

Ottimizzazione della terapia nel paziente con comorbidità psichiatrica

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Management issues

1. Effects of AEDs on behavior
2. Pharmacologic interactions between AEDs and psychotropic drugs
3. Psychotropic drugs and seizure risk
4. Role of Epilepsy centers

1. EFFECTS OF AEDS ON BEHAVIOR

Mechanisms of action of AEDs

AED	Blockade of VOC Na	Increase GABA	Selective potentiation of GABA-A	Direct facilitation of Cl	Blockade of VOC Ca	Antiglutamate rgic	Other actions
BDZ	-	-	++	-	-	-	-
CBZ	++	?	-	-	+ (L-type)	+(NMDA)	+
ETX	-	-	-	-	++ (T-type)	-	-
PHB	-	+	+	++	?	-	+
PHT	++	-	-	-	?	?	+
VPA	?	+	?	-	+ (T-type)	+(NMDA)	++
FLB	++	+	+	-	+ (L-type)	++(NMDA)	+
GBP	?	?	-	-	++ (N, P/Q-type)	-	?
LTG	++	+	-	-	++ (N, P/Q, R, T-type)	++(NMDA, AMPA)	+
LEV	-	?	?	-	+ (N-type)	?	++
OXC BZ	++	?	-	-	+ (N, P-type)	+(NMDA)	+
PGB	-	-	-	-	++ (N, P/Q-type)	-	-
TGB	-	++	-	-	-	-	-
TPM	++	+	+	-	+ (L-type)	++(AMPA)	+
VGB	-	++	-	-	-	-	-

Two AED categories of psychotropic profiles

Ketter et al., Neurology 1999

1.

GABA ergic

Sedating

Depressogenic

Antimanic, anxiolytic

Barbiturates,
Benzos, Valproate, Vigabatrin,
Tiagabine, Gabapentin,
Pregabalin

Topiramate
Zonisamide

Levetiracetam ?

2.

Anti glutamatergic

Anxiogenic

Activating

Antidepressive

Felbamate, Lamotrigine

Psychotropic effects of AED in epilepsy

- **Direct (drug-related)**
 - Mechanism of action of the drug
 - Drug toxicity
 - Drug withdrawal
- **Indirect (epilepsy-related)**
 - Forced normalization
 - Postictal and periictal psychoses
 - Severity of the epilepsy
 - Limbic system abnormalities

Prevalence of AED related depression and psychosis

	Depression	Psychosis
Total	25	26
Preictal	-	1
Ictal	-	1
Postictal	6	16
Interictal	12	4
Forced normalisation	6	2
AED withdrawal	1	1
AED toxicity	0	1
	28 %	15 %

