



Psychiatric and behavioral side effects of antiepileptic drugs

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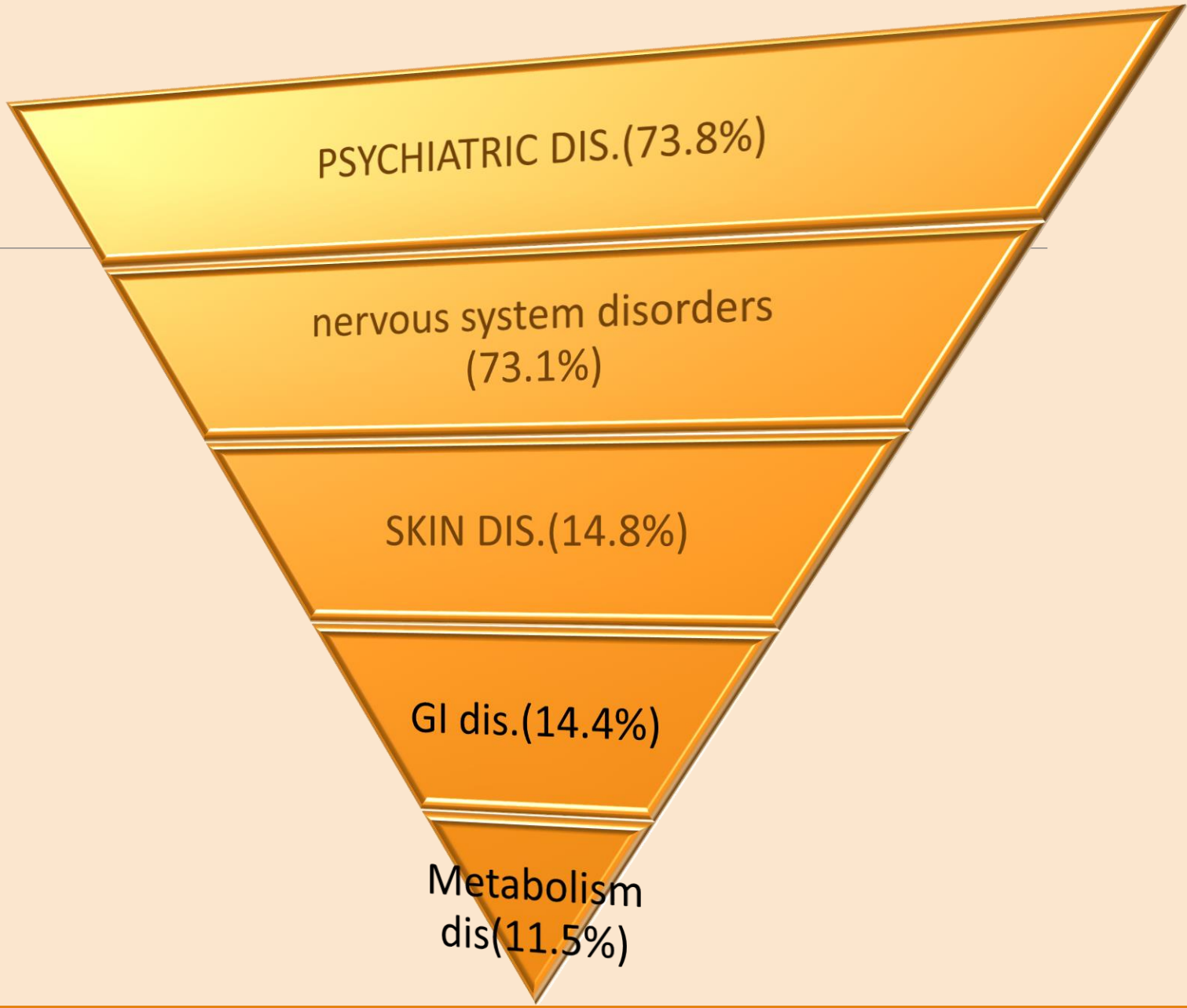
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Evaluation of adverse drug reaction profile of antiepileptic drugs in persons with epilepsy: A cross-sectional study

Epilepsy & Behavior 105 (2020)





As per individual ADRs' prevalence analysis among AEDs monotherapy were reported more with **LEV.**

anger and aggression (59.1%),

depression (4.9%),

suicidal tendency
(1.8%)

CBZ

- Insomnia (16.1%)

PHT

- Somnolence (24.6%).

