may be associated with lower risks
- At least a standard vitamin D supplement (400IU/day) in all patients early on, guided by serum levels checked every 2–5 years

Epilepsy and sexual dysfunction

- 30% to 66% in men
- 14% to 50% in women
- Patients treated with older ASMs (CBZ, PHT and barbiturates)
- Herzog et al. →Nearly 25% of men with epilepsy had sexual dysfunction (in men taking enzyme-inducing ASMs, CBZ or PHT, compared to men with epilepsy taking LTG or compared to controls)

Epilepsy and sexual dysfunction

Table 2 Summary of antiepileptic drugs and reported effects on sexual function

Drug	Most commonly reported types of sexual dysfunction	How common?
Carbamazepine	Decreased libido	***
	Erectile dysfunction	
	Orgasmic dysfunction	
Phenytoin	Decreased libido	***
	Erectile dysfunction	
Phenobarbital	Decreased libido	***
	Erectile dysfunction	
Primidone	Decreased libido	***
	Erectile dysfunction	
Sodium valproate	Decreased libido	**
	Erectile dysfunction	
	Increased libido	**
Oxcarbazepine	Anorgasmia/anejaculation	*
	Improved sexual function (especially if switching from carbamazepine)	**
Lamotrigine	Increased libido (especially in women switching to it from other antiepileptic drugs)	**
Levetiracetam	Improved sexual function (especially in women)	**
	Decreased libido (men only) and erectile dysfunction	*
Topiramate	Erectile dysfunction	*
	Decreased libido	
	Orgasmic dysfunction	
Pregabalin	Erectile dysfunction	*
	Orgasmic dysfunction	
Gabapentin	Orgasmic dysfunction	*
Zonisamide	Erectile dysfunction	*
Lacosamide	Erectile dysfunction	*
	Decreased libido	

Asterisks indicate frequency of side effects relative to other AEDs. *, rare; **, common; ***, very common. Note that the relative frequency of side effects noted in the table is based on a qualitative assessment of the literature.

Epilepsy and sexual dysfunction

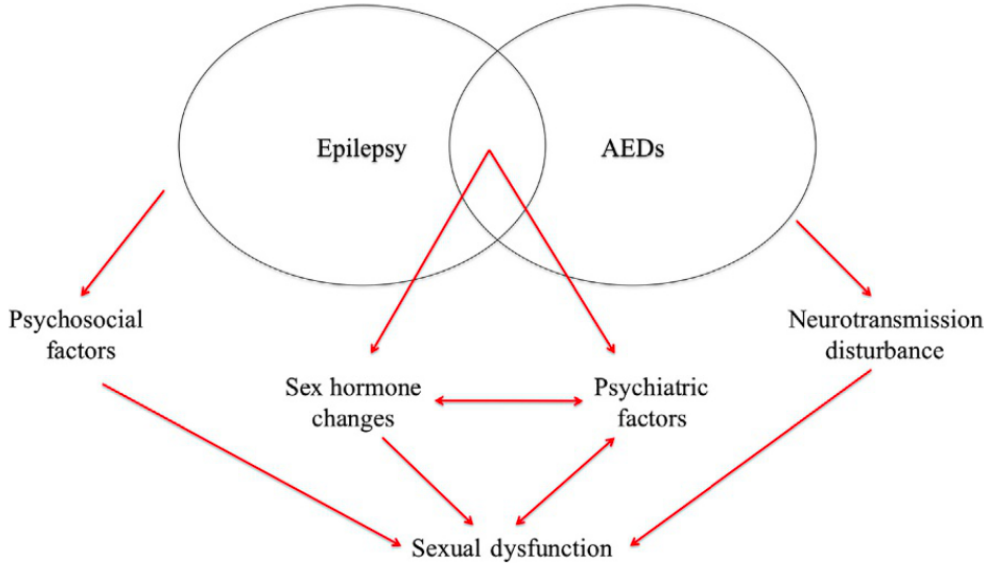


Fig. 1 The multifactorial nature of sexual dysfunction in epilepsy. Both epilepsy (which includes ictal/interictal discharges +/− any structural cause of epilepsy) and AEDs can give rise to sexual dysfunction, which is mediated by changes in sex hormones. However, both epilepsy and AEDs can also cause mood disturbances, which can lead to sexual dysfunction and may also be mediated by changes in sex hormones. Conversely, sexual dysfunction and hypogonadism may lead to mood disturbance. AEDs can also cause sexual dysfunction directly by affecting neural transmission in those pathways that are important for the sexual response. Finally, social factors caused by epilepsy can also lead to sexual dysfunction. *From Yogarajah M, Mula M. Sexual dysfunction in epilepsy and the role of anti-epileptic drugs. Curr Pharm Des 2017;23(37):5649–61.*