| Review article

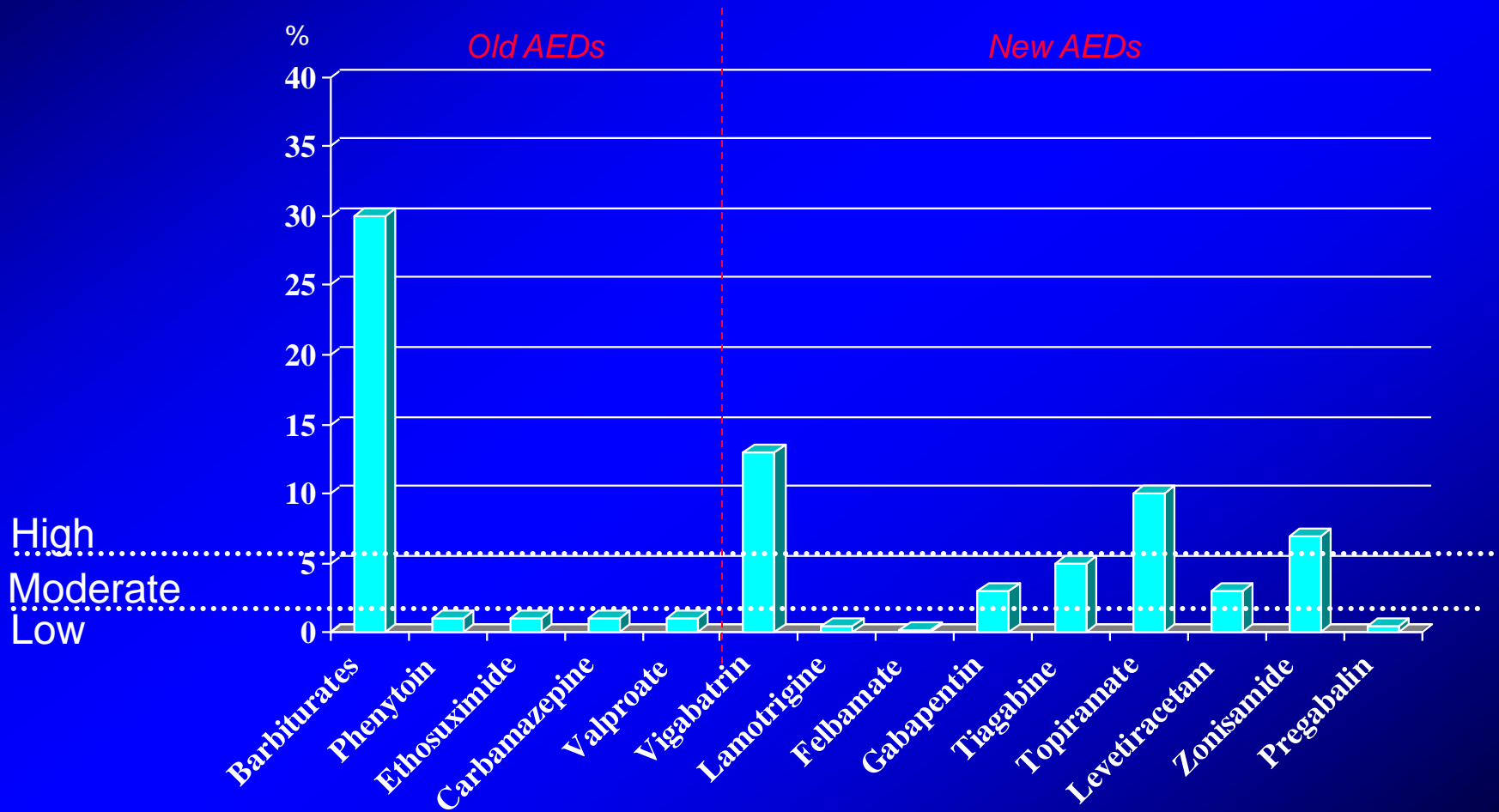
Epileptic Disord 2009; 11 (1): 1-9

Antiepileptic drugs and psychopathology of epilepsy: an update

Marco Mula, Francesco Monaco

AEDs and Depression

Phase III Trials



Mechanisms for AEDs-related depression

1. GABA enhancement
2. Polytherapy
3. Folate deficiency
4. Hippocampal sclerosis (febrile seizures?)
5. Past psychiatric history
6. Forced normalization phenomenon

FULL-LENGTH ORIGINAL RESEARCH

The role of titration schedule of topiramate for the development of depression in patients with epilepsy

*Marco Mula, †Dale C. Hesdorffer, ‡Michael Trimble, and ‡§Josemir W. Sander

Factor ^a	Depressed n = 44 (%)	Not depressed n = 379 (%)	OR (95% CI)
Rapid TPM titration and FS			
Rapid TPM titration only	16	66	5.9 (2.5–13.5)
History of FS only	8	52	3.7 (1.4–9.9)
Both	10	19	12.7 (4.7–34.4)
Neither	10	242	1.0 (Referent)
Rapid TPM titration and history of depression			
Rapid TPM titration only	18	78	4.7 (2.2–10.0)
History of depression only	5	29	3.5 (1.2–10.6)
Both	8	7	23.3 (7.3–74.1)
Neither	13	265	1.0 (Referent)
Rapid TPM titration and HS			
Rapid TPM titration only	18	66	4.9 (2.3–10.4)
HS only	4	41	1.7 (0.5–5.6)
Both	8	19	7.6 (2.8–20.4)
Neither	14	253	1.0 (Referent)

What about mania?