VPA

- Memory loss (26.6%)
- tremor (16.5%)

PERSONS WITH EPILEPSY ON AED TAPERING

- ❖ PWE who have undergone AED tapering (as a routine tapering protocol) vs. unattempted tapering significantly higher psychiatric disorder ($p = 0.002$) and nervous system disorder ($p = 0.02$).
- ❖ This may be the reason for tapering in those subjects.

Adverse drug reactions among newer and conventional AEDs

There is no significant difference in ADRs between newer vs. conventional AEDs except in skin disorder.

- there is evidence suggesting that secondarily generalized seizure is associated with
- negative preictal (as auras) and postictal behavioral and psychiatric symptoms such as

presence of psychiatric history is a strong predictor of PBSE.

depressed mood

psychosis

Anger

irritability, aggression

nervousness

AED load

The average AED load of patients when they experienced PBSE was not significantly different from the average AED load of patients when they did not experience PBSE

significantly more PBSEs and IPBSE
than average.

1-LEV

2-ZNS

LEV use

❖ irritability has been found to be the **most common PBSE**

❖ Incidence of irritability has been shown to be similar across different LEV doses

❖ depression,

❖ anxiety, and

❖ emotional liability

❖ have been reported to occur in **around 3%**

❖ suicidal events had been reported **lower at around 1%**

lower rates of PBSEs were associated with

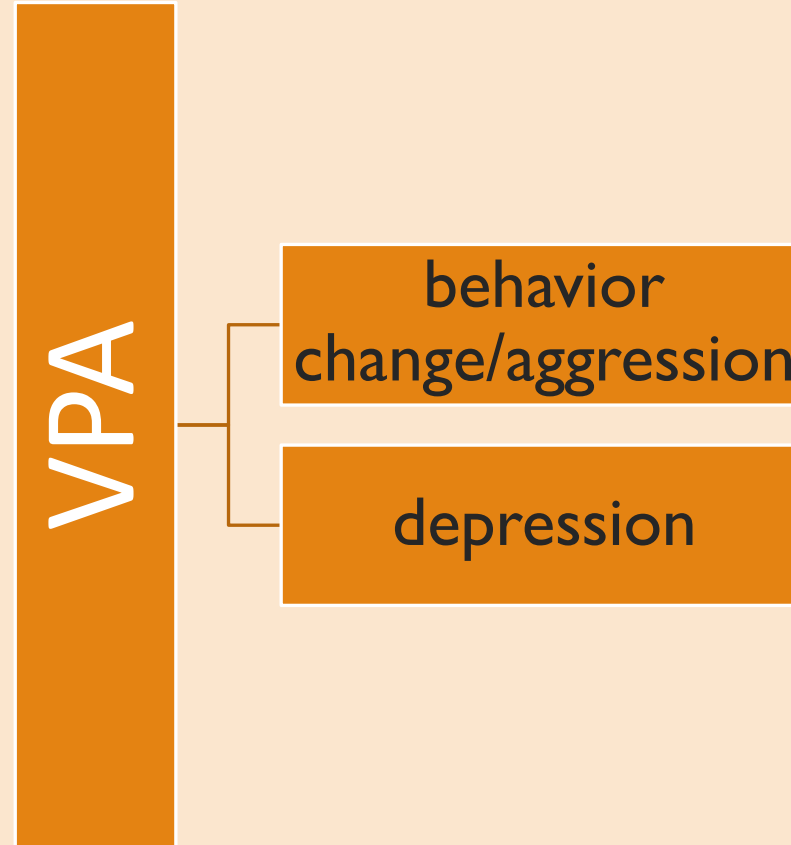
CBZ, CLB, GBP, LTG, OXC, PHT, and VPA.

