مقایسه داروهای مؤثر در درمان اختلال دوقطبی

دکتر امیر شعبانی

گروه روانپزشکی دانشگاه علوم پزشکی ایران

Treatment Challenges in BD

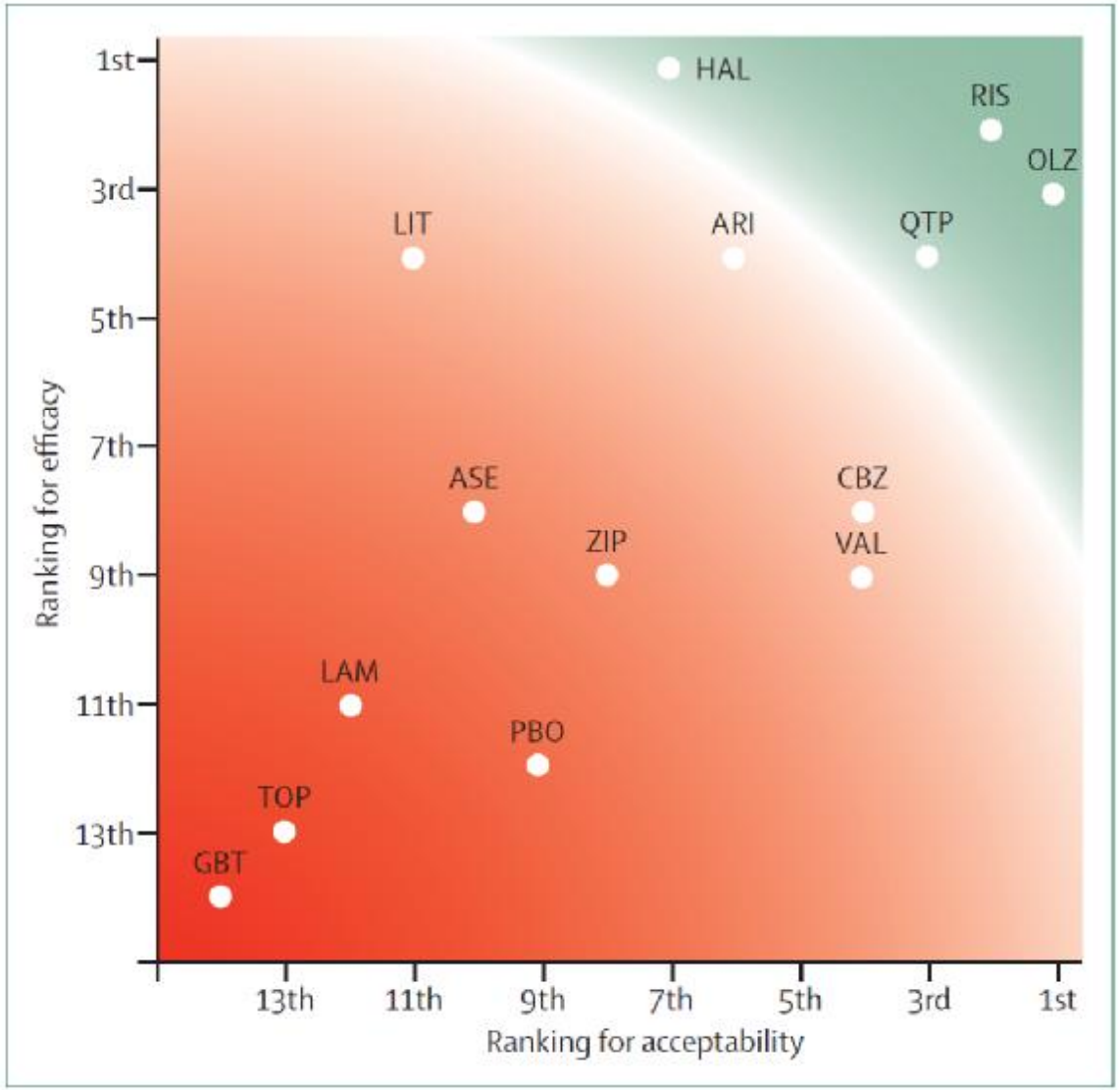
- Major depressive episode
- Mixed states= 20%
- Rapid cycling= 18% (annually), 31.5% (lifetime)
- Psychiatric Comorbidity (substance abuse, personality dis., OCD, ...)
- Non-psychiatric Comorbidity (diabetes, cardiovascular, cognitive, ...)
- Residual and subsyndromal symptoms
- Cognitive symptoms

