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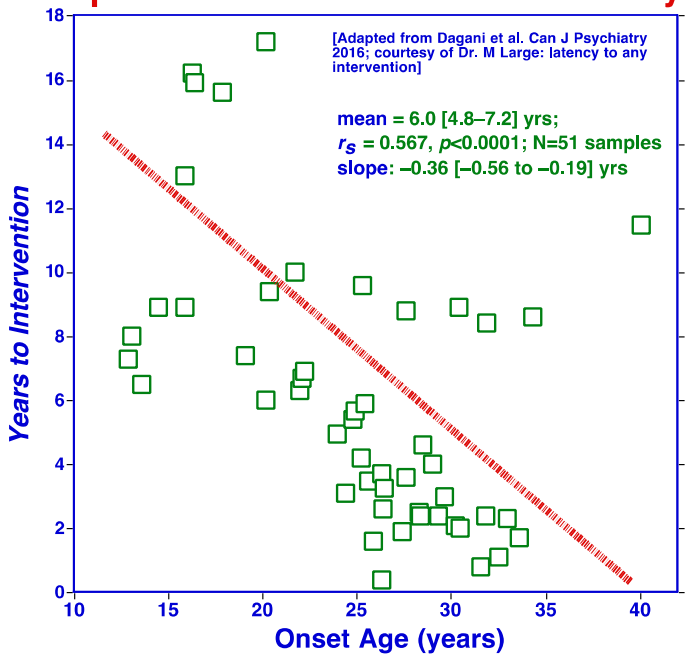
Pharmacological Treatment of Bipolar Disorder

Ross Baldessarini, M.D.

Professor of Psychiatry & Neuroscience
Harvard Medical School

[Neither Dr. Baldessarini nor any immediate family member has financial relationships with commercial organizations that might appear to represent a conflict of interest with material presented here]

Bipolar Disorder: Treatment Latency



Treatments: bipolar disorder

Lithium

- Std. "mood-stabilizer" vs. all phases, esp. long-term
- US popularity highly eroded by competitive marketing

Anticonvulsants

- Carbamazepine less effective than Li in all phases
- Divalproex antimanic, but widely used long-term
- Lamotrigine esp. effective vs. depressive recurrences
- Others: Efficacy not proved

Antidepressants

- Overused (understandably), limited efficacy, risky alone
- More useful & safer in type-II BPD
- Modern preferred, all risk dose-dependent switching

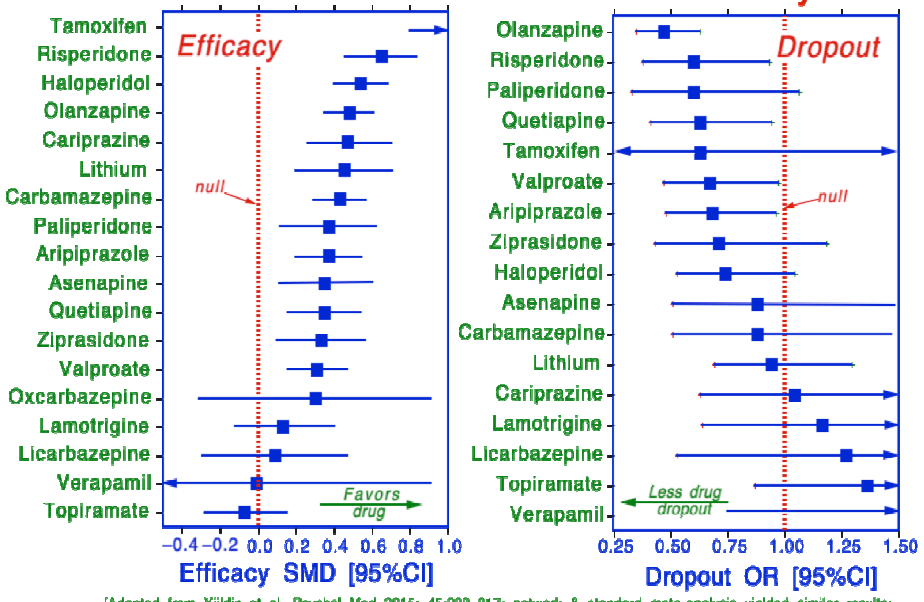
Antipsychotics

- All antimanic (CPZ vs. all better-marketed atypicals)
- Bipolar depression: CRP, LUM, LUR, ONZ-FLX, QTP
- Long-term use FDA-approved: APZ, ONZ, QTP