- In our study, the only AED with lower PBSE rate compared with LTG was CBZ

LTG had been found in a study to be **protective against**
PBSEs associated with LEV when both AEDs

Psychiatric adverse events during levetiracetam therapy
Neurology. 2003

two most common PBSEs



Adult patients using LEV and ZNS for treatment of epilepsy

- may also be at a higher risk of developing PBSEs compared with those using other available AEDs and are also more likely to stop or reduce dose of AED because of PBSEs.

The findings in our study may serve as preliminary guidelines for clinicians

when prescribing AEDs for patients with epilepsy and considering side effect profiles of AEDs.

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- Patients who are mainly concerned about PBSEs associated with AED may consider replacing LEV and/or ZNS with AEDs associated with lower incidences of PBSEs such as LTG, CBZ, or GBP.

PSYCHIATRIC AND BEHAVIORAL SIDE
EFFECTS OF ANTIEPILEPTIC DRUGS IN
ADULTS WITH EPILEPSY

EPILEPSY BEHAV (2017)

Psychiatric and behavioral side effects (PBSEs) are highly prevalent in patients taking antiepileptic drugs (AEDs).

- ❖ These adverse effects can lead to
- ❖ suboptimal dosing for seizure control,
- ❖ poor adherence to AEDs
- ❖ early AED discontinuation in up to 25% of patients
- ❖ Between 15% and 20% experience PBSEs

depressive mood

psychosis

increase in irritability

and aggressive behavior

Columbia Comprehensive Epilepsy Center

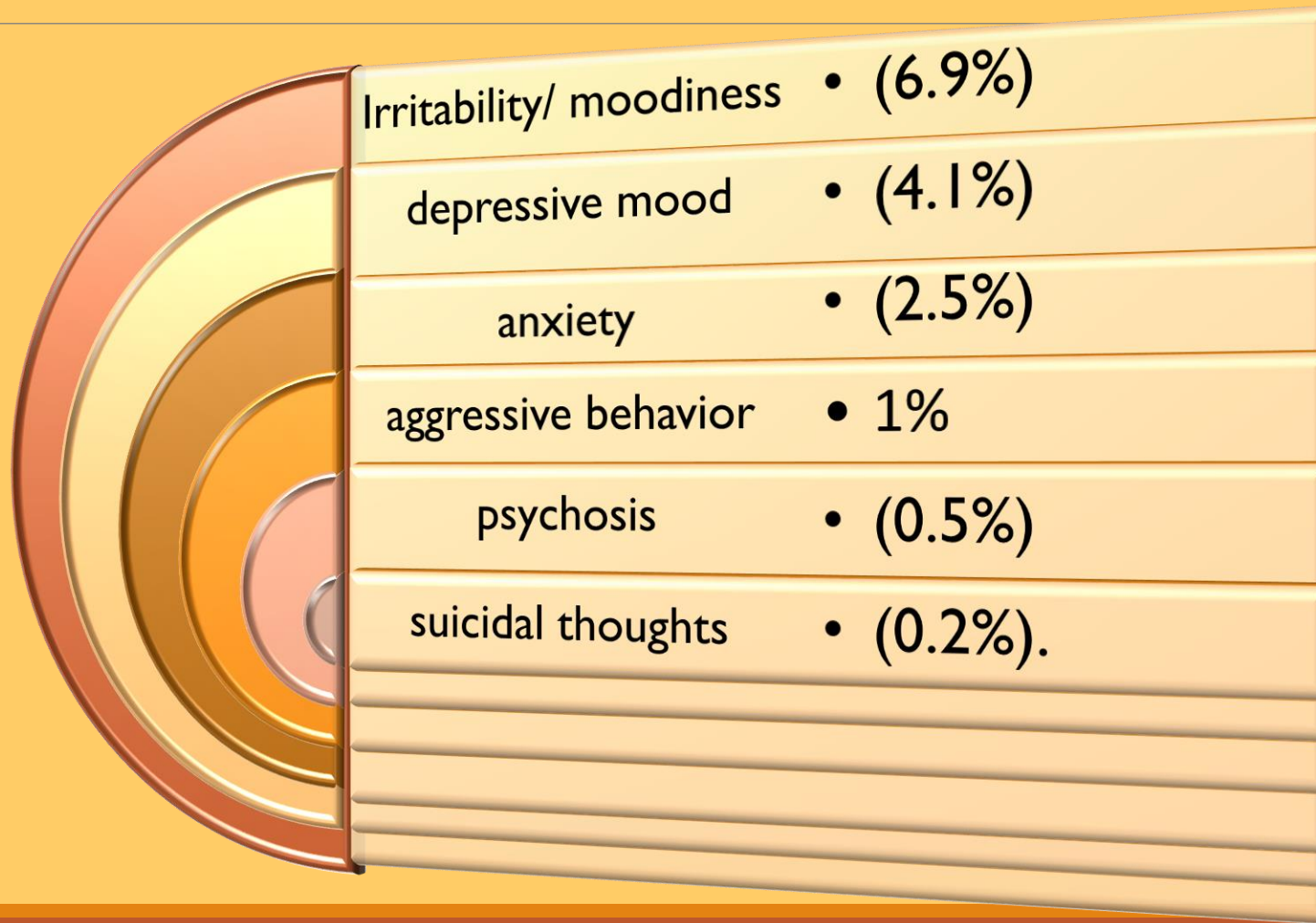
4085 adult patients newly started on an AED regimen.