Pharmacotherapy

Mood stabilizers	SGAs	Antidepressants	Others
Lithium	Quetiapine	SSRIs	FGAs
Valproate	Olanzapine	Bupropion	Topiramate
Divalproex	Risperidone		Gabapentine
Lamotrigine	Aripiprazole		Benzodiazepines
Carbamazapine	Ziprasidone,		
	Lurasidone		
	Asenapine		
	Paliperidone		

FDA	Mania	Depression	Maintenance
Lithium	X		X
Divalproex	X		
Lamotrigine			X
Carbamazepine (ER)	X		
Aripiprazole	X		X
Asenapine	X		
Chlorpromazine	X		
Lurasidone		X (BID)	
Olanzapine	X		X
Olanzapine-fluoxetine		X (Also for pediatric BID)	
Paliperidone	X		
Quetiapine (IR, XR)	X	X	Adjunctive
Risperidone	X		(Long acting)
Ziprasidone	X		Adjunctive

Manic Episode



(Geddes and Miklowitz, 2013)

Manic Episode

- Antipsychotic drugs seem to be better than anticonvulsants and lithium in the treatment of manic episodes.
- Olanzapine, risperidone, and haloperidol seem to have the best profile of presently available agents.
- However, a drug with better long-term evidence of efficacy such as lithium might be preferred when continued drug therapy is planned.

(Geddes and Miklowitz, 2013)

Manic Episode (CANMAT, 2012)

First line	Other options	
Lithium	CBZ	Risperidone + CBZ
Divalproex	ECT	Olanzapine + CBZ
OLZ, RSP, QTP	Haloperidol	Tiagabine
APZ, ZPS	Lithium + DVP	Topiramate
Asenapine, Paliperidone	Lamotrigine	Gabapentine
Li/DVP + OLZ/RSP/QTP/APZ/Asenapine	Antidepressants	Verapamil
	ECT	

Depressive Episode

- Recommendations in clinical practice guidelines for treatment-resistant bipolar depression are still often based on extrapolation from the evidence on augmentation and switching strategies in unipolar major depression.

- A recent review of strategies for patients who do not respond to first-line treatments reported just seven small trials; one each for ketamine, pramipexole, LTG, and RSP, and two each for modafinil and ECT.

- The place of LTG in acute treatment remains uncertain. (Geddes Miklowitz, 2013)

- Lithium, LTG, and QTP are the recommended as a first-line choice in bipolar depression.

(Vieta and Valentı, 2013)

Depressive Episode (CANMAT, 2012)

First line	Other options	
Lithium	Divalproex	~~Antidepressant monotherapy~~
LTG	Lurasidone	~~LMT + Antidepressant~~
Quetiapine	QTP+SSRI	~~Typical antipsychotics~~
Olanzapine + SSRI	Adjunctive Modafinil	~~Gabapentin, Aripiprazole~~
Li/DVP + SSRI/Bupropion	Li/DVP+LTG/Lurasidone	~~Ziprasidone, Adjunctive ziprasidonec~~
Li + DVP	ECT	~~Adjunctive levetiracetam~~

Depressive Episode

FDA Approved	Unapproved with some evidence	Unapproved lacking substantive evidence	Unapproved with negative evidence
Olanzapine-fluoxetine	Lithium	Antidepressants	Aripiprazole
Quetiapine	Lamotrigine		Ziprasidone
Lurasidone	Valproate		
	Armodafinil (add-on)		
	Modafinil (add-on)		
	Pramipexole (add-on)		(Beyer, Ketter, et al., 2013)

Antidepressants in Bipolar

- Antidepressants should be avoided in bipolar cases through:
  - Rapid cycling
  - Mixed states
  - Monotherapy
  - Long-term maintenance treatment
  - Starting to treat depressive episode

Antidepressants in Bipolar

- No class effect
- No fixed response for any targets
- Need to be tried in many cases of depression; if not the majority

- To conclude that no antidepressant agent is effective in bipolar depression is probably premature, although the emerging evidence suggests that paroxetine is ineffective.

