Common Psychiatric Syndromes in Epileptic Patients and PNES

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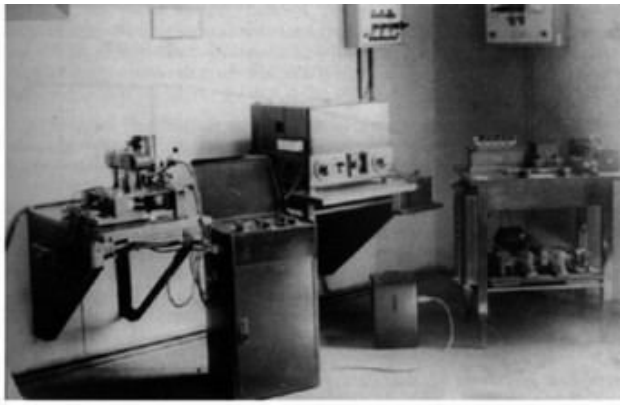
Prevalence of Psychiatric Disorders in Epilepsy and the General Population

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%

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

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



Über das Elektrenkephalogramm des Menschen.

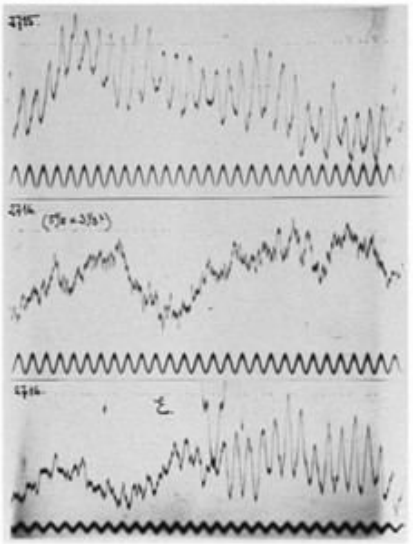
Von

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.