2000 - 2015, and were followed up for at least 1 year:

Most of the patients were diagnosed with:

- ❖ **focal epilepsy (71.1%)**
- ❖ **idiopathic generalized epilepsy (17.4%)**
- ❖ **symptomatic generalized epilepsy (3.6%)**

**17.2% (701/4085) of patients developed PBSE attributed to an AED,
and 13.8% (565/4085) experienced intolerability**



History of **any psychiatric condition**

secondarily generalized seizures

remained significantly associated with incidence of PBSE

absence seizures, intractable epilepsy

Table 3Comparison of specific AED-attributed PBSEs in adults with epilepsy taking one of the AEDs[†].

AED	n	Behavioral side effects % (n)				Psychiatric side effects % (n)			
		Irritability (280)	Aggression (n=39)	Tantrum (n=21)	Other behavioral problems (n=64)	Depressive mood (n=168)	Psychosis (n=19)	Anxiety (n=103)	Suicidal thoughts (n=7)
CBZ	1103	0.5 (6)^a	0.2 (2)	0.1 (1)	0.2 (2)^a	0.9 (10)^a	–	0.2 (2)^a	–
CLB	645	1.7 (11)^a	0.8 (5)	0.3 (2)	0.8 (5)	1.4 (9)	0.2 (1)	0.5 (3)	0.2 (1)
FBM	184	2.7 (5)	–	–	1.1 (2)	0.5 (1)	0.5 (1)	–	–
GBP	606	1.0 (6)^a	–	–	0.2 (1)	0.7 (4)^a	0.2 (1)	–	–
LCM	354	1.4 (5)^a	0.6 (2)	0.6 (2)	0.6 (2)	1.1 (4)	0.3 (1)	1.4 (5)	0.3 (1)
LEV	1890	12.5 (236)^b	1.4 (27)^b	0.7 (14)^b	2.5 (47)^b	7.3 (138)^b	0.6 (11)^b	2.5 (47)^b	0.2 (4)
LTG	2337	1.2 (27)^a	0.1 (3)^a	0.1 (3)	0.5 (11)^a	1.2 (28)^a	0.1 (3)	1.5 (34)^b	–
OXC	566	0.5 (3)^a	0.2 (1)	–	0.4 (2)	1.8 (10)	–	0.5 (3)	–
PB	234	0.4 (1)	0.9 (2)	0.4 (1)	0.4 (1)	4.7 (11)	–	1.3 (3)	–
PGB	502	1.6 (8)^a	0.2 (1)	0.6 (3)^b	0.6 (3)	1.8 (9)	–	0.8 (4)	–
PHT	816	0.5 (4)^a	0.1 (1)	–	0.4 (3)	1.6 (13)	–	0.7 (6)	0.1 (1)
PRM	94	1.1 (1)	–	–	–	2.1 (2)	–	–	–
RFM	131	1.5 (2)	1.5 (2)	–	3.1 (4)^b	–	0.8 (1)	–	–
TGB	46	10.9 (5)^b	–	–	–	4.4 (2)	2.2 (1)^b	4.4 (2)^b	–
TPM	639	2.8 (18)	0.5 (3)	0.2 (1)	1.1 (7)	2.2 (14)	0.2 (1)	0.8 (5)	–
VGB	75	2.7 (2)	–	1.3 (1)^b	4.0 (3)	–	2.7 (2)^b	5.3 (4)	–
VPA	868	1.3 (11)^a	0.1 (1)	–	0.7 (6)	1.5 (13)	–	0.5 (4)	0.1 (1)
ZNS	760	3.2 (24)	0.4 (3)	0.1 (1)	1.1 (8)	4.3 (33)^b	0.8 (6)^b	1.3 (10)	–
Average		3.2	0.5	0.2	0.9	2.5	0.2	1.1	0.1
Statistical significance: P < 0.003		Statistical trend: 0.003 < P < 0.005							