Table 1
Relationship between antiepileptic drugs and the occurrence of manic or hypomanic symptoms in patients with epilepsy

Syndrome	Type of effect	Effect of AED	Seizure pattern
Secondary mania	Toxic effect	Direct	May or may not be associated with seizure worsening
Postictal states	Drug withdrawal	Indirect	Seizure worsening
Alternative psychopathology	Force normalization	Indirect	Sudden seizure control or improvement
Interictal psychopathology	No effect	No effect	No change in seizure frequency and pattern

Mechanisms for AED-related behavior abnormalities

- Polytherapy
- Severity of epilepsy
- Mental retardation (release phenomenon)
- Biological vulnerability in the limbic system
- Mainly activating AEDs

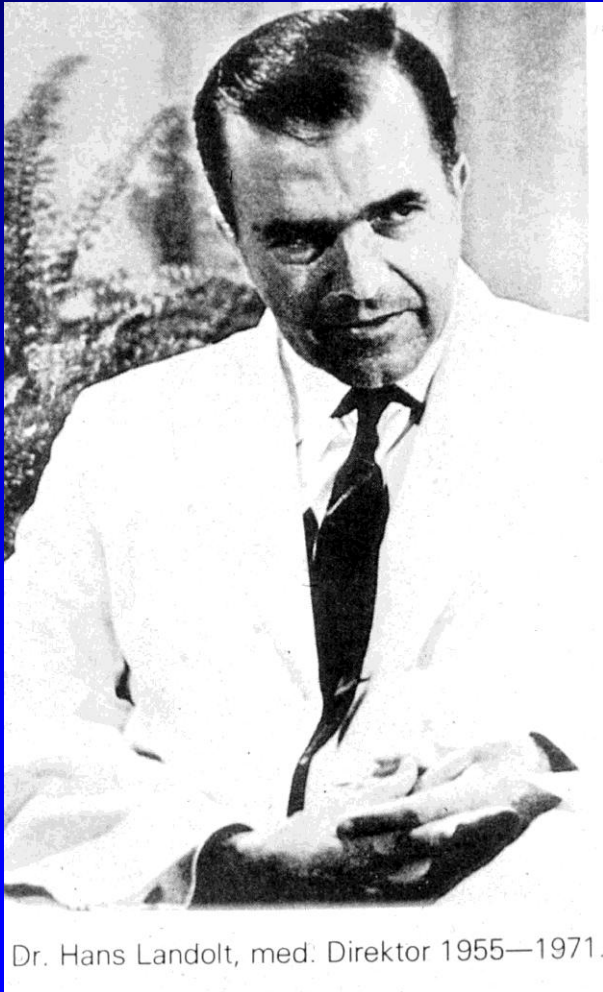
Behavior abnormalities

- Barbiturates and gabapentin in children
 - Agitation, conduct disorder (Vining et al. 1987; Bhaumik et al. 1997)
- Lamotrigine and levetiracetam
 - Emotion lability, irritability (White et al. 2003; Mula et al. 2003)

Mechanisms for AED-related psychosis

- Forced normalization
- Drug toxicity (periictal psychoses)
- Drug withdrawal (postictal psychoses)

