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Long-Term Treatment in Bipolar Disorder: Fall 2025 Update

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Disclosures

"My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:"

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Genomind – Scientific Advisor
Circular Genomics – Scientific Advisor
Alkermes – Scientific Advisor

JAMA+ AI – Editor in Chief
JAMA Network Open – AI Editor

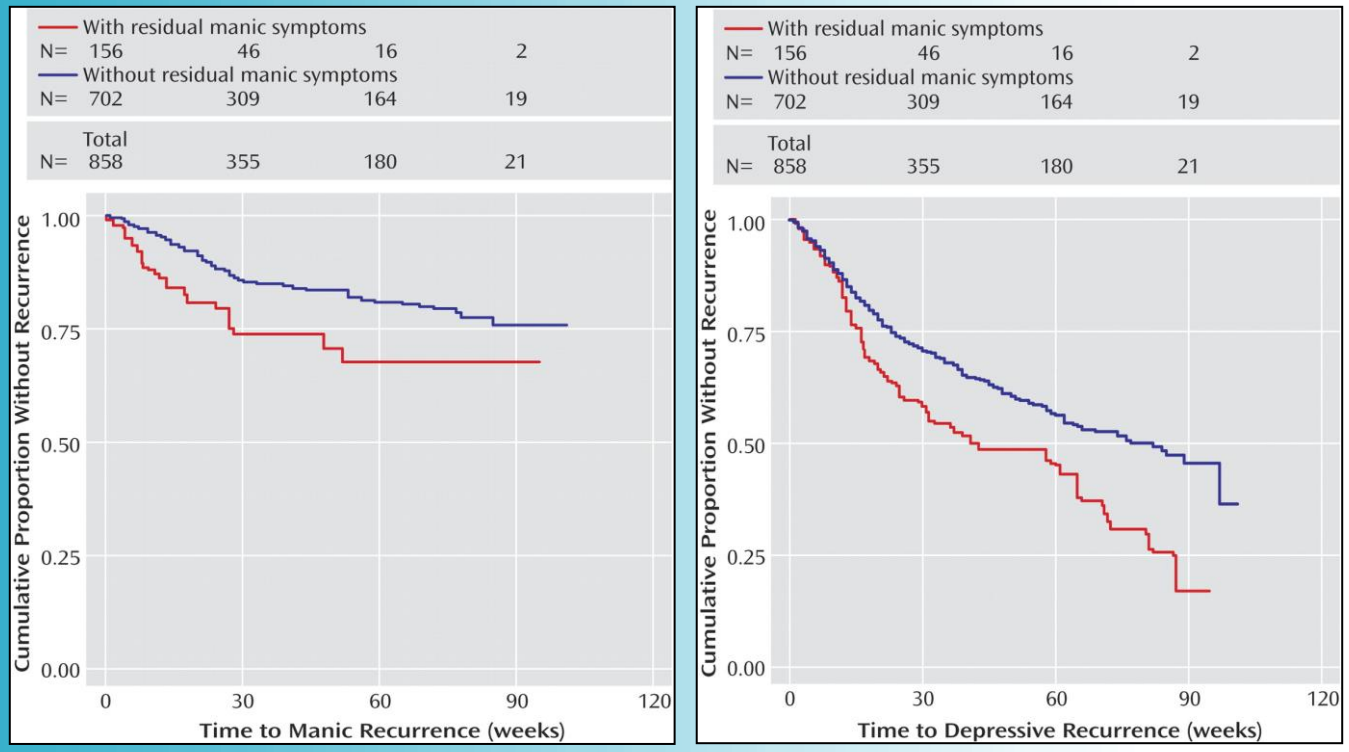
Overview

- Guideline-based care
- Using lithium
- Role of antidepressants
- Subtypes and treatment resistance
- Optimizing care
  - Psychosocial interventions
  - Apps
  - Managing residual symptoms and side effects
- Practicing stratified medicine

About Half of Patients with Bipolar Recur Within 2 Years

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(Left panel = mania; right panel = depression)



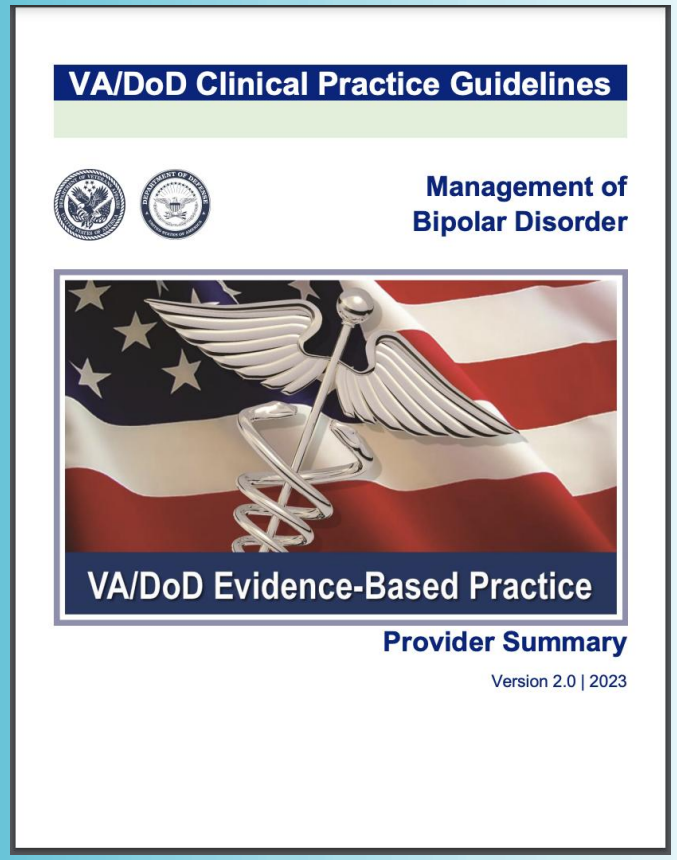
Perlis et al. *Am J Psychiatry.* 2006;163:217-224.

General Approach to Preventing Recurrence

- Choose med(s) on the basis of efficacy data for pole you are trying to treat/prevent, maximizing tolerability
- Add psychotherapy

Comprehensive Review of Evidence – VA 2023

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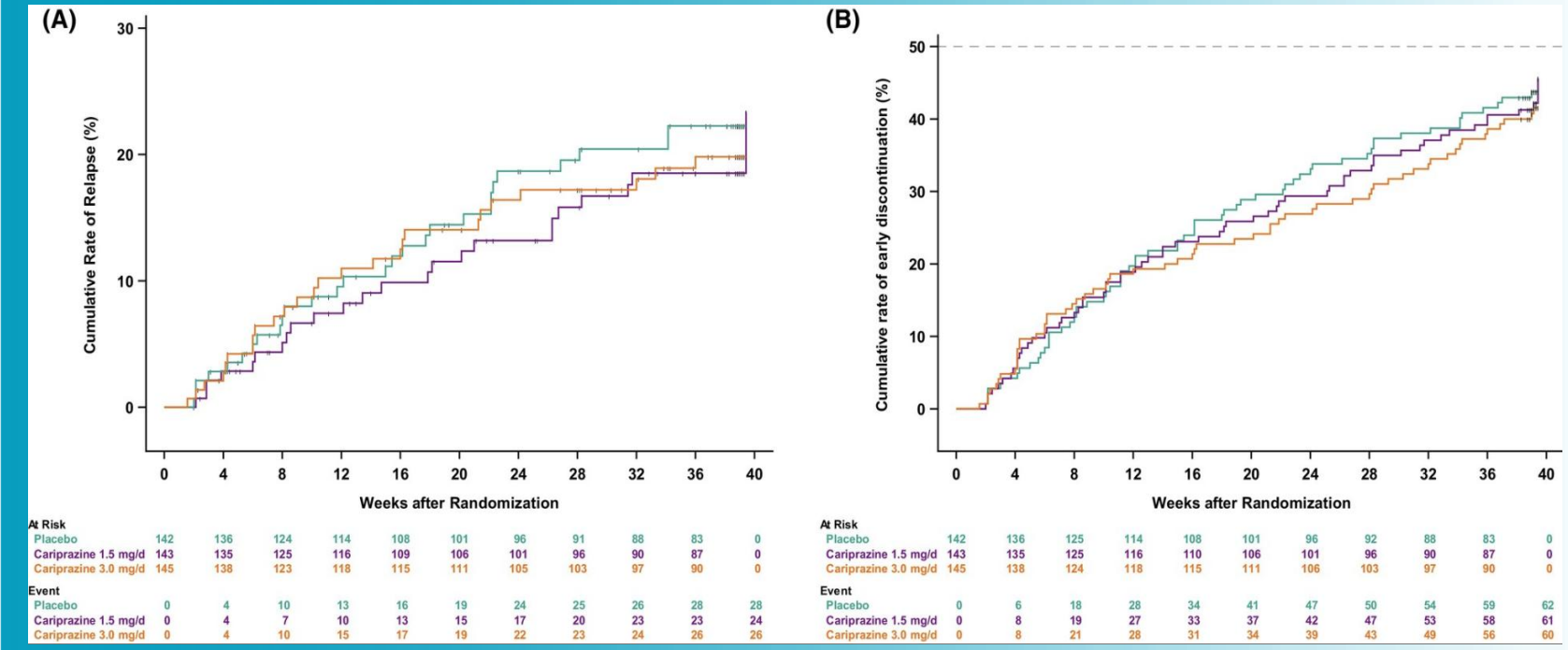
https://www.healthquality.va.gov/guidelines/MH/bd/VA-DoD-CPG-BD-Provider-SummaryFinal508.pdf

Medication	Effective for Bipolar Disorder Phase/Indication[b]			
	Acute Treatment of Mania	Prevention of Mania	Acute Treatment of Bipolar Depression	Prevention of Bipolar Depression
Quetiapine	x	x	x	x
Olanzapine	x	x	x	x
Lithium	x	x		x
Cariprazine	x		x	
Paliperidone	x	x		
Risperidone	x	x		
Aripiprazole	x			
Asenapine	x			
Carbamazepine	x			
Haloperidol	x			
Valproate	x			
Ziprasidone	x			
Lumateperone			x	
Lurasidone			x	
Lamotrigine				x

https://www.healthquality.va.gov/guidelines/MH/bd/VA-DoD-CPG-BD-Provider-SummaryFinal508.pdf

Cariprazine as a maintenance therapy in the prevention of mood episodes in adults with bipolar I disorder

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Rates of relapse in the cariprazine 1.5 mg/day, cariprazine 3.0 mg/day, and placebo groups were 16.8%, 17.9%, and 19.7%, respectively

N = 436 patients with BD (type I) with acute manic or depressive episodes (1.5mg cariprazine, n=144; 3.0mg cariprazine, n= 147; placebo, n=145)

Results: Cariprazine was not superior to placebo in the prevention of relapses in this study. Relapse rates were unusually low in the placebo group. Cariprazine was well-tolerated.

McIntyre et al. *Bipolar Disord. April 2024*

VA Guidelines: Preventing Mania

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Prevention of Recurrence of Mania	18.	We recommend lithium or quetiapine for the prevention of recurrence of mania.	Strong for
	19.	If lithium or quetiapine is not selected based on patient preference and characteristics, we suggest oral olanzapine, oral paliperidone, or risperidone long-acting injectable for the prevention of recurrence of mania.	Weak for
	20.	There is insufficient evidence to recommend for or against other first-generation antipsychotics, second-generation antipsychotics, and anticonvulsants (including valproate) for the prevention of recurrence of mania. (See Recommendations 18, 19, and 30).	Neither for nor against
	21.	We suggest against lamotrigine as monotherapy for the prevention of recurrence of mania.	Weak against
	22.	We suggest aripiprazole, olanzapine, quetiapine, or ziprasidone in combination with lithium or valproate for the prevention of recurrence of mania.	Weak for

https://www.healthquality.va.gov/guidelines/MH/bd/VA-DoD-CPG-BD-Provider-SummaryFinal508.pdf

VA Guidelines: Preventing Depression

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Prevention of Recurrence of Bipolar Depression	23.	We recommend lamotrigine for the prevention of recurrence of bipolar depressive episodes.	Strong for
	24.	We suggest lithium or quetiapine as monotherapy for the prevention of recurrence of bipolar depressive episodes.	Weak for
	25.	If lithium or quetiapine is not selected based on patient preference and characteristics, we suggest olanzapine as monotherapy for the prevention of recurrence of bipolar depressive episodes.	Weak for
	26.	We suggest olanzapine, lurasidone, or quetiapine in combination with lithium or valproate for the prevention of recurrence of bipolar depressive episodes.	Weak for
	27.	There is insufficient evidence to recommend for or against other first-generation antipsychotics, other second-generation antipsychotics, and anticonvulsants (including valproate) as monotherapies for the prevention of recurrence of bipolar depressive episodes.	Neither for nor against
	28.	There is insufficient evidence to recommend for or against other first-generation antipsychotics, other second-generation antipsychotics, and anticonvulsants in combination with a mood stabilizer for the prevention of recurrence of bipolar depressive episodes.	Neither for nor against

https://www.healthquality.va.gov/guidelines/MH/bd/VA-DoD-CPG-BD-Provider-SummaryFinal508.pdf

Other Guidelines for Long-Term Treatment Are Similar…

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Level 1 Options for initial treatment:

- Periodic evaluation: frequency based on clinical needs
- Continue with effective and well-tolerated treatment
- Lithium* monotherapy
- Quetiapine monotherapy
- Lamotrigine* (evidence strongest for prevention of depression)
- If initially stabilized on divalproex*†, maintain.
- Oral aripiprazole or aripiprazole long-acting injectable, long-acting risperidone monotherapy
- Quetiapine (for recurrence prevention) or ziprasidone (for relapse prevention) adjunctive to (lithium* or divalproex*†)
- Asenapine monotherapy
- Olanzapine/samidorphan monotherapy
- Manual-based psychotherapy (e.g., interpersonal social rhythm therapy, CBT, mindfulness best evidence along with psychoeducation during the maintenance phase)

Florida Guidelines 2023. floridabhcenter.org

A Different Perspective on Longer-Term Treatment: Focus on Tolerability

- 32 mania studies, 16 depression, 13 maintenance
- 3 outcomes:
  - discontinuation due to adverse effects
  - 7%+ weight gain
  - somnolence

Bai. *J Clin Psychopharm.* 2020.

Tolerability Is Poor for Atypical Antipsychotics in Depression…

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TABLE 5. Ranking of the Risk for DAEs, 7% or More WG, and Self-reported Somnolence Based on the Number Needed to Harm From Pooled Analyses of Randomized, Double-Blind, Placebo-Controlled Trials in the Acute Treatment of Bipolar Depression

	DAEs		≥7% WG		Self-reported Somnolence	
Ranking	Medications	NNH Mean (95% CI)	Medications	NNH Mean (95% CI)	Medications	NNH Mean (95% CI)
1	**QTP-IR 600 mg/d**	**11 (8, 18)**	**Olanzapine**	**5 (4, 6)**	**QTP-XR 300 mg/d**	**3 (3, 4)**
2	**Aripiprazole**	**14 (9, 36)**	**OFC**	**5 (3, 8)**	**QTP-IR 300 mg/d**	**6 (5, 8)**
3	**QTP-XR 300 mg/d**	**17 (11, 46)**	**QTP-IR 600 mg/d**	**15 (11, 25)**	**QTP-IR 600 mg/d**	**7 (5, 9)**
4	Ziprasidone	23 (12, ∞, −1488)	**QTP-XR 300 mg/d**	**17 (10, 39)**	**Olanzapine**	**8 (6, 12)**
5	**QTP-IR 300 mg/d**	**25 (15, 91)**	**QTP-IR 300 mg/d**	**27 (17, 73)**	**Ziprasidone**	**8 (6, 12)**
6	**Lamotrigine**	**27 (14, 514)**	Lurasidone	55 (24, ∞, −89)	**OFC**	**12 (5, 326)**
7	**Olanzapine**	**32 (17, 578)**	Aripiprazole	69 (22, ∞, −67)	Lithium	20 (9, ∞, −94)
8	Cariprazine	87 (20, ∞, −28)	Ziprasidone	76 (30, ∞, −124)	Aripiprazole	29 (14, ∞, −6789)
9	Lithium	181 (13, ∞, −16)	Cariprazine	88 (23, ∞, −28)	Lamotrigine	57 (19, ∞, −52)
10	Lurasidone	−495 (25, ∞, −19)	Lithium	−112 (26, ∞, −17)	Cariprazine	61 (20, ∞, −30)
11	OFC	−37 (30, ∞, −17)			Lurasidone	79 (20, ∞, −30)

Note: Significant difference of ARI and NNH between active treatment and its respective placebo was shown in bold.
Abbreviation: IR, immediate release; OFC, olanzapine fluoxetine combination; QTP, quetiapine; XR, extended release.