Sedative-hypnotics

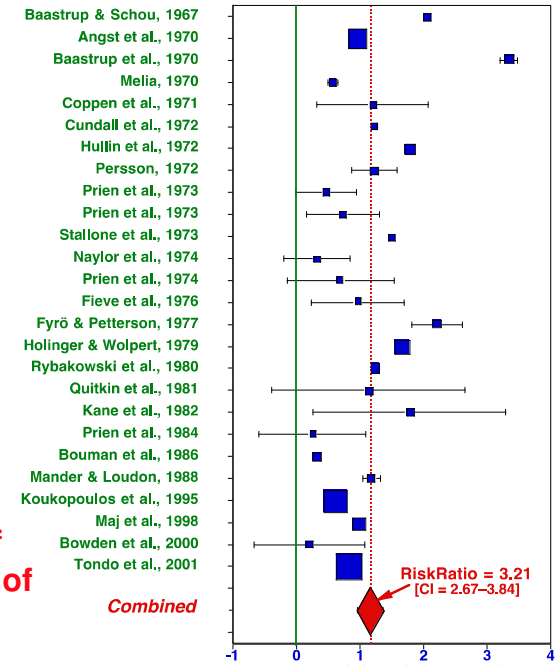
- High-potency preferred antimanic adjuncts
- May limit late anxiety, emerging irritability

Antimanics vs. Placebo: Network Meta-Analysis



[Adapted from Yildiz et al. Psychol Med 2015; 45:299–317; network & standard meta-analysis yielded similar results: r=0.944, with efficacy 12.2% lower by network analysis]

Meta-analysis of efficacy studies of lithium in MDI



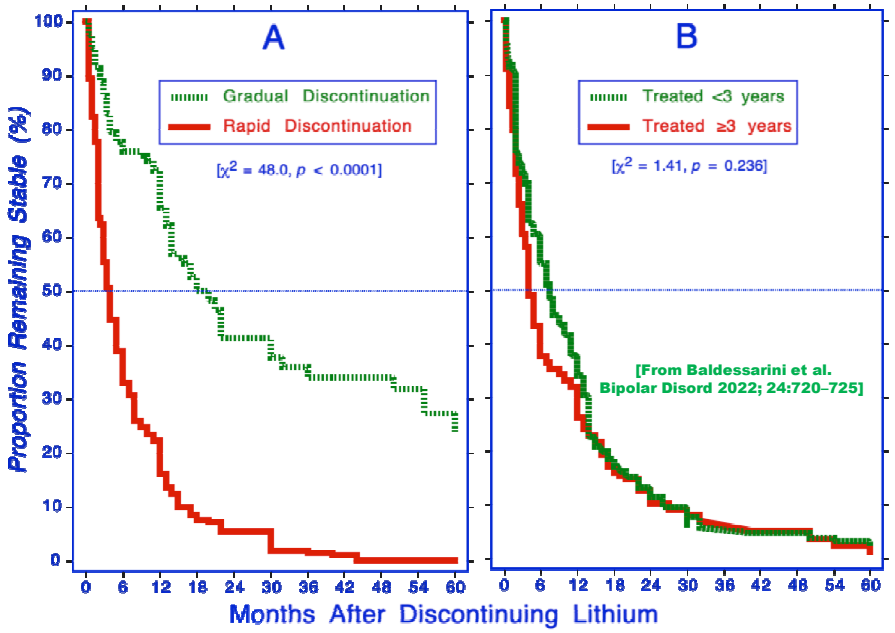
[From Baldessarini et al.: Harvard Rev Psychiatry 2002; 10: 59–75]

Long-term efficacy: lithium for bipolar disorder

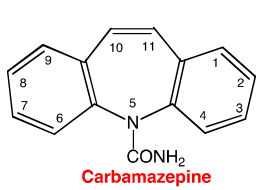
Outcome	Trials (n)	Subjects (N)	RR [95%CI]	Favors	*p*-value
Lithium vs. Placebo					
vs. Any polarity	7	1580	0.66 [0.53–0.82]	Li > Pbo	<0.001
vs. Mania	6	1375	0.52 [0.36–0.71]	Li > Pbo	<0.001
vs. Depression	6	1375	0.78 [0.59–1.03]	Li ≥ Pbo	0.08
Dropout risk	7	1580	1.33 [1.07–1.65]	Pbo > Li	0.01
Lithium vs. Anticonvulsants					
vs. Any polarity	7	1305	0.89 [0.79–1.01]	Li ≥ ACs	0.07
vs. Mania	5	941	0.66 [0.44–1.00]	Li > ACs	0.05
vs. Depression	5	941	1.15 [0.92–1.43]	ACs ≥ Li	0.23
Dropout risk	6	1085	1.19 [0.87–1.63]	ACs ≥Li	0.27

Data adapted from Severus et al. *Int J Bipolar Disord* 2014; 2: 10–14, based on random effects meta-analyses.

