

تداخل داروها و بیماریهای مؤثر بر مغز در مدیریت اختلال دوقطبی

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تداخل داروها و
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در مدیریت اختلال دوقطبی

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• اختلال دو قطبی و

CVA •

Migrane •

Epilepsy •

Bipolar disorder and **CVA**

Bipolar disorder and **CVA**

- stroke was twice as great amongst patients with bipolar disorder as patients undergoing an appendectomy

H. C. Lin, S. Y. Tsai, and H. C. Lee, "Increased risk of developing stroke among patients with bipolar disorder after an acute mood episode: a six-year follow-up study," *Journal of Affective Disorders*, vol. 100, no. 1–3, pp. 49–54, **2007**.

Bipolar disorder and **CVA**

- Patients with bipolar disorder were **1.24** times more likely to have a stroke (95% CI = 1.12–1.38; p,0.0001)

Hung-Chi Wu and et al. The Incidence and Relative Risk of Stroke among Patients with Bipolar Disorder: A Seven-Year Follow-Up Study. PLOS ONE. August **2013** | Volume 8 | Issue 8 | e73037

Bipolar disorder and **CVA**

- Post-stroke mania
 - 50 years we found only 74 reported cases
 - 188 consecutive acute stroke patients, our group found 3 (**1.6%**) cases of mania

Bipolar disorder and **CVA**

- Post-stroke mania
 - (1) predisposing genetic factor
 - (2) subcortical brain atrophy
 - (3) damage to the right corticolimbic pathways

Raquel Calvão de Melo and et al. Bipolar Disorder after Stroke in an Elderly Patient. Hindawi Publishing Corporation Case Reports in Psychiatry Volume **2014**, Article ID 741934, 5 pages

Bipolar disorder and **CVA**

- Pharmacotherapy
 - Antipsychotics
 - Lithium
 - Anticonvulsant
 - Valproate
 - Carbamazepine
 - Lamotrigine

Bipolar disorder and CVA

antipsychotic

	Amisulpride	Clozapine	Risperidone	Olanzapine	Quetiapine	Ziprasidone	Aripiprazole	Paliperidone	Asenapine
QTc	-/+	-	-/+	-	+++	-/+	-	-/+	-/+
Anti-cholinergic	-	+++	-	+	+	-/+	-	-	-
Diabetes	-	+	-/+	+?	-	-	-	-/+	-/+
Hyper-triglyceridemia	-	+	-/+	+	-	-	-	-/+	-/+

Pietro Gareri and et al. Use of atypical antipsychotics in the elderly: a clinical review. *Clinical Interventions in Aging* **2014**;9 1363–1373

Bipolar disorder and **CVA**

antipsychotic

- **second-generation** antipsychotic was found not to be associated with increased risk of cerebrovascular adverse events compared to **first-generation** agents in older adults
- long-term use of second- and first-generation antipsychotic agents is associated with **increased risk** of cerebrovascular adverse events.

Mehta S and et al. Risk of cerebrovascular adverse events in older adults using antipsychotic agents: a propensity-matched retrospective cohort study. *J C psychiatry* 2010 Jun;71(6):689-98. doi: 10.4088/JCP.09m05817yel.

Bipolar disorder and CVA

Quetiapine

TABLE 1. Serious Adverse Events With Four Atypical Antipsychotics^a

Event	Treatment Group (randomly assigned)				Total
	Aripiprazole (N=64)	Olanzapine (N=54)	Quetiapine (N=65)	Risperidone (N=50)	
Medical hospitalization					
Cardiovascular event	3	1	3	2	9
Cerebrovascular event	0	0	1	0	1
Pneumonia	0	3	6	0	9
Seizure	0	0	2	0	2
Infection	1	0	2	0	3
Other	7 ^b	4 ^c	10 ^d	4 ^e	25
Total	11	8	24	6	49
Psychiatric hospitalization					
Worsening of psychiatric condition	4	4	5	1	14
Suicidal event	0	0	1	0	1
Total	4	4	6	1	15
Emergency room visit	0	1	3	1	5
Death	1	3	2	0	6
Other	1	1	2	0	4
Total	17	17	37	8	79

Jeste DV, Jin H, Golshan S, et al. Discontinuation of quetiapine from an NIMH-funded trial due to serious adverse events. *Am J Psychiatry*. Aug; 2009 166(8):937–938.