Obesity

- Conflictive evidence between epilepsy and obesity

- Overall, the prevalence of obesity is higher in those with epilepsy than in the general population

Obesity

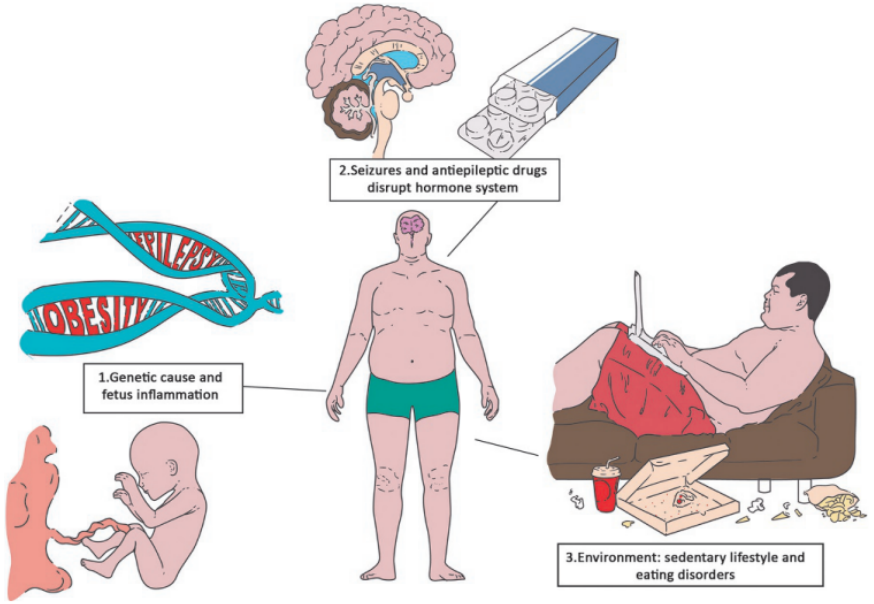


Fig. 1 Factors involved in obesity and epilepsy association. The association between epilepsy and obesity can be explained in three ways. The first factor is the genetic link between both diseases demonstrated by known genetic syndromes described in mice and humans. There is an increased prevalence of epilepsy in children with obesity, but also an increased prevalence of epilepsy in the offspring of obese mothers. The second factor is the well-known hormonal and neuronal alterations produced by seizures and antiepileptics drugs leading to overweight and obesity. The third factor is the hypothesis that environmental effects can lead to an imbalance in energy intake and expenditure. High-fat diet, fast food consumption and supersized portions, sedentary lifestyle, and lack of physical activity are elements described in people with epilepsy associated with overweight and obesity.

Drug group	Antiepileptic drug	Potential action mechanism
Antiepileptic drugs associated with weight gain	Valproic acid	• Enhance GABA transmission within the hypothalamus, causing appetite stimulation (carbohydrate craving and modified thirst), hyperinsulinemia and hyperleptinaemia • Decrease concentrations of ghrelin and adiponectin • Led to ineffective leptin action despite high leptin levels (leptin-resistance) • Defective sympathetic nervous system activity • Decrease the capacity for luxury consumption or facultative thermogenesis • Alter adipokine (adipose tissue cytokine) transmission • Direct stimulation of pancreatic beta cells • Indirect enhancement of insulin resistance by suppressing insulin-mediated peripheral glucose uptake • Elevation in fasting and postprandial insulin levels • Increase binge eating and motivation to eat • Modulation on a genetic basis for obesity • Carnitine deficiency causing impaired beta-oxidation of fatty acids
	Gabapentin	Enhancement of GABA-mediated inhibition in the medial hypothalamus
	Vigabatrine	Enhancement of GABA-mediated inhibition in the medial hypothalamus
	Carbamazepine	Induce overeating Increase fat deposition Induce water retention and edema
	Pregabalin	• Inhibit appetite-regulating effects in the CNS • Decrease energy consumption by sedation • Antidiuretic effect
	Levetiracetam	• Modify insulin secretion in response to glucose throughout its molecular target the synaptic vesicle protein 2A
Antiepileptic drugs associated with weight	Topiramate	• Reduce the food intake • Reduce energy deposition in the absence of alterations in food intake • Increase energy expenditure • Increase lipoprotein lipase activity in brown adipose tissue and muscle, which could indicate ability to enhance regulatory thermogenesis and promote substrate oxidation
	Felbamate	Reduction in food intake
	Zonisamide	Decrease leptin levels
	Rufinamide	Reduce food intake, through loss of appetite and nausea