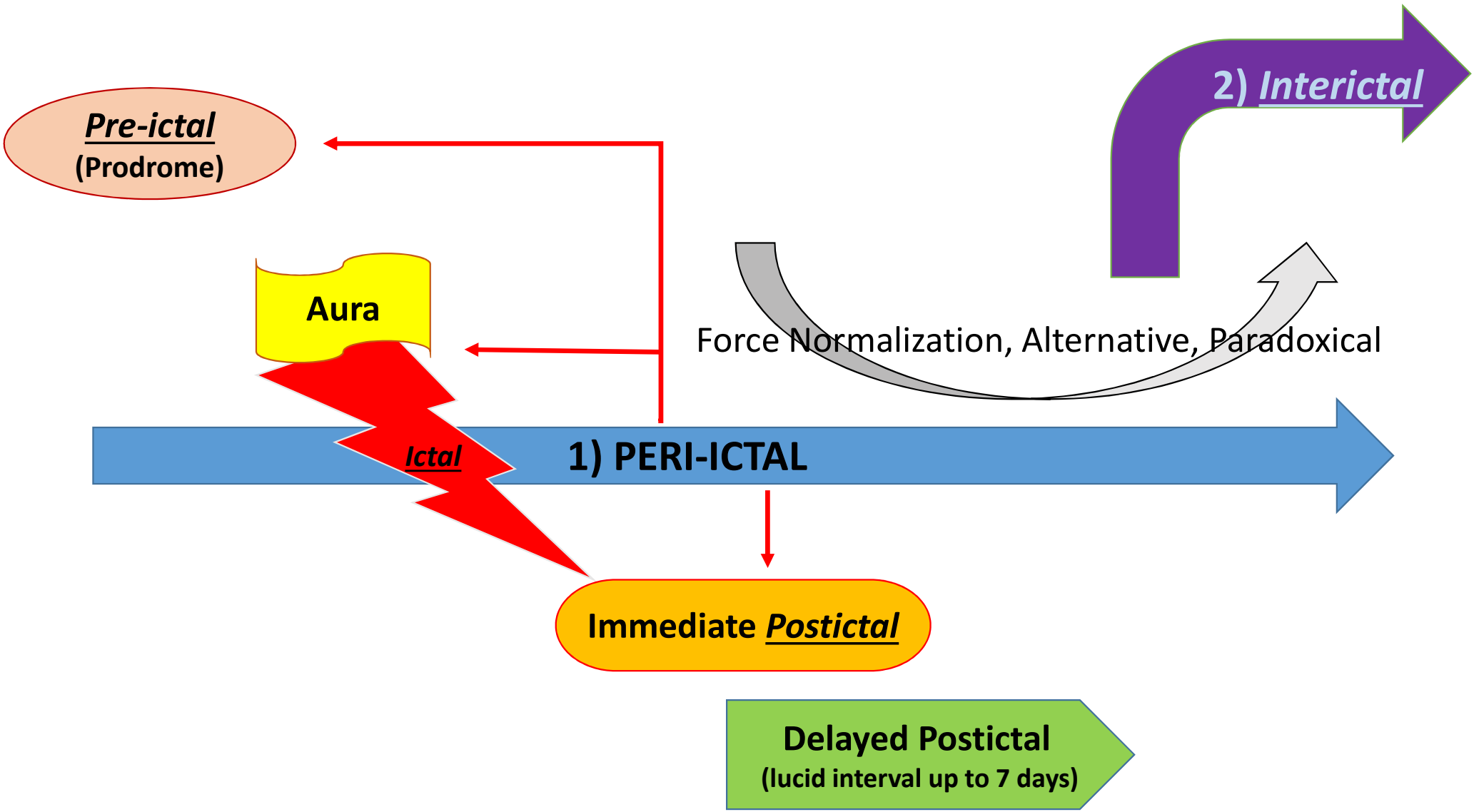


Millett D. Perspect Biol Med. 2001 Fall;44(4):522-42.

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 impact on the patient's QOL?
- What is the potential seizure x AEDs x psychotropic drugs pharmacokinetic/dynamic interaction?