Bipolar disorder and **CVA**

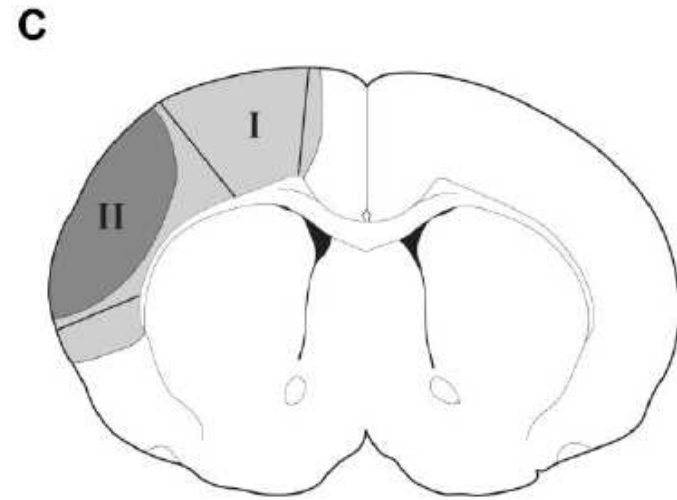
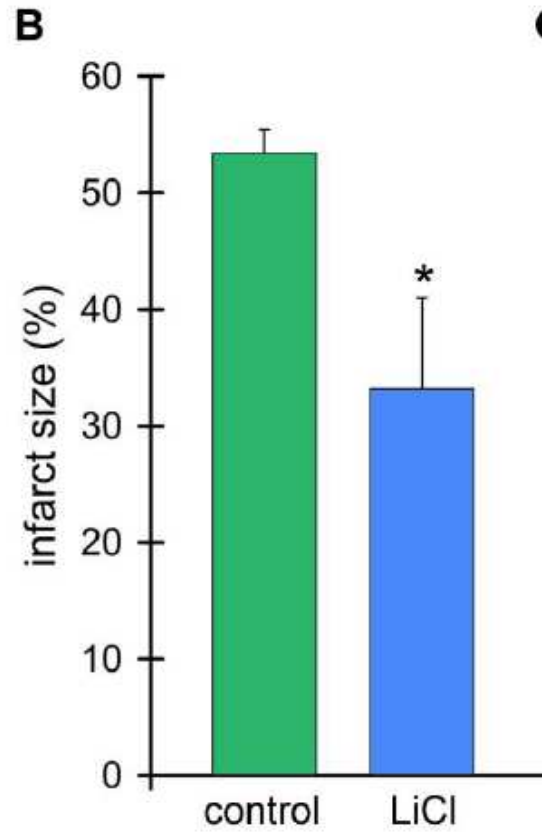
lithium

- mild negative effects on cognitive performance in immediate verbal learning and memory and creativity

Wingo AP, Wingo TS, Harvey PD, Baldessarini RJ. Effects of lithium on cognitive performance: a meta-analysis. **Journal of Clinical Psychiatry** 2009; 70(11): 1588-1597

Bipolar disorder and CVA

lithium



Administration of lithium reduced infarct size.

Bipolar disorder and **CVA**

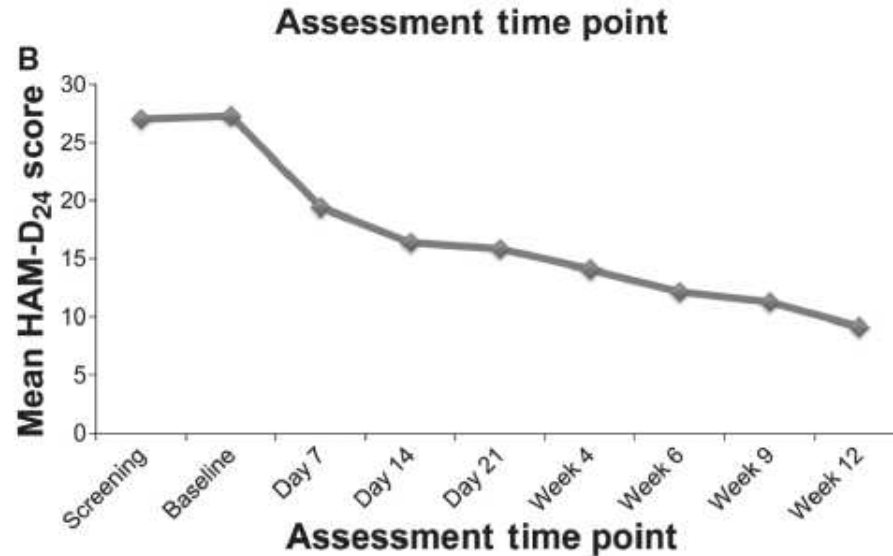
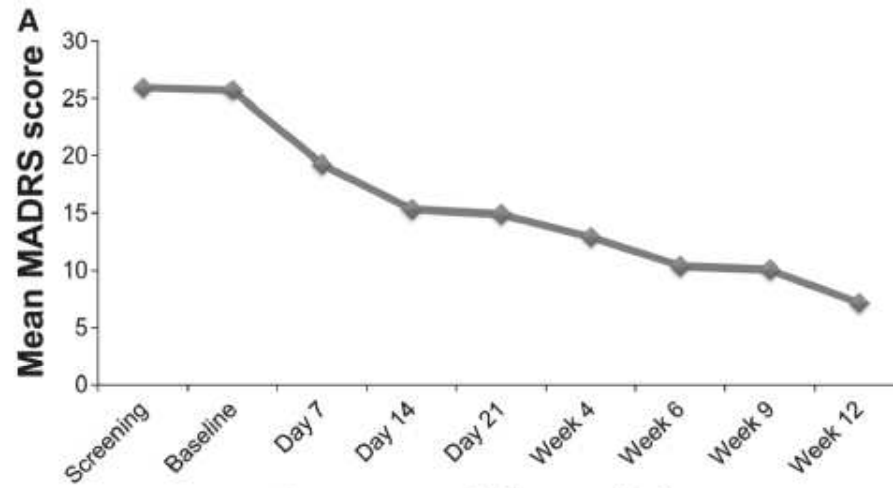
lithium