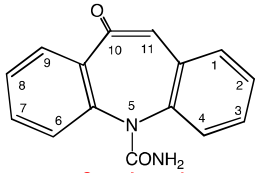
Risk in Bipolar Disorder After Discontinuing Lithium



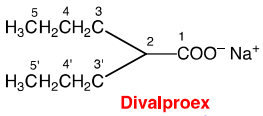
MOOD-ALTERI NG ANTICONVULSANTS



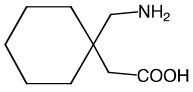
Carbamazepine
(Tegretol®)



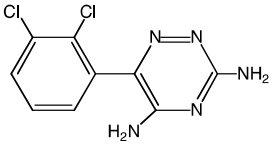
Oxcarbazepine
(Trileptal®)



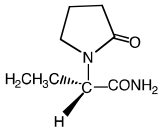
Divalproex
(Depakote®)



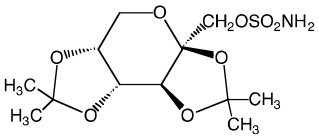
Gabapentin
(Neurontin®)



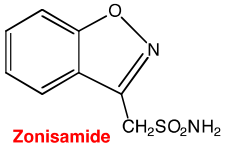
Lamotrigine
(Lamictal®)



Levetiracetam
(Keppra®)



Topiramate
(Topamax®)



Zonisamide
(Zonegran®)

[Only CBZ, VPA, LTG are approved for BD]

Controlled trials of valproate: Adult mania

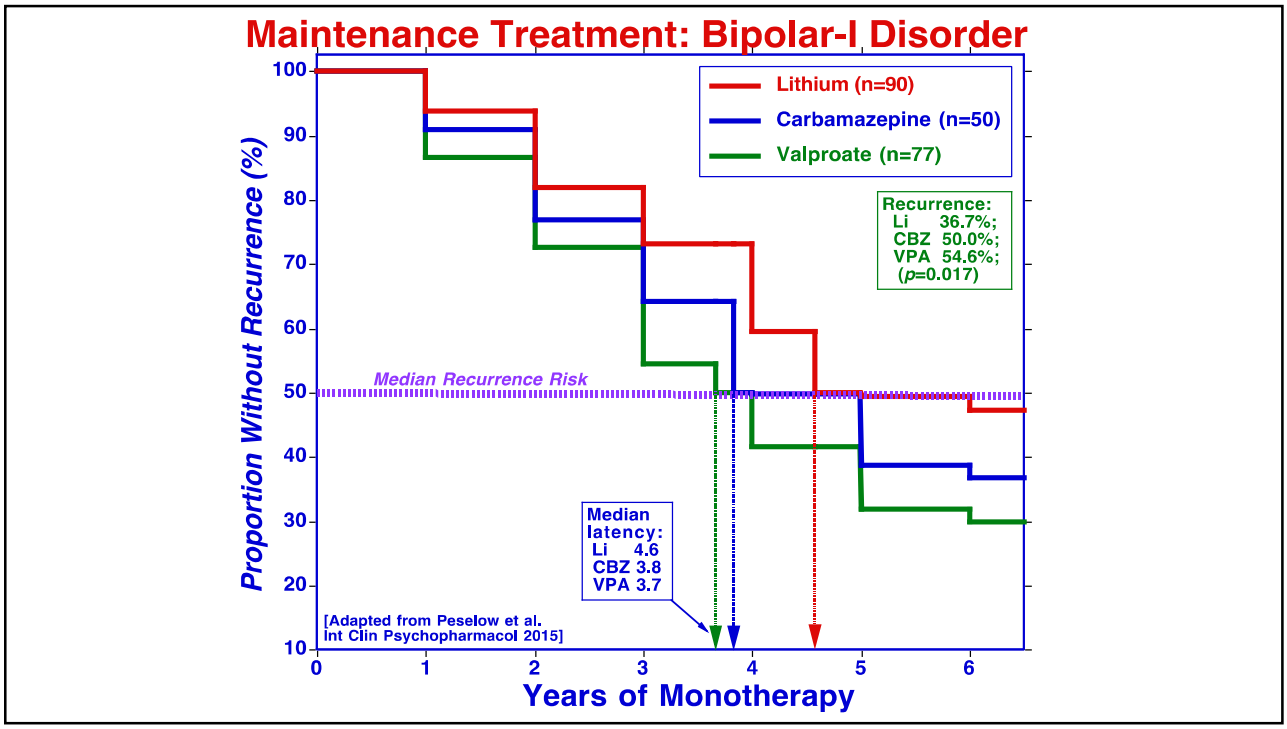
Study	Response Rates (%) *Valproate*	*Standard*	*Placebo*
Brennan et al. 1984	6/8	——	3/8
Emrich et al. 1985, 1992	3/5 (+Li)	5/7 (OxCBZ+Li)	0/8
Pope et al. 1991	10/17	——	2/19
Freeman et al. 1992	9/14	12/13 (Li)	———
Bowden et al. 1994	28/53	23/59 (Li)	16/30
Vasudev et al. 2000	11/15	8/15 (CBZ)	———
Müller et al. 2000	48/68 (+APD)	31/68 (APD)	——
Totals (7 trials; 407 Ss)	115/180	79/162	21/65
Means	63.9%*	48.8%	32.3%