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


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

Psychiatric comorbidities; temporally correlated, but atypical

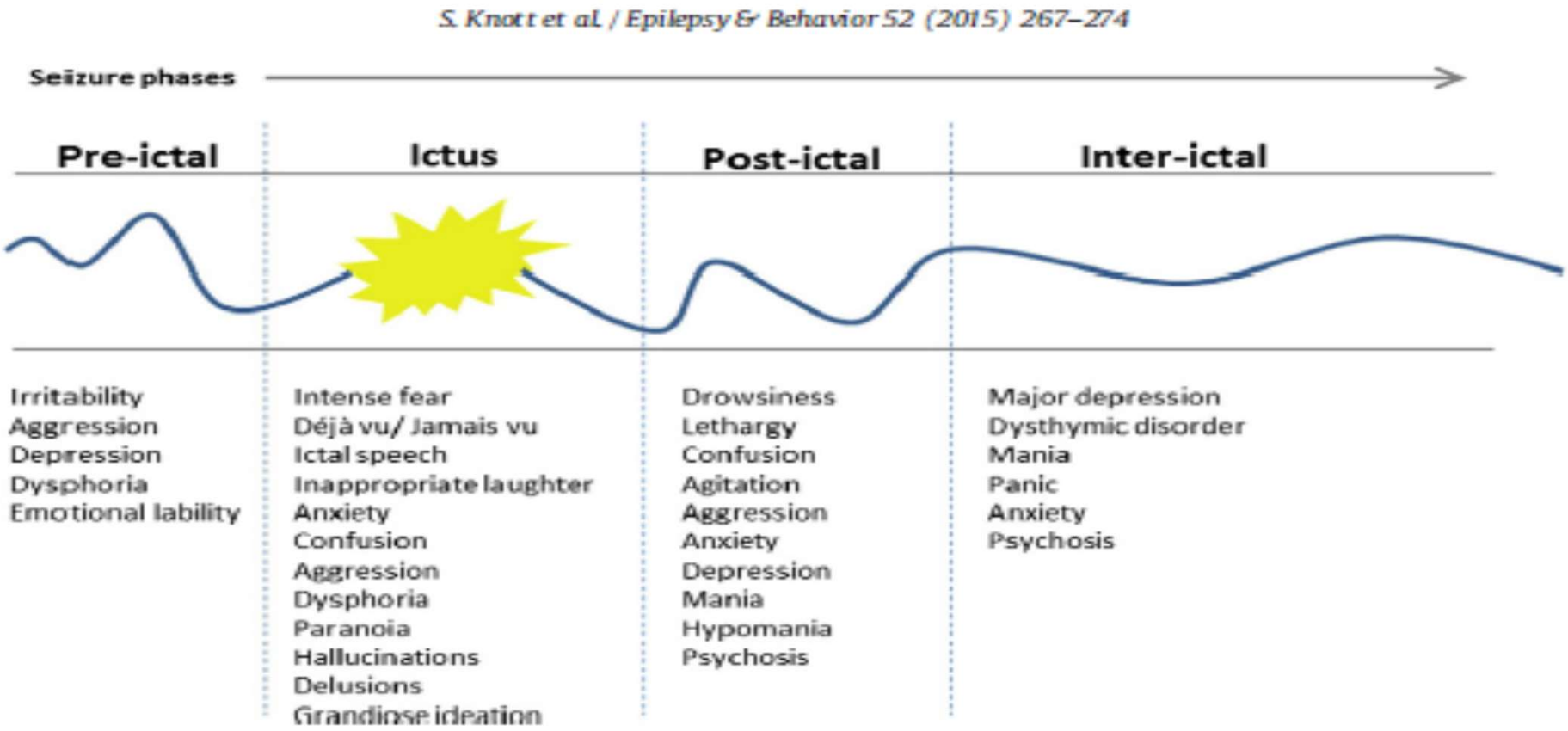
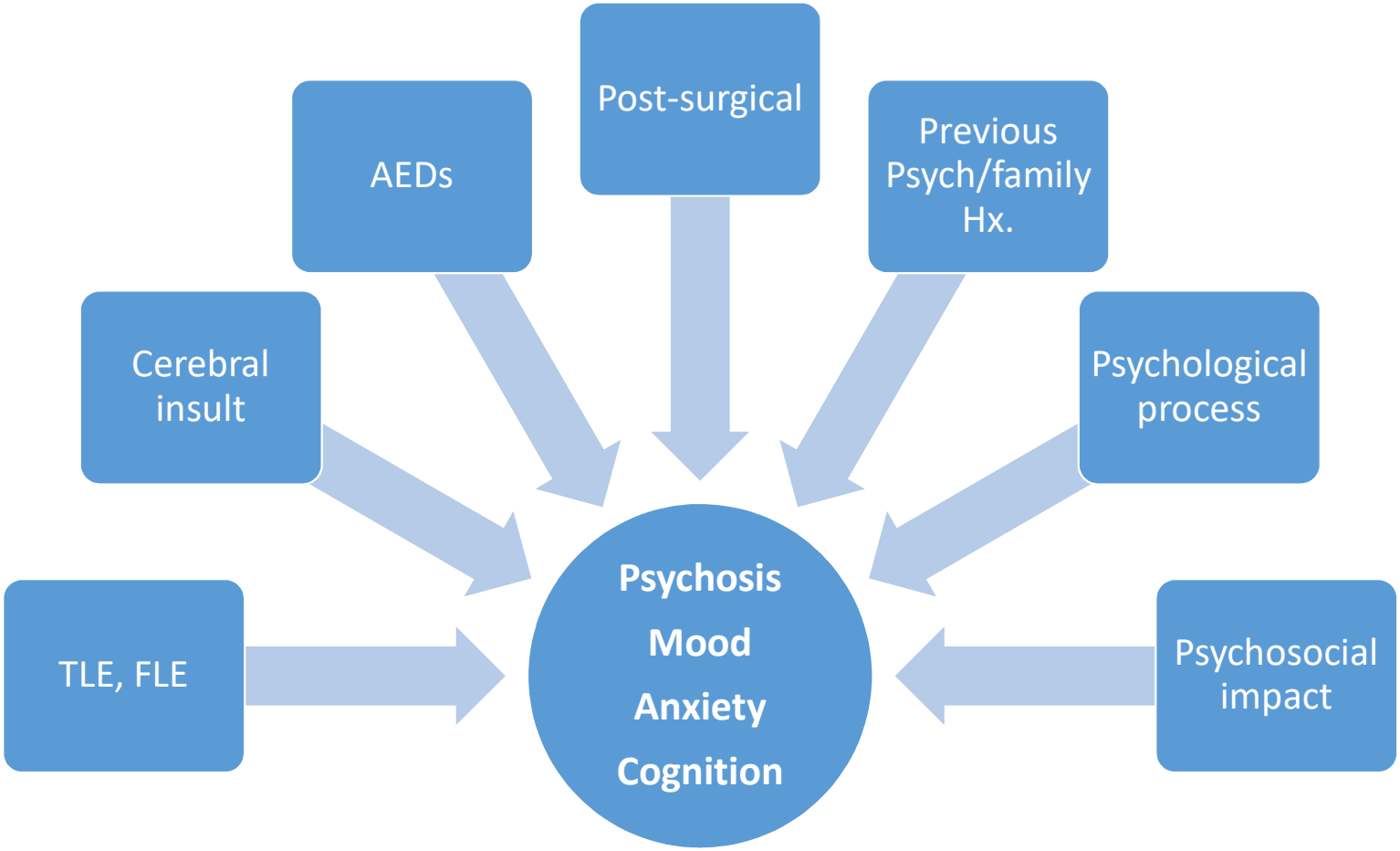
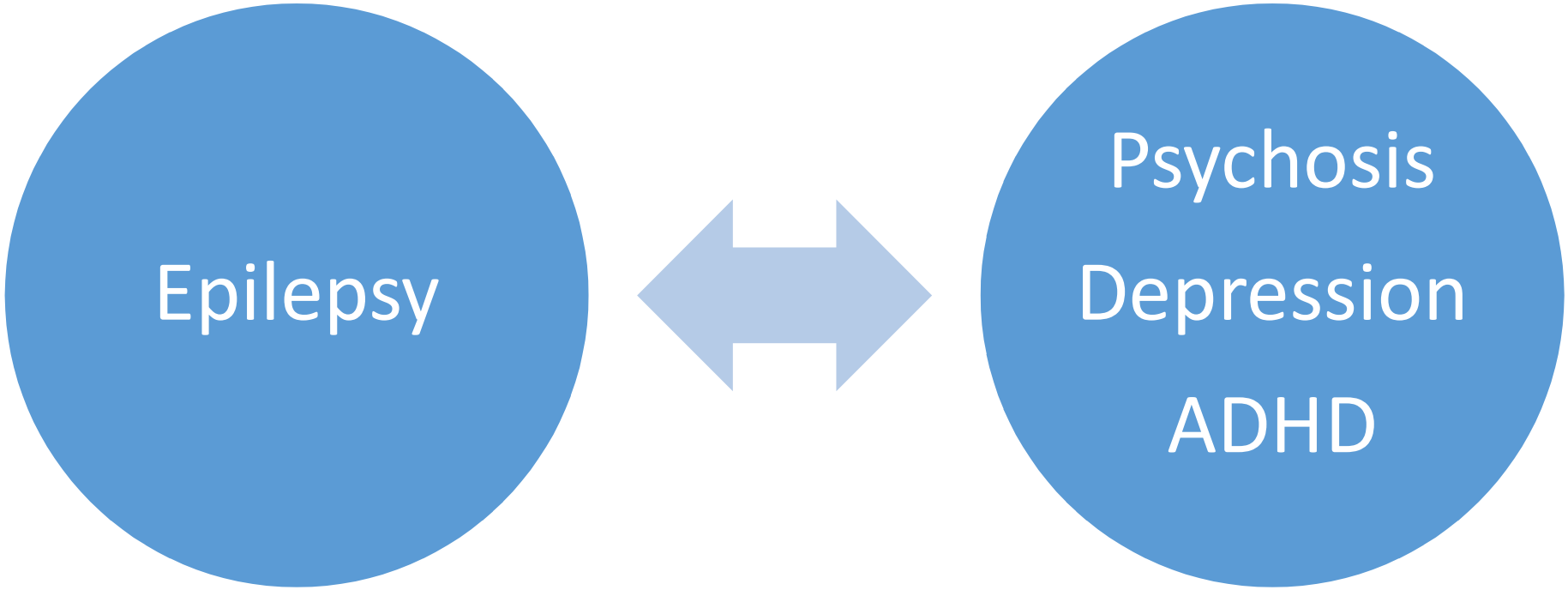