- patients with cortical strokes in the lithium group had significantly better improvement in both mNIHSS and hFMA in comparison to the placebo group (P=0.003)

Mohammadianinejad and et al. The Effect of Lithium in Post-Stroke Motor Recovery: A Double-Blind, Placebo-Controlled, Randomized Clinical Trial. *Clinical Neuropharmacology*. **2014** May-Jun;37(3):73-8

Bipolar disorder and CVA

lamotrigine



Bipolar disorder and **CVA**

lamotrigine

- Lamotrigine appears to work best in depressed elderly patients with BD who have high cardiometabolic risk and low level of mania

Ariel Gildengers, MD and et al. Correlates of Treatment Response in Depressed Older Adults With Bipolar Disorder. *J Geriatr Psychiatry Neurol.* **2012** March ; 25(1): 37–42.

Bipolar disorder and **CVA**

valproate

- VPA monotherapy is associated with the increase in plasma homocysteine levels in patients with epilepsy

Ni G, et al. **BMJ Open** 2014;4:e004936. doi:10.1136/bmjopen-2014-004936

Bipolar disorder and **CVA**

Anticoconvulsant

- **CBZ**, **PHT**, and **VPA**, caused significantly increased **CCA IMT** in patients with epilepsy
- no significant alterations in the markers of vascular risk or CCA IMT were observed in patients who received long-term **LTG** monotherapy

CCA IMT: common carotidartery intima media thickness

Chuang Y-C and et al. Effects of Long-Term Antiepileptic Drug Monotherapy on Vascular Risk Factors and Atherosclerosis. *Epilepsy Currents*, Vol. 12, No. 6 (November/December) **2012** pp. 229–23 © American Epilepsy Society