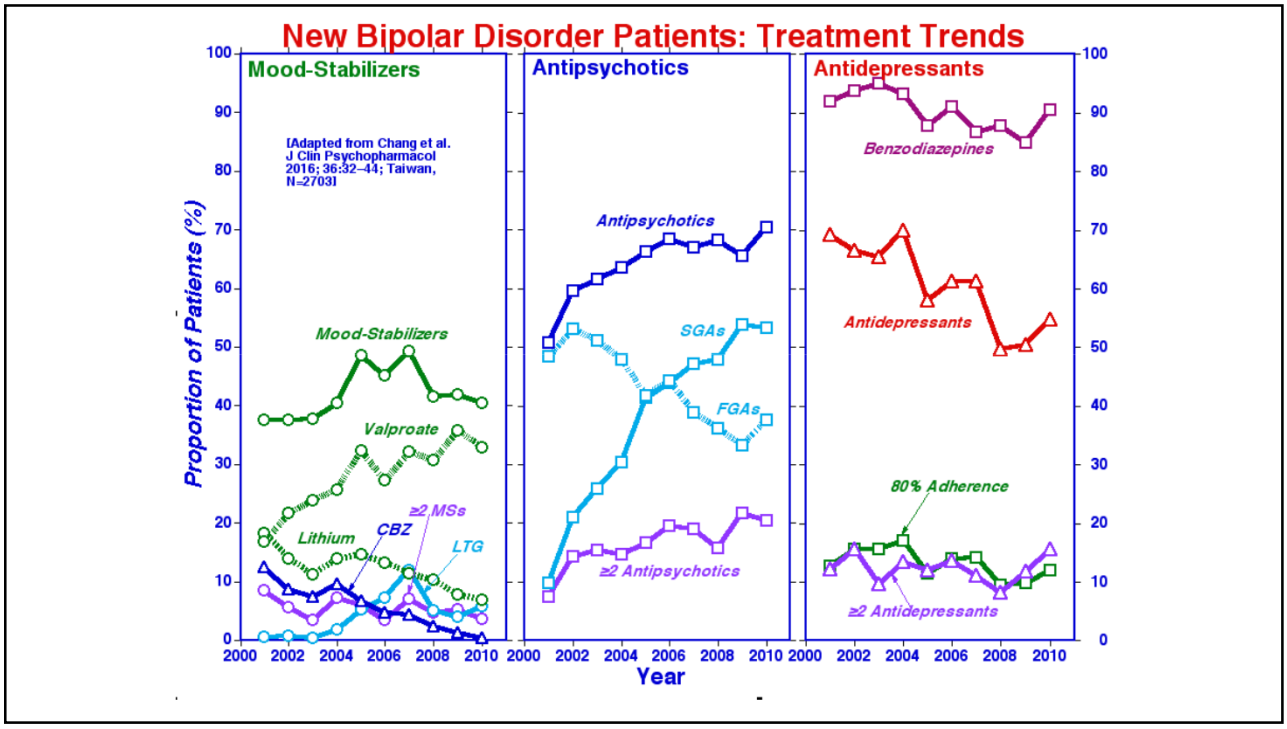
Adapted from De León: Harvard Rev Psychiatry 2001; 9: 209–222. (*) $p<0.001$.