Systemic Autoimmune disease and epilepsy

Rheumatological disorders

- **SLE:**

- Seizures are associated with worse systemic disease severity (Andrade et al., 2008)
- SLE was associated with 5.6-fold increased risk of epilepsy in one study (Chan et al., 2016)
- Acute symptomatic seizures less likely to have recurrent seizures compared to “unexplained”(not attributed to neurolupus) seizures (Hanly et al., 2012)
- MTLE accounts for more than 1/3 of chronic epilepsy in SLE and rarely can precede SLE diagnosis (Toyota et al., 2013)

Rheumatological disorders

- **<u>Rheumatoid arthritis (RA):</u>**

- 2 studies showed an increased risk of epilepsy (Ong et al., 2014; Chang et al., 2015)
- A higher risk of early or late childhood epilepsy through maternal exposure to RA (Rom et al., 2016)
- The increased risk of epilepsy in children of mothers with clinical RA was higher than in those with maternal preclinical RA (90% vs. 30%) → Cytokine fetal transmission? (Rom et al., 2016)

Endocrinological disorders

- **<u>Type 1 DM:</u>**

- 4 population-based studies → the risk of developing seizures is up to 3 x greater than in controls (Ong et al., 2014; Fazeli Farsani et al., 2015; Chou et al., 2016; Dafoulas et al., 2017)

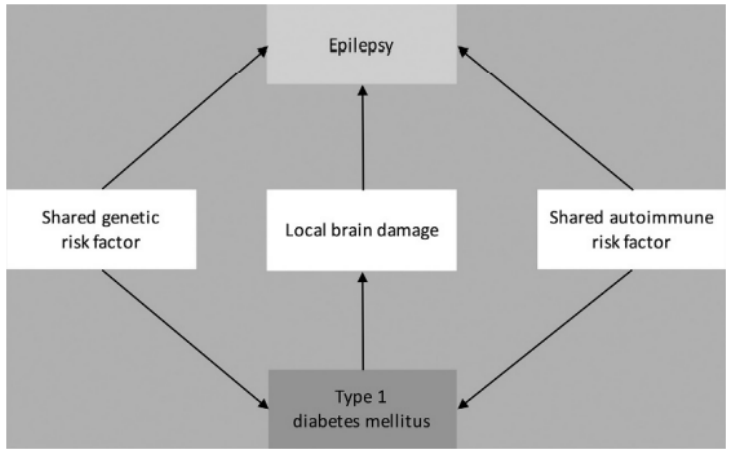


Fig. 3 The mechanisms proposed to explain the association between epilepsy and type 1 diabetes mellitus (T1DM). Genetic factors not yet identified may constitute a shared risk factor for both epilepsy and T1DM. A shared underlying autoimmune process may also contribute to this association. Diabetes mellitus could indirectly lead to epilepsy through the production of local brain damage.

Endocrinological disorders

- **<u>Hashimoto's thyroiditis:</u>**

- Higher risk for seizures (Ong et al., 2014)
- May present with Hashimoto's encephalopathy (Laurent et al., 2016)
- SREAT (steroid responsive encephalopathy associated with autoimmune thyroiditis) → Acute symptomatic seizures are the most common presenting symptom and occur in 47% of all cases (Laurent et al., 2016)

Gastrointestinal disorders

- **<u>Celiac disease:</u>**

- Swedish cohort study of 28 885 subjects with biopsy-verified coeliac disease → a 1.42-fold risk of developing epilepsy after a diagnosis of coeliac disease over a mean follow-up of 10 years (Ludvigsson et al., 2012)
- Children >adults (Ong et al., 2014)
- ? Adults with temporal lobe epilepsy with hippocampal sclerosis and children with occipital epilepsy might have a higher risk of comorbid coeliac disease (Julian et al., 2018)
- ? comorbid coeliac disease can present without gastrointestinal symptoms in up to 40% of patients with epilepsy (Julian et al., 2018)