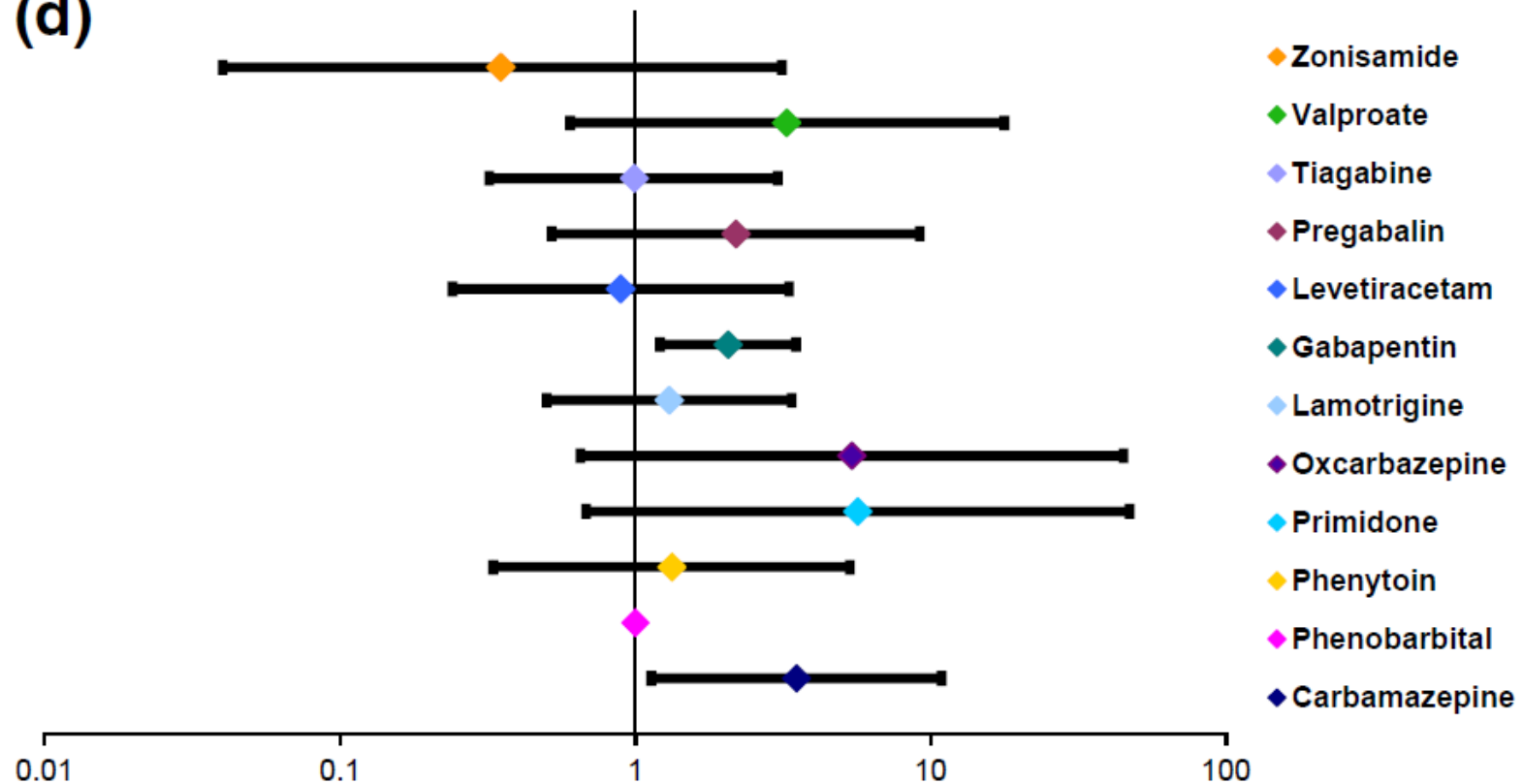
Bipolar disorder and CVA



valproate

at day 90

(d)



Elisabetta Patorno, MD and et al. Risk of Ischemic Cerebrovascular and Coronary Events in Adult Users of Anticonvulsant Medications in Routine Care Settings. *J Am Heart Assoc.* **2013**;2:e000208

Bipolar disorder and **CVA**

Drug of choice

1-Lithium

- Neuroprotective
- Neurogenesis
- Note : Need to readjustment

Bipolar disorder and **CVA**

Drug of choice

2-Lamotrigine

- Low vascular risk
- Note: no antimanic

Bipolar disorder and **CVA**

Drug of choice

3-Valproate and Carbamazepine

-valproa → homocysteine ↑

-Carbamazepine → warfarine ↓

Bipolar disorder and **Headache**

Epidemiology

- Migrane in B2D(34.8%)
- Migrane in B1D (19.1%)
- B1D in Migrane (4.9%)
- B2D in Migrane (7.8%)

A. Ortiz, P. Cervantes, G. Zlotnik et al., "Cross-prevalence of migraine and bipolar disorder," *Bipolar Disorders*, vol. 12, no.4, pp. 397–403, 2010.

Epidemiology

- BD patients with comorbid migraine had significantly higher rates of suicidal behaviour, social phobia, panic disorder, GAD, and OCD
(all $p < 0.05$)

A. Ortiz, P. Cervantes, G. Zlotnik et al., "Cross-prevalence of migraine and bipolar disorder," *Bipolar Disorders*, vol. 12, no.4, pp. 397–403, 2010.

Antipsychotics

Possible rationale for antipsychotic use for headaches and nausea

Condition	Possible rationale
Migraine	Patients are hypersensitive to dopamine agonists or dopamine transporter dysfunction. Some evidence that the dopamine D2 (DRD2) gene is involved
Cluster headache	Pain alleviation possibly related to dopamine receptor antagonism
Nausea	D2 and H1 receptor blockage

Matthew Macaluso and et al . Antipsychotics for migraines, cluster headaches, and nausea . **Current Psychiatry** February **2013** Vol. 12, No. 2

Antipsychotics**Antipsychotics for headache and nausea: Strength of the evidence**

Condition	Strength of evidence ^a
Migraine	Intermediate: Chlorpromazine, ²⁻⁵ droperidol, ⁶⁻⁸ prochlorperazine ^{1,10-12}
	Weak: Haloperidol ^{13,14}
	Very weak: Aripiprazole, ¹⁵ olanzapine, ^{16,17} quetiapine, ¹⁸ ziprasidone ¹⁹
Cluster headache	Weak: Chlorpromazine ²⁰
	Very weak: Clozapine, ²¹ olanzapine ²²
Nausea/vomiting	Intermediate: Droperidol, ²³ metoclopramide, ²⁴ prochlorperazine, ²⁵ promethazine ²⁵
	Weak: Olanzapine ^{26,27}

Matthew Macaluso and et al . Antipsychotics for migraines, cluster headaches, and nausea . **Current Psychiatry** February **2013** Vol. 12, No. 2

Lithium

- (two RCTs) 900mg showed significant improvement in the cluster headache
- No significant differences were found in cessation of attacks between lithium 800mg and placebo (one RCT).