Long-term trial: Bipolar-I disorder

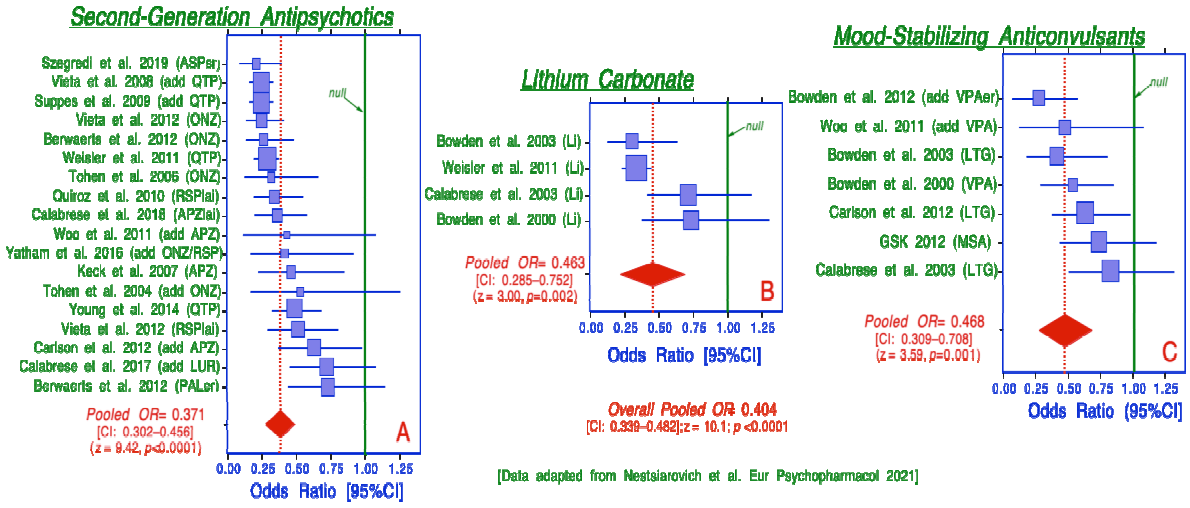
Measures	Valproate	Lithium	Both
Subjects (N)	110	110	100
Survival (mos)	6.2	10.6	14.7
Failures (%)	69.1	59.1	53.6
New mania (%)	44.6	36.4	27.3
New depression (%)	45.5	31.8	35.5

Adapted from Geddes et al. Balance trial. Lancet 2010; 375:385–395.
Duration: 1.8 yrs.


Maintenance Treatment: Bipolar-I Disorder
Lithium (n=90)
Carbamazepine (n=50)
Valproate (n=77)
Recurrence:
Li 36.7%;
CBZ 50.0%;
VPA 54.6%;
(p=0.017)
Median Recurrence Risk
Median latency:
Li 4.6
CBZ 3.8
VPA 3.7
[Adapted from Peselow et al. Int Clin Psychopharmacol 2015]
Proportion Without Recurrence (%)
Years of Monotherapy


New Bipolar Disorder Patients: Treatment Trends
Mood-Stabilizers
Antipsychotics
Antidepressants
[Adapted from Chang et al. J Clin Psychopharmacol 2016; 36:32–44; Taiwan, N=2703]
Mood-Stabilizers
Valproate
Lithium
CBZ
≥2 MSs
LTG
Antipsychotics
SGAs
FGAs
≥2 Antipsychotics
Benzodiazepines
Antidepressants
80% Adherence
≥2 Antidepressants
Proportion of Patients (%)
Year

Placebo-Controlled, Randomized Preventive Trials for Bipolar Disorder



[Data adapted from Nestsiarovich et al. Eur Psychopharmacol 2021]

[Total N=7773; trial duration = 24–104 wks; overall efficacy ranked: Mixed ≥ Mania > Depression; duration of stabilization or trial had no effect; some treatments ("add") were added to lithium or valproate (Woo et al. 2011 [APZ+VPA] & Carlson et al. 2012 [APZ+LTG] added both SGA+MSA); efficacy was similar with monotherapy or add-ons; inter-trial heterogeneity was moderately high (80%–70%).]