The forced normalization phenomenon



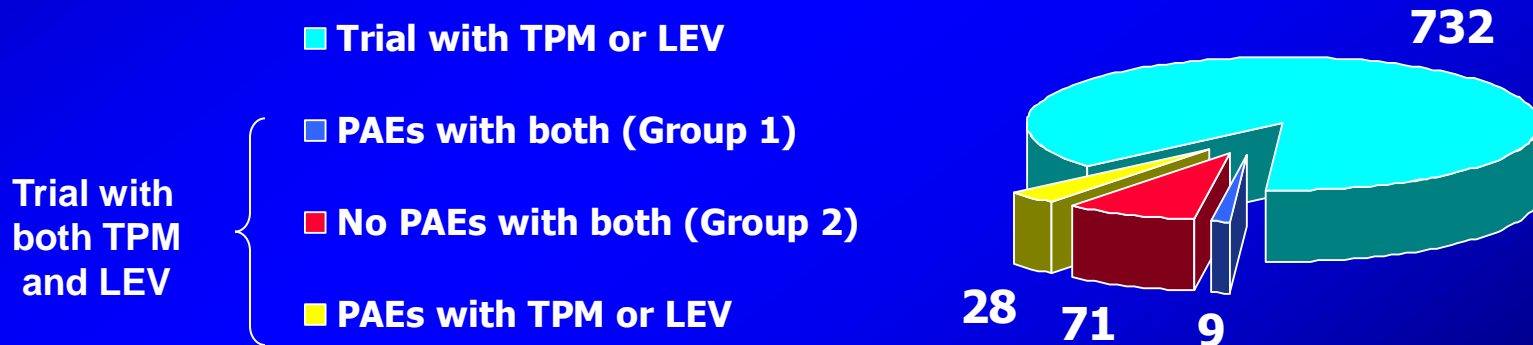
“Forced Normalization is the phenomenon characterised by the fact that, with the occurrence of the psychotic states, the EEG becomes more normal or entirely normal as compared with previous and subsequent EEG findings”

Dr. Hans Landolt, med. Direktor 1955—1971.

FULL-LENGTH ORIGINAL RESEARCH

Are psychiatric adverse events of antiepileptic drugs a unique entity? A study on topiramate and levetiracetam

*Marco Mula, †Michael R. Trimble, and †‡Josemir W. Sander



FULL-LENGTH ORIGINAL RESEARCH

Are psychiatric adverse events of antiepileptic drugs a unique entity? A study on topiramate and levetiracetam

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	Group 1 (9)	Group 2 (71)
Gender, males	5	37
Age (yr), mean (SD)	40.2 (9.6)	35.5 (10.0)
Age at onset of epilepsy (yr), mean (SD)	10.1 (8.1)	11.8 (7.3)
Duration of epilepsy (yr), mean (SD)	30.1 (5.6)	23.5 (9.6)
Epilepsy syndrome, CP/IG/SP/Others	2/1/6/0	25/10/35/1
Family history of epilepsy	1	11
History of febrile convulsions	5 [°]	11
Learning disabilities	1	11
Psychiatric history	6*	17
Family psychiatric history	2 [§]	0

[°]p=0.005; *p=0.008; [§]p=0.001



Nature Medicine 5, 888 - 894 (1999)

Febrile seizures in the developing brain result in persistent modification of neuronal excitability in limbic circuits

Kang Chen, Tallie Z. Baram, Ivan Soltesz

Positive psychotropic effects

Positive psychotropic effects of old AEDs

	Depression	Psychosis	Controls
Polytherapy	56	80*	46
Phenytoin	68	72*	48
Carbamazepine	44	48	46
Barbiturates	28	16	28
Primidone	20	36	12
Benzodiazepines	8	4	10
Valproate	4*	28	28
Ethosuccimides	0	0	6