Behavioral adverse events with
brivaracetam, levetiracetam, perampanel,
and topiramate:
A systematic review

EPILEPSY & BEHAVIOR 118 (2021)



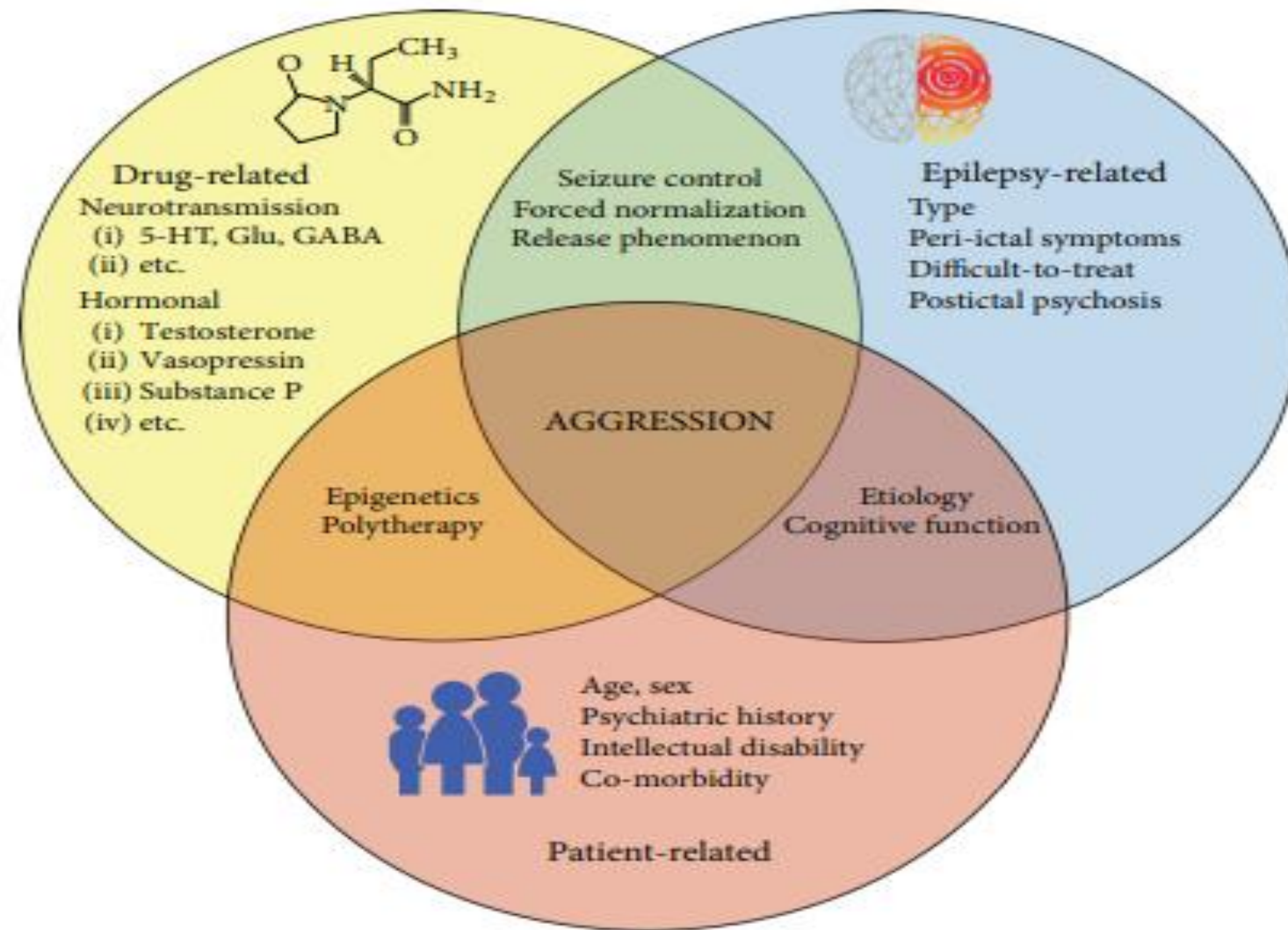
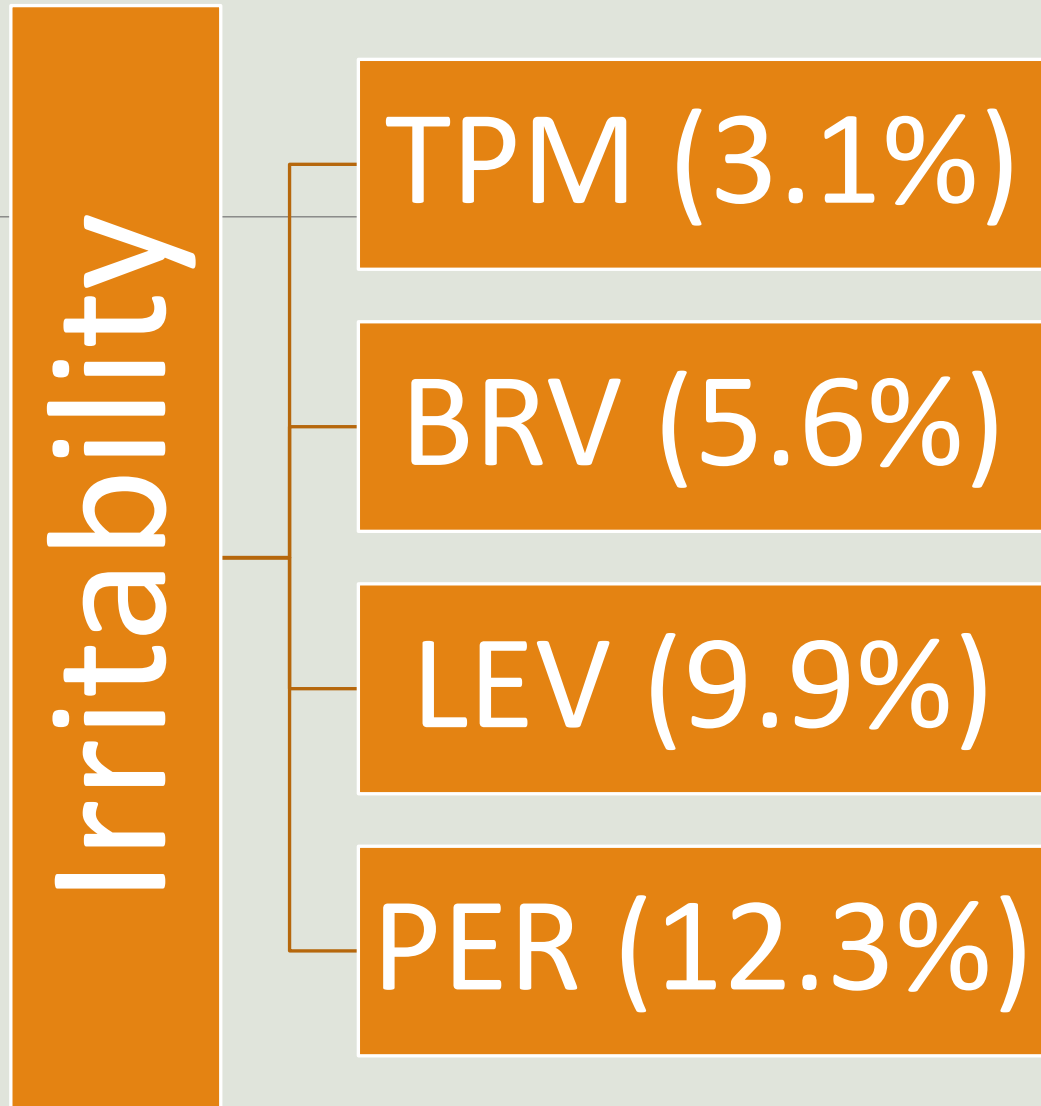


