Cognitive and Behavioral Comorbidities in Epilepsy: Assessment and Management

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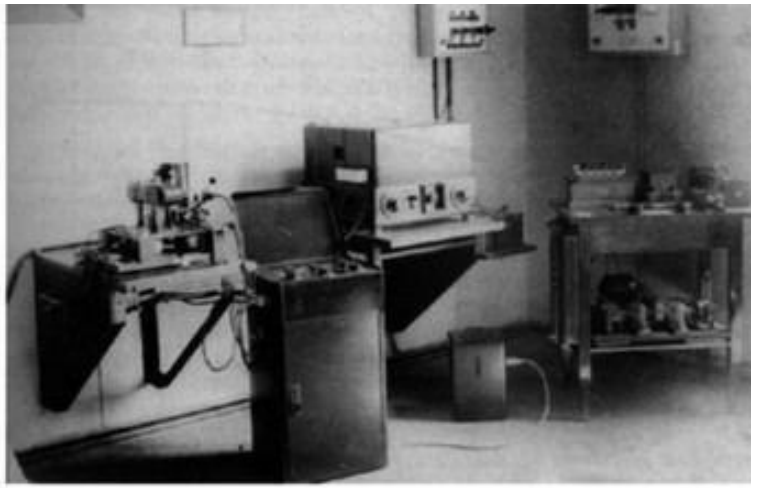
7th August, 2026

Outlines

- The general concepts of epilepsy and psychiatry
- Cognitive comorbidities
- Behavioral comorbidities
- Not PNES!

Hans Berger, a German psychiatrist (1873-1941);. "The father of electroencephalography"



Über das Elektrenkephalogramm des Menschen.

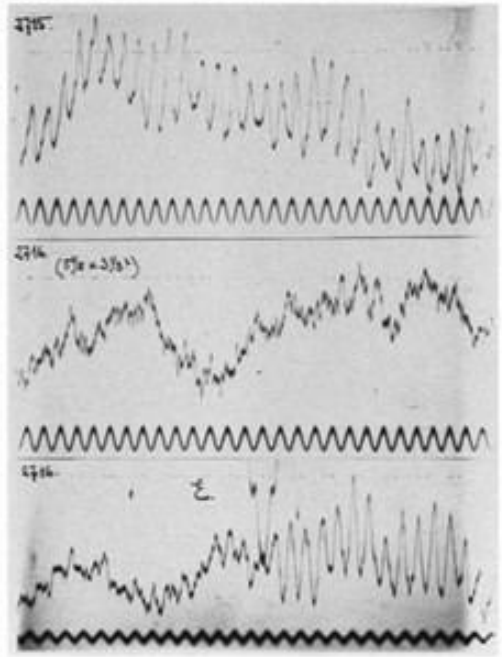
Von

Professor Dr. **Hans Berger**, Jena.

(Mit 17 Textabbildungen.)

(Eingegangen am 22. April 1929.)

Wie *Garten* [1], wohl einer der besten Kenner der Elektrophysiologie, mit Recht hervorgehoben hat, wird man kaum fehlgehen, wenn man jeder lebenden Zelle tierischer und pflanzlicher Natur die Fähigkeit zuschreibt, elektrische Ströme hervorzubringen. Man bezeichnet solche Ströme als bioelektrische Ströme, weil sie die normalen Lebenserscheinungen der Zelle begleiten. Sie sind wohl zu unterscheiden von den durch Verletzungen künstlich hervorgerufenen Strömen, die man als Demarkations-, Alterations- oder Längsquerschnittsströme bezeichnet hat. Es war von vornherein zu erwarten, daß auch im Zentralnervensystem, das doch eine gewaltige Zellanhäufung darstellt, bioelektrische Erscheinungen nachweisbar seien, und in der Tat ist dieser Nachweis schon verhältnismäßig früh erbracht worden.



Millett D. Perspect Biol Med. 2001 Fall;44(4):522-42.

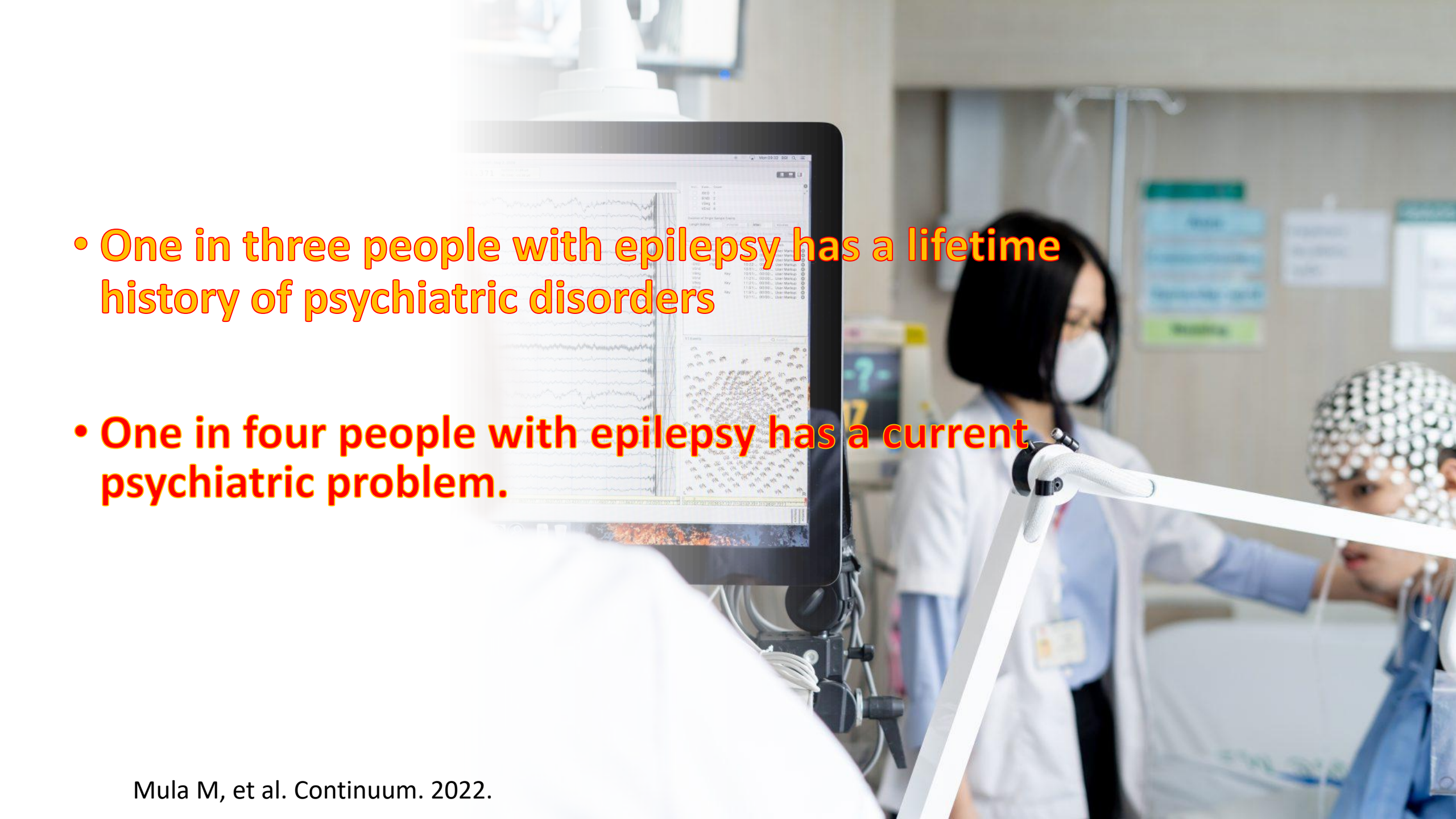
Special Article

Epileptic Seizures and Epilepsy: Definitions Proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE)

Epilepsia, 46(4):470–472, 2005
Blackwell Publishing, Inc.