Gastrointestinal disorders

- **<u>Inflammatory bowel disease:</u>**

- Increased risk of epilepsy in IBD (Virta and Kolho, 2013; Ong et al., 2014)

BUT

- Acute symptomatic seizures due to medication side effects, metabolic disturbance, and stroke may account for a significant proportion of seizures associated with IBD
- It remains thus uncertain whether IBD is indeed associated with an increased risk for epilepsy

Epilepsy and Cardiac disease

- **Cardiac arrhythmias:**

Table 1 Reported (post)ictal cardiac arrhythmias

Seizure-related arrhythmia	Reported in *n* cases	Associated seizure types	Reported in n cases	EEG seizure onset	Reported in *n* cases	SUDEP association
Ictal asystole	103	99% FDS 1% FAS	97	46% LT 31% RT 13% BT 10% Other	80	Unlikely
Postictal asystole	13	85% fbTCS 15% FDS	13	20% LT 60% RT 20% Other	10	Likely, accompanied or preceded by PGES/apnea (Ryvlin et al. [9])
Ictal bradycardia	25	100% FDS	8	52% LT 38% RT 10% Other	21	Unlikely
Ictal AV block	11	90% FDS 10% FAS	10	73% LT 18% BT 10% Other	11	Unlikely
Postictal AV block	2	100% fbTCS	2	100% RT	1	Unlikely
Atrial fibrillation	13	46% GTCS 46% fbTCS 8% FDS	13	33% LT 33% Gen 33% Non loc	3	Unlikely
(Post)ictal ventricular fibrillation	4	100% fbTCS/ GTCS	4	Insufficient data	0	Probable, but in a minority of cases

FDS, focal dyscognitive seizure; *FAS*, focal autonomic seizure; *fbTCS*, focal seizure evolving to bilateral tonic-clonic seizure; *GTCS*, generalized tonic clonic seizure; *LT*, left temporal; *RT*, right temporal; *BT*, bitemporal; *Gen*, generalized; *Non loc*, nonlocalizing; *PGES*, postictal generalized EEG suppression; *in people with refractory focal epilepsy admitted for a vEEG recording. For more details see [8]. For VF/VT a recent case was added [10].

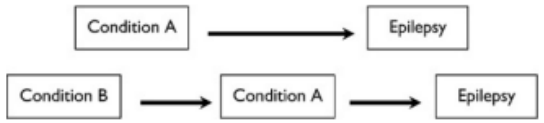
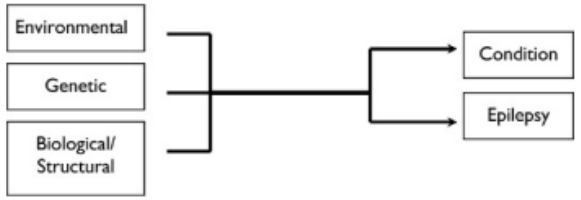
Epilepsy and Cardiac disease

- **<u>Structural cardiac conditions:</u>**

- People with epilepsy have a higher prevalence of structural cardiac disease than those without epilepsy
- Cardiovascular disease seems to be a significant contributor to the increased mortality in people with epilepsy, compared with the general population
- People with a history of epilepsy are more likely to be obese, physically inactive, and current smokers and have a worse cardiovascular risk profile

Epilepsy and Cardiac disease

Table 3 Putative mechanisms of associations between epilepsy and structural cardiac disease

Mechanisms of association	Conditions	References
Causal 	Cardiac conditions (e.g., embolism and congenital cardiac abnormalities) ➔ Stroke	Attar et al. [113], Ferlazzo et al. [114], Gaitatzis et al. [36]
Shared risk factor 	Genetic ➔ Malformation of cortical and cardiac development	Miller and Vogel [112]
	Shared cardiovascular risk factors ➔ Myocardial infarction, Stroke	Centers for Disease Control and Prevention (CDC) [103], Elliott et al. [104], Gaitatzis et al. [36], Kobau et al. [97]
Resultant 	AED ➔ Arteriosclerosis	Brodie et al. [108], Katsiki et al. [109], Lopinto-Khoury and Mintzer [110], Mintzer et al. [111]
	AED ➔ Weight gain, nonalcoholic fatty liver disease, and metabolic syndrome	Katsiki et al. [109]
	Seizures ➔ Transient myocardial ischemia	P-Codrea Tigaran et al. [121], Schuele [78]
	Seizures ➔ Seizure-triggered Takotsubo syndrome (TTS)	Finsterer and Wahbi [123], Finsterer and Bersano [124], Lemke et al. [126]