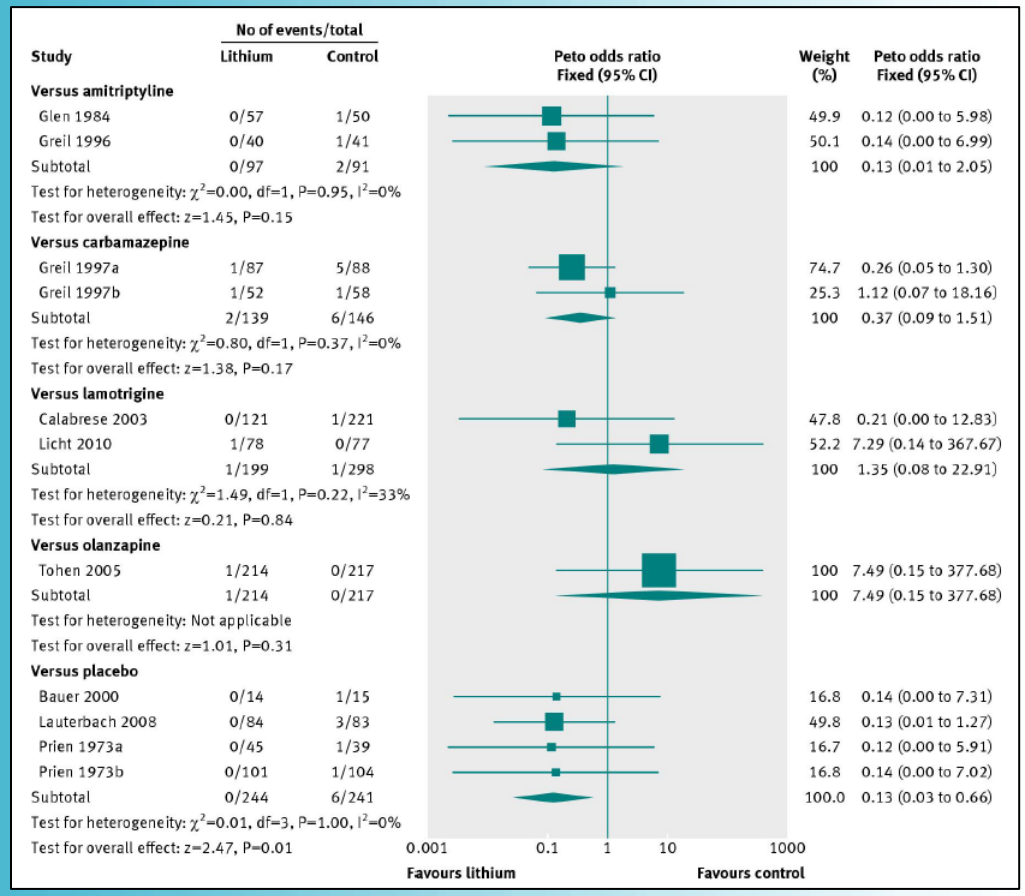
Bai. *J Clin Psychopharm.* 2020.

Begin with Lithium Unless There's a Good Reason Not to

- "In general**, lithium is the gold standard for maintenance treatment**…"
  - Prevents mania>depression
  - Anti-suicide benefit (?)

CANMAT. *Bipolar Disorders.* 2018.

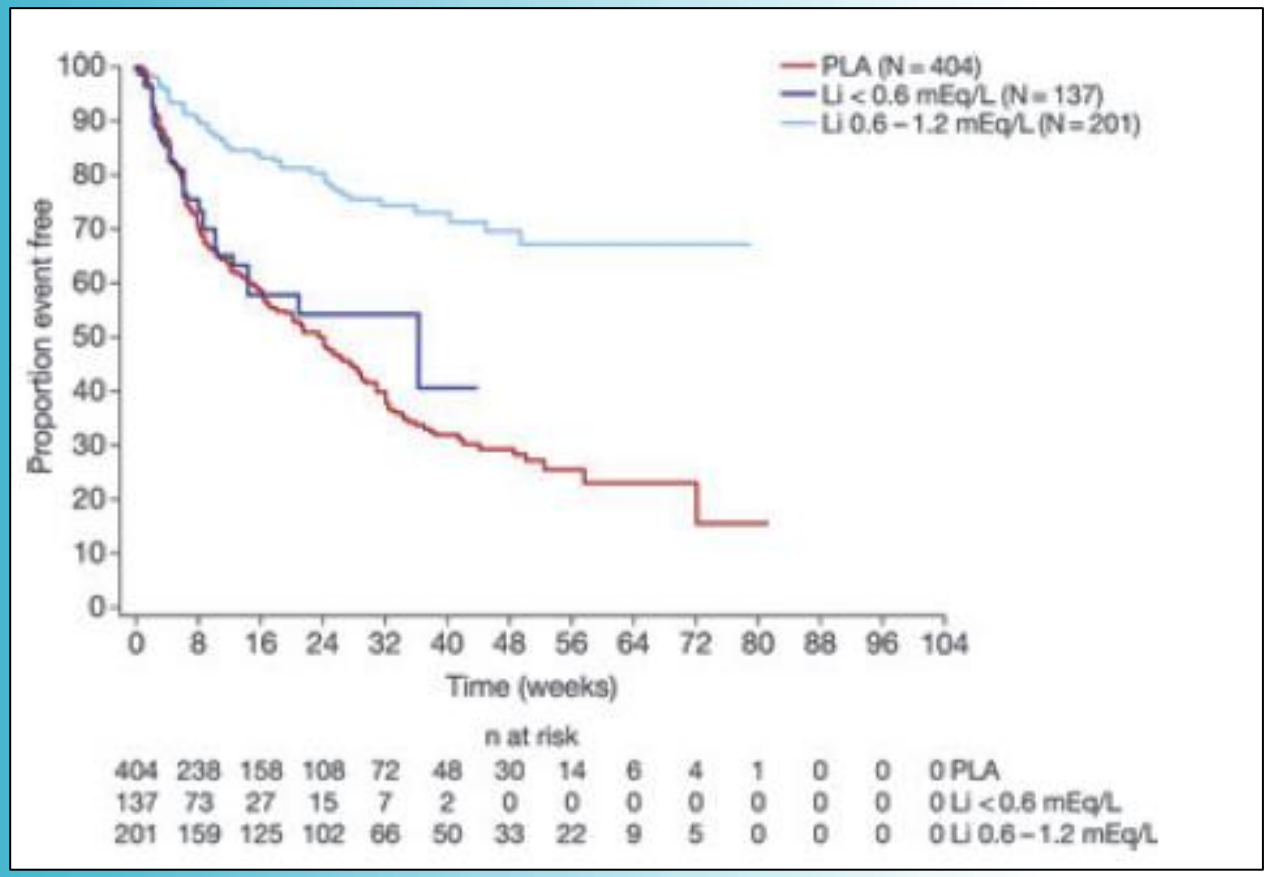
Lithium Reduces Suicide Attempt Risk by >60%



Cipriani. *BMJ.* 2013.

Aim for Li level of 0.6+

Post Hoc Analysis of SPaRCle Trial – Time to Recur



Nolen. *Bipolar Disord*. 2013.

Minimizing Risk for Renal Insufficiency on Lithium

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- Case-control study of 1,445 lithium-treated adults with GFR<60, and 4,306 lithium-treated adults with normal GFR
- **Dosing and concomitant treatments may influence lithium risk**
  - Decrease risk:
    - Once-daily dosing (but not extended release…)
  - Increase risk:
    - Lithium levels exceeding 0.6 mEq/L (risk increases as level increases)
    - Concomitant first-generation antipsychotic?

Castro. *Neuropsychopharmacology.* 2016.

Key Risk Factors for Renal Insufficiency: Age, Psychosis, Hypertension, Smoking

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Table 2 Multiple Logistic Regression Model of Baseline Clinical and Demographic Features Associated with Renal Failure ($N = 3850$)

	Univariate, odds ratio	Adjusted			
		Odds ratio	*p*-value	[95% Conf. interval]	
Sex, male	0.68	0.57	<0.001	0.48	0.67
Race/ethnicity, white	1.63	1.53	<0.001	1.21	1.94
Age (per decade)	1.80	1.55	<0.001	1.45	1.65
Charlson index (Log 10)	2.68	1.46	<0.001	1.31	1.64
Insurance, private	1.01	1.29	0.006	1.08	1.53
Lifetime hypertension	4.74	2.62	<0.001	2.18	3.16
Lifetime smoking	1.79	1.27	0.01	1.06	1.53
Lifetime diabetes mellitus	3.16	1.17	0.166	0.94	1.46
Any schizophrenia/schizoaffective	1.72	1.63	<0.001	1.31	2.03

Specificity 68% with sensitivity=80%; AUC=0.81

Castro. *Neuropsychopharmacology.* 2016.

Summary of Lithium Principles

- *Every patient deserves a lithium trial*
  - Even if rapid cycling or mixed episodes
- Aim for lithium levels as low as feasible:
  - ≤ 0.6 if possible, 0.6-0.8 if not
- Dose *once daily at bedtime* if possible

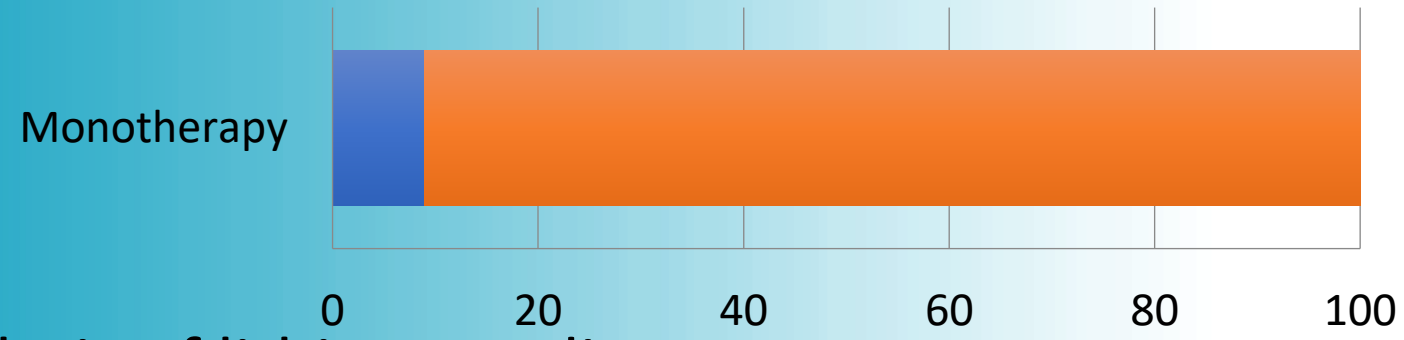
Extended vs. Immediate Release

- Can still dose immediate release once daily
- No need for extended release unless gastric discomfort/nausea with immediate release
- *Tremor may be improved by switch to extended release* (Pelacchi. *Brain Behav*. 2022.)
- Amiloride for nephrogenic diabetes insipidus/polyuria (Batlle. *NEJM*. 1985.)

But in the Real World, Few Patients Stay on Lithium Monotherapy

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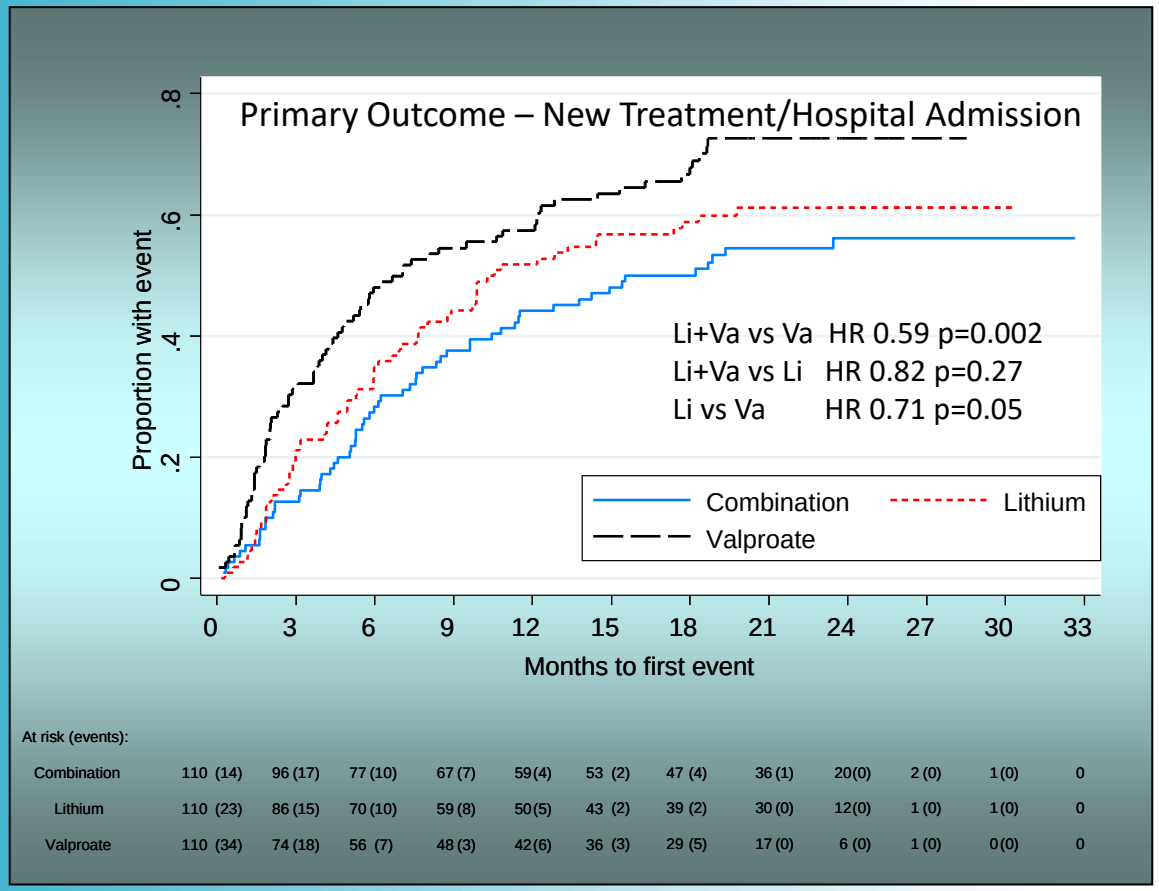
- Danish registry study:
  - 5 years later, only 8.9% still on lithium monotherapy



- Meta-analysis of lithium studies
  - 67% all-cause discontinuation rate

Kessel. *Int Clin Psychopharm.* 2011.
Kishi. *J Clin Psychopharm.* 2020.

Lithium, Alone or with Valproate, Is Better Than Valproate



BALANCE Investigators. *Lancet.* 2010.

How to Choose Combinations?