An **epileptic seizure** is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure.



- One in three people with epilepsy has a lifetime history of psychiatric disorders
- One in four people with epilepsy has a current psychiatric problem.

Mula M, et al. Continuum. 2022.

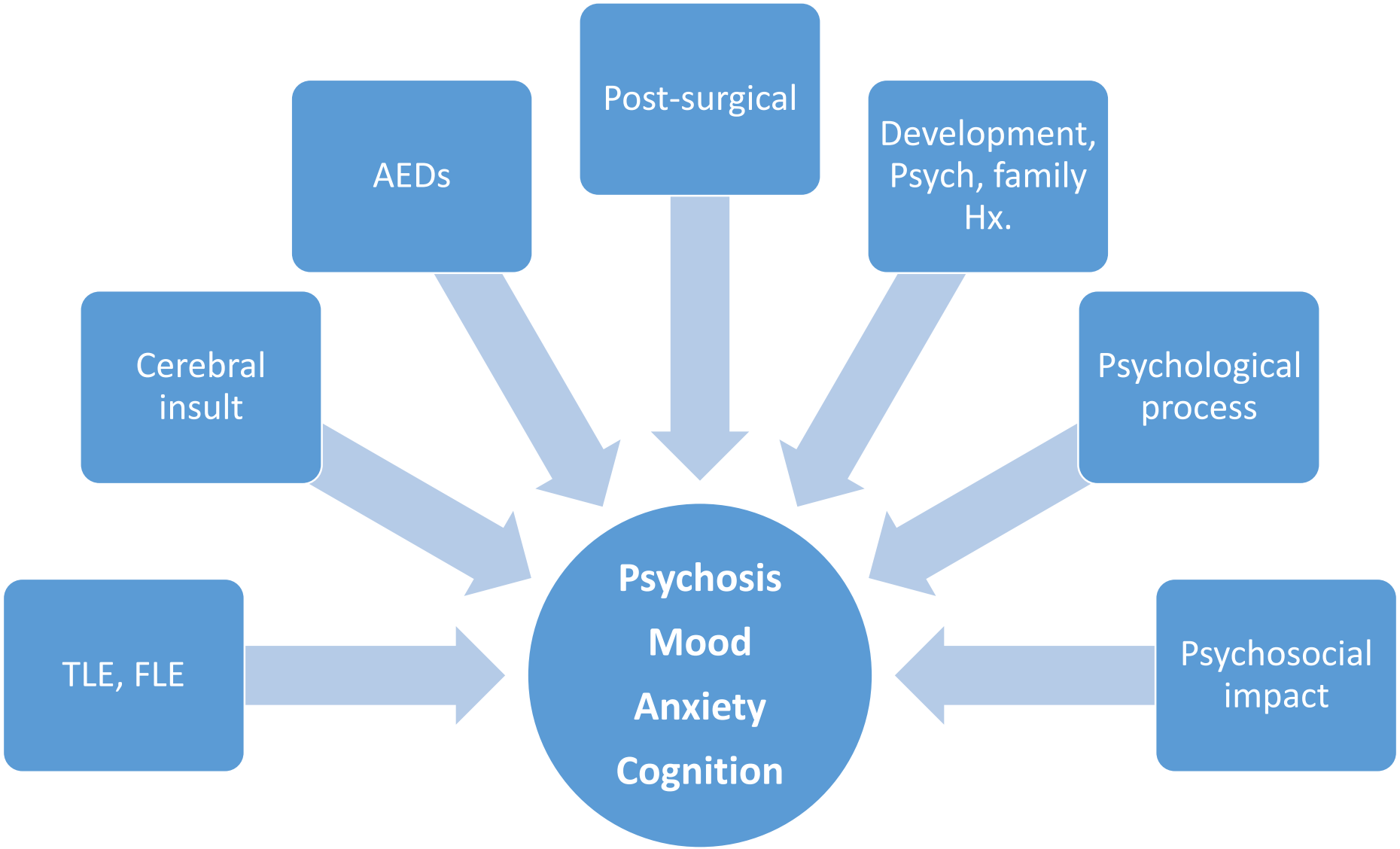
Prevalence of Psychiatric Disorders in Epilepsy vs. the General Population

Psychiatric Disorders	Prevalence	
	Epilepsy	General Population
Depression	11-80%	4.9-17% (MDD)
Psychosis	2-9.1%	1% (Schizophrenia)
GAD	15-25%	5.1-7.2%
Panic disorder	4.9-21%	0.5-3%
ADHD	12-37%	4-12%

"4 fold increased of psychiatric disorder in epilepsy than non-epilepsy patients."

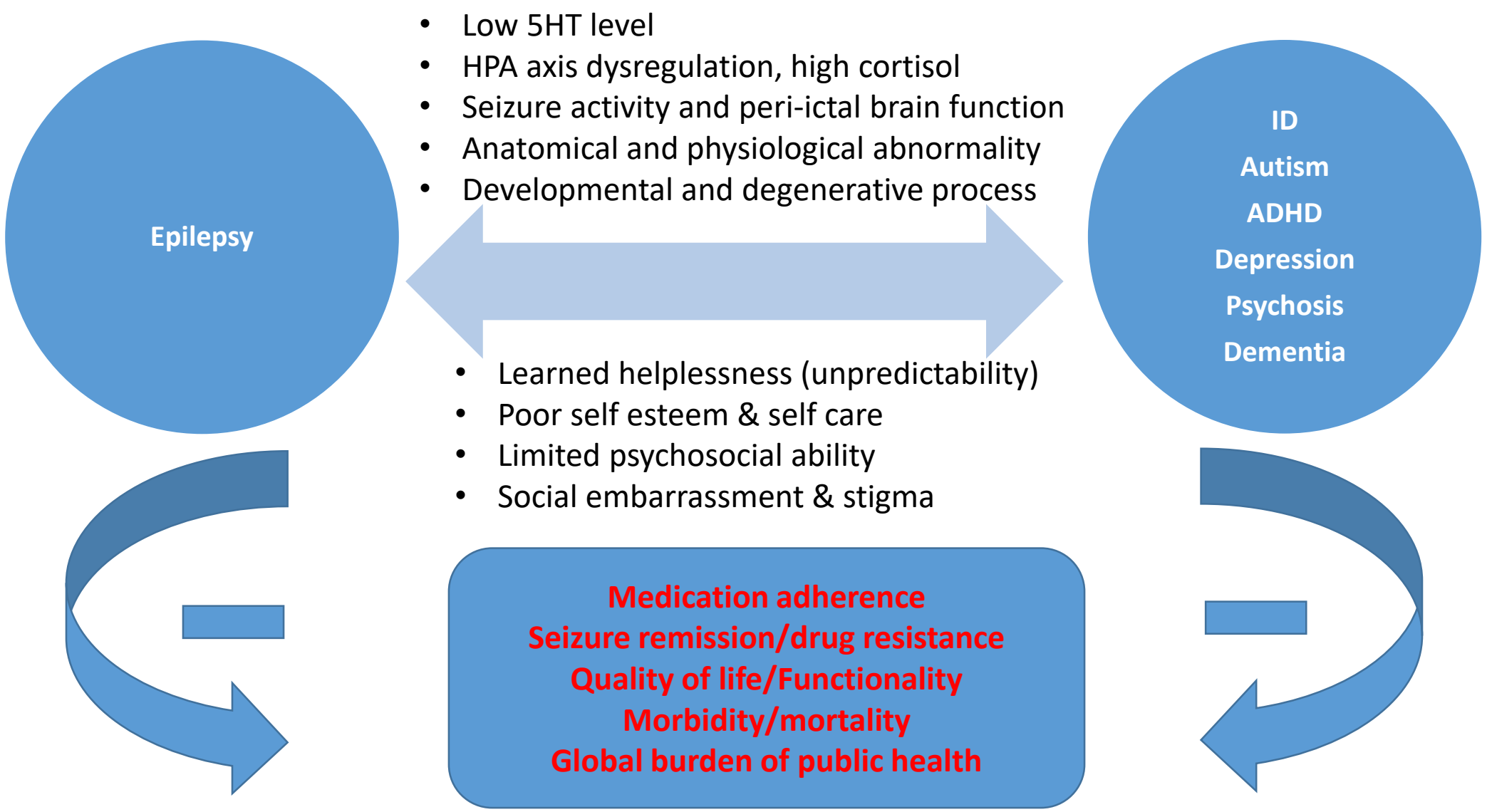
Fogel BS, Greenberg DB. Psychiatric care of the medical patient. Oxford University Press. 2015.