Fig. 1. The spectrum of behavioral and psychiatric disturbances that can occur throughout the phases of a seizure.

Potential risk factors of psychiatric symptoms in PWE.



Bidirectional Relationship



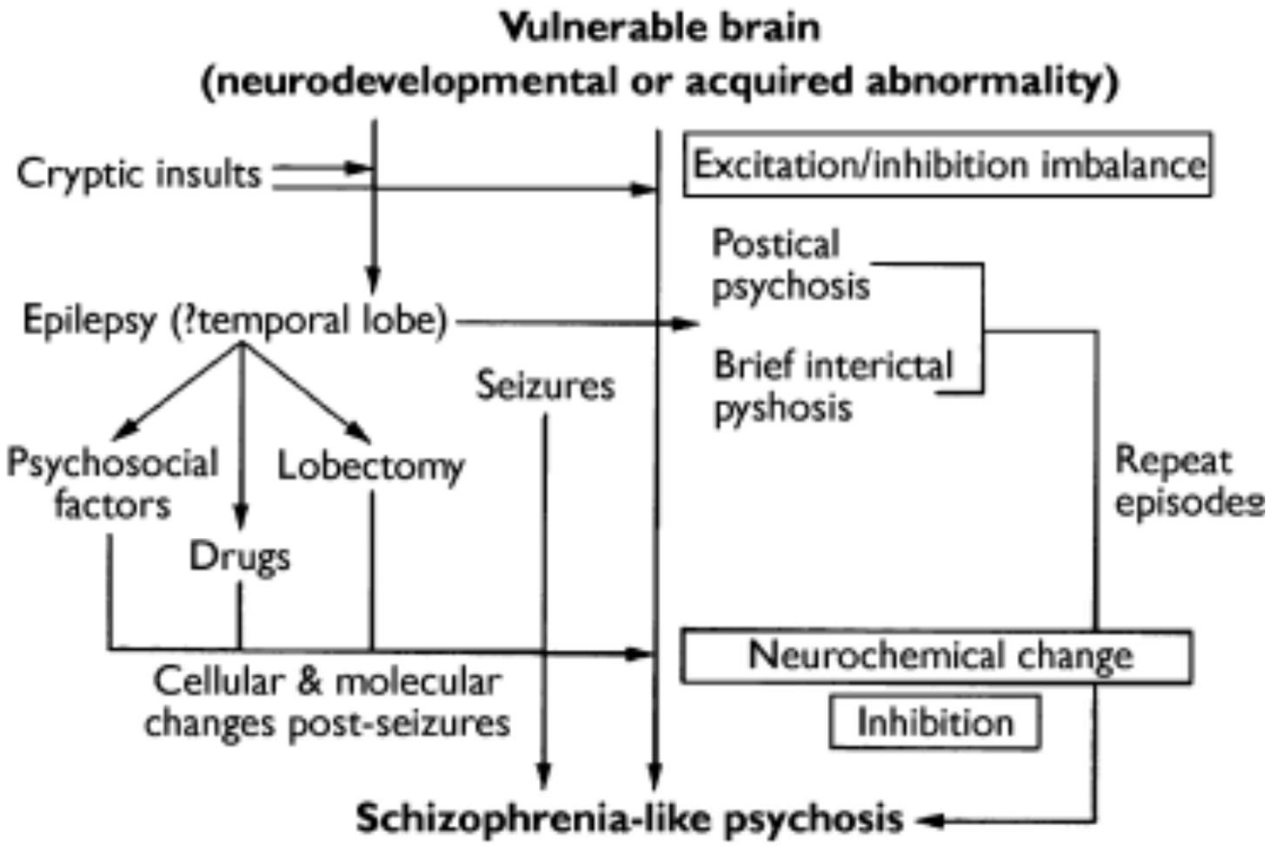


Figure 1.

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

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

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

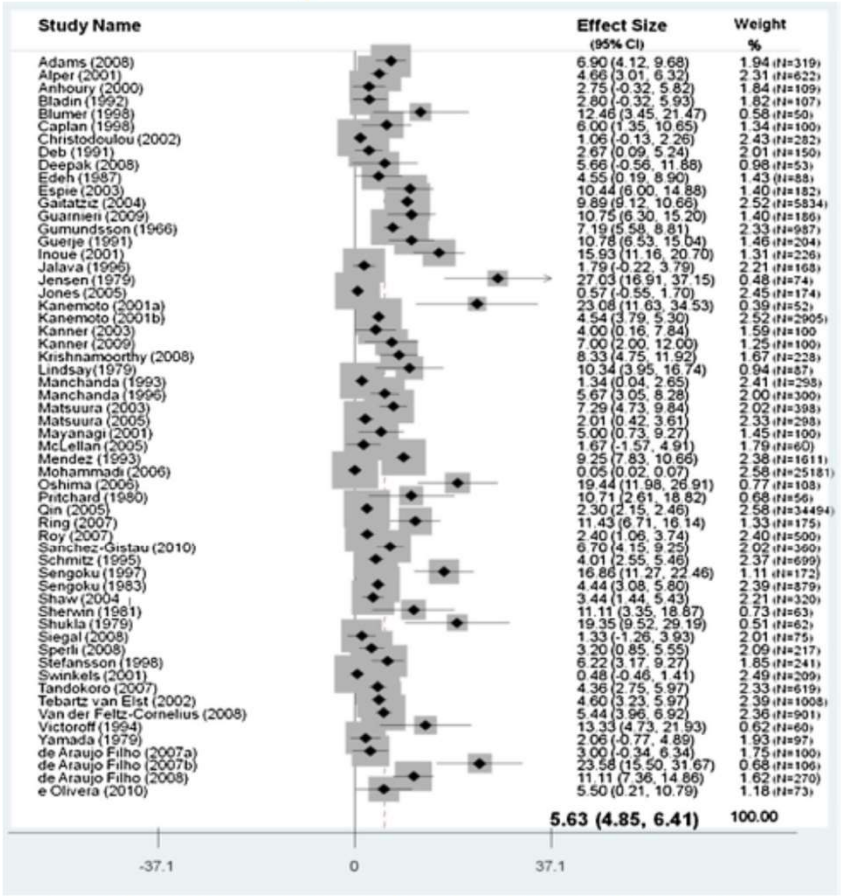


Figure 2 Pooled prevalence of psychosis in individuals with epilepsy..