Epilepsy and other neurological conditions

- CVD:
- In elderly, CVD is the most frequent cause of epilepsy
- Acute seizures varies between 3% and 13% (2.4% with ischemic stroke and 4.8% with hemorrhagic stroke)
- Late onset poststroke seizures was 1.5% at 3months, 3.5% at 1 year, 9% at 5years, and 12.4% at 10 years (risk higher below age 65)

Epilepsy and other neurological conditions

- MS:
- Annual incidence of 2.28%
- Annual prevalence of 3.09%

Epilepsy and other neurological conditions

Cerebral tumors:

-Incidence of brain tumors as a cause of epilepsy is around 4% of patients with epilepsy

-Approximately 30%–50% of patients with cerebral tumors will have seizures as a first sign of tumor and an additional 10%–30% will experience a seizure during the course of disease

-In patients who have never had seizures, routine prophylactic use of ASMs is not recommended

-Epilepsies caused are more often drug resistant. Seizure freedom in about 40% (lower than the overall epilepsy population)

Table 2 Seizure frequency by tumor type

Tumor type	Seizure frequency
Dysembryoplastic neuroepithelial tumor	100%
Ganglioglioma	80%–90%
Low-grade astrocytoma	75%
Meningioma	29%–60%
Glioblastoma multiforme	29%–49%
Metastasis	20%–35%
Leptomeningeal tumor	10%–15%
Primary CNS lymphoma	10%

van Breemen MS, Wilms EB, Vecht CJ. Epilepsy in patients with brain tumours: epidemiology, mechanisms, and management. Lancet Neurol 2007;6(5):421–30.

Epilepsy and other neurological conditions

- Dementia:
- Epilepsy in AD is significantly higher than in the normal population
- Degeneration of the noradrenergic nucleus locus coeruleus seems also to be involved in the pathogenesis of dementia and seizures

Mortality and SUDEP

Mortality

- 2-3 times Increased mortality compared to the general population
- Higher in medically refractory epilepsy (12% within 2 years of being refractory, 1.2% after epilepsy surgery) *Burneo et al, 2016*
- Patients who are seizure free after surgery have mortality similar to the general population *Sperling et al., 1999*

Mortality

- The National General Practice Study of Epilepsy:

- 23% →underlying cause of death was directly related to the epilepsy etiology (more likely if death occurred within 2 years of the index seizure)
- Specific comorbidities independently associated with increased risk of mortality were neoplasms, certain neurologic diseases, and substance abuse *Keezer et al, 2016*

SUDEP

- Sudden unexpected death in epilepsy
- Death in a patient with epilepsy that is not due to trauma, drowning, status epilepticus, or other known causes but for which there is often evidence of an associated seizure
- Each year there are about 1.16 cases of SUDEP for every 1,000 people with epilepsy
- Highest prevalence between the age of 20-45

SUDEP
Risk Factors

- Recurrent Seizures (BTC>FIAS>FAS)
- Onset of epilepsy at an early age
- Ongoing frequent seizures
- Frequent tonic clonic seizures
- Long duration of epilepsy
- IQ < 70 in the presence of a major neurologic insult
- Neurologic pathologic abnormality (i.e. stroke)
- Multiple ASMs
- Poor adherence to medication regimen (low drug Levels)
- Male>female

SUDEP

The most important risk factor is continued generalized tonic seizures

Many deaths have occurred in bed and a significant number appear to be related to the prone position of sleep

SUDEP

- Prevention:
- **BETTER SEIZURE CONTROL,** Cessation of GTCs dramatically reduces risk
- “Avoid Prone position”
- Not missing medications
- Surgery or seizure alerting mechanisms (VNS/RNS)