- Choose med(s) on the basis of efficacy data for pole you are trying to treat/prevent, maximizing tolerability

VA Guidelines: Combination

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Medication		Effective for Bipolar Disorder Phase/Indication[a]			
Medication 1	Medication 2	Acute Treatment of Mania	Prevention of Mania	Acute Treatment of Bipolar Depression	Prevention of Bipolar Depression
Quetiapine	Lithium or valproate	x	x		x
Olanzapine	Lithium or valproate	x	x		x
Haloperidol	Lithium or valproate	x			
Asenapine	Lithium or valproate	x			
Risperidone	Lithium or valproate	x			
Aripiprazole	Lithium or valproate		x		
Ziprasidone	Lithium or valproate		x		
Lurasidone	Lithium or valproate				x
Lamotrigine	Quetiapine or lithium			x	

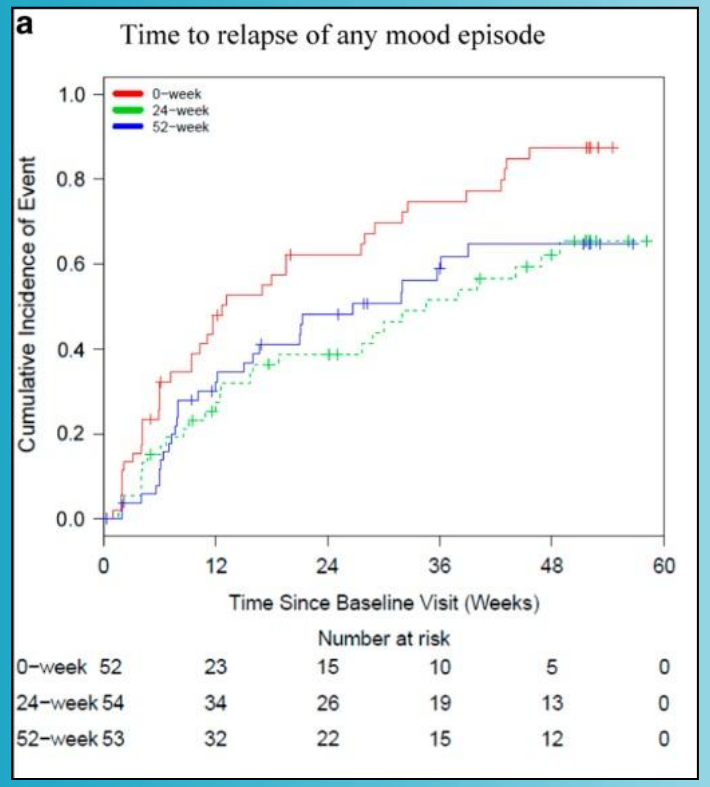
https://www.healthquality.va.gov/guidelines/MH/bd/VA-DoD-CPG-BD-Provider-SummaryFinal508.pdf

When Treatments Are Added Acutely, Beware Early Discontinuation!

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- Note that *nearly all long-term treatment studies in bipolar disorder exaggerate benefit* (particularly with lamotrigine and atypical antipsychotics)!!!
- Because – these studies randomize people stabilized on acute treatment to early discontinuation.

Consider Continuation of Acute Medication: Early Discontinuation of Atypical Antipsychotic = Greater Risk



n=159 bipolar 1 patients on mood stabilizer plus recent addition of olanzapine or risperidone, randomized to 0, 24, or 52 week discontinuation

(n.b.: only olanzapine showed clear benefit beyond 24 weeks!)

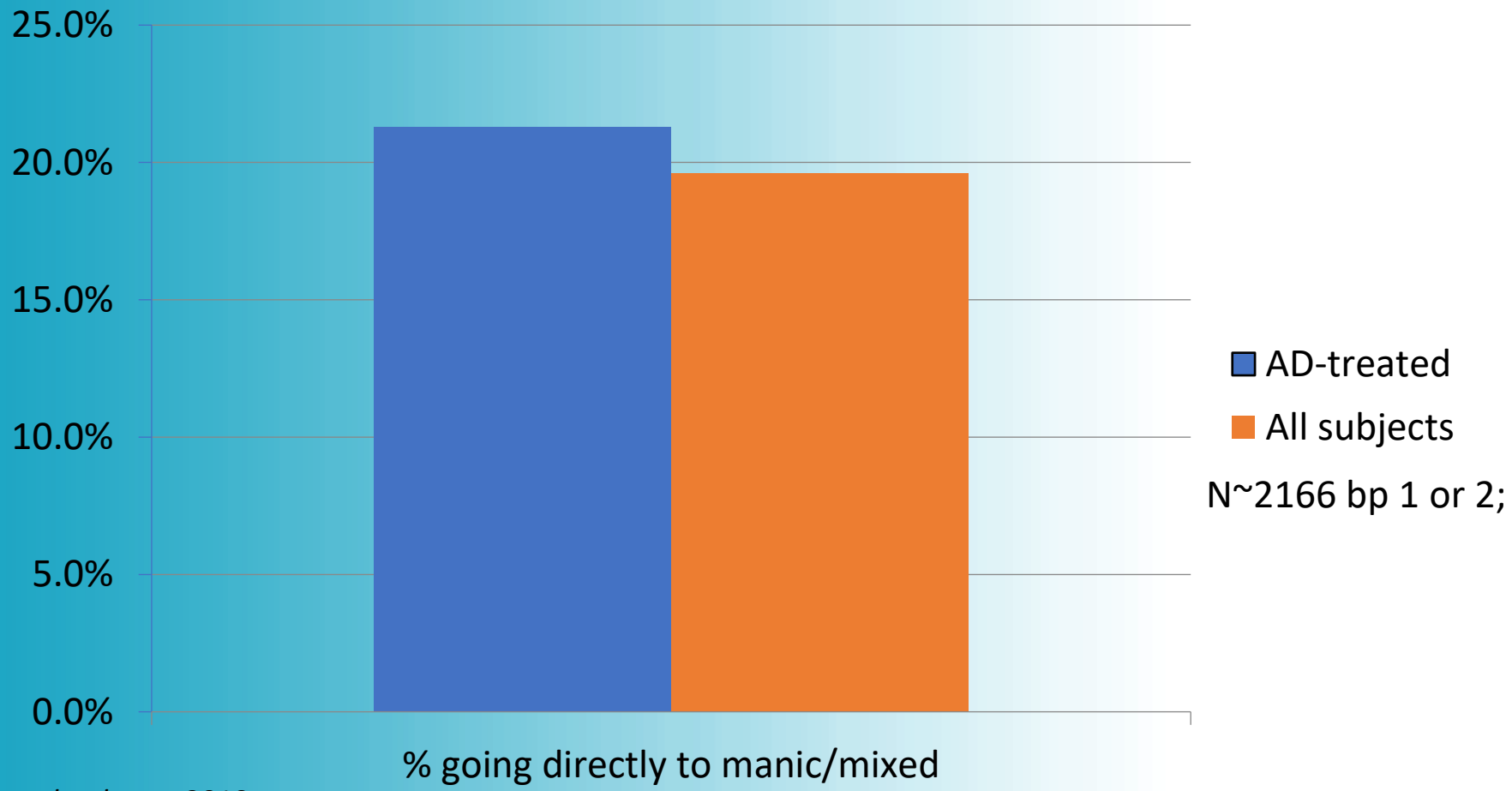
Yatham. 2016.

What About Longer-Term Treatment with Antidepressants?

Risk Associated with Antidepressants in Long-Term Treatment

- Acute data *consistently* shows no increase in risk vs placebo (when combined with AAP or mood stabilizer), or in large registry studies (e.g., Viktorin. *AJP*. 2014.)
- Debate: Risk associated with longer-term use
- **BUT:** Key to recognize that depression -> mania transitions are a core part of the illness, *regardless of treatment!*

Transition from Depression to Mania Is Part of the Course of Illness



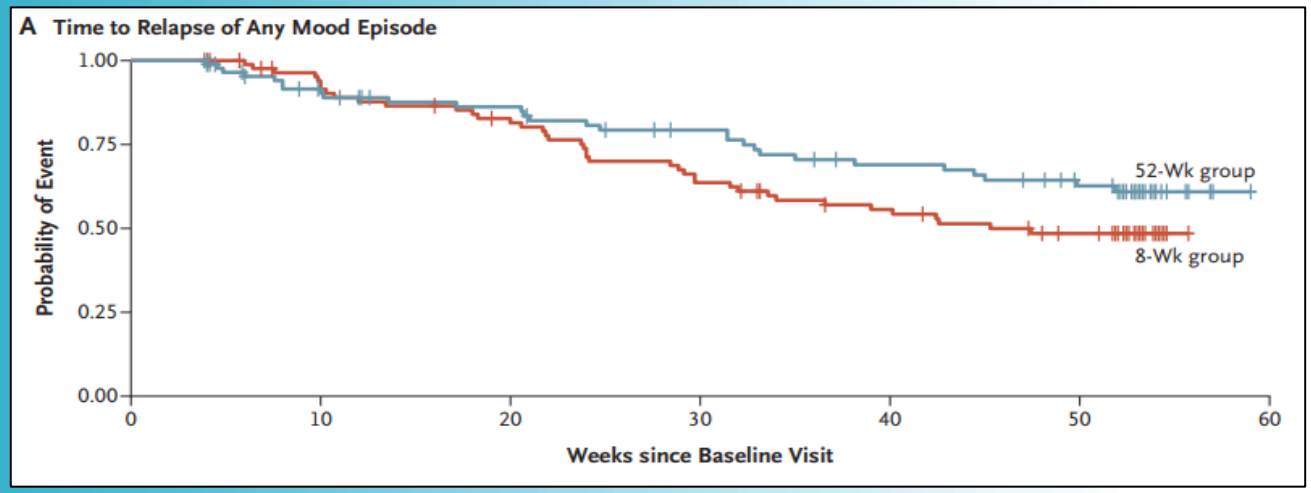
Perlis. *Neuropsychopharm.* 2010.

Risk Factors for Switch to Mania

- 2+ prior depressions
- Rapid cycling, past year
- History of suicide attempt
- Younger age
- Earlier age at onset
- More manic symptoms during depressive episode (subthreshold mixed symptoms)
- Days elevated or irritable, prior year
- Days anxious, prior year

N~2166
Perlis. *Neuropsychopharm.* 2010.
See also: Frye. *AJP*. 2009.
Gorwood. *Psychiatry Res*. 2016.

Adjunctive Antidepressants Ineffective in Preventing Relapse in Bipolar I Disorder Patients Who Are in Remission from a Depressive Episode



Methods:

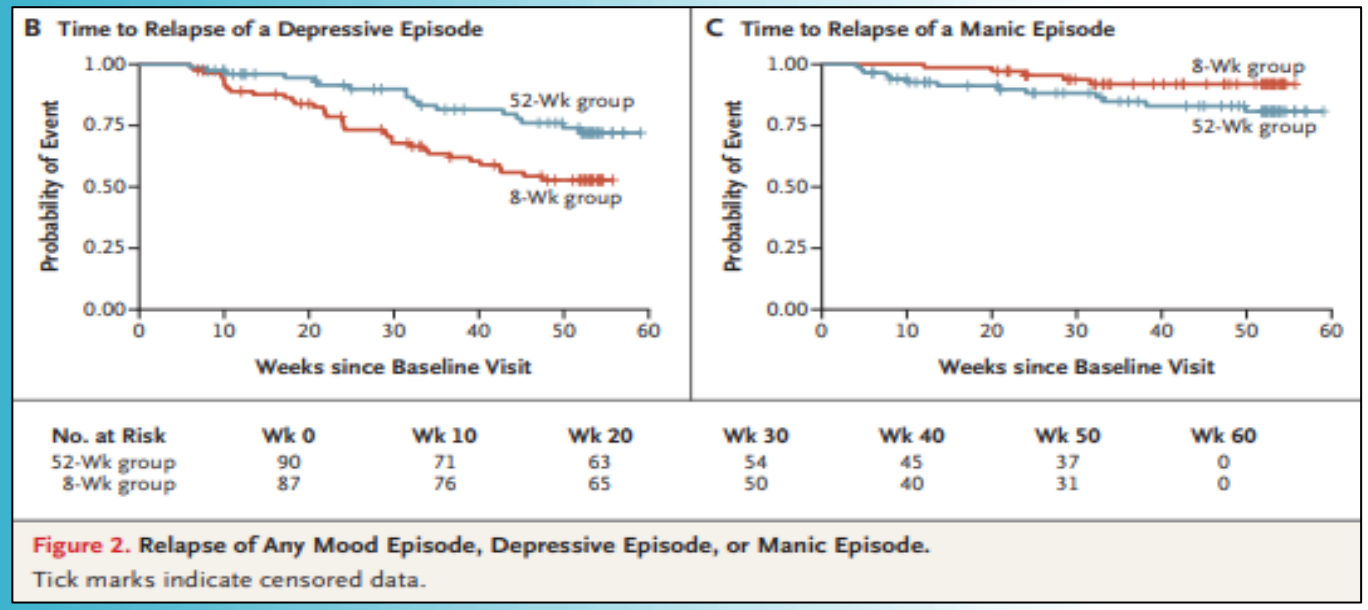
n = 187 patients with bipolar I disorder recently remitted from depressive episode; adjunctive escitalopram or bupropion XL: randomized 1:1 to

– 52 weeks of continued antidepressant, or

– Placebo substitution after 8 weeks

Yatham. *N Engl J Med*. 2023.

But…May Be Some Benefit?



No. at Risk	Wk 0	Wk 10	Wk 20	Wk 30	Wk 40	Wk 50	Wk 60
52-Wk group	90	71	63	54	45	37	0
8-Wk group	87	76	65	50	40	31	0

Figure 2. Relapse of Any Mood Episode, Depressive Episode, or Manic Episode.
Tick marks indicate censored data.

Results:

Continuing adjunctive antidepressant therapy for 52 weeks as compared with discontinuing antidepressants at 8 weeks was not more beneficial with regard to the primary outcome of the occurrence of any mood episode.

Continuing antidepressant therapy for 52 weeks may prolong the time to a depressive episode. However, this result from a prespecified sensitivity analysis was not adjusted for multiplicity and causal inferences can therefore not be drawn.

Yatham. *N Engl J Med*. 2023.