Anticonvulsant

The American Academy of Neurology and the American Headache Society list:

- **topiramate** and **valproic acid** among first-line prophylactics
- **lamotrigine** as ineffective (Level A)
- **carbamazepine** as possibly effective (Level C)
- **clonazepam** and **oxcarbazepine** as possibly not effective (Level C)
- **Gabapentin** list it as Level U (inadequate or conflicting data to support or refute medication use)

Linde M, Mulleners WM, Chronicle EP, McCrory DC. Antiepileptics other than gabapentin, pregabalin, topiramate, and valproate for the prophylaxis of episodic migraine in adults (Review) Copyright © 2014 The Cochrane Collaboration. Published by JohnWiley & Sons, Ltd.

Bipolar disorder and **Epilepsy**

Epidemiology

- In the reported cases mania is mostly
 - peri-ictal state
 - improved seizure control
 - with an epileptic focus in the nondominant hemisphere (right temporal focus?)

Epidemiology

- 1.5% for mania in patients with temporal lobe epilepsy

Barry JJ, Lembke A, Huynh N: Affective disorders in epilepsy, in *Psychiatric Issues in Epilepsy: A Practical Guide to Diagnosis and Treatment*. Edited by Ettinger AB, Kanner AM. Philadelphia, Lippincott Williams & Wilkins, 2001, pp 45–71

Epidemiology

- Bipolar symptoms occurred in 12% of community-based epilepsy patients (MDQ)

Alan B. Ettinger, MD, Michael L. Reed, PhD, Joseph F. Goldberg, MD and Robert M.A. Hirschfeld, MD: Prevalence of bipolar symptoms in epilepsy vs other chronic health disorders. **Neurology** August 23, 2005 vol. 65 no. 4 535-540

Epidemiology

Table 3. Frequency (%) of mood disorders

	epileptic	control	P-value	OR ⁺	CI ⁺⁺
major depressive disorder	36.7	18.3	0.025	2.57	1.1 to 5.9
Depressive Disorder NOS	8.3	0	0.02	-----	-----
Dysthymic Disorder	5	8.3	0.72	0.5	0.1 to 2.5
Bipolar Disorder	1.7	0	0.5	-----	-----
Bipolar Disorder NOS	3.3	0	0.49	-----	-----

+ Odds Ratio

++ Confidence Interval (95%)

Amir Shabani, MD et al:Frequency of Psychiatric Comorbidities in Epilepsy in an Iranian Sample. **Iran J Psychiatry 2006; 1: 148-152**

Epidemiology

- Depression
 - Peri-Ictal
 - Ictal
 - Postictal
 - Interictal (most common type)

Bipolar treatment

- Anticonvulsants
- Antipsychotics
- Lithium

Bipolar treatment

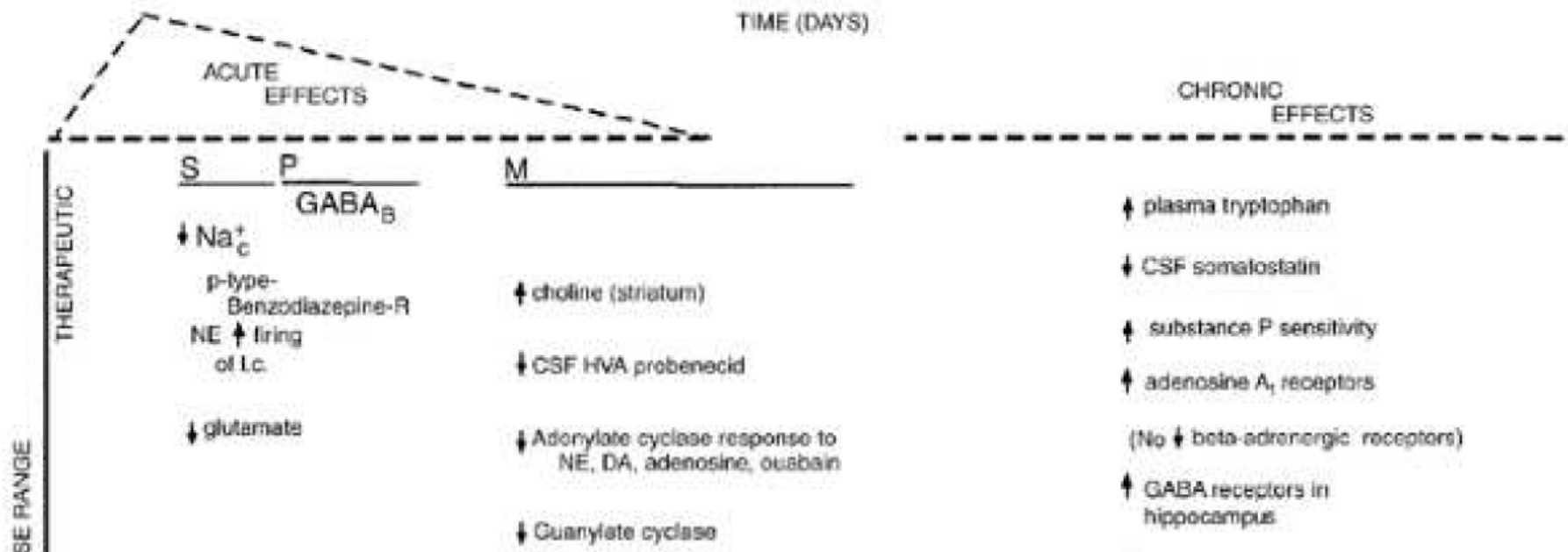
- **Anticonvulsants**
 - Carbamazepine
 - Lamotrigine
 - Valproate
 - Others