Potential risk factors of neurocognitive-psychiatric symptoms in PWE.



Kanner AM, et al. European Journal of Epilepsy 83 (2020) 216-222

Bidirectional Relationship Between Epilepsy & Neurocognitive-Psychiatric Disorders

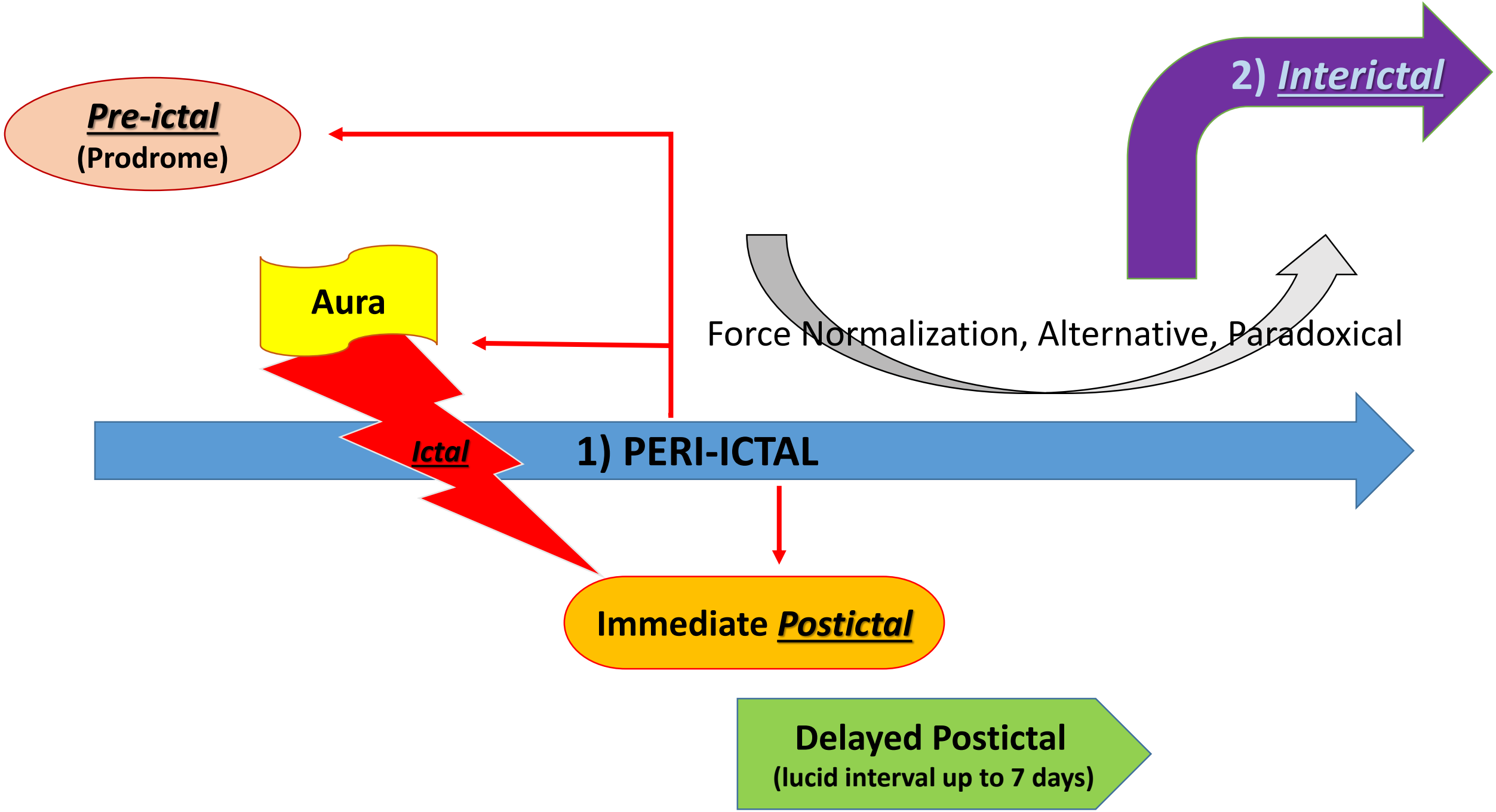


Hesdorffer et al. Ann Neurol. 2012 Aug;72(2):184-91.

Psychiatric Approach In The Patient With Epilepsy (PWE)

- Epileptic VS non-epileptic seizure?
- Atypical psychiatric syndrome VS DSM-5 syndrome?
- How the occurrence and remission of seizure and psychiatric symptoms temporally correlated?
- AED initiation/discontinuation → psychiatric symptoms?
- What is the potential seizure x AEDs x psychotropic drugs pharmacokinetic/dynamic interaction?
- What is the impact on the patient's QOL?

International League of Epilepsy (ILAE) Commission on the Neuropsychiatric Aspects of Epilepsy. Epilepsia. 2011 Nov;52(11):2133-8.


Pre-ictal
(Prodrome)
Aura
Ictal
1) PERI-ICTAL
2) Interictal
Force Normalization, Alternative, Paradoxical
Immediate Postictal
Delayed Postictal
(lucid interval up to 7 days)