Systematic Meta-analysis: Long-term Trials for Bipolar Disorder

Long-term randomized controlled trials: bipolar disorder

Treatments	Trials (n)	OR [95% CI]
Drug Types		
SGAs	18	0.370 [0.300–0.451]
Lithium	4	0.461 [0.280–0.752]
MSAs	5	0.610 [0.451–0.840]
Individual Agents		
Olanzapine	4	0.280 [0.200–0.391]
Quetiapine	4	0.290 [0.210–0.400]
Aripiprazole	2	0.380 [0.260–0.571]
Risperidone	3	0.410 [0.290–0.559]
Valproate	1	0.490 [0.290–0.840]
Lamotrigine	3	0.639 [0.451–0.971]

Selective prevention of recurrences of mania vs. bipolar depression

Treatments	Polarity Index [CI]	Favors
MSAs	0.38 [0.19–0.59]	D > M
SGAs	1.57 [1.12–3.25]	M > D
Lithium	2.29 [1.43–5.06]	M > D
All agents	1.08 [1.02–1.20]	M ≥ D

Abbreviations: *D*, bipolar depression; *M*, [hypo] mania
SGAs, second-generation antipsychotics (aripiprazole, asenapine, lurasidone, olanzapine, paliperidone, quetiapine, risperidone);
MSAs, mood-stabilizing anticonvulsants (lamotrigine, valproate).
Trials with 7773 subjects averaged 58.5 weeks, usually following 6.7 weeks of stabilization in discontinuation trials.
Smaller OR = greater prophylactic efficacy vs. placebo.
Polarity Index = [NNT for D/NNT for M]; >1.00 favors M.

Data adapted from Nestsiarovich et al. Eur Psychopharmacol 2021.

Responses to mood-stabilizer treatment in BPD with a M-D-I vs. D-M-I course: meta-analysis

Study	Response Rate Difference (RD) [95%CI]	Weight (%)	χ^2	*p* - value
Kukopulos et al. 1980	0.29 [0.15 to 0.44]	24.3	14.2	0.0002
Grof et al. 1987	0.39 [0.14 to 0.64]	13.3	7.26	0.007
Haag et al. 1987	0.42 [0.18 to 0.64]	14.2	10.7	0.001
Maj et al. 1989	0.42 [0.16 to 0.69]	12.5	5.84	0.02
Faedda et al. 1989	0.23 [–0.21 to 0.66]	5.72	1.03	0.31
Koukopoulos et al. 2013	0.14 [0.04 to 0.25]	30.1	7.67	0.006
Pooled RD	0.29 [0.18 to 0.40]	100	41.9	<0.0001
NNT [CI]	3.4 [2.5 to 5.6]	---	---	---

Better responses (≥50% reduction of recurrences) were found when the dominant polarity sequence was mania before depression in 5/ 6 studies. From Koukopoulos et al. J Affect Disord 2013; 151:105–110.

Trials of Treatments for Acute Bipolar Depression

Monotherapies

Treatment	Trials (n)	RR [95%CI]
Fluoxetine	1	1.41 [0.22–2.55]
Valproate	3	1.25 [0.47–2.03]
Lurasidone	2	1.15 [0.37–1.92]
Imipramine	2	0.86 [0.01–1.72]
Cariprazine	2	0.85 [0.08–1.62]
Olanzapine	3	0.72 [0.09–1.35]
Quetiapine	11	0.48 [0.14–0.82]

Ineffective agents included: CBZ, GPN, Li, LTG, OFC, other SSRIs, other SGAs, VNX. Adapted from Bahji et al. J Affect Disord 2020; 269:154–184.

Adjunctive treatments

Treatment	Trials (n)	SMD [95%CI]
Ketamine	2	12.5 [3.96–50.9]
Coenzyme-Q10	1	5.96 [2.03–17.5]
Pramipexole	2	4.17 [1.32–13.2]
Fluoxetine	4	1.51 [1.11–2.06]
Lamotrigine	2	1.43 [1.00–2.04]

Ineffective agents included: inositol, lithium, modafinil, SAMe SGAs, SSRIs, TCAs, valproate. Treatments added mainly to mood-stabilizers. Adapted from Bahji et al. Can J Psychiatry 2021; 66: 274–288.