Cognitive issues in epilepsy

Cognitive issues

- Intelligence/ID:
- 1/3 have IQ<70
- ADHD:
- Several studies found ADHD prevalence rates between 23% and 40% (compared to 6%–12% in controls)
- Boys and girls equally affected
- Risk factors/associations:

Some ASMs (polytherapy, PB/barbiturates>PH,CBZ,VPA, TPM)

Maybe FLE, CAE

Nocturnal seizures

Cognitive issues

- Language:

-TLE: word finding problems

- Can have lower academic achievement and executive functioning
- ID is also common
- Autism:

- Prevalence of epilepsy in autism ranges from 6%-30% (7% in preschoolers and up to 20%-30% in adulthood)
- Incidence of epilepsy in autism: 13.7%

Cognitive issues
Factors

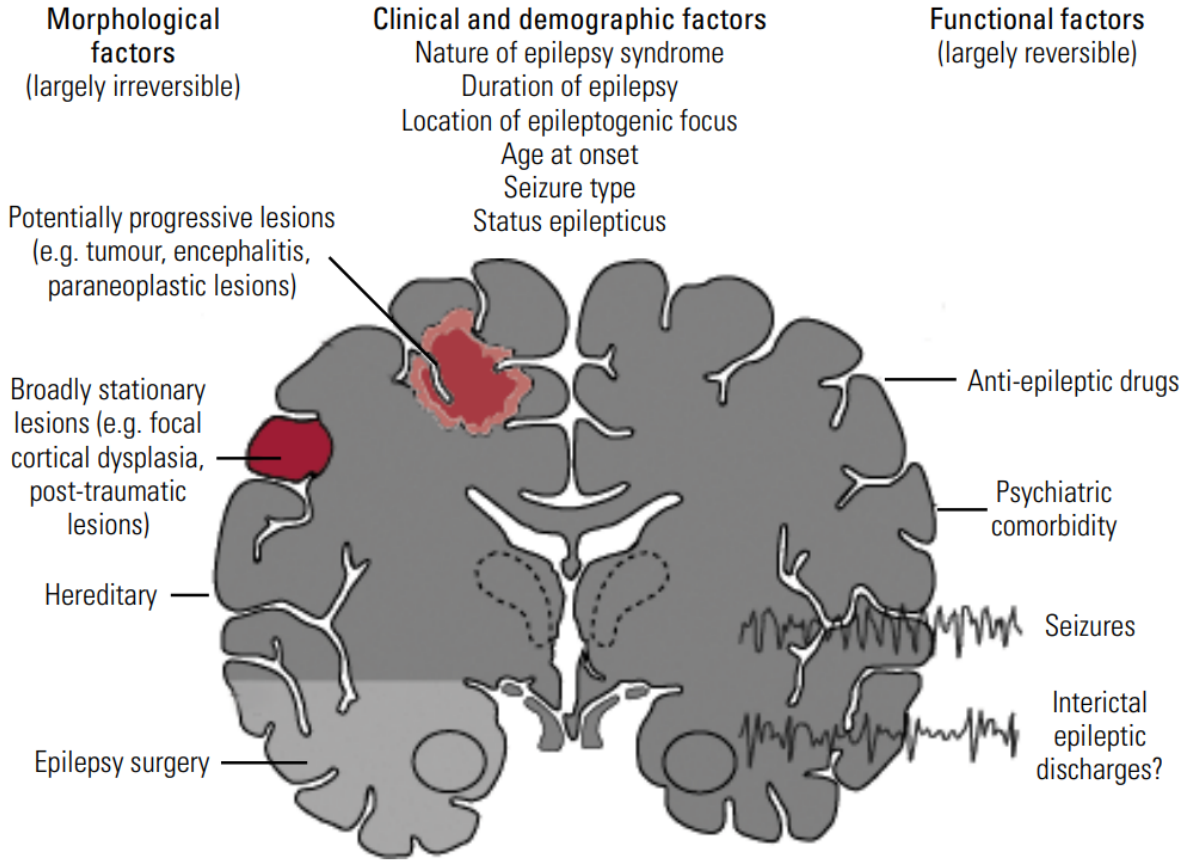


FIG 1 Factors affecting cognition in epilepsy (adapted from Elger et al 2004, with permission).