BIID (CANMAT, 2012)

	Depression	Maintenance
First line	QTP	Li, LTG, QTP
Second line	Li LTG DVP Combination (±ADP)	DVP Combination (±ADP)
Third line	ADP (primarily for those with infrequent hypomanias) Switch to alternate ADP QTP+LTG Adjunctive ECT, adjunctive NAC, adjunctive T3	

Maintenance Treatment

- A meta-analysis of five placebo-controlled lithium maintenance trials (n=770) showed that lithium reduces the risk of manic relapses by 38% (RR=0·62) and depressive relapse by 28%. (Geddes, et al., 2004)
- The BALANCE trial found that lithium was better than VLP in the prevention of mood episodes (RR=0·71).
- Lithium plus VLP is better than VLP monotherapy (RR=0·59). (Geddes, Goodwin, et al., 2010)
- A pooled analysis of two randomized LTG versus placebo trials reported a 36% reduction for lamotrigine in the risk of relapse over 18 months. (Goodwin, Bowden, et al., 2004)
- There are few long-term trials, most use enrichment designs, and none have the same degree of independent replication of efficacy as lithium. Thus, the role of antipsychotics as long-term mood stabilizers remains uncertain.

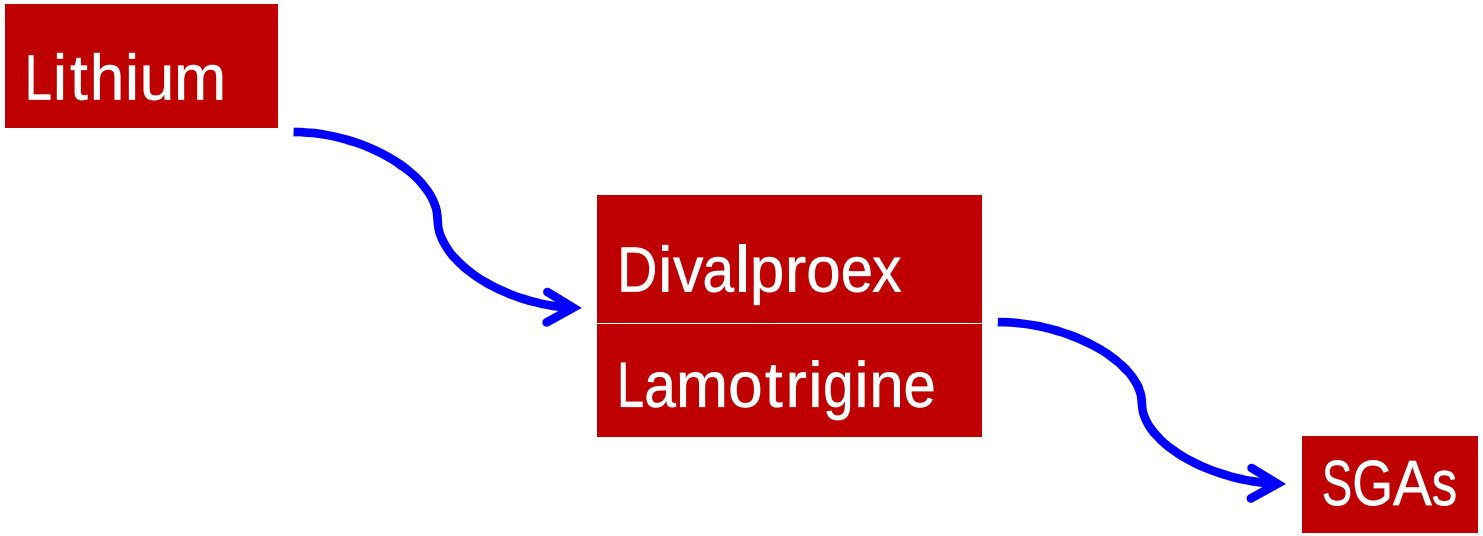
Numbers needed to treat

- Mania: The NNT for lithium and the SGAs for 3 weeks lay between 3 and 13 for a response greater than that found for placebo.