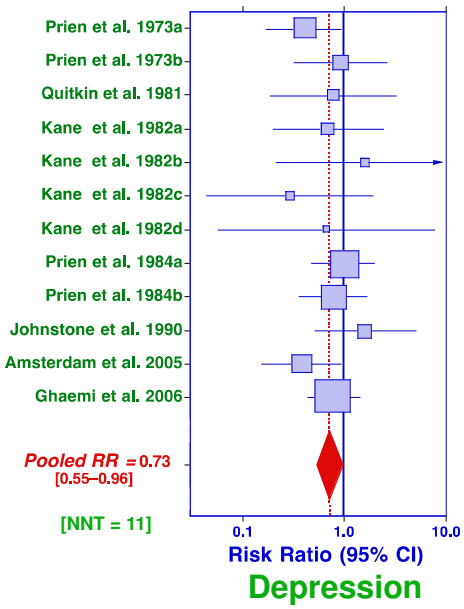
Randomized controlled trials: acute bipolar depression

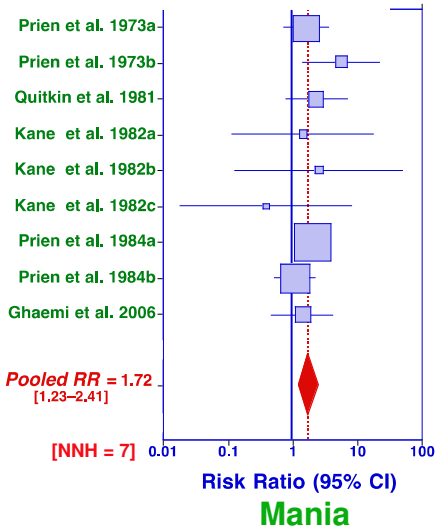
Treatment	Trials	Subjects	% Responders		RR [95%CI]
			Drug	Placebo	
Mood-Stabilizing Anticonvulsants (MSAs)					
Valproate	4	140	40.6	18.3	2.22 [1.26–3.91]
Carbamazepine	1	70	63.8	34.8	1.84 [1.01–3.34]
Lamotrigine	5	1071	47.1	30.2	1.56 [1.33–1.83]
All MSAs	10	1281	47.6	24.0	1.61 [1.39–1.87]
Second-Generation Antipsychotics (SGAs)					
Lurasidone	1	485	52.0	30.2	2.50 [1.68–3.73]
Quetiapine	5	2485	64.5	44.4	2.27 [1.91–2.71]
Cariprazine	1	236	44.4	31.1	1.81 [0.91–3.62]*
Olanzapine	2	1220	45.7	35.2	1.55 [1.23–1.96]
Aripiprazole	2	690	43.9	41.6	1.10 [0.81–1.48]*
Ziprasidone	2	928	50.7	50.0	1.03 [0.79–1.34]*
All SGAs	13	6044	55.3	41.4	1.28 [1.09–1.51]
Lithium Carbonate (Lithium)					
Lithium	1	263	62.5	55.8	1.12 [0.92–1.37]*
All Treatments					
Overall	13	6044	55.3	41.4	1.34 [1.17–1.53]

Data derived from random-effects meta-analysis; [*] not significant. Adapted from Baldessarini et al. Mol Psychiatry 2019; 24(2):198–217. Note the effects of high placebo responder rates.

Meta-analyses: Long-Term Antidepressant Trials in BPD

[Ghaemi et al. Acta Psychiatr Scand 2008;118:347–356]