Carbamazepine

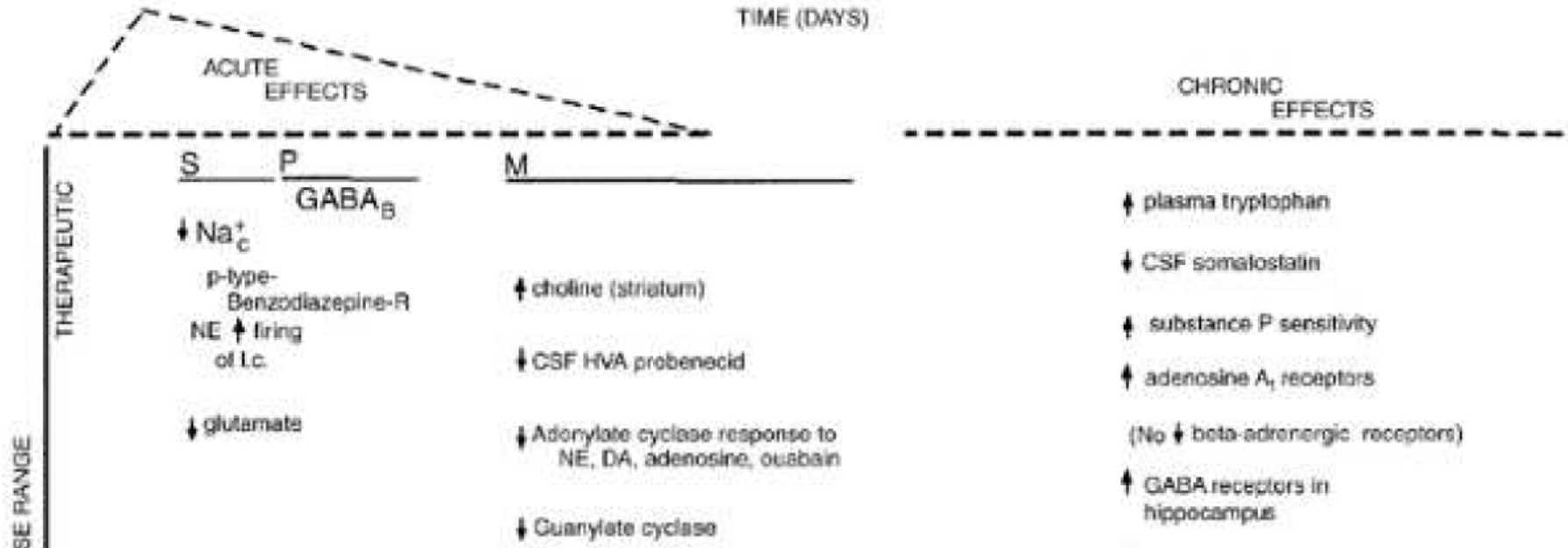
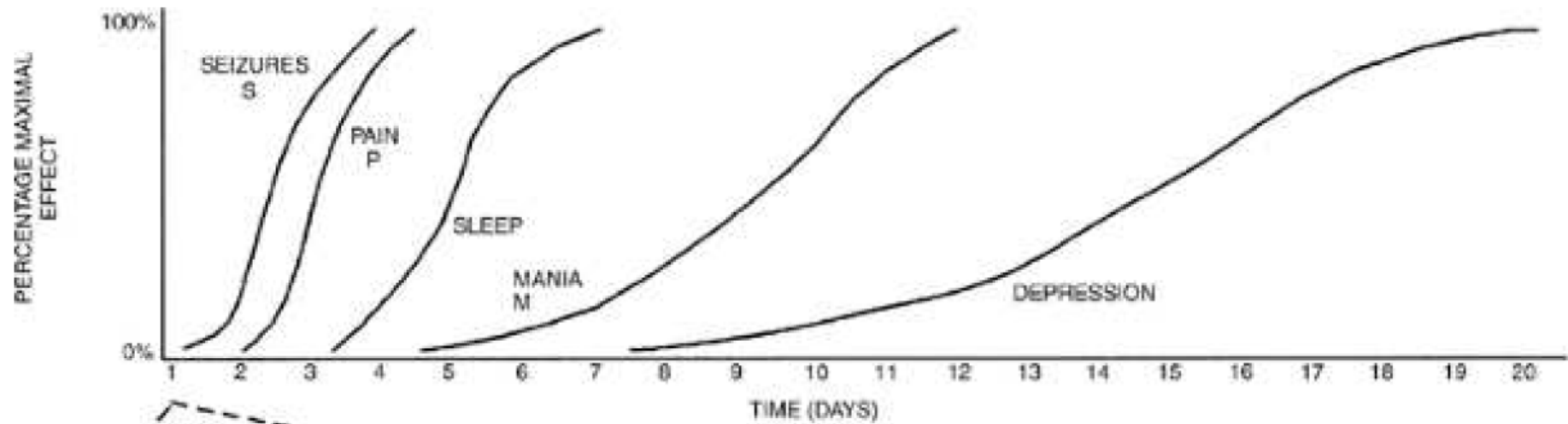
Carbamazepine