Another Reason to Consider Antidepressants? Anxiety Comorbidity Is Common in Bipolar Disorder…

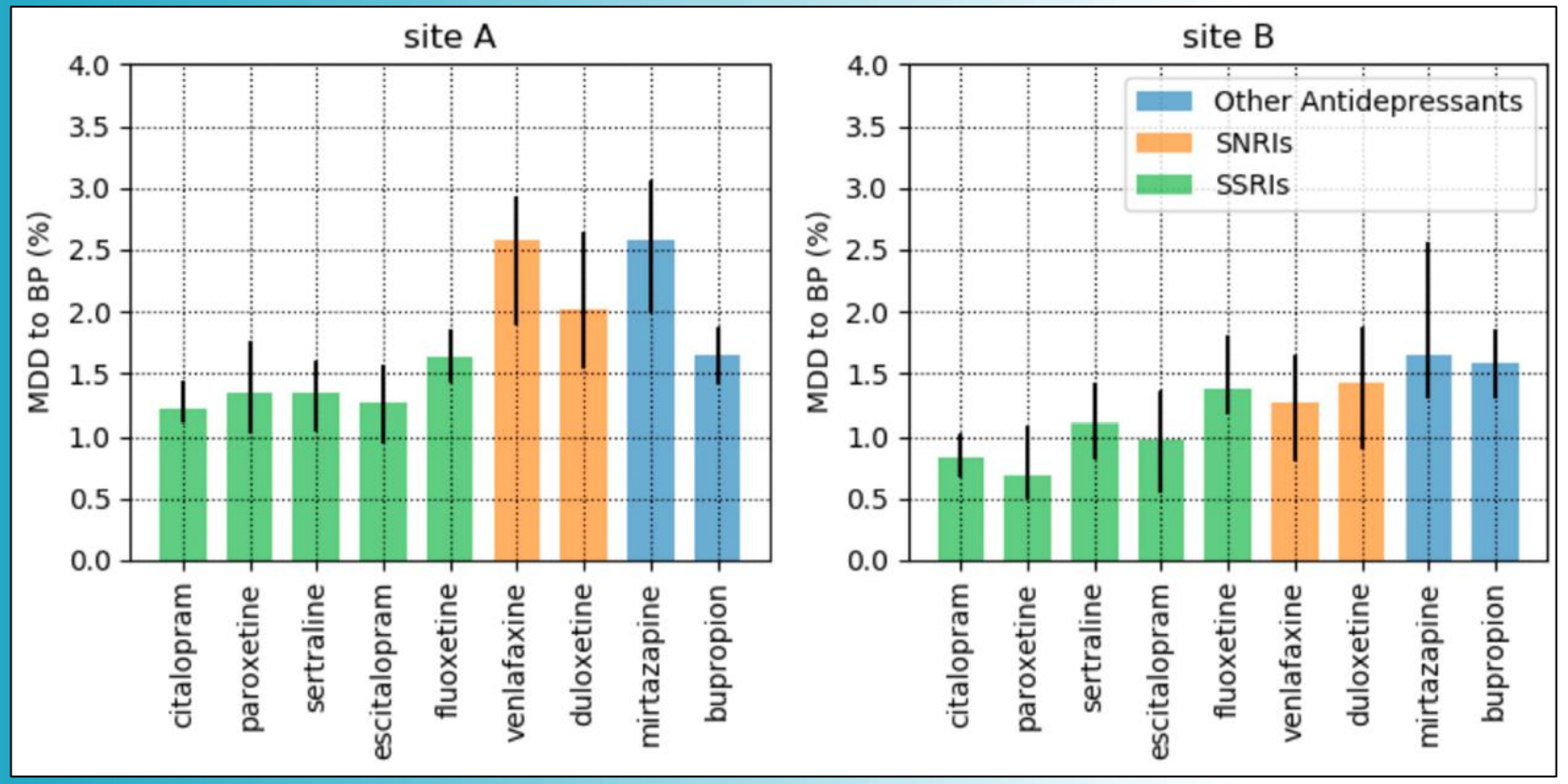
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	Studies (n)	Individuals (n)	Rate (95% CI)
Any anxiety disorder	40	14 914	0·453 (0·400–0·506)
Panic disorder	40	14 960	0·193 (0·153–0·234)
Agoraphobia	17	9066	0·117 (0·078–0·156)
Social phobia	31	13 329	0·199 (0·150–0·248)
Generalised anxiety disorder	31	11 196	0·204 (0·147–0·262)
Specific phobia	24	5093	0·108 (0·080–0·136)
Obsessive compulsive disorder	35	11 619	0·106 (0·086–0·126)
Post-traumatic stress disorder	22	8371	0·173 (0·128–0·217)

NOTE: Current symptoms are associated with greater recurrence risk (Perlis. *AJP*. 2006).
Use of benzodiazepines may be associated with greater recurrence risk (Perlis. *JCP*. 2010).

Pavlova. *Lancet Psych*. 2015.

Rates of Transition from MDD to BPD, by Antidepressant



Pradier. *Neuropsychopharmacology.* 2021.

Even the Experts Are Confused

- "Because of limited data, the task force could not make broad statements endorsing antidepressant use but…
- *Individual bipolar patients may benefit from antidepressants.*
- Serotonin reuptake inhibitors and bupropion may have lower rates of manic switch than tricyclic and tetracyclic antidepressants and norepinephrine-serotonin reuptake inhibitors
- The frequency and severity of antidepressant-associated mood elevations appear to be greater in bipolar I than bipolar II disorder.
- In bipolar I patients antidepressants should be prescribed only as an adjunct to mood-stabilizing medications."

ISBD Task Force. *AJP*. 2013.

We Know Remarkably Little About Bipolar Subtypes

- Treatment resistance
- Rapid cycling
- Bipolar 2

Treatment Resistance

- No consistent/standardized definition exists!

Role of ECT in Mood Disorder Maintenance Remains Unclear

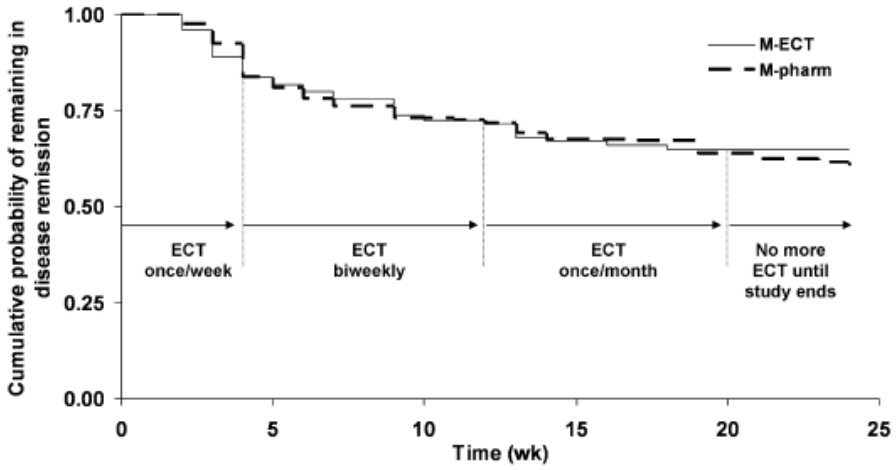


FIGURE 1. Proportion of patients remaining in remission during the maintenance phase in the CORE trial. Reprinted with permission from Kellner et al.[15] Log-rank test comparing distributions of time to relapse for M-ECT versus M-pharm: $\chi^2 = 0.30$; $P = 0.59$.

TABLE 4. CANMAT Recommendations for ECT in Bipolar Disorders

Diagnosis	Recommendations for ECT
Acute mania	Second line
Acute bipolar I depression	Third line
Maintenance therapy of bipolar disorder	Third line (adjunctively)
Maintenance therapy of bipolar II disorder	Third line

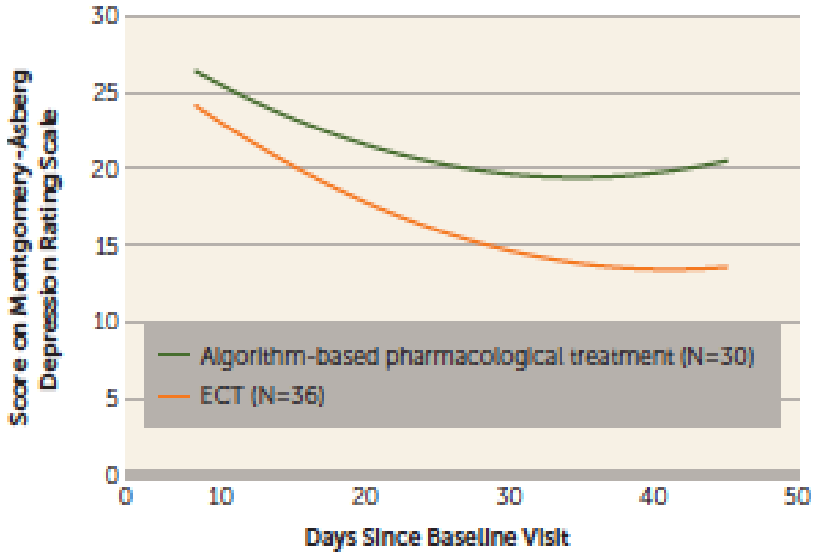
Adapted from Yatham et al.[26]

ECT side effects resulting in discontinuation: headache and memory loss. Pharmacologic side effects resulting in discontinuation: dry mouth, tremor, drowsiness, fatigue, constipation.

Kellner. *AGP*. 2006.

ECT Superior to Algorithm-Based Meds in Treatment-Resistant BP Depression

FIGURE 2. Change in Depression Severity in Patients With Treatment-Resistant Bipolar Depression Randomly Assigned to ECT or Algorithm-Based Pharmacological Therapy[a]



[a] Linear mixed-effects analysis showed that the mean score at 6 weeks was 6.6 points lower in the ECT group (SE=2.05, 95% CI=2.5–10.6, p=0.002).

(n=66 in ITT analysis; blinded raters only) - > 50% bipolar II; Minimal difference in cognitive measures between groups

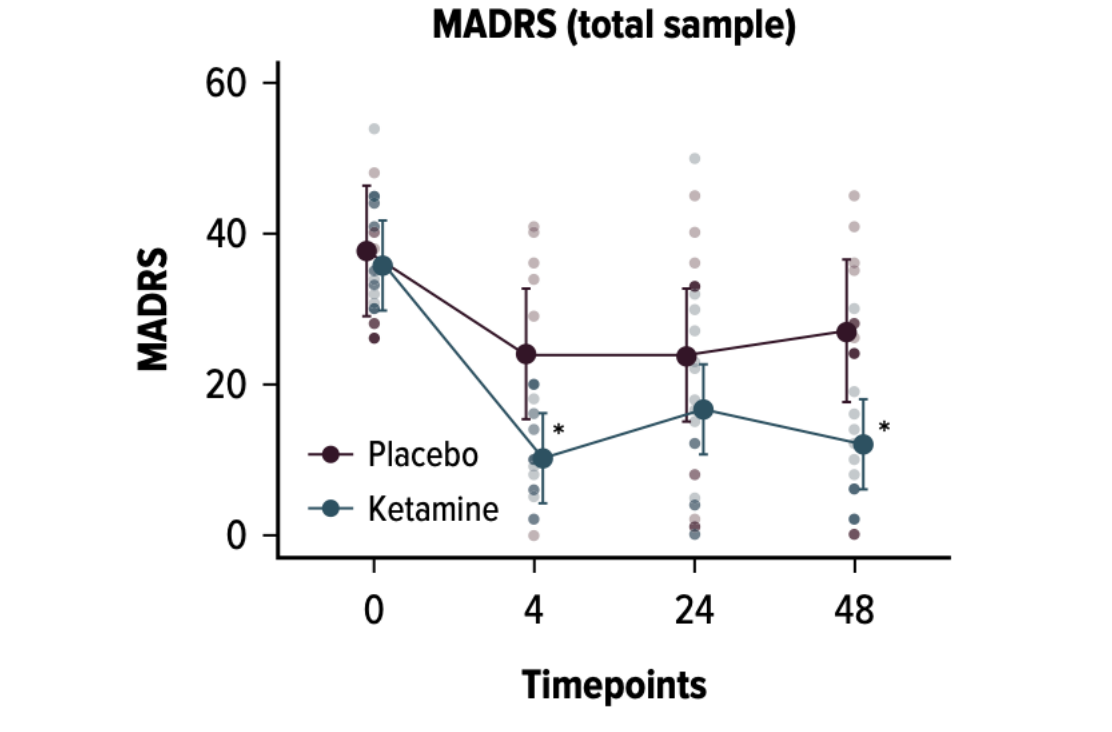
Kessler. *JCP*. 2014.
Schoeyen. *AJP*. 2015.

TMS, Ketamine?

- Some evidence of efficacy
- Unclear benefit in *treatment-resistant* BPD
- Main limitation is cost, need for maintenance

Intranasal Ketamine in Severe Unipolar and Bipolar Depression

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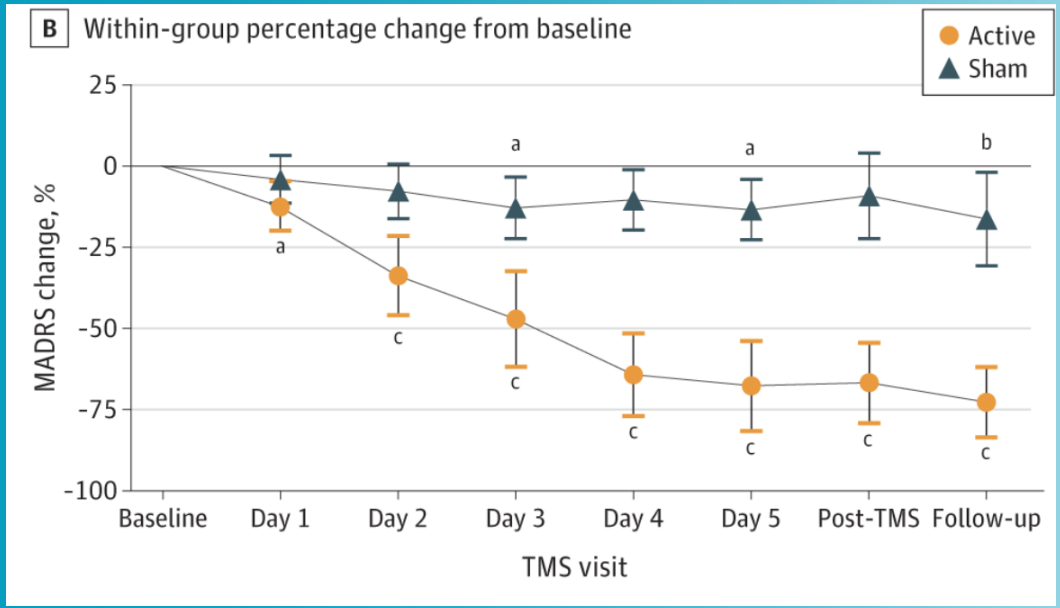
MADRS mixed-model regression effects plot

N = 29 patients with a depressive episode (bipolar or unipolar) with current SI and past attempt. (placebo, n=11; active treatment, n=18)

Results: Intranasal ketamine induced rapid antidepressant effects compared to placebo, but **did not significantly alter SI scores.**

Jones et al. *J Clin Psych.* June 2024.

Accelerated intermittent theta-burst stimulation



24 patients with treatment-resistant bipolar disorder were randomized 1:1 to active or sham conditions.

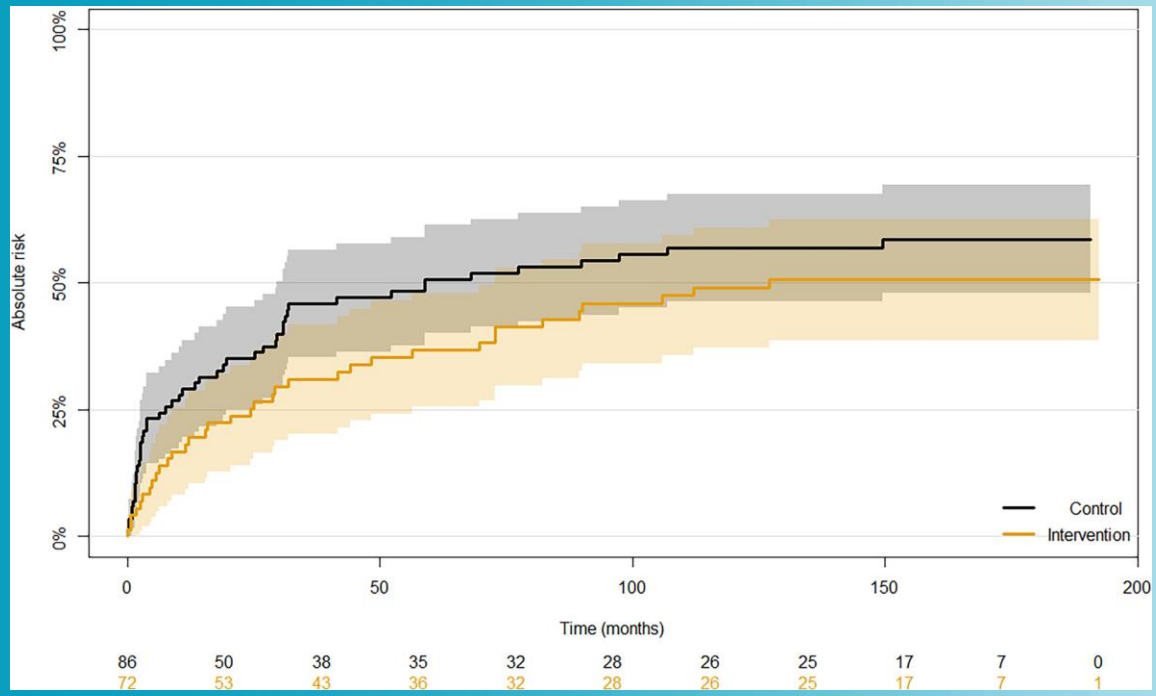
Compared to baseline, MADRS scores were significantly lower in the active group than the sham after treatment

Sheline, JAMA Psychiatry, July 2024
See also: Appelbaum, JAMA Psychiatry, Feb 2025

Consider Clozapine or Injectables Where Adherence Is Poor

- Injectables in the average patient may not be necessary – BUT might show benefit in nonadherent or brittle patients… (Suzuki letter. *NEJM*. 2011.)
- E.g., Paliperidone (Fu JCP 2015); aripiprazole once-monthly (Calabrese. *JCP*. 2017.); risperidone long-acting (Vieta. *Neuropsychopharm.* 2012.)