Psychiatric comorbidities; temporally correlated, but atypical

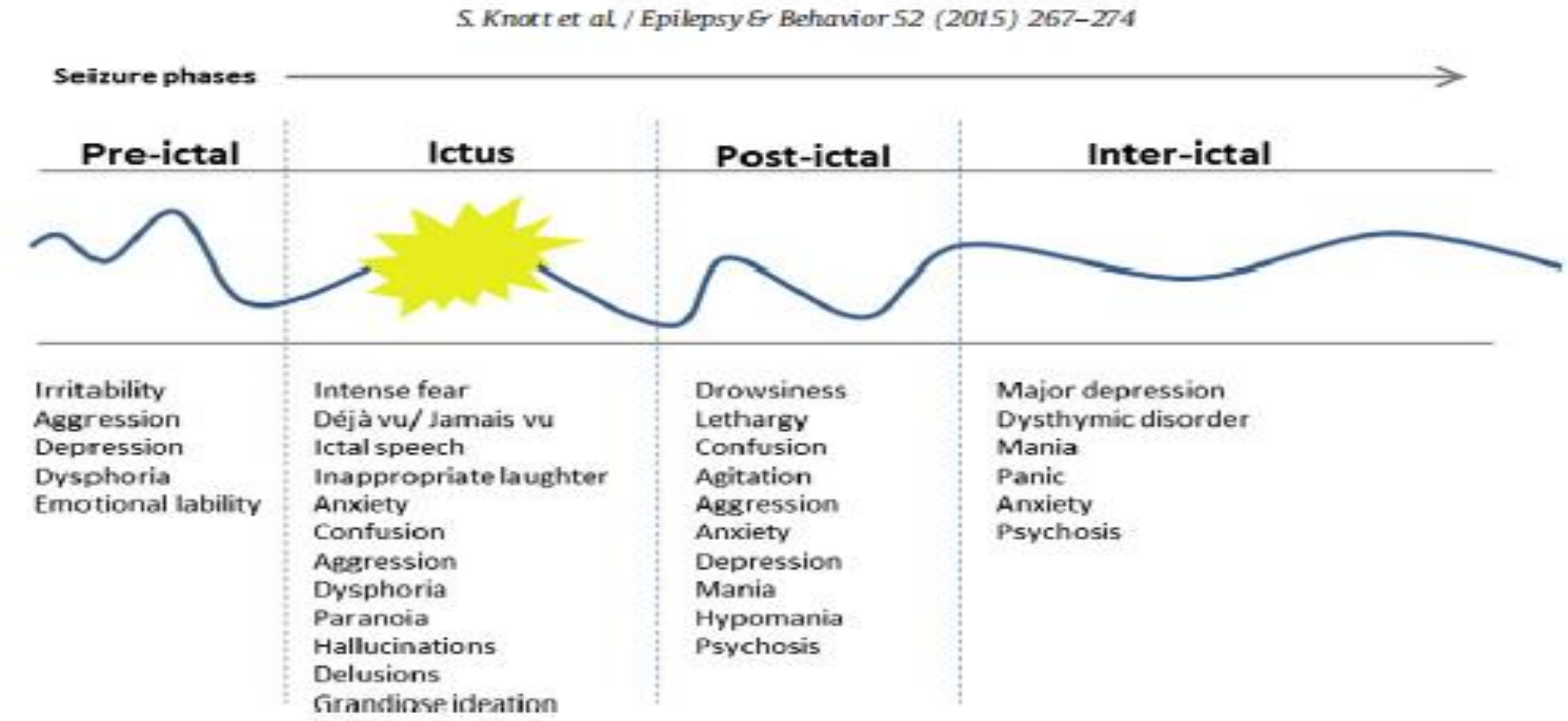


Fig. 1. The spectrum of behavioral and psychiatric disturbances that can occur throughout the phases of a seizure.

Intellectual disability (ID) and Epilepsy

- Children with epilepsy: 17.2% with autism, 7.8% with ADHD, 14.3% with ID.
- 1 in 5 adult individuals with ID diagnosed with comorbid epilepsy.
- Moderate ID → 16.7% epilepsy, severe ID → 27% epilepsy, profound ID → 50.9% epilepsy
- ID: IQ ≤ 70 → reasoning, problem solving, planning, abstract thinking, judgement, academic learning, etc.

- Comorbidity: speech handicap, motor handicap, joint/GI/neurovascular disease, aggression, self-injurious behaviors, anxiety, depression.
- Neuropsychological testing: WAIS, WISC

Mula M, et al. Continuum. 2022.
Robertson j, Hatton c, et al. Seirzure 2015

Kanner AM, et al. European Journal of Epilepsy 83 (2020) 216-222
Taniguchi et al. Psychiatry Clin. Neurosci. Rep. 2025

Seminar in Epileptology
Epileptic Disord 2021; 23 (1): 40-52
Epileptic Disorders

Developmental and epileptic encephalopathies: recognition and approaches to care

Sharika Raga [1,2], Nicola Specchio [3,4], Sylvain Rheims [4,5,6], Jo M. Wilmshurst [1,2]

- **Developmental encephalopathy (DE):** a person with developmental delay or intellectual disability, due to a non-progressive brain state, who also has co-existing epilepsy → Precision (genetic) therapy.

- **Epileptic encephalopathy (EE):** the abundance of epileptiform abnormalities and/or a high number of epileptic seizures contribute to cognitive regression. → (Aggressive) seizure medications.

- **Developmental and epileptic encephalopathy (DEE):** both developmental impairment and epileptic activity have an impact on the cognitive and behavioral state of the affected person → Both interventions.

▼ **Table 1.** Differentiation between patients with neurocognitive impairment and epilepsy whose DEE is, or is not, influenced by epileptic activity. Note that some conditions, such as TSC, may be assigned to more than one category depending on the impact of the epileptiform activity.

	Developmental encephalopathy (DE)	DEE with dual impact on cognition from developmental and epileptiform activity	DEE predominantly related to epileptic encephalopathy
Etiology	Condition due to underlying static etiology *e.g.* hypoxic brain insult	Condition due to underlying etiology *e.g.* TSC, Dravet syndrome, most commonly with gene mutations	Condition due to the impact of the epilepsy *e.g.* EE-CSWS
Clinical	May have systemic or focal neurological features, neurocutaneous markers. May be normal	May have systemic or focal neurological features, neurocutaneous markers. May be normal	May be normal or hypotonic, depending on seizure control
Age at onset	*In utero* or shortly after birth	Any age, most have onset in infancy or early childhood	Any age but most in childhood
Past medical history	Often abnormal	Either abnormal or normal	Usually normal
Cognition	Abnormal	Abnormal – but may be normal and regress, or deteriorate from a low baseline	Regression, improves with seizure control
EEG	Abnormal in established cases	Abnormal in established cases.	Abnormal. Can return to normal if seizures are controlled. Mostly slow with frequent epileptiform discharges.
Outcome	Neurocognition and neurobehavior remain impaired even with seizure control	Neurocognition and neurobehavior remain impaired even with seizure control although some improvement may occur	Neurocognition and neurobehavior may significantly improve with control of seizures and resolution of interictal epileptiform activity.

ADHD and Epilepsy

- ADHD is a risk factor for having epileptic seizures (but is not mediated by stimulants).
- A population-based study from Sweden (N=21,557) demonstrated a lower risk for subjects with ADHD to experience acute seizures when they were taking CNS stimulants compared to periods when they were not.
- CNS stimulants **(Methylphenidate)** and Atomoxetine are safe at therapeutic doses and worsen seizures at toxic doses.