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%

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 Lithium, 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.

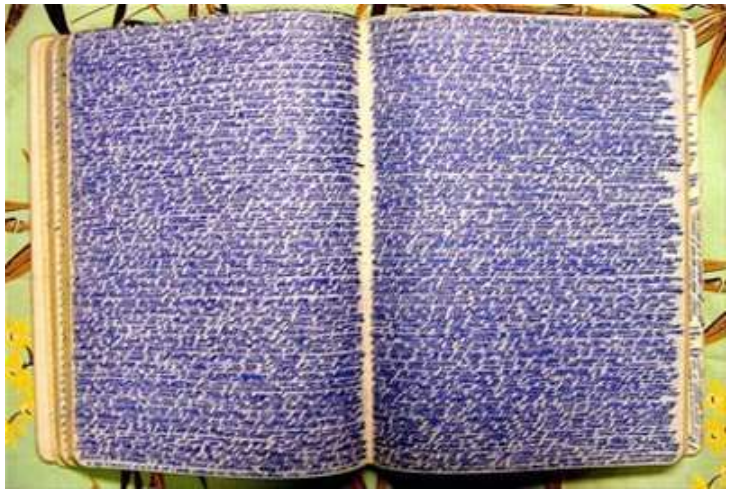
Anxiety & Epilepsy

- 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, Paroxetine, Venlafaxine).
- Pregabalin (1st choice in epilepsy with GAD), Gabapentin.

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

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 absolute psychiatric contraindications

Physical & emotional support

- Pain
- Insomnia
- Delirium
- Benzo withdrawal

Exacerbation or De novo Mx

- Depression
- Anxiety
- Psychosis
- Mania
- AEDs discontinuation

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

DSM-5; Conversion Disorder (Functional Neurological Disorder)

A) One or more symptoms of altered voluntary motor or sensory function.

B) Clinical findings provide evidence of incompatibility between the symptom and recognized neurological or medical conditions.

C) The symptom or deficit is not better explained by another medical or mental disorder.

D) The symptom or deficit causes clinically significant distress or impairment in social, occupational, or other important areas of functioning or warrants medical evaluation.

- Specify symptom type; with weakness or paralysis, with abnormal movement, with swallowing symptoms, with speech symptom, with **attacks or seizures**, with anesthesia or sensory loss, with special sensory symptom, with **mixed symptoms**.
- Specify if; acute episode vs persistent (>6 months)
- Specify if; with or without psychological stressor

Table 1 Some clinical semiological features of epileptic and dissociative seizures

	Dissociative seizures	Epileptic seizures
Duration over two minutes	common[1 7 28–30]	rare
*Stereotyped attacks	common[7 31 32]	common
Motor features		
Gradual onset	common[7 28 31 33 34]	rare
Fluctuating course	Common[7]	very rare
Thrashing, violent movements	common[28 35–37]	rare
Side to side head movement	common[29 35]	rare
Asynchronous movements	common[29 38]	very rare
Eyes closed	common[28 39]	rare
Pelvic thrusting	occasional[1 29 40]	rare
Opisthotonus, "arc de cercle"	occasional[28 31 41]	very rare
Automatisms	rare[41]	common
Weeping	occasional[42 43]	very rare
*Incontinence	occasional[7 35 44]	common
*Injury		
Biting inside of mouth	occasional[7 35 39 41 44]	common
Severe tongue biting†	very rare[7 35 39 41 44]	common
Recall for period of unresponsiveness	common[1 7 41]	very rare

Mellers JD.Postgrad Med J. 2005 Aug;81(958):498-504.