* $p < 0.05$

Schmitz et al. 1999

Positive psychotropic effects of lamotrigine in epilepsy

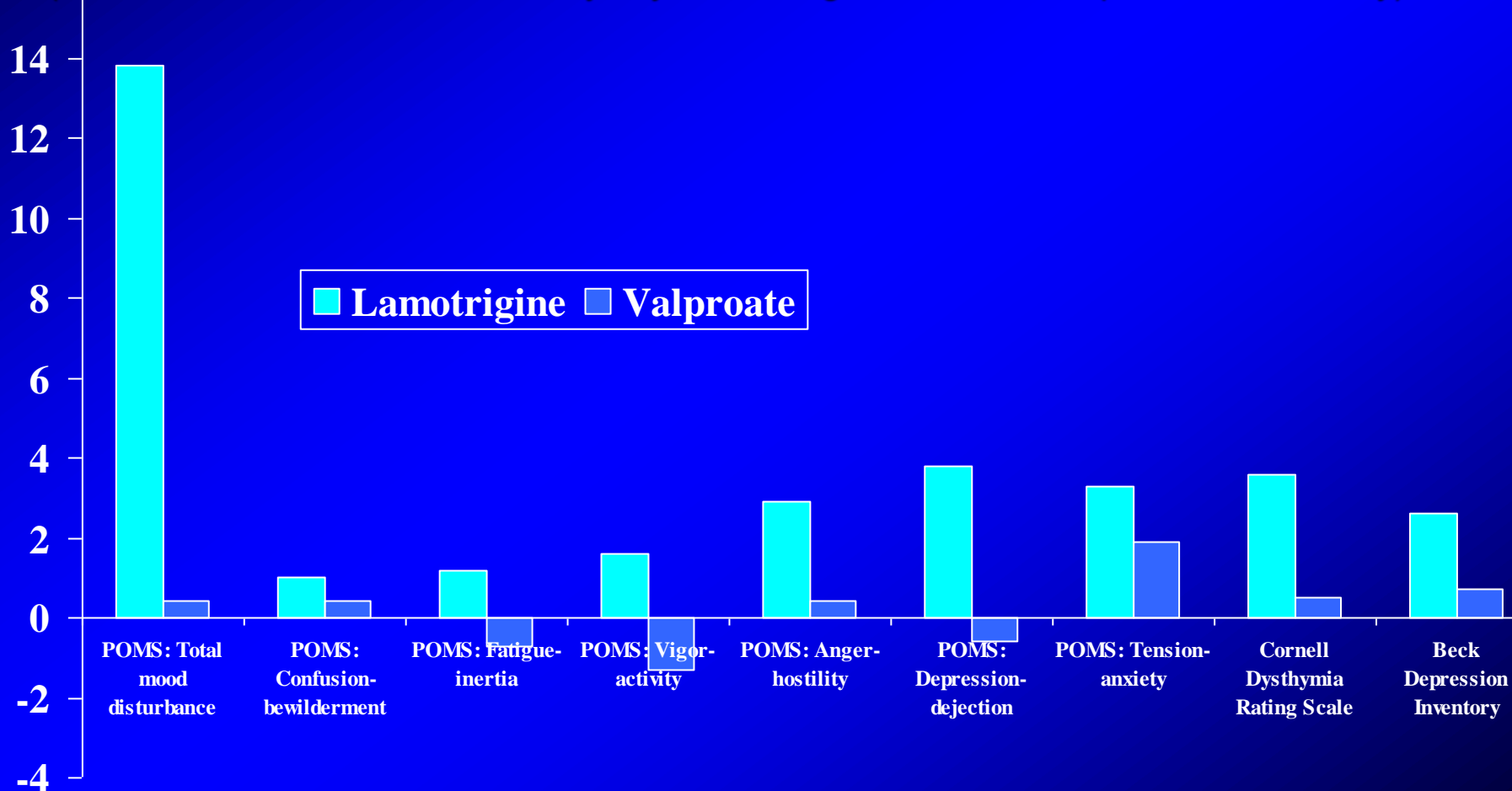
1. Smith et al. 1993* - versus Placebo (QOL)
2. Matsuo et al. 1993
3. Davanzo et al. 1996
4. Brodie et al. 1995
5. Jacoby et al. 1996
6. Schapel et al. 1996
7. Gillham et al. 1996* - versus Carbamazepine (SEALS)
8. Bhaumik et al. 1997
9. Maxoutova et al. 1997
10. Pellicia et al. 1997
11. Serra et al. 1997
12. Edwards et al. 2000* - versus Valproate (QOL + mood)