FIGURE 1: Summary of factors involved in aggressive behavior associated with antiepileptic drug treatment of epilepsy.

INCIDENCES OF IRRITABILITY, ANGER, AND AGGRESSION

42 STUDIES



ANGER

PER (2%)

LEV(2.5%)

AGGRESSION

PER (4.4%)

LEV (2.6%)

BRV (2.5%)

TPM (0.5%)

switching from LEV to BRV may improve
LEV-associated BAEs in clinical practice

MEDICATION-INDUCED PSYCHOTIC DISORDER

A REVIEW OF SELECTED DRUGS SIDE EFFECTS

Psychiatria Danubina, 2022



Psychotic symptoms seem to be
less common than **mood disturbances**,
but they are reported in clinical trials.

The diagnosis of antiepileptic drug-induced psychosis (ADIP) can be challenging.

It needs to be distinguished from other psychotic states related to seizures.



The diagnosis of antiepileptic drug-induced psychosis (ADIP) can be challenging.



Psychotic symptoms are reported after

levetiracetam

lamotrigine

tiagabine

vigabatrin

zonisamide

Clinicians should pay attention to interactions and seizure risk when choosing an antipsychotic drug.

the combination of clozapine and carbamazepine is contraindicated due to agranulocytosis

Clozapine is also associated with the highest risk of seizures.

Guidance for the treatment of psychotic symptoms in epilepsy is scant in the literature.

Risperidone can be considered a first-line treatment for psychotic patients with epilepsy.

Psychotic disorders
induced by
antiepileptic drugs
in people with
epilepsy
BRAIN 2016

2630 patients

1993 to 2015

Melbourne

- ❖ In our study one in seven patients with epilepsy who presented with psychosis had AIPD.

- ❖ **female gender, temporal lobe involvement and current use of levetiracetam** were significantly associated with AIPD compared to other types of psychosis,
- ❖ while carbamazepine had a negative association.

- ❖ Disorganized behaviours and abnormal disorganized thinking were predominant symptoms of AIPD.

- ❖ AIPD had an overall better outcome than that of other psychotic disorders in people with epilepsy.

ANTIEPILEPTIC DRUGS AND SUICIDE: THE ROLE OF PRIOR SUICIDAL BEHAVIOR AND PARENTAL PSYCHIATRIC DISORDER.

Antiepileptic drugs and suicide: role of prior suicidal behavior and parental psychiatric disorder. *Annals of neurology*. 2019



In 2008, FDA issued a **warning** that the use of **antiepileptic** drugs was associated with an **increased risk** of suicidality.

This alert was based on a **meta-analysis including nearly 200 placebo-controlled trials** of antiepileptic drugs. However, the FDA report was **quickly criticized** for several methodological issues, and numerous epidemiological investigations have since attempted to resolve these issues.

Methods:

Using the Danish National Prescription Register, we identified all incident users of antiepileptic drugs aged 15 years or older in Denmark between 1997 and 2015.

516,019 patients

1,759 comple suicide

- phenobarbital, clonazepam, carbamazepine, oxcarbazepine, valproic acid, lamotrigine, gabapentin, levetiracetam, and pregabalin.

- ❖ current treatment with phenobarbital was associated with the highest suicide risk among the nine drugs considered.
-
- ❖ Treatment with pregabalin and clonazepam was associated with an increased risk of suicide
 - ❖ Prior studies have not identified any significant associations between use of pregabalin and suicidal events
 - ❖ Use of valproic acid was consistently associated with a lower risk of suicide
 - ❖ no increased risk of suicide associated with lamotrigine treatment.