Diagnosis levels of certainty for PNES

- Rule of 2; >=2 normal EEG, >= 2 seizures/week, >=2 AED resistant → 85% PPV of PNES

Diagnostic level	History	Witnessed event	EEG
Possible	+	By witness or self-report/description	No epileptiform activity in routine or sleep-deprived interictal EEG
Probable	+	By clinician who reviewed video recording or in person, showing semiology typical or PNES	No epileptiform activity in routine or sleep-deprived interictal EEG
Clinically established	+	By clinician experienced in diagnosis of seizure disorders (on video or in person), showing semiology typical of PNES, while not on EEG	No epileptiform activity in routine EEG or ambulatory ictal EEG, capturing a typical ictus*
Documented	+	By clinician experienced in diagnosis of seizure disorders, showing semiology typical of PNES, while on video EEG	No epileptiform activity immediately before, during or after ictus captured on ictal video EEG with typical PNES semiology

Gold Standard

Perez and LaFrance *CNS Spectr*. 2016 June ; 21(3): 239–246. doi:10.1017/S109285291600002X.

PNES in the nutshell

- 5-20% of people diagnosed with epilepsy is PNES.
- Female, 30 year-old, unemployed, with comorbid psych issues, with other medically unexplained symptoms.
- 10% with mixed PNES and epilepsy.
- Diagnostic accuracy and good communication by neurologist is important as 1/3 of the patients stopped having the PNES shortly after this step.
- Although, some other patients do have resistance, short exacerbation of PNES and other psych issues, or have no PNES free at 3-6 months.
- Correct PNES diagnosis also decreases the healthcare utilization.
- Early tapering and discontinuation of AEDs is recommended.
- RCT showed PNES can be effectively treated with psychotherapy (CBT, psychodynamic, family therapy, etc.) +/- pharmacotherapy (SSRI).

LaFrance WC Jr, Reuber M, Goldstein LH. Epilepsia. 2013 Mar;54 Suppl 1:53-67.

Bio-Psycho-Social and 3P Approach of PNES

	Predisposing	Precipitating	Perpetuating
Bio	genetic vulnerability of psych illness, history of seizure/TBI, IQ	accident, illness, illicit substance use	uncontrolled symptoms, illnesses or problematic health management
Psycho	abuse, trauma, loss, alexithymia, cluster b/c	psychological stress ex. school, family, work, relationship	comorbid depression, anxiety, PTSD, vicious maladaptive coping
Social	high emotional expression family, epileptic family member	conflict with spouse, peer, family member, co-worker	ongoing conflict without support, misunderstanding of the family

How to (empathically) communicate the PNES diagnosis

- Showing and explaining the vEEG.
- “Good news, the episode is not epilepsy”.
- “Although it is a true spell, not putting on or faking the event”.
- “Many people in this center suffered and disabled from it”
- “It is still unclear about the cause of this seizure but can possibly explain by the stress-emotion-brain dysfunction”.
- “PNES is the mind-brain overloading, patient is not mad or crazy”.
- “AEDs do not work, and cause serious side effects”.
- “Evidence and experience show the psychiatric care such as talk therapy and psychiatric medication are effective”.
- “Many people are able to manage their stress and seizure better, even seizure free in the cases we referred to our mental health colleague”.

LaFrance WC Jr, Reuber M, Goldstein LH. Epilepsia. 2013 Mar;54 Suppl 1:53-67.

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
Zonisamide	Irritability, Depression, Psychosis
Topiramate	Cognitive impairment, Depression
Phenobarbital	Depression, Irritability, Cognitive impairment
Phenytoin	Delirium, Mood change, Psychosis