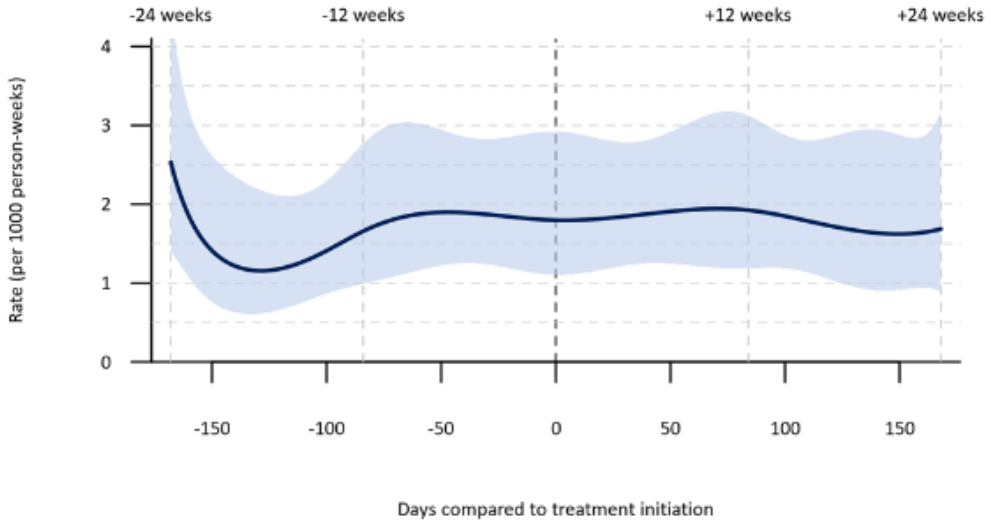


FIGURE 1 Incidence rate (IR) of seizures in the 24 weeks before and after ADHD medication initiation among 995 individuals with a seizure history who initiated ADHD medication treatment between 2007 and 2013. The blue line is the estimated IR per 1000 person-weeks presented with 95% confidence interval. IRs are estimated with natural cubic splines with knots at −24, −12, 0, 12, and 24 weeks

Kanner AM, et al. European Journal of Epilepsy 83 (2020) Brikell I, et al. Epilepsia. 2019 Robertson j, Hatton c, et al. Seizure 2015

Dementia and Epilepsy

- Increased risk of dementia in epilepsy (8.1- 17.5 per 100 PWE).
- Increased risk of seizure in VaD & AD (as well as DLB & FTD).
- Seizure mimics in demented older adult patients: stroke, TIA, delirium, syncope, migraine, panic attack, sleep disorders, etc.
- MMSE, MoCA screening → Neuropsychological testing.
- Donepezil did not improve memory/cognitive/psychological functions in PWE with memory problems.
- Cognitive impairment → limited informed consent & decisional capacity, lifestyle, school, driving, employment, etc.
- Levetiracetam!!! (> _ <) (T - T)

Mula M, et al. Continuum 2022
Hamberger MJ, et al. Epilepsia, 2007

The prevalence of psychosis in epilepsy; a systematic review and meta-analysis

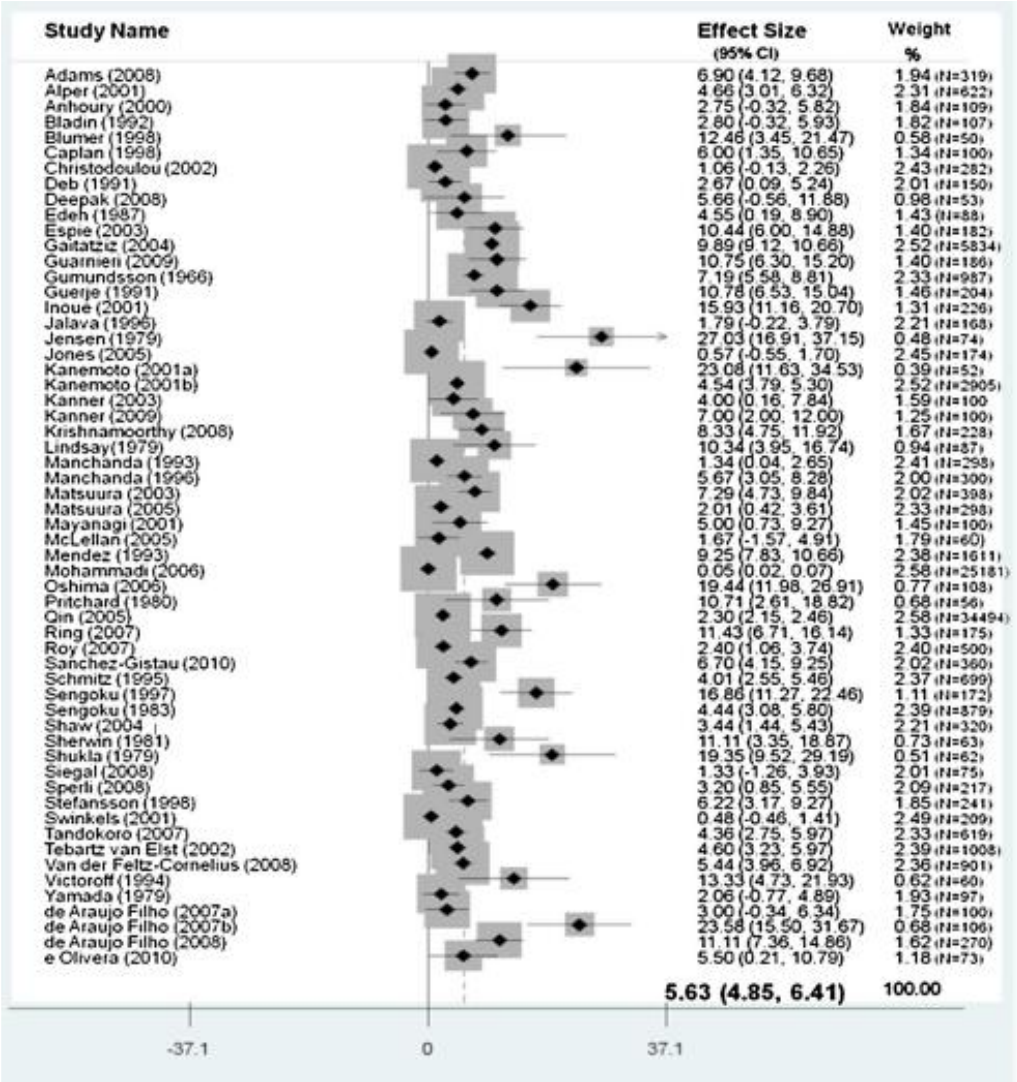


Figure 2 Pooled prevalence of psychosis in individuals with epilepsy.

Clancy *et al. BMC Psychiatry* 2014, **14**:75

- Pooled OR for risk of psychosis among PWE compared with controls = 7.8
- Pooled prevalence of psychosis in PWE = 5.6%
- Prevalence of psychosis in TLE = 7%
- Prevalence of interictal psychosis in PWE = 5.2%
- Prevalence of postictal psychosis in PWE = 2%