❖ Levetiracetam was not associated with an increased risk of suicide in spite of its reported negative effects on mood.

❖ In fact, even though levetiracetam was used nearly as often as phenobarbital, the number of suicides among users of this drug was low; indeed too low to allow examination of the role of prior suicidality and familial predisposition for psychiatric disorder on suicide risk.

❖ The low number of suicides in users of levetiracetam may reflect that physicians avoid this drugs in individuals considered to be at high risk of suicidality or that they may be more observant of signs of suicidality in persons treated with this drug.

the choice of drug may be influenced by patient history and clinical characteristics (prior suicidality and familial predisposition to psychiatric disorder).

Thus, in individuals considered to be at high risk of psychiatric disease and suicidality, physicians may avoid prescribing drugs with known negative psychotropic effects

such as phenobarbital, topiramate, and levetiracetam and instead recommend treatment with drugs like lamotrigine that are considered to have mood-stabilizing effects.

-
- we found current versus previous treatment with antiepileptic drugs was associated with an elevated risk of completed suicide, which is consistent with finding from other studies

We found that the risk of suicide associated with antiepileptic drugs was present

❖ **both** in high-risk individuals predisposed via family history of psychiatric disorders and prior suicidal behavior, and in individuals without such predisposing factors.

❖ These findings suggest that neither prior suicidality nor familial predisposition to psychiatric disorder explains the association between antiepileptic drug treatment and suicide

❖ substantially higher risk of suicide within the **first 15 years in individuals with prior suicidal behavior** or a **parental history of** psychiatric disorders .

❖ This higher suicide risk was however, **independent of whether they continued or stopped treatment.**

❖ Thus, although our findings confirm that **prior suicidality and parental history of psychiatric disorders** are important risk factors for suicide, we also find that these conditions seem to **neither magnify nor reduce the suicide risk associated** with antiepileptic drug treatment.

**Effects of antiseizure medications on alternative psychosis
and strategies for their application.**

World J Psychiatry 2022



Alternative psychosis is also known as forced normalization (FN).

This phenomenon is characterized

- ❖ by abnormal mental behavior and disordered emotions after the seizures of active epilepsy patients are controlled and their EEGs have significantly improved.
- ❖ FN is unique to the pharmacotherapy of epilepsy and often leads to the failure of epilepsy treatment. Although FN is still an entity with uncertain pathophysiology.

the causes included anti seizure medications (ASMs), epilepsy surgery and vagus nerve stimulation (VNS), with ASMs being the **most common** cause.

When ASMs such as LEV, LTG, and VPA are used to control epileptic seizures

if abnormal mental behavior occurs despite successful seizure control and normal EEG results, the possibility of FN should be considered.

TREATMENT

❖ Dose reduction or drug withdrawal

❖ **Control** of mental symptoms

Table 1 Clinical features and treatment of forced normalization.

Classification		Ref.	
Clinical features	LEV	Abnormal mental behavior and dissociative personality	[11,19,21]
	ESM	Mania; visual and olfactory hallucinations; paranoid psychosis	[9,24,25]
	VPA	Paranoid thoughts, agitation, sleep disturbances, confusion	[26,27]
	LTG	Irritable, inattention, insomnia, paranoid thoughts, and hallucinations appearing	[3,10]
	LCM	Paranoid behavior and psychotic symptoms	[3,28,29]
	TPM	Abnormal mental behavior	[20]
	ZNS	Communication disorders, interpersonal tension and stereotyped behaviors	[20,30]
	VGB	Hallucinations and anxiety	[1,31]
	PHT	Paranoia, restlessness, aggressiveness, command hallucinations, and stereotyped, short-term psychomotor excitement and impulsive violent events, irritability	[3,12,32]
	ESL	Behavioral disturbances, psychosis	[3]
	BRV	Dysthymia, generalized anxiety disorder	[3]
Treatment	Dose reduction or drug withdrawal		[3-5,10,11,15,21]
	Control of mental symptoms (haloperidol, risperidone)		[2,3,5,25,26,33]
	Electroshock		[19]