Lodhi, Shruti, and Niruj Agrawal. "Neurocognitive Problems in Epilepsy." Advances in Psychiatric Treatment, vol. 18, no. 3, 1 May 2012

Sleep and epilepsy

Sleep

- Excessive daytime sleepiness, which is multifactorial (Manni and Tartara, 2000)
- Approximately 30%–40% of people with focal epilepsy describe a disturbance of sleep in the past 6 months
- Most ASMs do not usually have a clinically relevant impact on sleep
- Insomnia:
- sleep-maintenance insomnia
- reduced percentage of sleep time spent in rapid eye movement (REM) sleep, increased waking after sleep onset, prolonged REM latency, and increased number of stage shifts (Touchon et al., 1991)

Insomnia

- Insomnia (predominantly sleep maintenance) affects about 40%–70% of people with epilepsy

- Risk factors consist of poor seizure control, nocturnal seizures, treatment with lamotrigine and posttraumatic epilepsy

Sleep apnea

- OSA prevalence maybe higher (Kaleyias et al., 2008; Manni and Terzaghi, 2010; Manni et al., 2003)
- Affects approximately 10% of people with epilepsy referred to an Italian epilepsy center
- More prevalent in individuals with drug-resistant epilepsy (Malow et al., 2000b) and may play a role in drug resistance
- May worsen seizure control by fragmenting nocturnal sleep and mimicking sleep deprivation
- Older epilepsy patients→ obstructive sleep apnea was more common in those with new-onset or newly worsened epilepsy than in individuals with stable or well-controlled epilepsy (Chihorek et al., 2007)
- Treatment of the sleep apnea may have a beneficial effect on seizure control (Malow et al., 2008)

Sleep and epilepsy

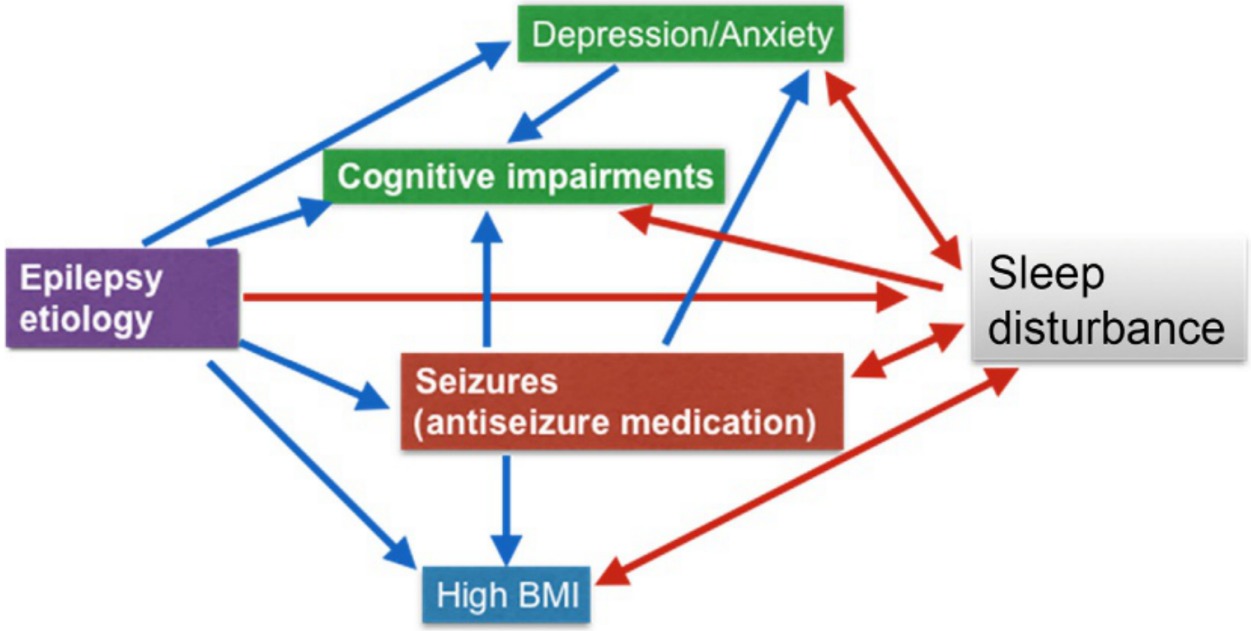


Fig. 1 Complex interaction between sleep epilepsy, seizures, and other comorbidities. Sleep often has a bidirectional association.