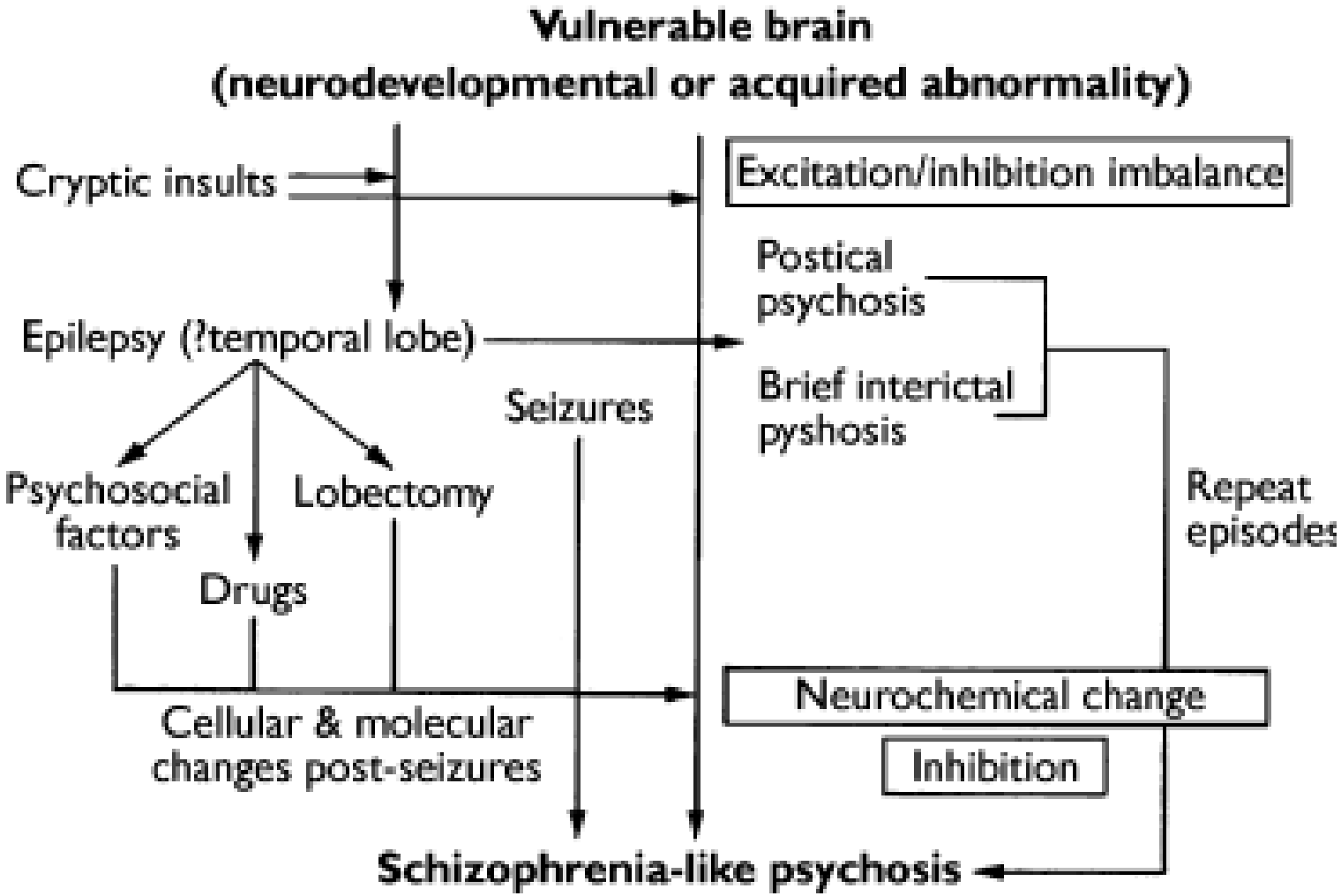


Figure 1.

Possible pathophysiologic mechanisms for the association between epilepsy and schizophrenia-like psychosis

Sachdev P. Am J Psychiatry. 1998 Mar;155(3):325-36.

Post-ictal Psychosis (PIP)

- Develops within 1 week (mostly 3 days) after seizure.
- Lucid interval may present.
- Psychosis (+ mania + depression + anxiety + confusion + agitation/aggression/violence + suicide + dissociation + personality change).
- Mostly resolves in 1 week - 1 month. 1/2 of PIP recurs.

- Aggressive seizure control (AEDs, Sx.) prevent PIP!!!
- Early treatment (Observation + environmental control + Med) during the development of PIP may prevent full-blown psychosis.
- Benzo, Antipsychotic (PO, IV, IM)
- Psych meds tapering in 5 days (rapid episode) or 1-3 months (prolonged episode).

Adachi N, et al. Epilepsia. 2013 Mar;54 Suppl 1:19-33.
Kerr MP, et al. Epilepsia. 2011 Nov;52(11):2133-8.

Inter-ictal Psychosis (IIP)

- Psychosis in clear consciousness occurs in PWE, the periictal/postictal psychosis is excluded.
- Schizophrenic-like with limited negative symptoms.
- Longer; median duration = 17 weeks.
- 75% of IIP lasted more than 1 month.
- Only 15% remitted w/o treatment.

- Early APD treatment is recommended.
- Months – years course of treatment.
- 2/3 of IIP recurs.

Adachi N, et al. Epilepsia. 2013 Mar;54 Suppl 1:19-33.
Kerr MP, et al. Epilepsia. 2011 Nov;52(11):2133-8.

Depression and Epilepsy

- 1/3 of PWE experiences a depressive disorder in their life.
- Atypical presentation is common; depression + irritability + anxiety + cognitive impairment.
- Temporal correlation; prodrome, ictal, postictal, interictal, alternative depression, postsurgical depression, AED initiation, AED discontinuation, enzyme inducing AED and AD.

- Consider Lamotrigine, Valproic acid, Carbamazepine, Oxcarbazepine.
- SSRI > SNRI > TCA.
- Avoid Bupropion, Clomipramine!!!
- Caution with CYP450 interaction between AEDs & Ads.
- Counseling, Psychoeducation, Supportive psychotherapy, CBT.

Kanner AM. Epilepsia. 2013 Mar;54 Suppl 1:3-12.
Kerr MP, et al. Epilepsia. 2011 Nov;52(11):2133-8.

Anxiety & Epilepsy

- TLE; amygdala/hippocampus → fear & anxiety (aura, ictal, postictal, interictal).
- Ictal fear (panic) is the most frequent ictal psychiatric symptom.
- Interictal anxiety ; panic, agoraphobia, GAD, OCD, PTSD.

- Psychotherapy; CBT (Cautious with deep breathing exercise!!!)
- Benzo (short-term); Clobazam, Clonazepam, Lorazepam, Diazepam.
- SSRIs (Sertraline, Escitalopram, Venlafaxine).
- Pregabalin (1st choice in epilepsy with GAD), Gabapentin.

Mula M. Epilepsia. 2013 Mar;54 Suppl 1:13-8.

Screening tools: Neurological Disorders Depression Inventory for Epilepsy (NDDI-R)

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____

=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

GAD-7

Over the last 2 weeks, how often have you been bothered by the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

(For office coding: Total Score T____ = ____ + ____ + ____)

Hospital Anxiety and Depression Scale (HADS)

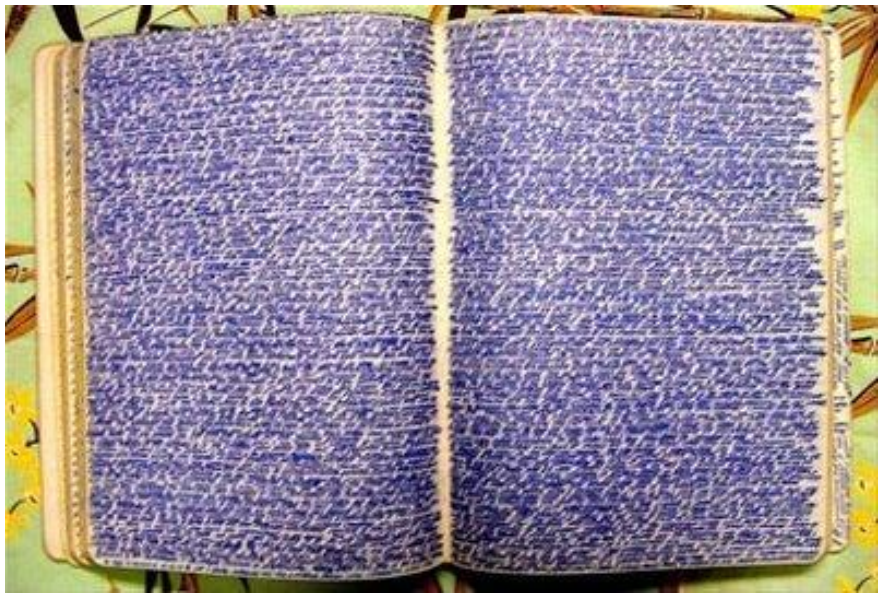
Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Scoring:
Total score: Depression (D) _____ Anxiety (A) _____
0-7 = Normal

Personality disorder & Epilepsy



- **TLE (Epileptoid personality);**

-Hyper/hypo-sexuality, hyper-religiosity, hyper-graphia, circumstantiality, viscosity (interpersonal adhesiveness).