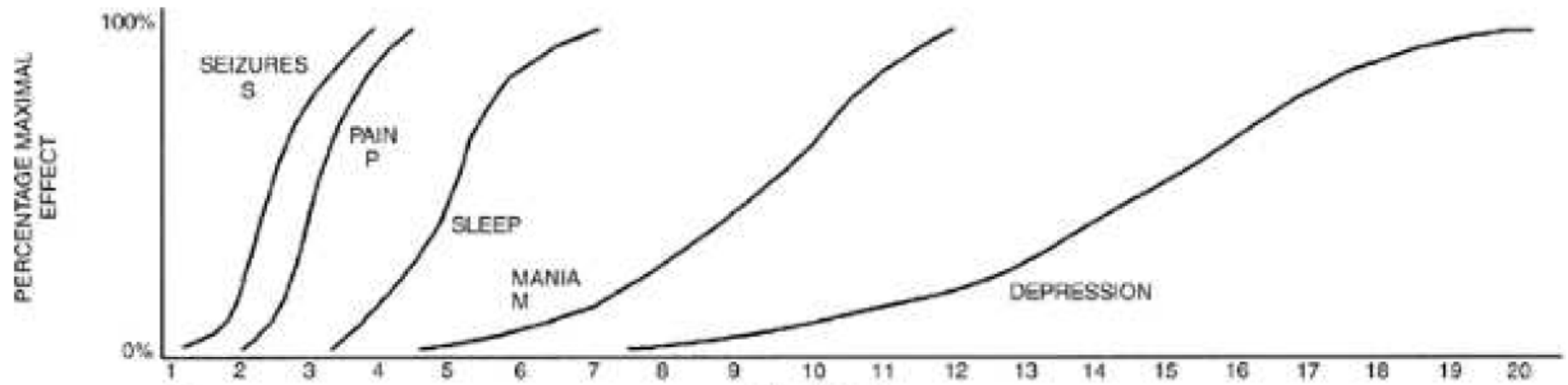
Carbamazepine



Carbamazepine



Carbamazepine



Carbamazepine

- In epilepsy, a series of studies indicate that **higher doses** and blood levels of **carbamazepine** are correlated with greater **reductions in anxiety**

Valproate

Valproic acid	Lamotrigine	<p>1) Inhibition of lamotrigine metabolism and elevated serum concentrations giving rise to skin rashes, or neurotoxic effects if lamotrigine is added to valproic acid</p> <p>2) A synergistic pharmacological effect and improved seizure control</p>	Level 2: Dosage adjustments and monitoring are needed	<p>1) Low initial dose and slow titration of lamotrigine dose when initiating therapy, about 50 % of the dose used in monotherapy is required</p> <p>2) A dose reduction of both drugs may reduce risk of adverse effects without affecting the efficacy</p>
Valproic acid	Phenobarbital	Inhibition of phenobarbital metabolism resulting in elevated serum concentrations, and risk of intoxication if valproic acid is added as a second drug	Level 2: Dosage adjustments and monitoring are needed	A reduction in phenobarbital dose by up to 80 %

Antiepileptic drugs and suicidality

- suicidality risk of 0.43 per 1000 patients in active drug arms placebo arm of 0.22

January 31, 2008



FDA warning

Antiepileptic drugs and suicidality



- suicidality in patients who take drugs called antiepileptics to treat epilepsy, bipolar disorder, migraine headaches, and other conditions.