16 years long-term outcomes after randomization of the participants in the EIA trial

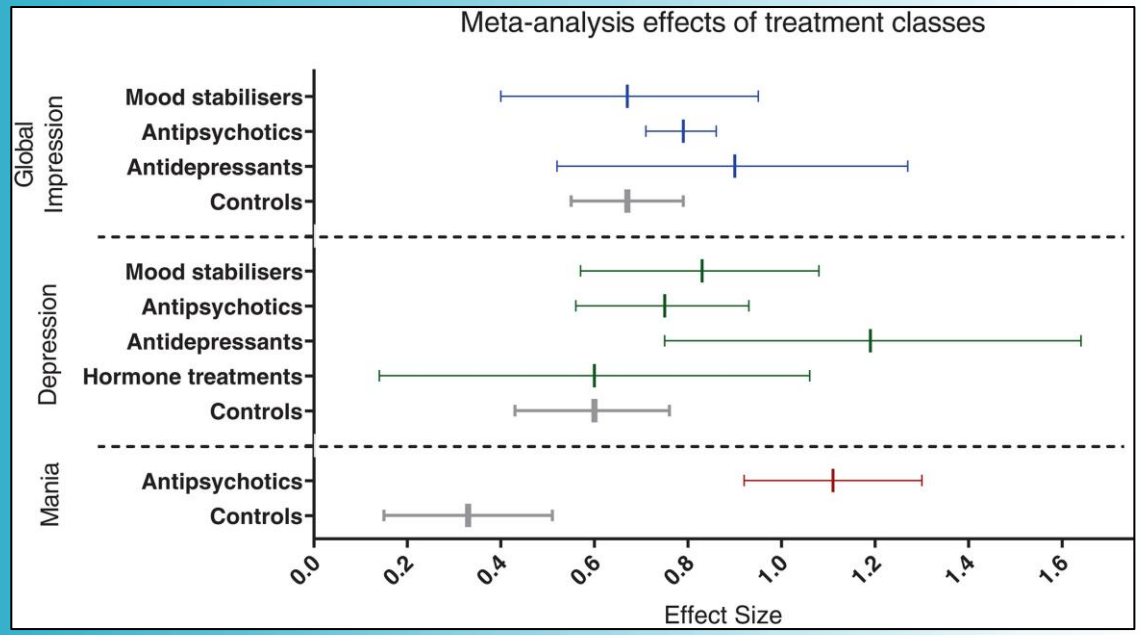


Risk of re-admission in participants in the intervention- and control group

N = All 158 participants of the EIA trial (Trial Registration Number NCT00253071) were followed from time of randomization (2005–2009) to end of study (31 December 2021).

Results: The absolute mean risk of psychiatric readmission was 49.3% in the intervention group and 59.8% in the control group, with no statistically significant difference between the groups. Fewer patients in the intervention group had an event of intentional self-harm or suicide attempt or suicide during follow-up compared with the control group.

Rapid Cycling



- No reason to believe lithium less effective than anticonvulsants (Fountoulakis. *BPD*. 2013.)
- Very small study suggested L-T4 increased until FT4I 4.5-7.5 or TSH<0.1)
  - (n=32; Walshaw. *Bipolar Disorders.* 2018.)

Strawbridge. *Acta*. 2022.
See also: Fountoulakis. *Bipolar Disord.* 2013.

What About Bipolar II?
Far Less RCT Data

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Strength of evidence and treatment recommendations for maintenance treatment of bipolar II disorder

Recommendation	Agent	Evidence level
First-line	Quetiapine	Level 1
	Lithium	Level 2
	Lamotrigine	Level 2
Second-line	Venlafaxine	Level 2
Third-line	Carbamazepine	Level 3
	Divalproex	Level 3
	Escitalopram	Level 3
	Fluoxetine	Level 3
	Other antidepressants	Level 3
	Risperidone[a]	Level 4

Rule of thumb: More focus on acute/maintenance depression treatment.

CANMAT. *Bipolar Disorders*. 2018.

Lack of Consensus Regarding Management of Bipolar 2 Disorder

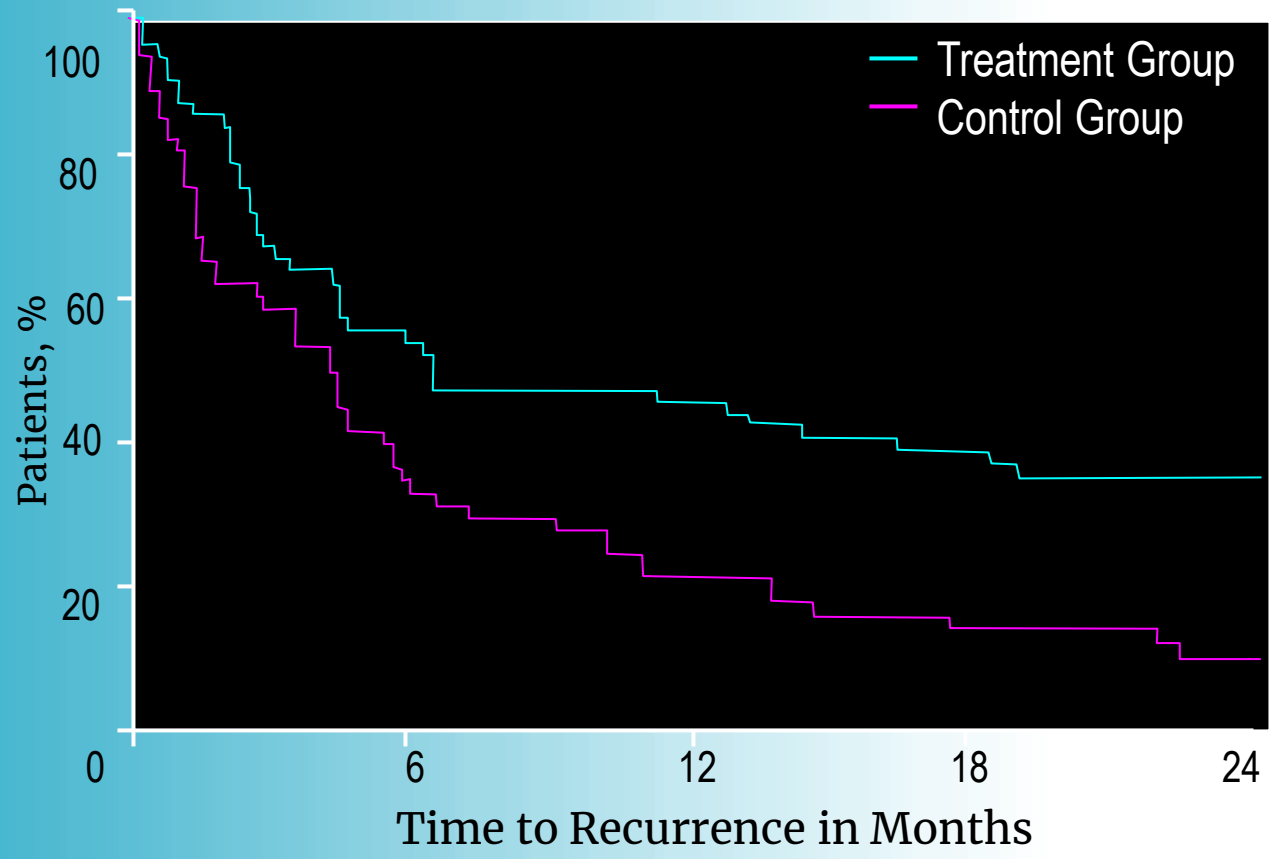
- N=18 expert clinicians
- Asked 14 questions regarding management of aspects of bipolar disorder
- "To all questions, the independently derived recommended strategies demonstrated distinct divergence."

Parker. *Australasian Psychiatry*. 2020.

Optimizing Care

- Psychosocial interventions and apps for prevention of recurrence
- Residual symptoms
  - Cognition
  - Sleep
  - Functioning
- Adverse effects
  - Weight gain

We've Known for 2 Decades That Psychoeducation Groups Reduce Recurrence



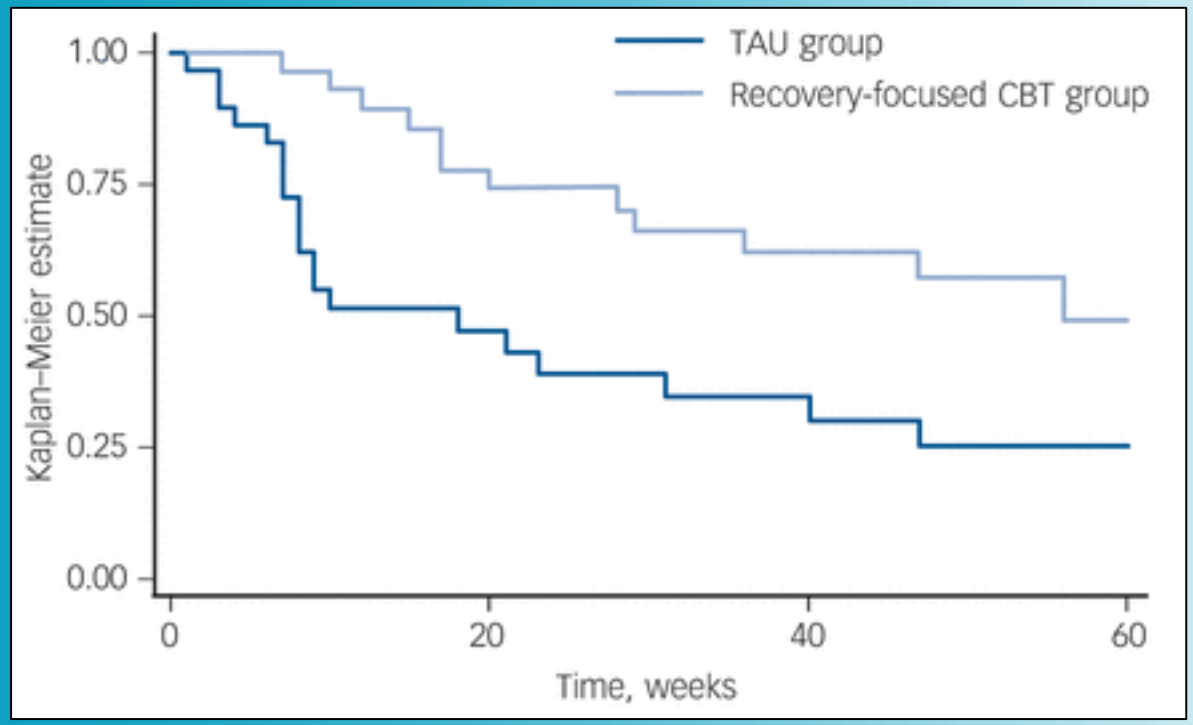
Colom et al. *Arch Gen Psychiatry.* 2003; 60(4):402-407.

VA Guidelines: Psychotherapy

34.	For individuals with bipolar 1 or bipolar 2 disorder who are not acutely manic, we suggest offering psychotherapy as an adjunct to pharmacotherapy, including cognitive behavioral therapy, family or conjoint therapy, interpersonal and social rhythm therapy, and non-brief psychoeducation (not ranked).	Weak for
35.	For individuals with bipolar 1 or bipolar 2 disorder, there is insufficient evidence to recommend for or against any one specific psychotherapy among cognitive behavioral therapy, family or conjoint therapy, interpersonal and social rhythm therapy, and non-brief psychoeducation.	Neither for nor against

https://www.healthquality.va.gov/guidelines/MH/bd/VA-DoD-CPG-BD-Provider-SummaryFinal508.pdf

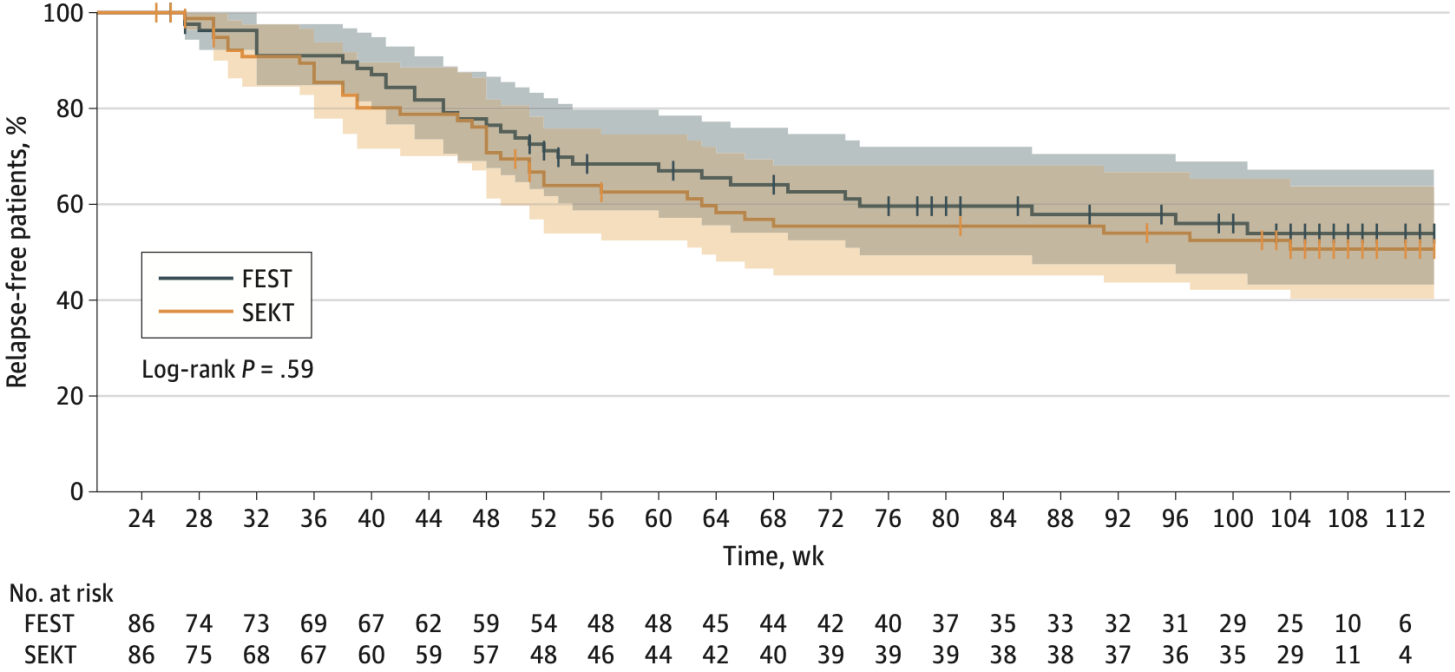
Recovery-Focused CBT in Recent-Onset Bipolar Patients Decreases Recurrence



n=67 single-blind RCT, CBT vs TAU; benefit in depression>mania

Jones. *BJP*. 2015.