- Depression: The NNT for 8 weeks lay between 5 and 7 for a response greater than that found for placebo.

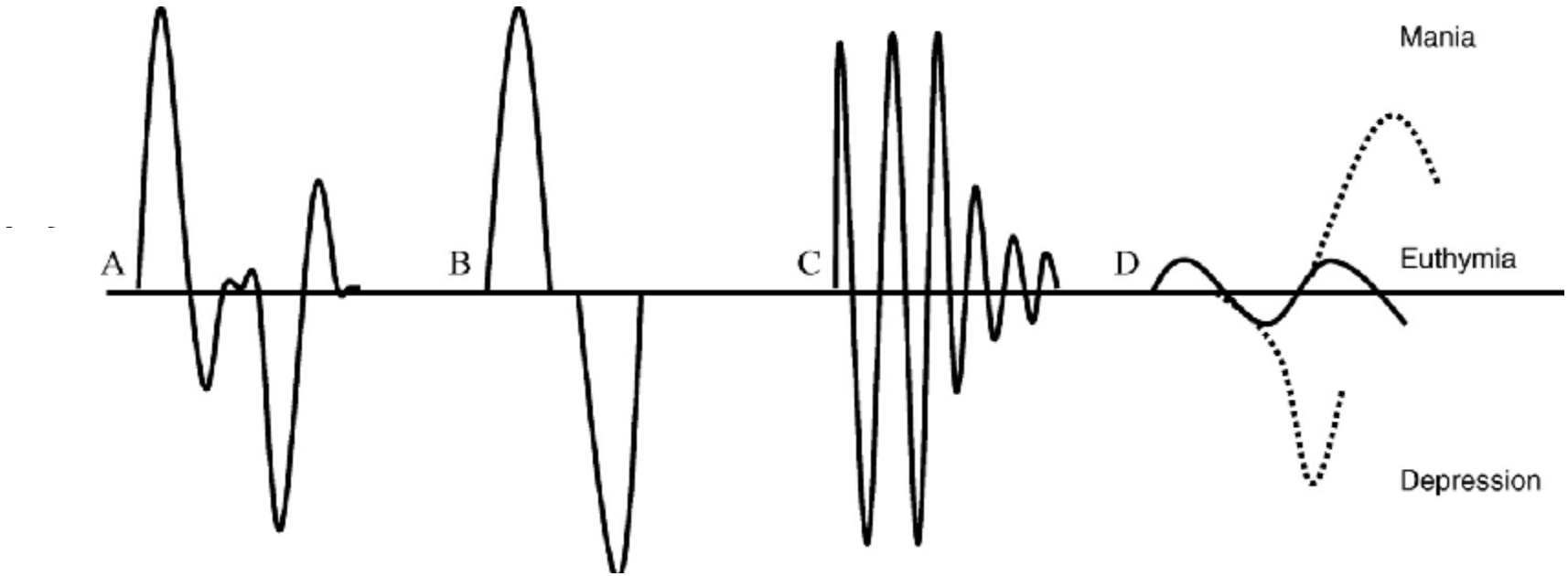
- Maintenance: The NNT for 12 months was 14 for an additionally prevented episode compared to placebo, and for 24 months it was 3.

Evidence for Maintenance Treatment



(Geddes and Miklowitz, 2013)

- **Unpredictable course!**



Maintenance (CANMAT, 2013)

First line	Other options	
Lithium	**CBZ**	~~**Antidepressants**~~
Lamotrigine	**Paliperidone**	~~**Fluphenthixol**~~
Divalproex	**Lith+DVP/CBZ/RSP/LTG**	~~**Topiramate**~~
OLZ, QTP, RSP_{LA} (for mania), APZ (for mania)	**Lith/DVP+ OLZ**	~~**Gabapentine**~~
Lith/DVP+QTP/RSP_{LA}/APZ/ZPS	**OLZ+FLX**	**ECT**