Antiepileptic drugs and suicidality

- The higher risk of suicidal thoughts and behaviors was observed at one week after starting a drug and continued to at least 24 weeks

Antiepileptic drugs and suicidality

	Hazard
Adjusted analysis ^b	Ratios
Carbamazepine	1.19
Gabapentin	1.42
Lamotrigine	1.86
Levetiracetam	1.66
Oxcarbazepine	2.12
Phenobarbital	0.96
Phenytoin	1.19
Pregabalin	1.44
Primidone	1.84
Tiagabine	2.40
Valproate	1.69
Zonisamide	1.37

Elisabetta Patorno and et al. Anticonvulsant Medications and the Risk of Suicide, Attempted Suicide, or Violent Death. **JAMA**, April 14, **2010**—Vol 303, No. 14

Antiepileptic drugs and suicidality

	Study design	Comparison drug	Results
Olesen et al ³¹	Cohort/ case-crossover	CBZ/No AED	Increased risk for CLB, VPA, LTG, PB, LEV
VanCott et al ³²	Nested matched case-control	GBP	Increased risk for LEV, LTG
Patorno et al ³³	Cohort	TPM/CBZ ²	Increased risk for GBP
Andersohn et al ³⁴	Nested case-control	No AED	Increased risk for LEV, VGB, TGB, TPM
Arana et al ³⁰	Cohort/ case-control	No AED	No increased risk
Gibbons et al ³⁵	Cohort	No drug ⁷	No increased risk

Antiepileptic

- Seizure aggravation by antiepileptic drugs
 - rare phenomenon
 - Generalized epilepsies treated with drugs that are more efficacious against partial seizures
 - Absence seizures may be aggravated by carbamazepine
 - Myoclonic and atonic seizures

Antipsychotics

High

- Chlorpromazine (Thorazine)
- Clozapine (Clozaril)

Moderate

- Most piperazines
- Thiothixene (Navane)

Low

- Fluphenazine (Prolixin)
- Haloperidol (Haldol)
- Loxapine (Loxitane)
- Molindone (Moban)
- Pimozide (Orap)
- Thioridazine (Mellaril)
- Risperidone (Risperdal)
- Olanzapine (Zyprexa)
- Ziprasidone (Geodon)
- Aripiprazole (Abilify)

Seizure Threshold

lithium

High

Moderate

lithium

Low

**Seizure
Threshold**

lithium

- Proconvulsant (moderate)
- Encephalopathy (in combination with CBZ)

Barry JJ, Lembke A, Huynh N: Affective disorders in epilepsy, in *Psychiatric Issues in Epilepsy: A Practical Guide to Diagnosis and Treatment*. Edited by Ettinger AB, Kanner AM. Philadelphia, Lippincott Williams & Wilkins, 2001, pp 45–71

lithium

- Lithium can be a second-line alternative treatment and may prove useful when part of an augmentation strategy

lithium

- 1,411 patients registered at our lithium clinic between 1980 and 2000

lithium

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 - 201 death

lithium

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 - 201 death
 - Renal failure 2

lithium

- 1,411 patients registered at our lithium clinic between 1980 and 2000
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 - Renal failure 2
 - Definite suicides

lithium

- 1,411 patients registered at our lithium clinic between 1980 and 2000
 - 201 death
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 - Definite suicides 43

lithium

- 1,411 patients registered at our lithium clinic between 1980 and 2000
 - 201 death
 - Renal failure 2
 - Definite suicides 43
 - 42 of which committed after abandoning lithium prophylaxis

lithium

- 1,411 patients registered at our lithium clinic between 1980 and 2000
 - 201 death
 - Renal failure 2
 - Definite suicides 43
 - 42 of which committed after abandoning lithium prophylaxis

Bocchetta A, Fadda D, Satta G, Del Zompo M, Gessa GL, Cocco P: Longterm lithium treatment and survival from external causes including suicide. J Clin Psychopharmacol 2007, 27:544-546.

lithium

- Lithium can be a second-line alternative treatment and may prove useful when part of an augmentation strategy

Epidemiology

- Depression
 - Peri-Ictal
 - Ictal
 - Postictal
 - Interictal (most common type)

Epidemiology

- Depression
 - ~~• Peri-Ictal~~
 - ~~• Ictal~~
 - ~~• Postictal~~
 - Interictal (most common type)

Case

- بیمار مبتلا به Epilepsy+B1D که تشنجهایش با valproate کنترل شده است و افکار خودکشی دارد ، مورد مشاوره از بخش نورولوژی قرار گرفته است.
درمان؟

ECT

- most epileptic patients can be treated with ECT without dose adjustment in antiepileptic medications



Mary e lunde and et al. Electroconvulsive therapy in patients with epilepsy. *Epilepsy & Behavior* volume 9, issue 2, Pages 355–359, September **2006**

ECT

- ECT might be therapeutic strategy for the most resistant and severe cases of status epilepticus particularly after the failure of two inductions of anesthetic coma

Virgine Lambercq and et al. Refractory status epilepticus: Electroconvulsive therapy as a possible therapeutic strategy. *Seizure - European Journal of Epilepsy* . volume 21. issue 9. Pages 661–664, November **2012**

Drug of choice

- Valproate
 - Lamotrigine 
 - Phenobarbital 

Drug of choice

- Valproate+ Lamotrigine
 - excellent tolerability and efficacy in epilepsy
 - perhaps in affective illness

Drug of choice

- Valproate + Carbamazepine + **Lamotrigine**
 - Which dose of Lomotriginе?