Effectiveness of 2 types of group psychotherapy to prevent relapse in patients with euthymic BD



N = 305 patients with euthymic BD (type I or II) were randomized to SEKT (n = 154) or FEST (n = 151)

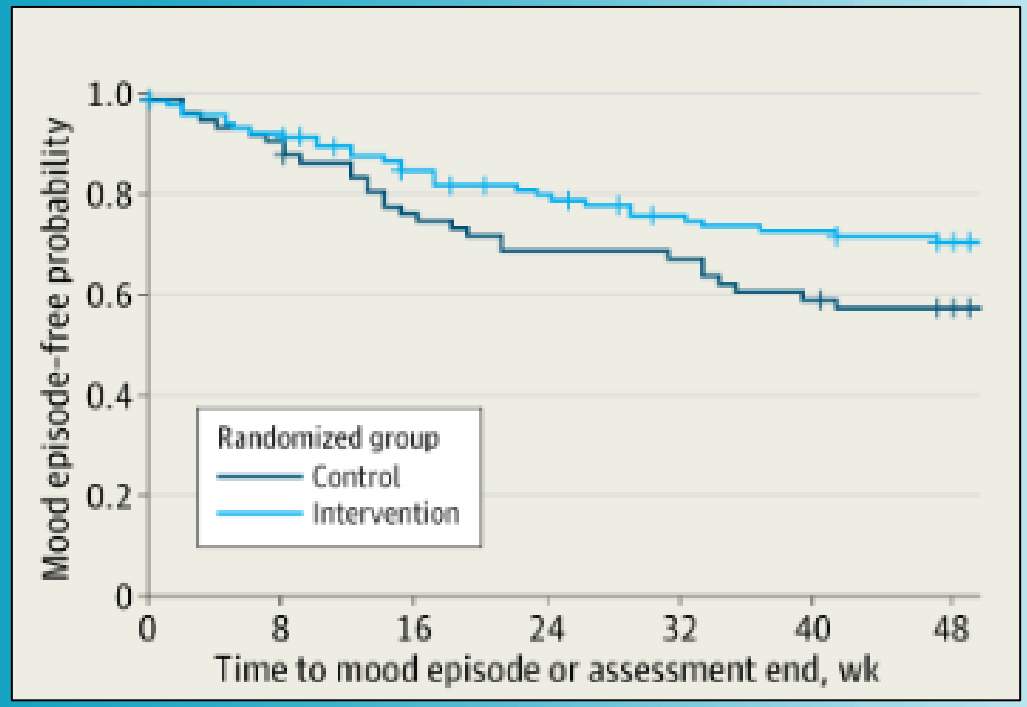
Results: structured, skill-oriented, material-based cognitive behavioral therapy (SEKT) and a supportive, patient-centered, emotion-focused therapy (FEST) were equally effective in preventing relapse of affective episodes when delivered in a new, intensive group format.

Hautzinger. *JAMA Psych*. June 2024

What About Apps? (*Hi-Roller*, Circa 2003)



Smartphone-Based Self-Management Intervention Shows Potential for Low Risk Patients



205 participants were randomized to TAU (n=81) or TAU + smartphone intervention (n=124)

Results: No significant *overall* reduction in relapse risk was observed in experimental group benefit significant only in **low risk individuals** (i.e., fully remitted at entry)

Goulding. *JAMA Psychiatry*. 2023.

Good Reference for Apps

- https://mindapps.org/
  - Implements APA app advisor framework
  - N=136 mood disorder
  - Majority address depression and focus on mood charting

Caveats…

- Beware iatrogenic injury from mood charting/quantified self.
- Goal is patient (and family) awareness of changes over time – but not obsession with minute-to-minute variability.
- Recipe for ultradian/ultrarapid cycling?

Current (Free) Favorite – but iPhone Only…

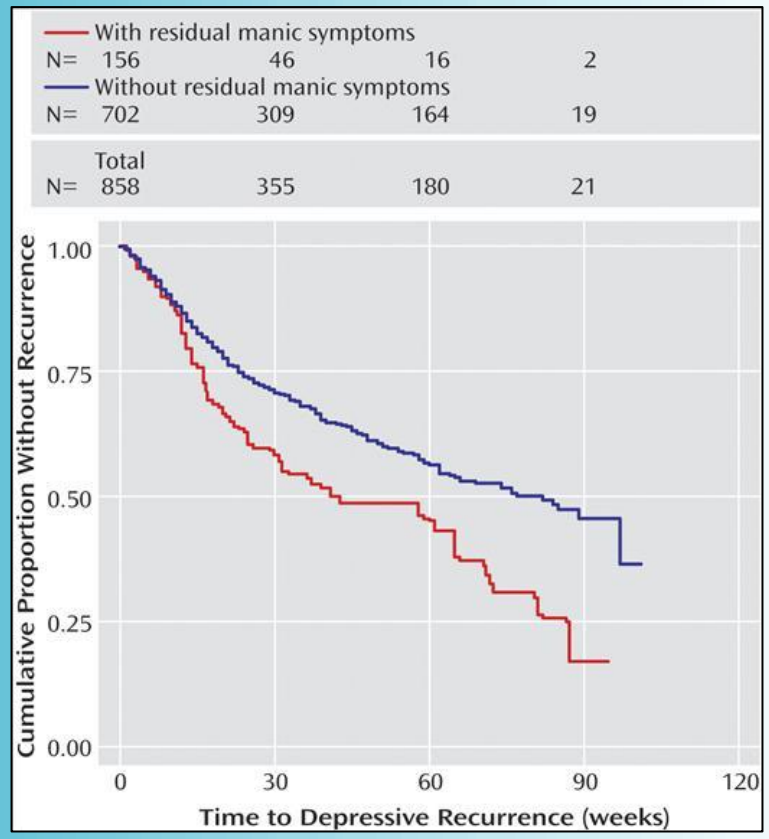
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Residual Symptoms

- Why worry about subthreshold symptoms?
  - Recurrence risk
  - Suicide risk

Residual Manic Symptoms Are Associated with Recurrence



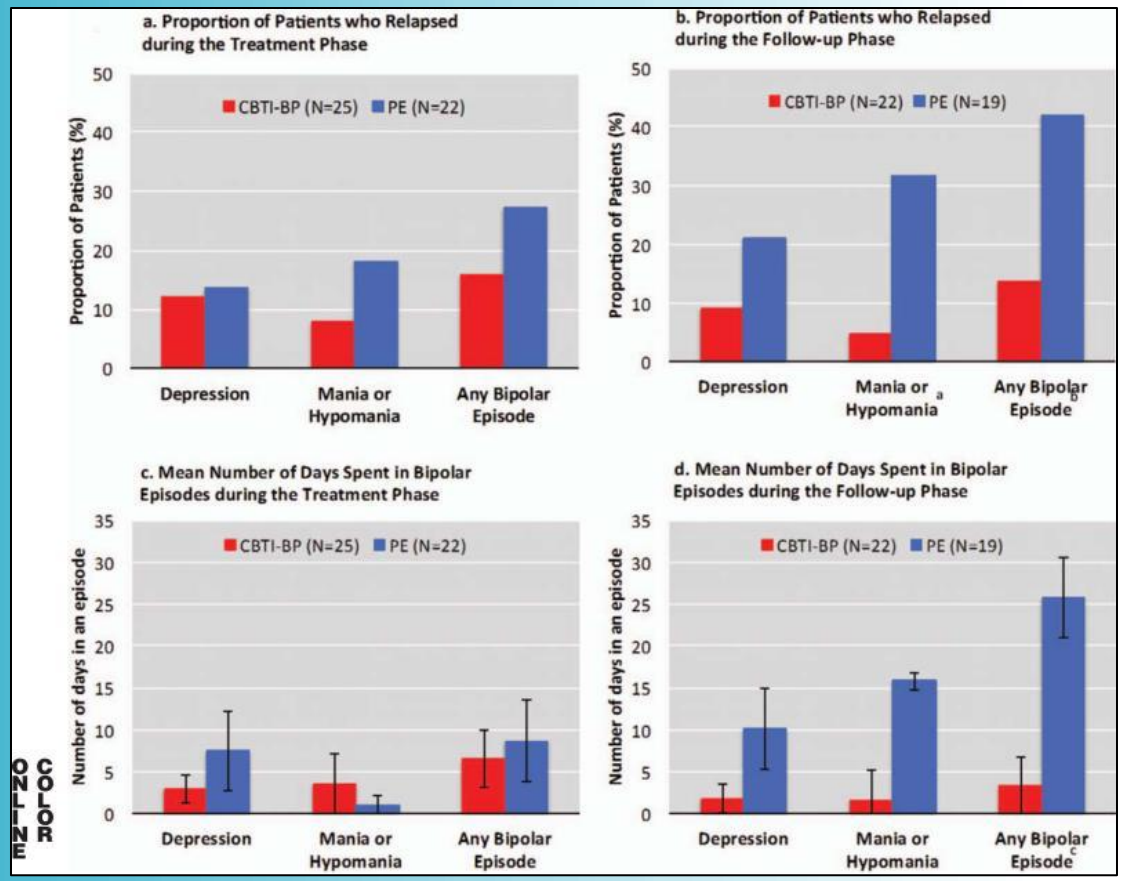
Perlis. *AJP*. 2006.

Sleep

Sleep Disruption in Bipolar Disorder

- Powerful precipitant of mania/depression
- Cause or effect? Both.
- Multifactorial
  - Medication adverse effects
    - Beware RLS – antidepressants and antipsychotics
  - Residual mood symptoms
  - Sleep disorders (incl sleep apnea)
    - Screens for OSA: STOP-BANG, ESS, …
      - Snoring, Tired, Observed apnea, blood Pressure elevation
- Standard insomnia treatments – including CBT – are effective

CBT for Insomnia in Bipolar Disorder



Harvey. *J Cons Clin Psychol.* 2015. (RCT, N=58 bipolar 1)

Cognition

“I Can’t Think Straight”: Persistent Cognitive Complaints

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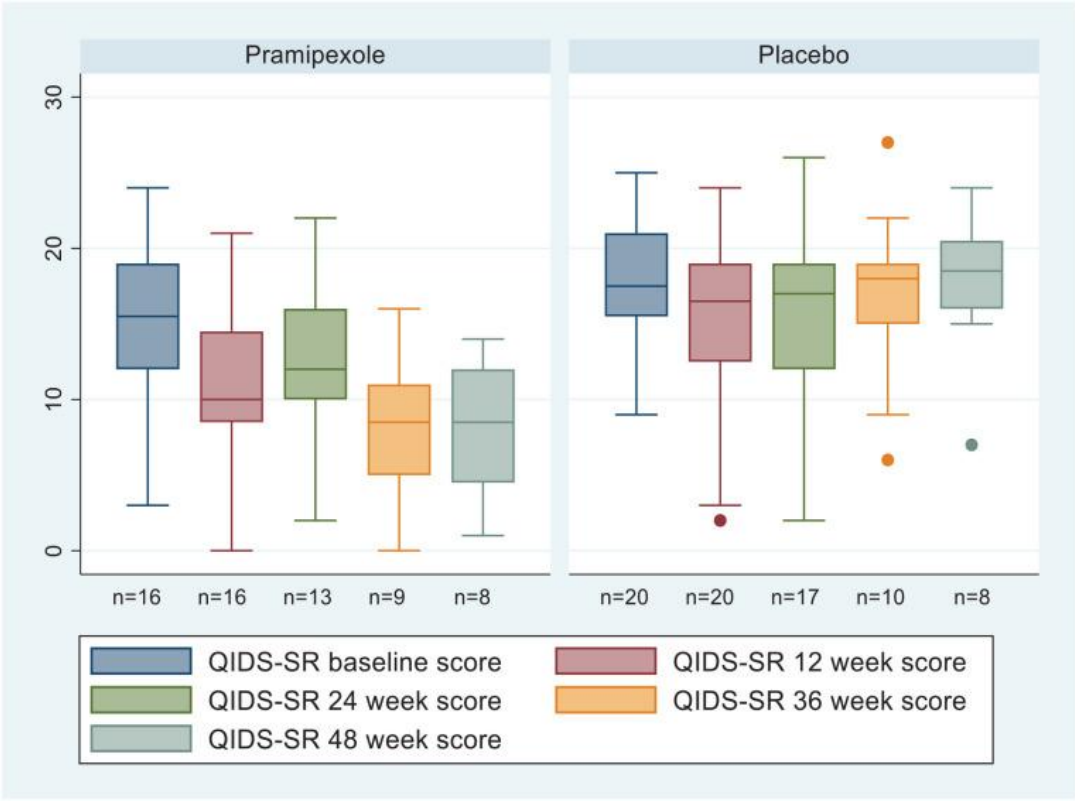
- Multifactorial
  - Medication adverse effects
  - Mood symptoms (including residual symptoms)
  - True comorbidity (ADHD)
  - Chronic features of disease

Ineffective for Cognition

- Memantine
  - 5mg x 12 weeks (n=325 bipolar 2), vs placebo
  - Exploratory analysis in 43 older patients suggested possible benefit (but exploratory, small subset)
- Pramipexole
  - Target dose 4.5mg/day x 8 weeks (n=60 bp/scz), vs placebo
  - No significant benefit on MATRICS

Lu. *JAD.* 2021.
Van Meter. *J Clin Psychopharm.* 2021.

Benefits with pramipexole treatment not observed until 36 weeks



39 patients with treatment-resistant bipolar depressions randomized to treatment with pramipexole (n = 18) or placebo (n = 21)

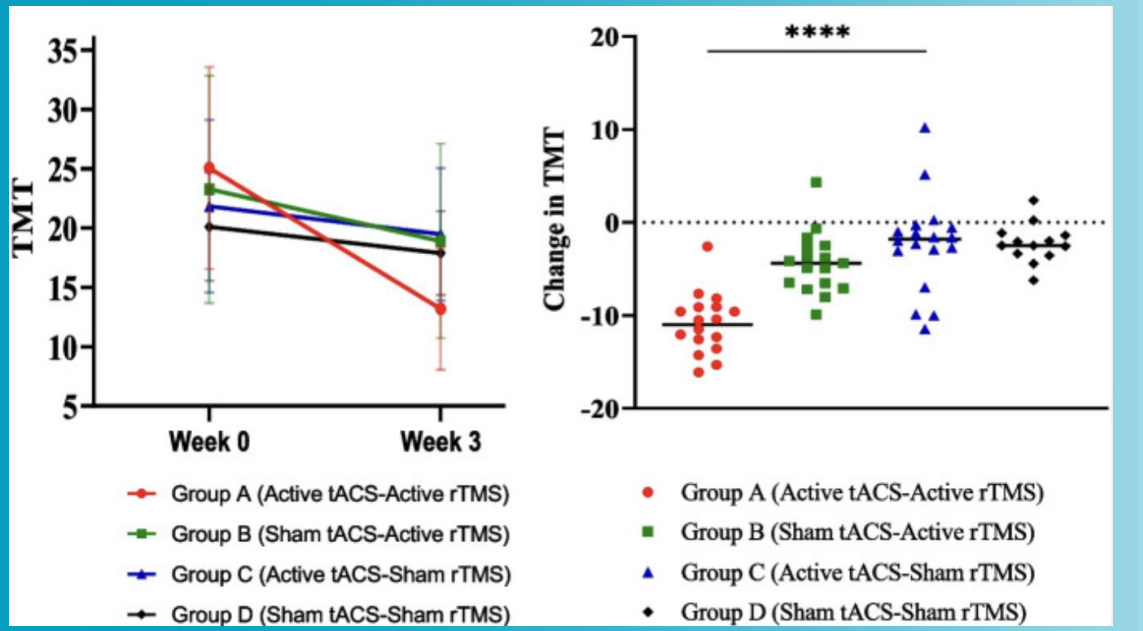
No significant difference in QIDS-SR score at 12 weeks between treatment groups

*** hypomania scores were significantly higher at 12 weeks for pramipexole group*

Significant long-term benefits identified at 36 and 48 weeks

McAllister-Williams, J Psychopharm, Jan 2025

Addressing cognitive symptoms with multimodal neurostimulation



N = 100 patients with BD randomized to four treatment groups (n = 25 for sham conditions)

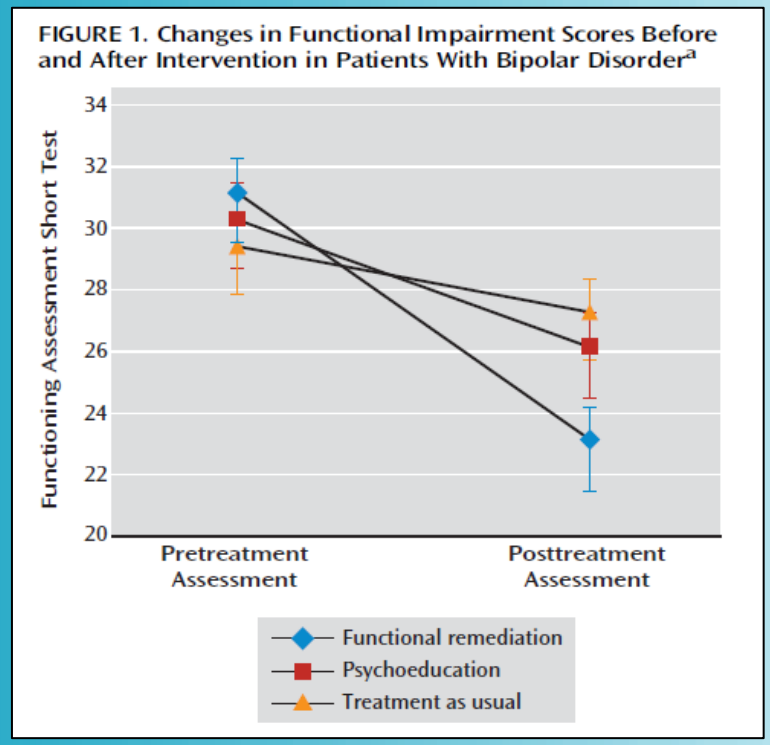
After 15 sessions of DTI-guided neurostimulation, the treatment group receiving both transcranial alternating current and magnetic stimulation showed the greatest improvement in cognitive assessment scores

Wang, BMC Med, June 2025

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Psychosocial Strategies to Improve Cognition and Function

Functional Remediation for Bipolar Disorder



N=239 euthymic outpatients (bipolar I or II); 21 weekly 90-minute sessions

Valls. *Psychol Med*. 2021. n=65
Torrent. *AJP*. 2013.
See also: Valls. *Psychol Med*. 2021.