* controlled design (randomised and double blind)

QOL = Quality of Life, SEALS = Side Effect and Life Satisfaction Inventory

Mean changes compared to baseline after 32 treatment weeks with Lamotrigine or Valproate in Monotherapy

16 (Profile of Mood States, Cornell-Dysthymia-Rating Scale, Beck-Depression Inventory)



		CBZ	GBP	LTG	OXC	VPA
<p>American Psychiatric Association Hirschfeld et al. Practice Guideline for the Treatment of Patients with Bipolar Disorder (Revision). Am J Psychiatry 2002;159(Suppl 4):1-50;</p>	Acute mania/Mixed mania	+	-	-	+	+
	Acute bipolar depression	-	-	+	-	-
	Acute rapid cycling	-	-	+	-	+
	Maintenance	+	-	+	+	+
<p>British Association of Psychopharmacology Goodwin GM. Evidence-based guidelines for treating bipolar disorder: Recommendations from the British Association for Psychopharmacology. Journal of Psychopharmacology 2003;17(2):149-173</p>	Acute mania/Mixed mania	+	-	-	-	+
	Acute bipolar depression	-	-	+	-	+
	Rapid cycling	-	-	+	-	+
	Maintenance	+	-	+	+	+

Psychopharmacology of topiramate: from epilepsy to bipolar disorder

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Abstract: Topiramate (TPM) is one of the novel antiepileptic drugs and exhibits a wide range of mechanisms of action. Efficacy of TPM has been demonstrated in partial-onset seizures and primary generalized seizures in adults and children, as both monotherapy and adjunctive therapy. More recently, TPM has been proposed as an add-on treatment for patients with lithium-resistant bipolar disorder, especially those displaying rapid-cycling and mixed states. This paper reviews the multiple mechanisms of action and the tolerability profile of TPM in the light of its therapeutic potential in affective disorders. Studies of TPM in bipolar disorder are evaluated, and the efficacy and tolerability issues as a mood stabilizing agent are discussed.

Keywords: topiramate, antiepileptic drugs, epilepsy, mood stabilizer, bipolar disorder

Table 1 Mechanisms of action and psychotropic spectrum of selected old and new anticonvulsants used in affective disorders

	Mechanisms of action				Psychotropic efficacy	
	Blockade of voltage dependent sodium channels	Antagonism of glutamatergic receptors (receptor type)	Potentiation of GABA transmission	Blockade of calcium channels (channel type)	Mania	Depression
CBZ	+	(+) (NMDA)	(+)	-	+	+
VPA	+	(+) (NMDA)	+	+ (T)	++	+
LTG	+	(+) (NMDA)	-	+ (L,N,P)	(+)	++
TPM	+	+ (AMPA/k)	+	+ (L)	+	(+)

Abbreviations: AMPA, α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; CBZ, carbamazepine; GABA, γ -aminobutyric acid; k, kainate; LTG, lamotrigine; NMDA, N-methyl-D-aspartate; TPM, topiramate; VPA, valproic acid.

The Role of Anticonvulsant Drugs in Anxiety Disorders

A Critical Review of the Evidence

Marco Mula, MD, Stefano Pini, MD, PhD, and Giovanni B. Cassano, MD

(J Clin Psychopharmacol 2007;27:263–272)

AEDs	PD	OCD	PTSD	SP	GAD
Gabapentin	II	IV	IV	II	
Lamotrigine		IV	II		
Pregabalin				II	I
Topiramate		III	II	III	
Valproate	III	IV	III	III	

Effects of AEDs on behavior

Take home message

- Start low and go slow
- Polytherapy to be minimized
- Barbiturates and GABAergic drugs to be avoided
- Lowest doses needed to control epilepsy
- Screen mental state before starting any AEDs
- History of depression = LTG
- History of mood disorder NOS = CBZ, OXCBZ, VPA
- History of psychosis = sudden seizure control NOT indicated! Avoid VGB, TPM, LEV