Mood Stabilizers

Lithium	Valproate	Lamotrigine	CBZ	SGAs
Renal failure, Toxicity, Diabetes insipidus, Hypothyroidism	Teratogenicity, Hepatotoxicity, Hypoalbuminemia effect	Serious rash, Interaction with VLP	Interactions, Bone marrow suppression	Diabetes mellitus, Hyperlipidemia, Fatal diabetic ketoacidosis (QTP/OLZ)
Slow symptom reduction	Pancreatitis, Hyperammonemic encephalopathy	Titration, No antimanic	SIADH	Weight gain, Cognitive (QTP] (Beyer, Ketter, et al., 2013)
Serum Levels, cognitive dulling	Osteoporosis, Thrombocytopenia, Menstrual irregularities		Muscle weakness, Ataxia, Visual disturbances	Loss of brain tissue [Ho, et al., 2011; Moncrieff, 2011]
Antisuicide, Best for maintenance	↑tolerance, Wide therapeutic window	↑tolerance, No weight gain, Low teratogenicity		Fast antimanic, Antipsychosis

	Current (M/MD/D/P)	Course (Md/Dm/RC)	Suicide	Personal /Family History	Comorbidity	Side effects	Interactions	Poor Compliance	Evidence
Lithium	+++	+++	++++	+++	?	----	---	---	++++
VLP/ DVP	++	++	++	+	?	--	-	-	++
LMT	+	+	?	+	?	-	-	-	++
SGAs	++	+	?	+	?	---	-	-	++

Suicide

- In 2009, the FDA issued an advisory that the use of AEDs for any indication can increase the risk of suicidal behavior or ideation, based on a meta-analysis of 199 RCTs yielding an odds ratio of 1.87 for patients on AEDs compared with patients on placebo. [the number needed to harm=769]

(Postmarket Drug Safety Information for Patients and Providers. Suicidal behavior and ideation and antiepileptic drugs, 2013)

- A 30-year prospective observational study found no evidence for increased suicide attempts or completions for bipolar patients while they were taking AEDs compared with these same patients during intervals when they were not.

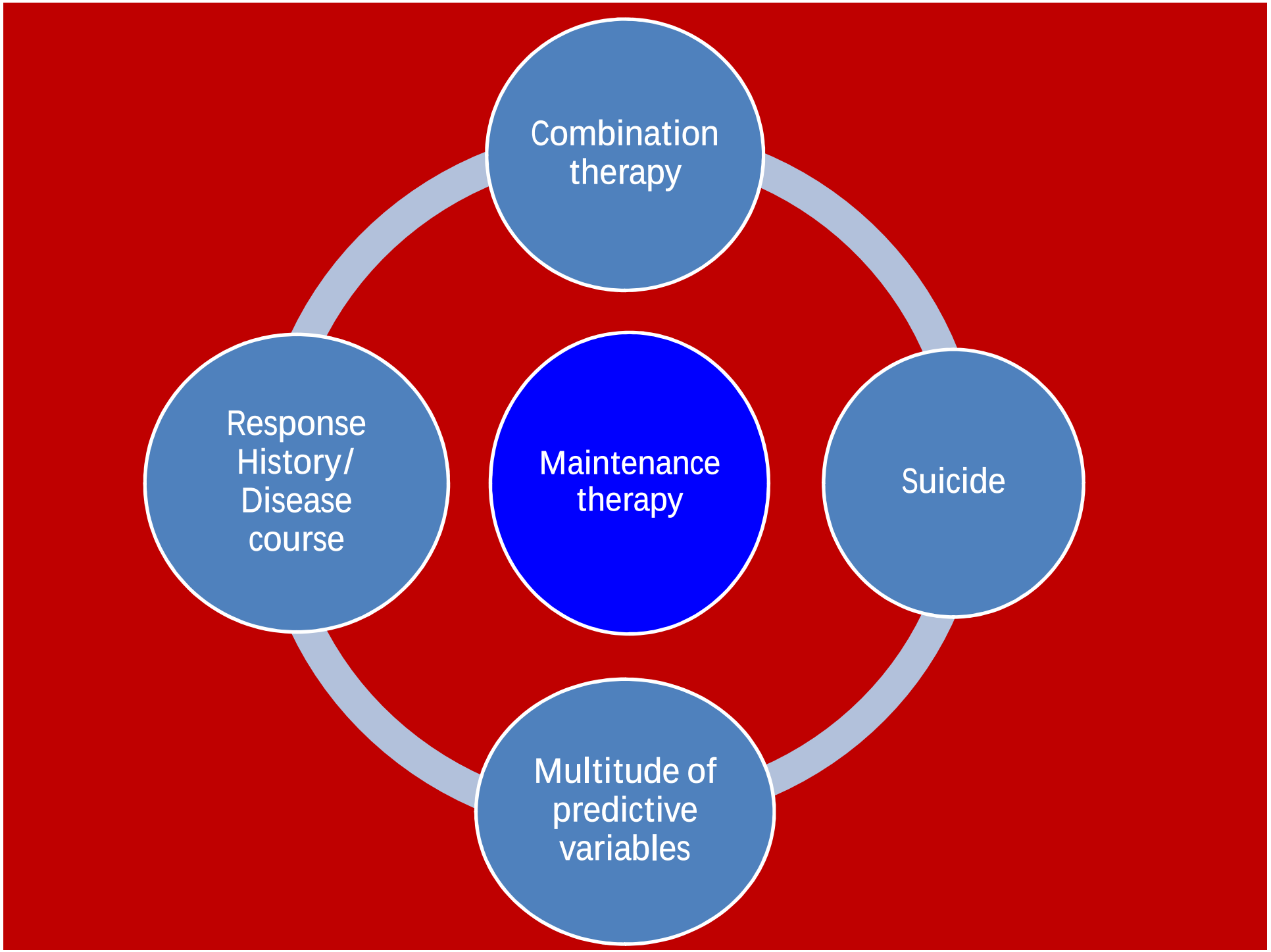
(Leon AC, Solomon DA, et al. Antiepileptic drugs for bipolar disorder and the risk of suicidal behavior: a 30-year observational study, 2012)