-Kluver-Bucy syndrome, Psychosis.

- **Juvenile myoclonic epilepsy;**

-Poor sleep habits, lack of discipline, hedonism, indifference of illness, attractive but labile, child-like behavior, mood swing.

-Cluster B-like.

- **Frontal lobe syndrome in PWE;**

-Irritability, impulsivity, aggressive outburst, social disorganization, emotional blunting, withdrawal, apathy.

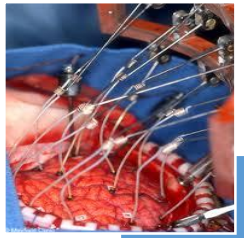
-Intermittent explosive disorder, aggressive episode.

Trimble M. Epilepsia. 2013 Mar;54 Suppl 1:41-5.

Post epilepsy surgery & Psychiatric complications

Previous risk stabilization

- Depression
- Anxiety
- Psychosis
- Personality
- No
  ps
  co



motional support

- Pain
- Insomnia
- Delirium
- Benzo withdrawal

n or De novo Mx

- Depression
- Anxiety
- Psychosis
- Mania
- AEDs

ation

4% incidence of De Novo interictal psychosis

→ 1.6% incidence in Thai cohort

"Epilepsy surgery improves epilepsy related psychosis, particularly aura & ictal and peri-ictal psychoses."

Koch-Stoecker S, et al. Epilepsia. 2013 Mar;54 Suppl 1:46-52.

Kanchanatawan B, et al. Psychiatry Res. 2016 Nov 30:245:333-339

Antiepileptics	Positive Psychiatric Effects
Carbamazepine	Bipolar disorder, Aggression
Oxcarbazepine	Bipolar disorder, Aggression
Valproic acid	Bipolar disorder, Aggression
Lamotrigine	Bipolar depression
Topiramate	Alcohol use, Weight gain, Binge eating
Gabapentin	Social anxiety, Alcohol use
Pregabalin	Generalized anxiety disorder

Antiepileptics	Negative Psychiatric Effects
Levetiracetam	Irritability, Depression, Psychosis
Perampanel	Hostility, Irritability, Anxiety, Psychosis
Topiramate	Cognitive impairment, Depression
Zonisamide	Cognitive impairment, Depression
Benzodiazepine	Cognitive impairment, disinhibition

Epilepsy Behav. 2017 Nov;76:24-31. Chen B et al.
Fogel BS, Greenberg DB. Psychiatric Care of the Medical Patient. 2015.
Taniguchi et al. Psychiatry Clin. Neurosci. Rep. 2025

TABLE 1 Common psychiatric adverse effects associated with antiseizure medications (based on references 15 and 46).

Drugs	Psychiatric adverse effects	Risk factors
Barbiturates (phenobarbital/primidone)	Depression (hyperactivity, irritability, and aggression)	Children and individuals with intellectual disabilities
Benzodiazepine	(Hyperactivity, irritability, and aggression)	Children and individuals with intellectual disabilities
Brivaracetam	Aggressive behavior, depression, and psychosis	
Carbamazepine	-	
Eslicarbazepine	-	
Ethosuximide	Psychosis	
Felbamate	Anxiety and psychosis	
Gabapentin	(Hyperactivity, irritability, and aggression)	Children and individuals with intellectual disabilities
Lacosamide	-	
Lamotrigine	(Hyperactivity, irritability, and aggression)	Individuals with intellectual disabilities
Levetiracetam	Irritability, aggression, anxiety, depression, and psychosis	
Oxcarbazepine	-	
Perampanel	Irritability, aggression, anxiety, depression, and psychosis	Blood concentration dependence
Phenytoin	Psychosis	At high serum levels
Pregabalin	Depression	
Rufinamide	-	
Stiripentol	Hyperactivity, irritability, and aggression	
Tiagabine	Irritability	
Topiramate	Depression, psychosis, irritability, and cognitive dysfunction	Dose dependent
Valproic acid	-	
Vigabatrin	(Hyperactivity, aggression, and agitation)	Children and individuals with intellectual disabilities
Zonisamide	Depression, psychosis, irritability, and cognitive dysfunction	Dose dependent

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REVIEW ARTICLE

PCN Reports

Redefining the practical roles of psychiatrists in epilepsy care: A framework for collaboration in Japan

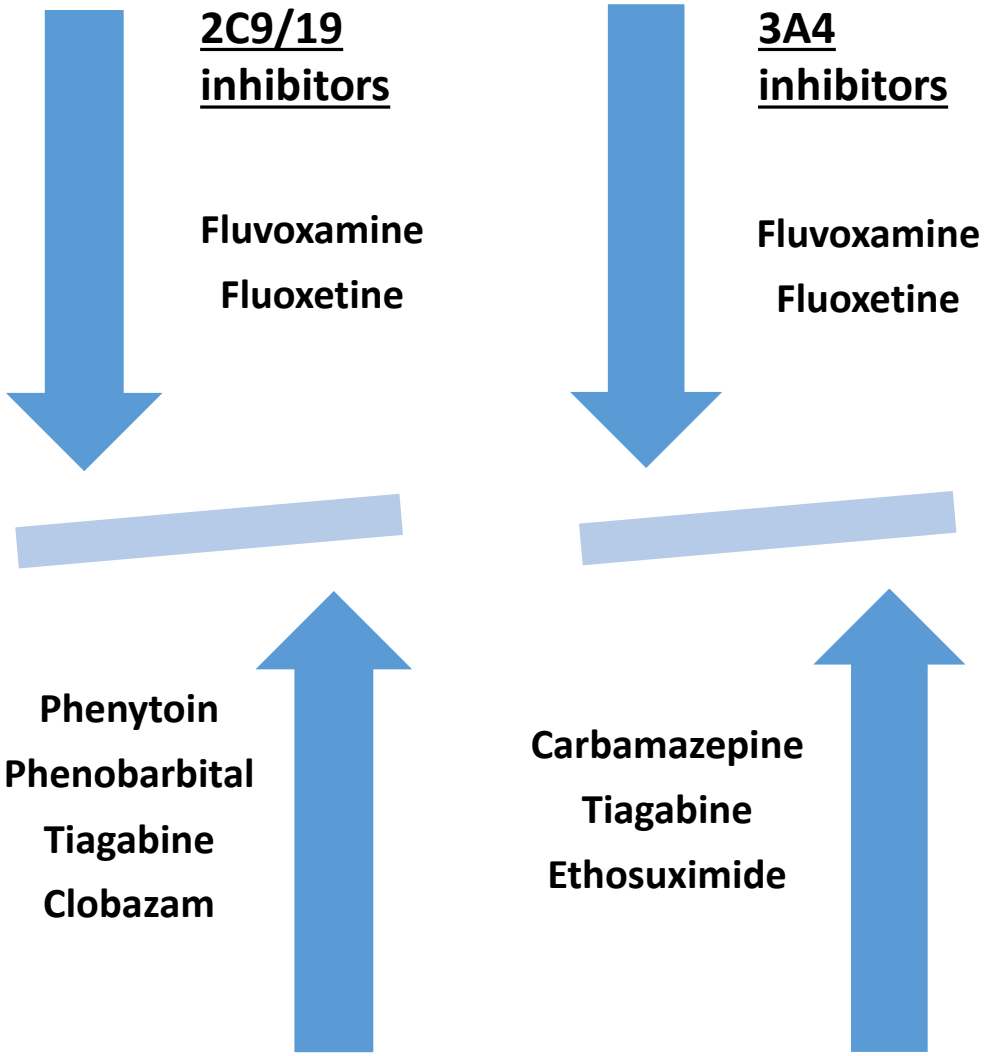
Go Taniguchi MD, PhD[1] | Hirotaka Iwaki MD, PhD[2] |