Cognitive Remediation in Remitted Bipolar Disorder

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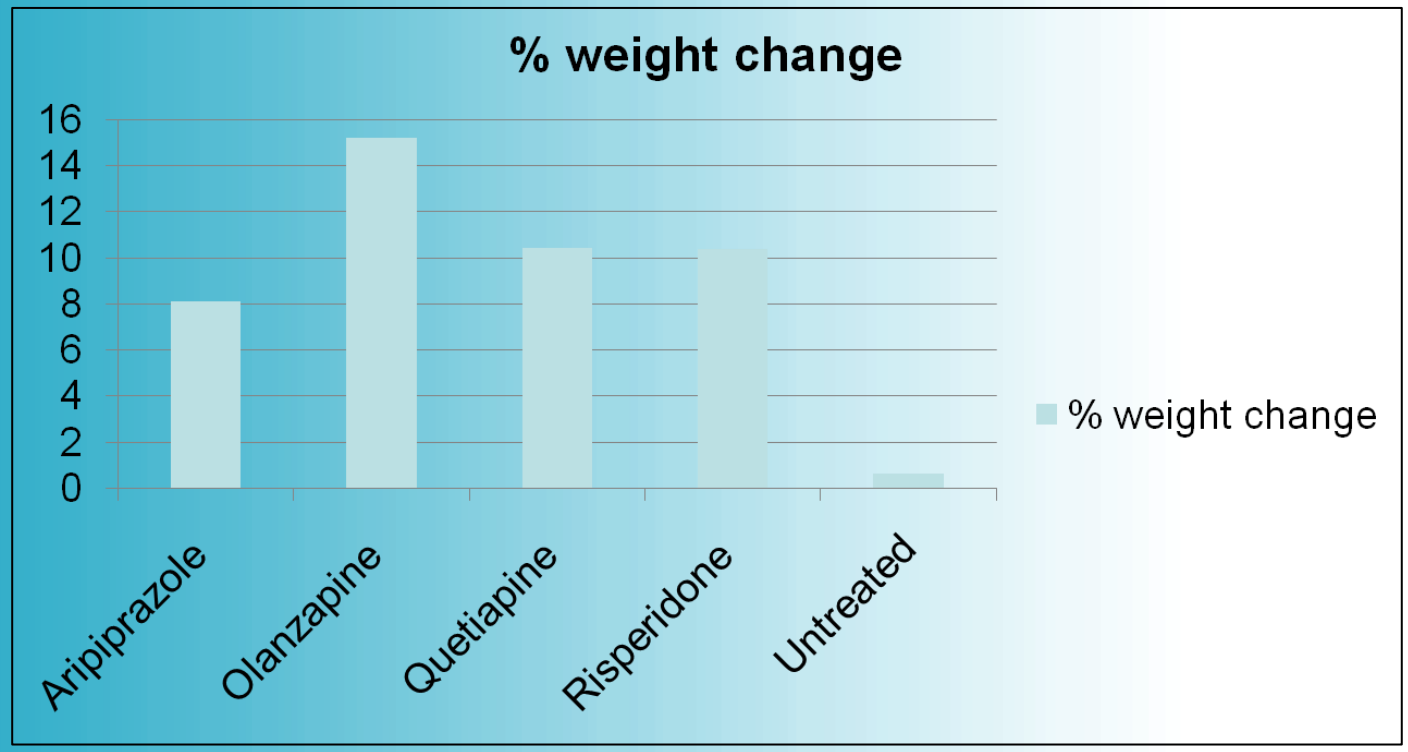
- Action-Based Cognitive Remediation (ABCR) x 11 weeks
- No benefit on composite cognitive score (primary); no benefit on functional measure
- BUT – secondary measures:
  - executive function measure (d = 0.65)
  - subjective cognitive functioning (d = 0.80)
- (and adding aerobic exercise did not improve outcomes)

Ott. *Bipolar Disorders*. 2020. n=61 bipolar
McGurk. *J Psych Res.* 2021. n=34 bipolar/schizophrenia

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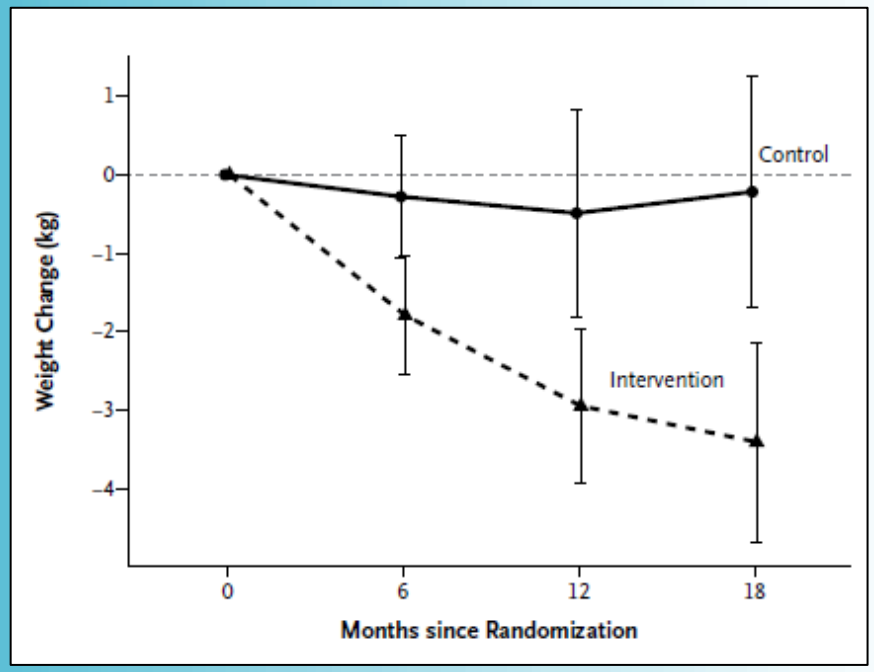
Managing Adverse Effects

Twelve Week Weight Change in Treatment – Naïve Children and Adolescents



Correll. *JAMA*. 2009.

Weight Loss Programs Work in Serious Mental Illness



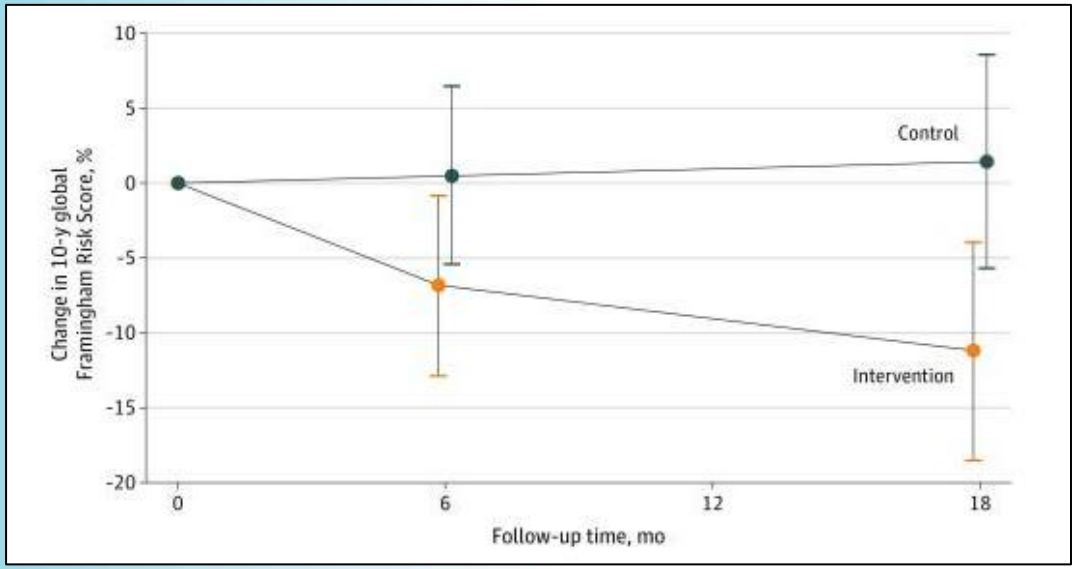
Mean 18-mo weight loss 3.2kg in intervention group (22% bipolar; ~82% on atypical antipsychotic)

Daumit. *NEJM*. 2013.
See also: Kilbourne. *JCP*. 2013. Bartels. *AJP*. 2015.

Psychosocial Interventions to Decrease Cardiovascular Risk in SMI

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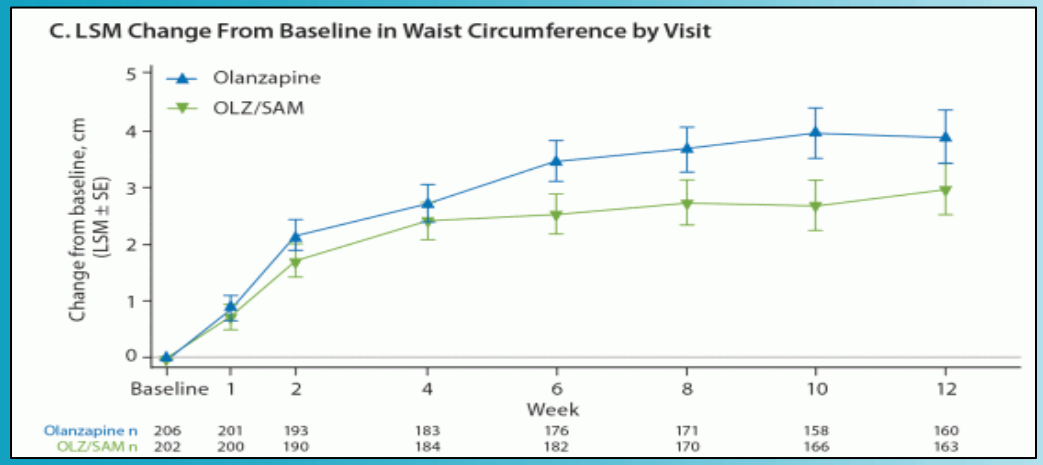
- Behavioral counseling, care coordination, and care management (vs treatment as usual)
- Estimated probability of cardiovascular event over 10 years decreased by >10%



Daumit. *JAMA Open*. 2020. n=269 SMI with 1+ cardiovascular risk factors.

Adjunctive Samidorphan Shown to Mitigate Weight Gain Associated with Antipsychotic Treatment

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N=428 young adults w/ recent diagnosis of BD, SZ, or schizophreniform disorder

n=211: these participants received both Olanzapine and Samidorphan

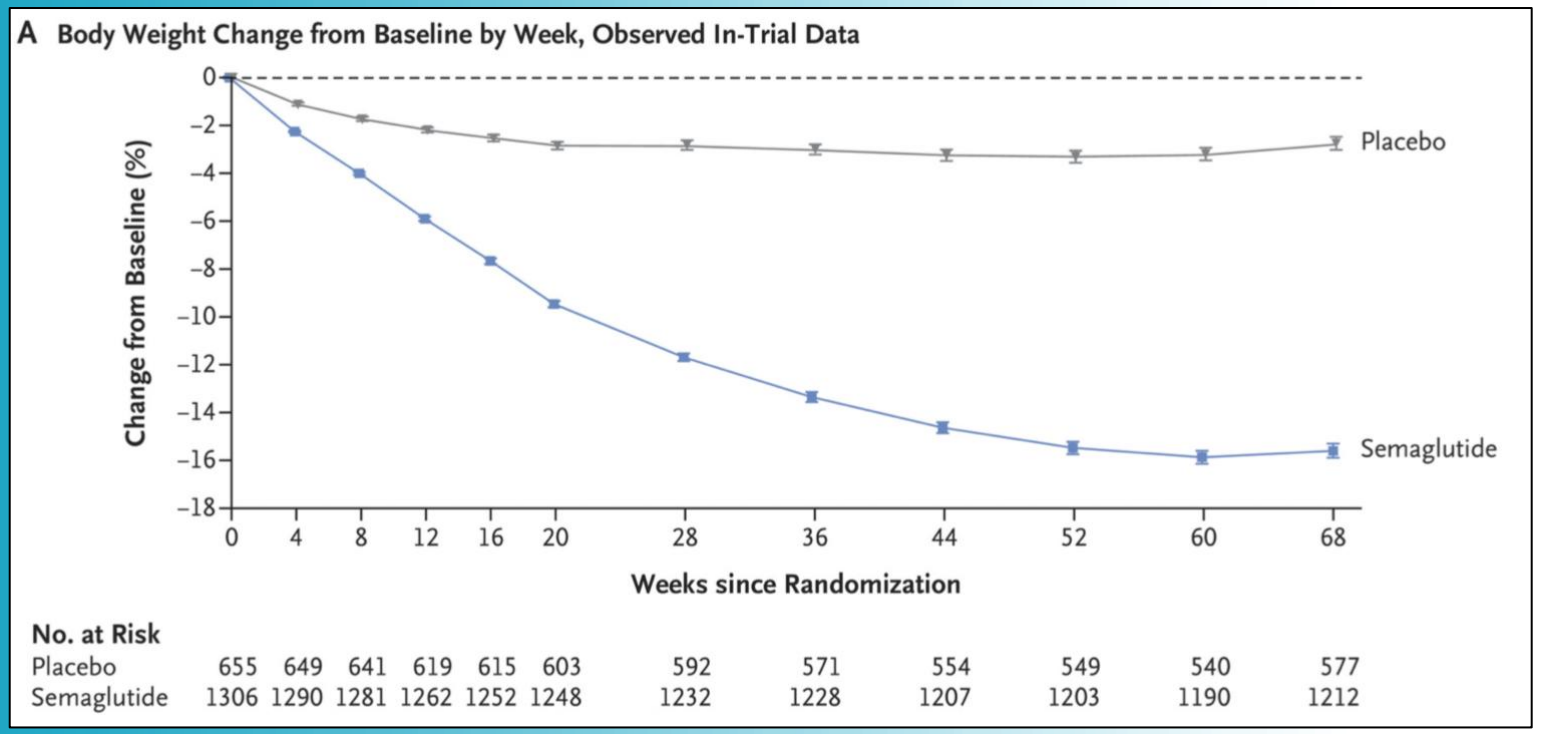
n=215: these participants received only Olanzapine

Patients with early-phase schizophrenia or bipolar I disorder are at a greater risk for antipsychotic-associated weight gain.