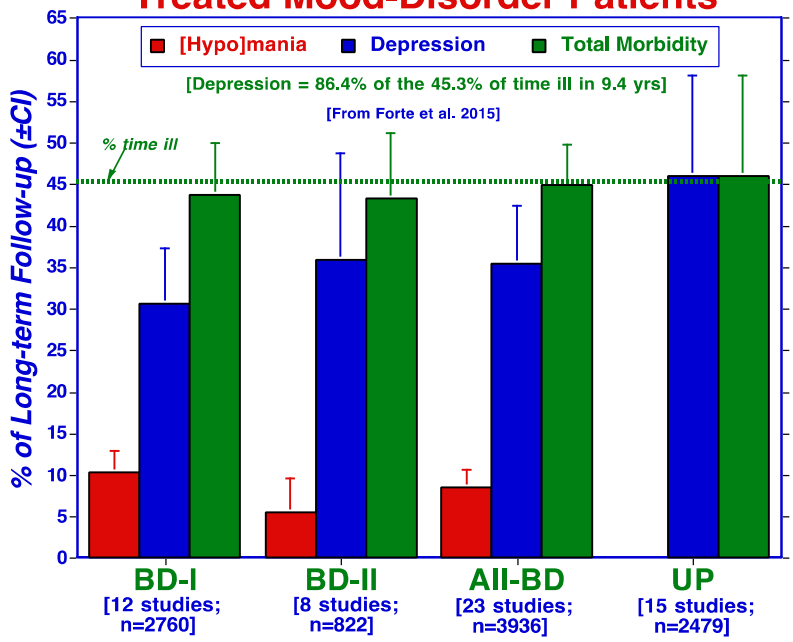


Intravenous ±-ketamine vs. acute treatment-resistant bipolar depression

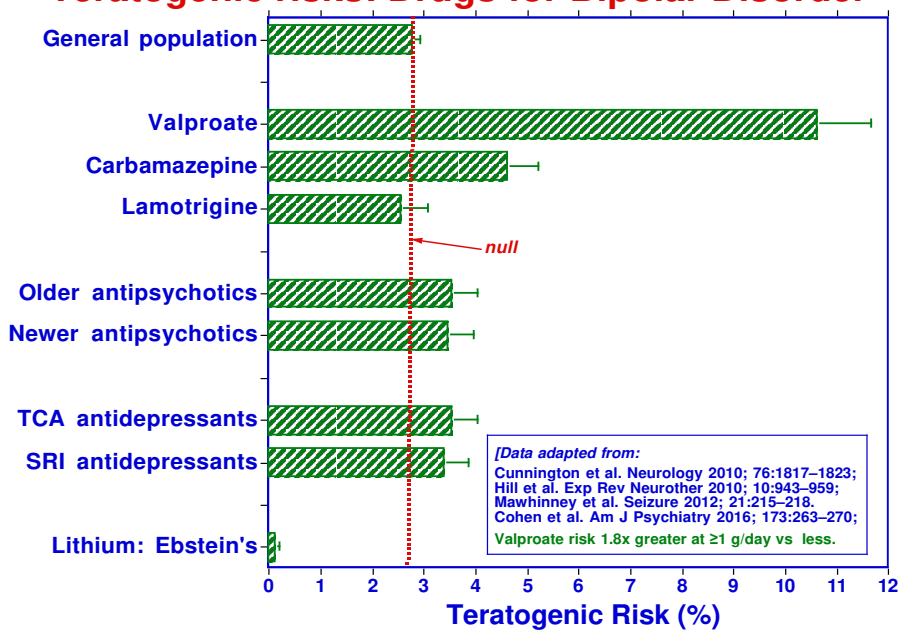
Outcome	% Change or Response [95%CI]
Improved depression (%)	
Overall (n=66)	31.7 [29.6–33.8]
BD1 (n=28	22.4 [19.3–25.8]
BD2 (n=35)	41.6 [37.7–45.6]
Response (%)	
≥50% improvement (response)	34.8 [21.4–50.2]
To ≤5% of initial score (remission)	19.6 [9.36–33.9]
Improved suicidal ideation (%)	48.5 [40.8–56.3]

Adapted from Fancy et al. Bipolar Disorders 2022; on-line 14 Dec, re. 66 BD depressed patients who failed two adequate treatment trials, given 2–4 IV infusions of ±-ketamine (0.50 or 0.75 mg/kg) over 2 weeks, based on depression scale (QIDS-SR$_{16}$) ratings.

Long-Term Morbidity in Clinically Treated Mood-Disorder Patients



Teratogenic risks: Drugs for Bipolar Disorder



Conclusions: Bipolar Disorder Rxs

- Lithium still a powerful option despite problems
- Anticonvulsants & antipsychotics successfully marketed for long-term use based on limited data
- All antipsychotics are useful for acute mania & probably for recurrent mania (lurasidone not tested)
- Antidepressants (& stimulants in children): far-overused & not well tolerated with BD
- Studies of Rx for BD-II disorder are limited
- Psychotherapy & rehabilitation efforts are emerging
- Despite modern poly-Rx, BD patients remain ill 40%–50% of follow-up (75% depressed-dysphoric), with increased disability, comorbidity, & death
- Poor integration: psychiatric & substance-abuse treatment
- BD-depression remains a major unsolved challenge, esp. for long-term prevention