Psychotropic drugs and seizure threshold

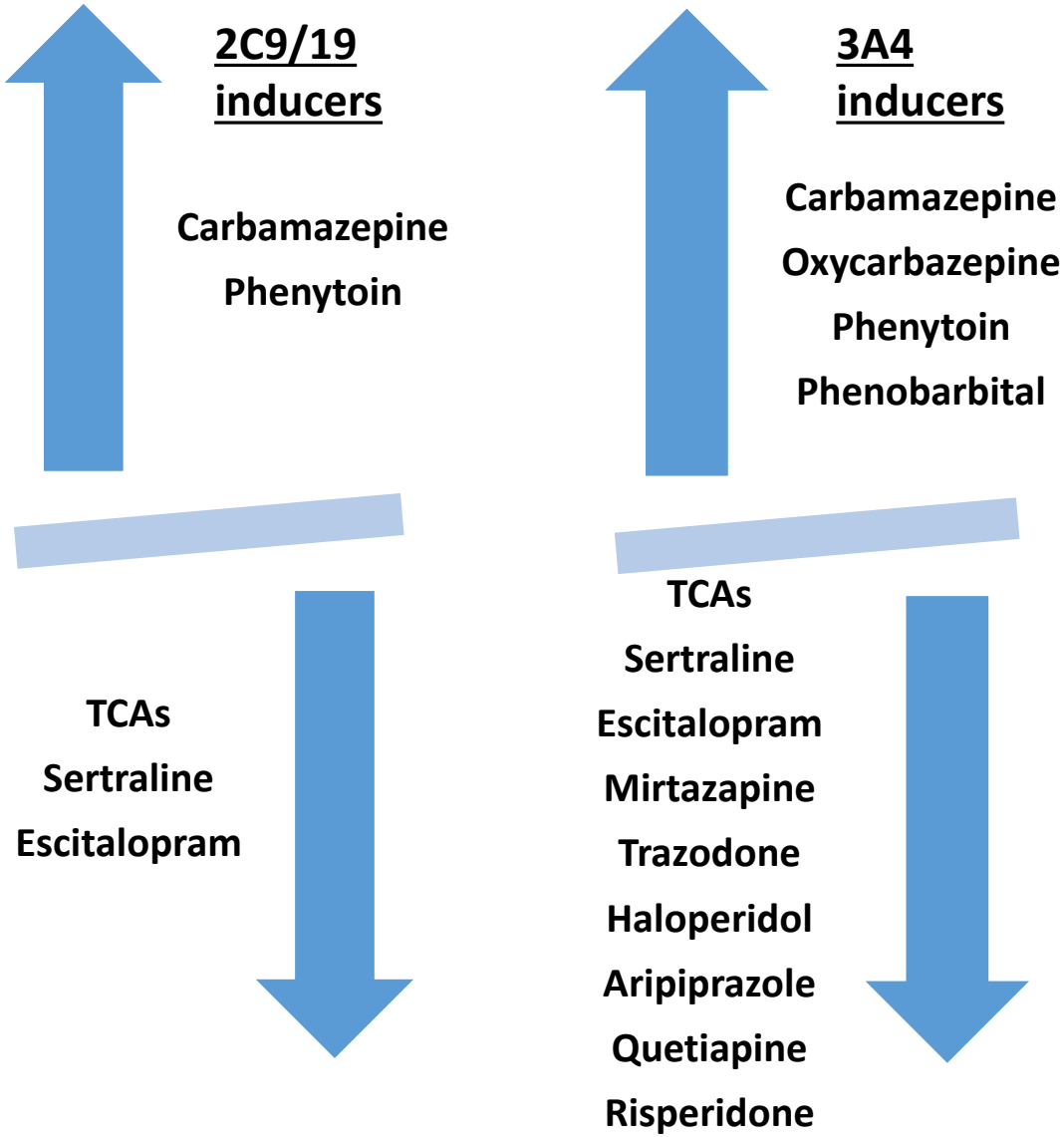
Drug Classes	Use	Avoid
Antidepressants	**SSRIs** (1-2% seizure risk when OD) > SNRIs > Mirtazapine > some TCAs (10-20% seizure risk when OD)	Amoxapine, Amitriptyline, **Clomipramine**, Maprotiline, **Bupropion**
Antipsychotics	Haloperidol = **Risperidone** = Paliperidone > Aripiprazole = Ziprasidone > Quetiapine > Olanzapine	**Chlorpromazine**, Loxapine, **Clozapine**
Mood stabilizers	**Valproic acid, Lamotrigine, Carbamazepine, Oxcarbazepine**, Benzodiazepine	Lithium (intoxication)
Stimulants	**Methylphenidate**	**Amphetamine**

Habibi M, Hart F, Bainbridge J. Curr Neurol Neurosci Rep. 2016 Aug;16(8):71.
Alper K, et al. Biol Psychiatry. 2007 Aug 15;62(4):345-54.
Mula M. Pharmacol Res. 2016 May;107:147-153.

Psych Drugs on AEDs



AEDs on Psych Drugs



Habibi M, Hart F, Bainbridge J. Curr Neurol Neurosci Rep. 2016 Aug;16(8):71. Levenson JL. Textbook of Psychosomatic Medicine, 2nd ed. 2011.

Psychotropic drugs & AEDs Pharmaco-dynamic interactions.

Psychotropics	AEDs	Side effects
TCAs, sedating ADs/APs	Almost all	Sedation, Cognitive impairment
TCAs, Mirtazapine, Olanzapine	Carbamazepine, Valproic acid	Weight gain
TCAs, Citalopram, Ziprasidone, Clozapine	Felbamate	Arrhythmia
Duloxetine, Chlorpromazine	Carbamazepine, Valproic acid	Hepatic impairment
SSRIs, SNRI, Antipsychotics, Lithium	Carbamazepine, Oxcarbazepine	Hyponatremia
Clozapine, Chlorpromazine	Carbamazepine, Valproic acid	Bone marrow suppression, Bleeding

Mula M. Pharmacol Res. 2016 May;107:147-153.
Levensen JL, Ferrando SJ. Clinical Manual of Psychopharmacology in the Medically Ill. 2nd ed. 2017.

Conclusion

- The cognitive and psychiatric presentations are common and adversely affect the outcome of epilepsy care as well as QOL of the PWE.
- Biological & psychosocial multi-factors between epilepsy and psychiatric disorders are bi-directionally related.
- Phenomenological, temporal, and etiologic approaches would promote the clinical understanding of this complex clinical situation and guide effective management.
- Choosing the antiepileptics, psychotropics, and psychological management for this population is challenging but may rewardingly enhance seizure/psychiatric symptom control as well as QOL improvement.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