No Class, but confusing, effect!

- Antidepressants may protect patients with BD but not unipolar depressive disorder from suicidal behavior. (Leon, et al, 2014)
- Lithium is effective in depression alone, not just BD. (Prien, et al, 1974)
- Atypical antipsychotics showed clear efficacy in acute mania, and in many cases, efficacy for depressive episodes, not limited to BD but even in MDD with some agents. (Nelson, et a, 2009)
- Aripiprazole does not seem to be efficacious in bipolar depression, but is apparently effective in unipolar depression.
- Quetiapine XR failed to demonstrate a statistically significant difference with a placebo in pediatric BD-I and/or BD-II depressive episodes.
- An anticonvulsant, lamotrigine, were much more effective in preventing depression rather than mania. (Goodwin, et al, 2004) And an antipsychotic, lurasidone, is FDA approved for treating bipolar depression, and not mania.
- The presumed strong efficacy of antidepressants in MDD was thrown into doubt with the discovery of a large number of negative unpublished studies. (Turner, et al, 2008)
- There are no class effect for antidepressants in treating MDD (Cipriani, et al, 2009), and for mood stabilizers/antipsychotics in treating BD.
- There is very little research on exactly which treatments are most effective among the neuroleptics and mood stabilizers, at which doses, and for how long.

Pharmacotherapy for BD
Key points

- Non-mood targets: Mortality reduction [suicide/ cardiovascular], neuroprotective effects, potential protection against the cognitive impairment that is a long-term consequence of multiple mood episodes
- Maintenance therapy is the most important aspect of treatment.
- As a rule, a long-term maintenance treatment strategy should not be modified in the event of recurrence within 6 months of its commencement.
- Suicide is possibly the most important recurrent risk conferred by mood disorders.
- It seems preferable to base the prognosis on a multitude of predictive variables.
- Mixed/rapid cycling BD generally have a poor treatment response to most agents.
- Combination therapy is a rule rather than exception. No particular treatment for BD is fully effective.



Maintenance Treatment

- Final suggestion:

Lithium + LTG OR VLP OR SGA OR Their combination

Depression predominance:
Lithium + LTG/QTP

Mania predominance:
Lithium + VLP/ARP/OLZ/QTP

Treatment should always be individualized.