Migraine and epilepsy

Migraine

- Rates of prevalence of epilepsy among migraineurs range from 1% to 17% (median value: 5.9%)
- Focal-onset and cryptogenic epilepsies are associated with a slightly higher rate of migraine compared to generalized onset seizures (relative risk = 1.3)
- A stronger association was found for cases of epilepsy occurring after a head trauma, with overall 1.8-fold increase in risk
- A positive family history for epilepsy (39%) and photosensitivity (12.5%) appear to be frequent in cases with comorbidity
- Around 7% of patients with Familial hemiplegic migraine suffer from epilepsy, but currently no conclusive data are available regarding the possible association between hemiplegic migraine and epilepsy

Migraine

- Children with epilepsy had a 4.5-fold increased risk of developing migraine over a tension-type headache (Toldo et al., 2010)
- The rate ratio for migraine was 2.4 for individuals with epilepsy in comparison with controls (Ottman and Lipton, 1994)
- A higher prevalence and frequency of migraine among patients with active epilepsy (45%) compared to those with epilepsy in remission or seizure-free status (14%)
- Several genes associated with specific, monogenic forms of migraine have been reported to be associated with epilepsy
- Migraine and epilepsy are shared comorbidities in patients with some specific gene mutations involving: CACNA1A, ATP1A2, SCN1A in FHM; SLC1A3 gene (channelopathy) in episodic ataxia type 6 (EA6); and MT-TL1, MT-ND5, POLG, C10orF2d mitochondrial diseases, and NOTCH3 in CADASIL

Questions

Question 1

SUDEP occurs in:

A- 1 in every 1000 person year with epilepsy

B- 10 in every 1000 person year with epilepsy

C- 1 in every 100 person year with epilepsy

D-1 in every 10000 person year with epilepsy

E- 5% of patients with epilepsy

Answer 1

- A- 1 in every 1000 person year with epilepsy

Question 2

- Which statement is false?

A- Epilepsy surgery reduces mortality in epilepsy

B- The risk of SUDEP is highest in patients younger than 20 years

C- The risk of SUDEP is associated with the duration of epilepsy

D- The highest prevalence of SUDEP is between the age of 20-45

E- The most common cause of death in drug resistant epilepsy is SUDEP

Answer 2

- B- The risk of SUDEP is highest in patients younger than 20 years

Question 3

- Which statement is correct about depression and epilepsy?

A- Depression is the second most common psychiatric comorbidity in epilepsy after anxiety

B- There is a bidirectional relationship between epilepsy and depression

C- There is no association between depression and seizure severity

D- Depression is equally present in drug resistant epilepsy and in medically controlled epilepsy

E- TCA and MOA are better tolerated in treatment of depression in epilepsy patients

Answer 3

- B- There is a bidirectional relationship between epilepsy and depression

Question 4

- Which statement is correct regarding Sleep and epilepsy?

A- Treatment of OSA has no effect on seizure frequency

B- OSA prevalence is similar in new onset epilepsy and long-standing stable epilepsy

C- OSA may worsen seizure control by sleep fragmentation similar to sleep deprivation

D- OSA prevalence is equally prevalent in both well controlled epilepsy and drug resistant epilepsy

E- Insomnia is uncommon in patients with epilepsy

Answer 4

- C- OSA may worsen seizure control by sleep fragmentation similar to sleep deprivation

Question 5

- Which statement is correct?

A- Migraine prevalence is higher in patients with medically refractory epilepsy

B- Migraine prevalence in patients with epilepsy is similar to the general population

C- Tension headache is more prevalent than migraine in children with epilepsy

D- Patients with generalized epilepsy have a slightly higher prevalence for migraines compared to patients with focal epilepsy

E- There is no genetic associations between migraine and epilepsy

Answer 5

- A- Migraine prevalence is higher in patients with medically refractory epilepsy

Question 6

- Which statement is correct?

A- 2/3 of patients with epilepsy have an IQ < 70

B- Language abnormalities are more common in generalized epilepsy

C- The incidence of epilepsy in autism is around 14%

D- Boys with epilepsy are more affected by ADHD compared to girls with epilepsy

E- Patients with CAE have a low risk to develop ADHD compared to other epilepsy syndromes

Question 6

- C- The incidence of epilepsy in autism is around 14%

Thank you