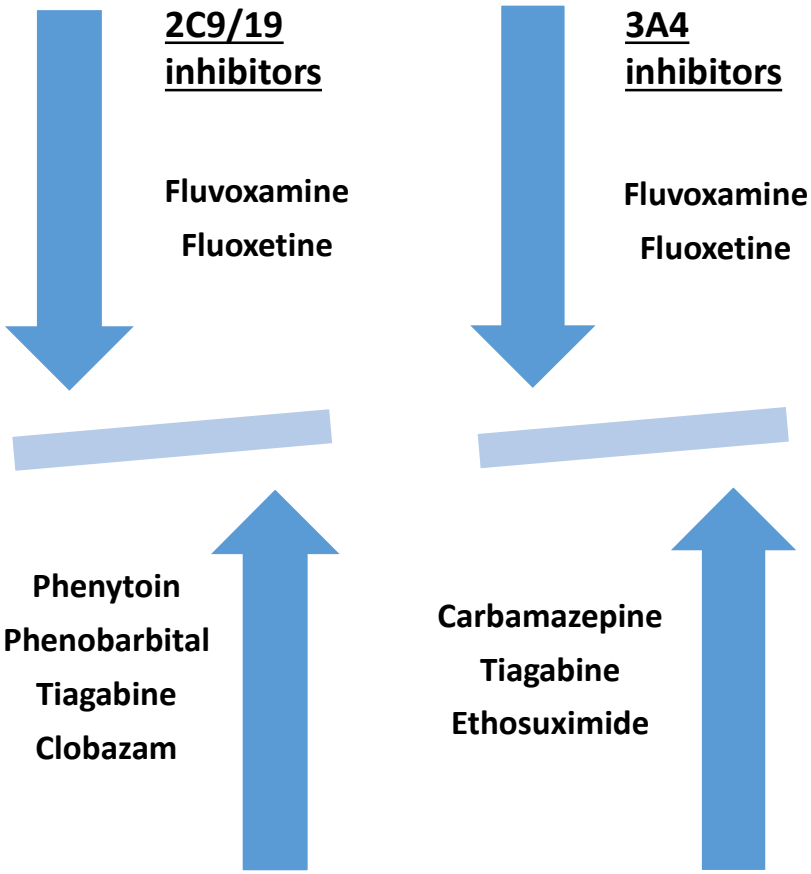
Epilepsy Behav. 2017 Nov;76:24-31. Chen B et al.
Fogel BS, Greenberg DB. Psychiatric Care of the Medical Patient. 2015.

Psychotropic drugs and seizure threshold

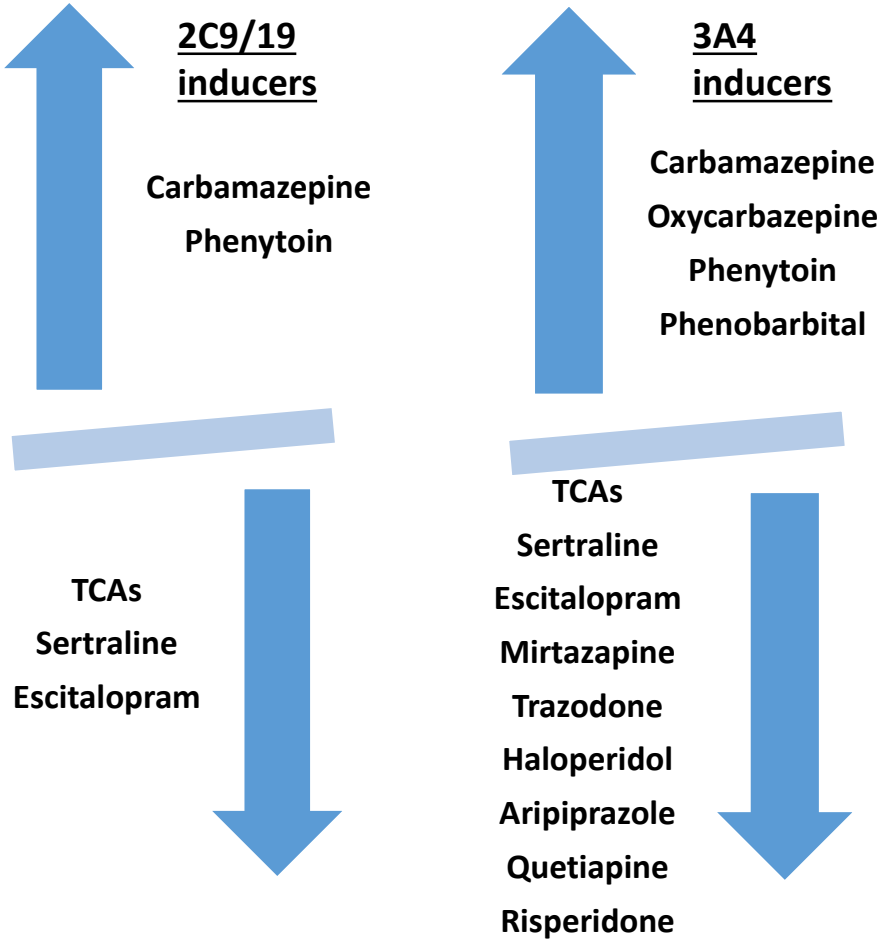
Drug Classes	Use	Avoid
Antidepressants	SSRIs (1-2% seizure risk when OD) > SNRIs > Mirtazapine > some TCAs (10-20% seizure risk when OD)	Amoxapine, Amitriptyline, Clomipramine, Maprotiline, Bupropion
Antipsychotics	Haloperidol = Risperidone = Paliperidone > Aripiprazole = Ziprasidone > Quetiapine > Olanzapine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

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

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.

Thank You

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