Results: 408 participants gained weight, but less weight gain observed in OLZ/SAM group
– suggests that OLZ/SAM mitigates olanzapine-associated weight gain

Khan. *J Clin Psychiatry*. 2023.

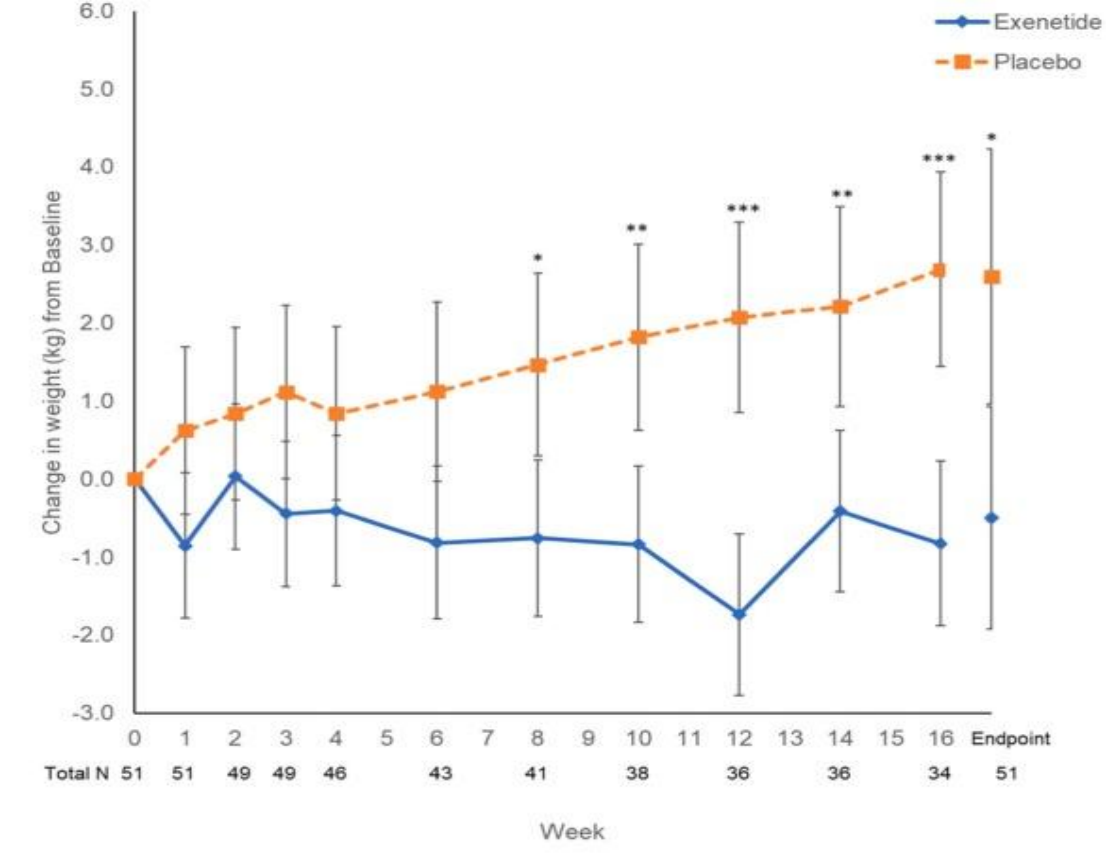
Semaglutide for Overweight or Obesity



BMI 30 or greater (≥27 in persons with ≥1 weight-related coexisting condition), without diabetes (most common AE nausea and diarrhea; d/c 2n GI 4.5% vs 0.8%).

Wilding. *NEJM*. 2021.

Adjunctive Exenatide May Mitigate Weight Gain Associated with Olanzapine Treatment



Adults with stable mood or psychotic disorders were randomized to adjunctive exenatide (n=24) or placebo (n = 30)

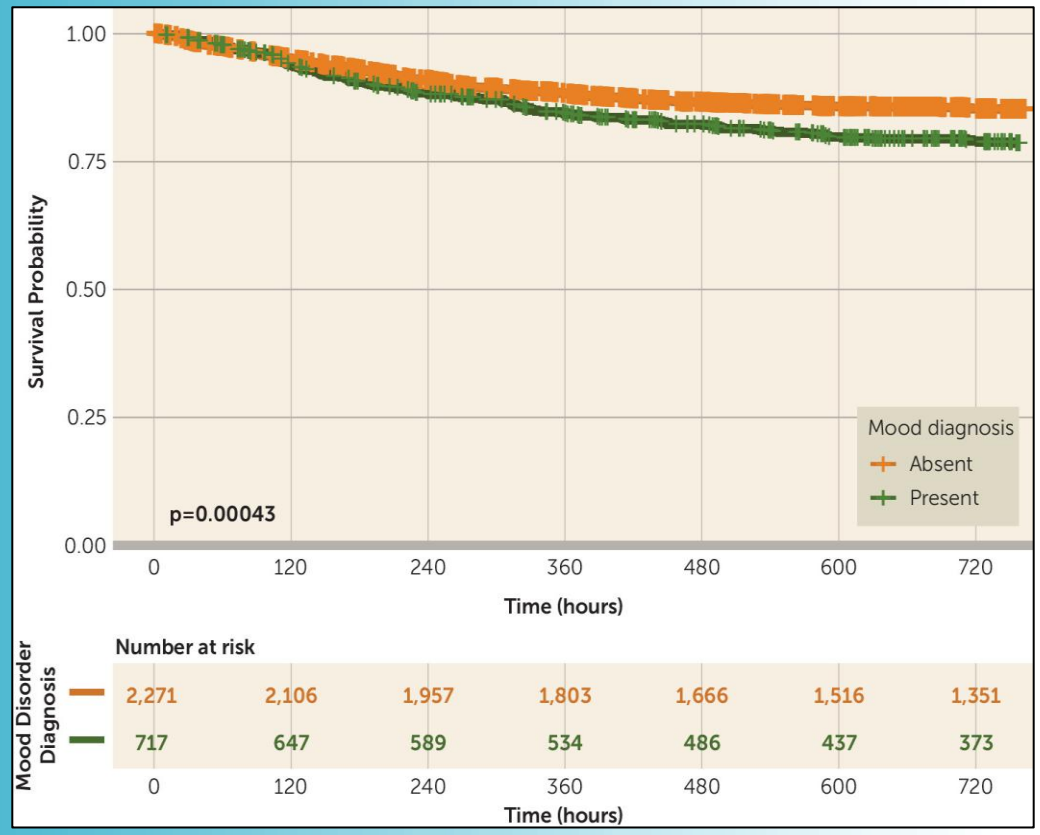
Participants in the placebo group demonstrated significant weight gain, while subjects in the exenatide group maintained stable weight during the 16-week study period

Patino, et al. JAD. August 2025.

Postscript: Do Not Forget Health Maintenance

Mood Disorders Are Associated with Poorer Outcome Among Individuals Hospitalized with COVID-19

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Castro. *AJP*. 2021.

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Personalized Medicine in Bipolar Disorder?

Personalized Medicine in Bipolar Disorder?

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- Still no *actionable* common genetic variants identified
- Family history is not diagnostic, but is useful in two ways
  - Increased suspicion for bipolar disorder
  - *Influences patient attitudes toward medication*
- CYP450 testing not well-studied for bipolar disorder – CANMAT considers useful in some treatment-resistant patients
  - Useful reference: medicine.iupui.edu/clinpharm/ddis/main-table/
  - 2 large RCT's of PGx testing in major depression **have not** demonstrated efficacy

Budde. *Eur Neuropsychopharm*. 2017.
Greden. *J Psych Res*. 2019.
Perlis. *Depression and Anxiety*. 2020.

For CYP450 Educational Purposes…

- https://sequence2script.com/
- Many missing meds (lithium, lamotrigine, …)
- Do not stop meds purely on the basis of CYP450 testing!

Current Medications

Medication Name	Description	Genes Affected	Recommendation	Strength of Recommendation	Source	Pathway
fluoxetine	CYP2C9 Substrate CYP2D6 Strong Inhibitor, Substrate CYP2C19 Moderate Inhibitor	CYP2D6	No action required. Initiate therapy with recommended starting dose (10 - 60 mg/d depending on indication and age).		DPWG	
aripiprazole	CYP3A5 Substrate CYP2D6 Substrate	CYP2D6	Consider testing for CYP2D6 prior to use.	OPTIONAL	FDA	N/A

*Note: Inhibitor and inducer information was based on the Drug Interactions Flockhart Table.

Bousman. *Front Pharmacol*. 2021.

Stratified Medicine in Bipolar Disorder

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- ~~Personalized medicine?~~
- ~~Precision medicine?~~
- ~~Genomic medicine?~~
- Stratified medicine!

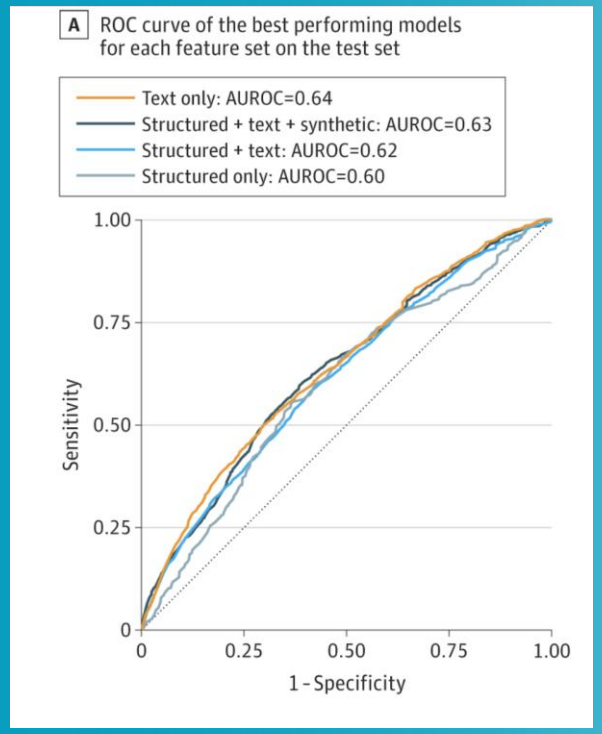
Rely on patient preference and clinical features for treatment selection:

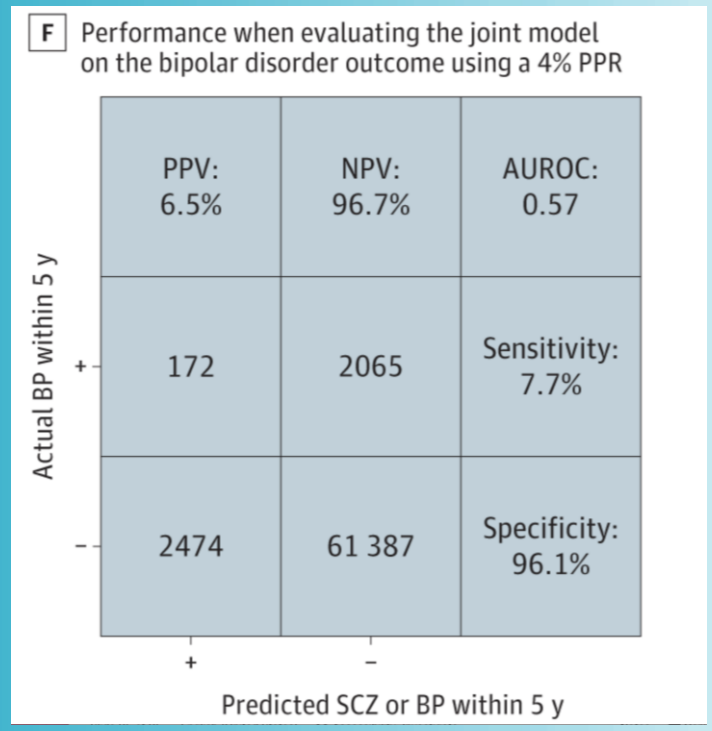
- Patient preference regarding side effects
- Comorbidities
- Residual symptoms

Preview of coming attractions?

Predicting diagnostic progression to SZ or BD

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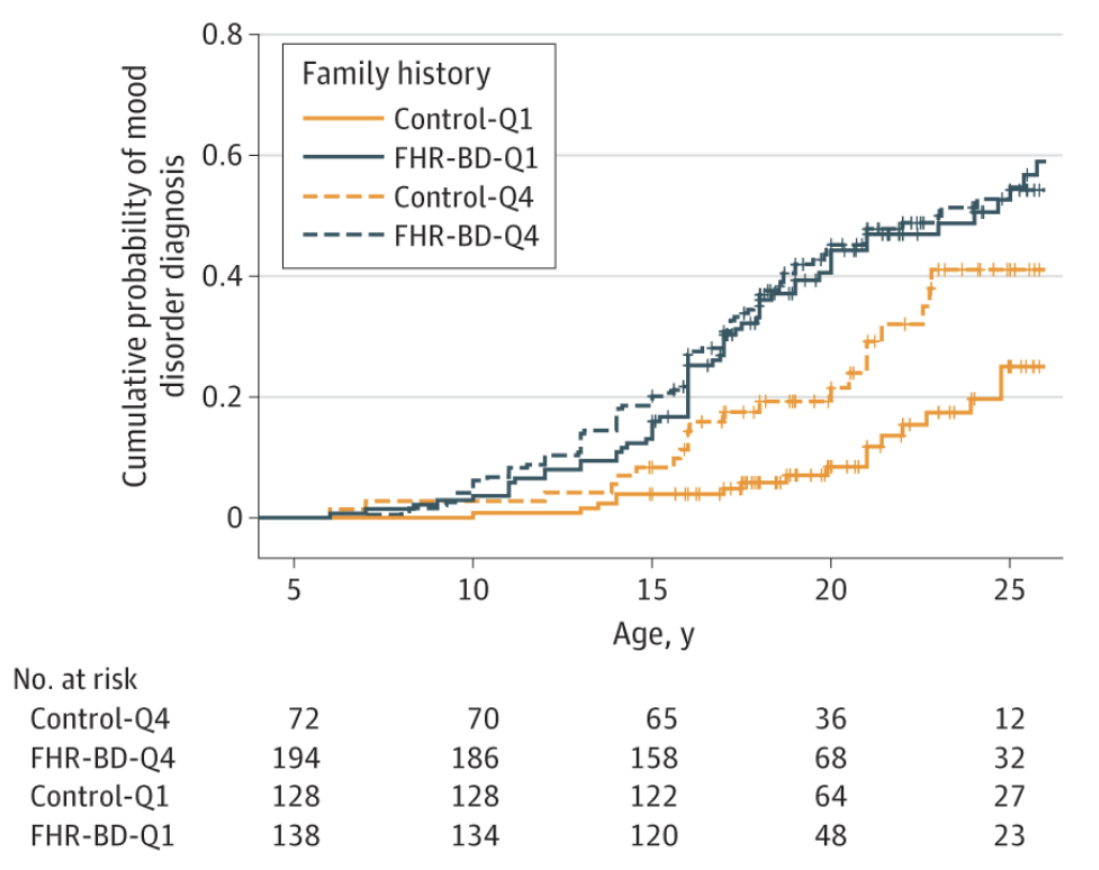


Hansen, JAMA Psych, April 2025

Diagnostic transition to schizophrenia or bipolar disorder within 5 years, predicted 1 day before outpatient contacts by means of elastic net regularized logistic regression and XGBoost models.

Predictors based on EHR data, including medications, diagnoses, and clinical notes.

Stratifying risk for patients without a family history of mood disorders.

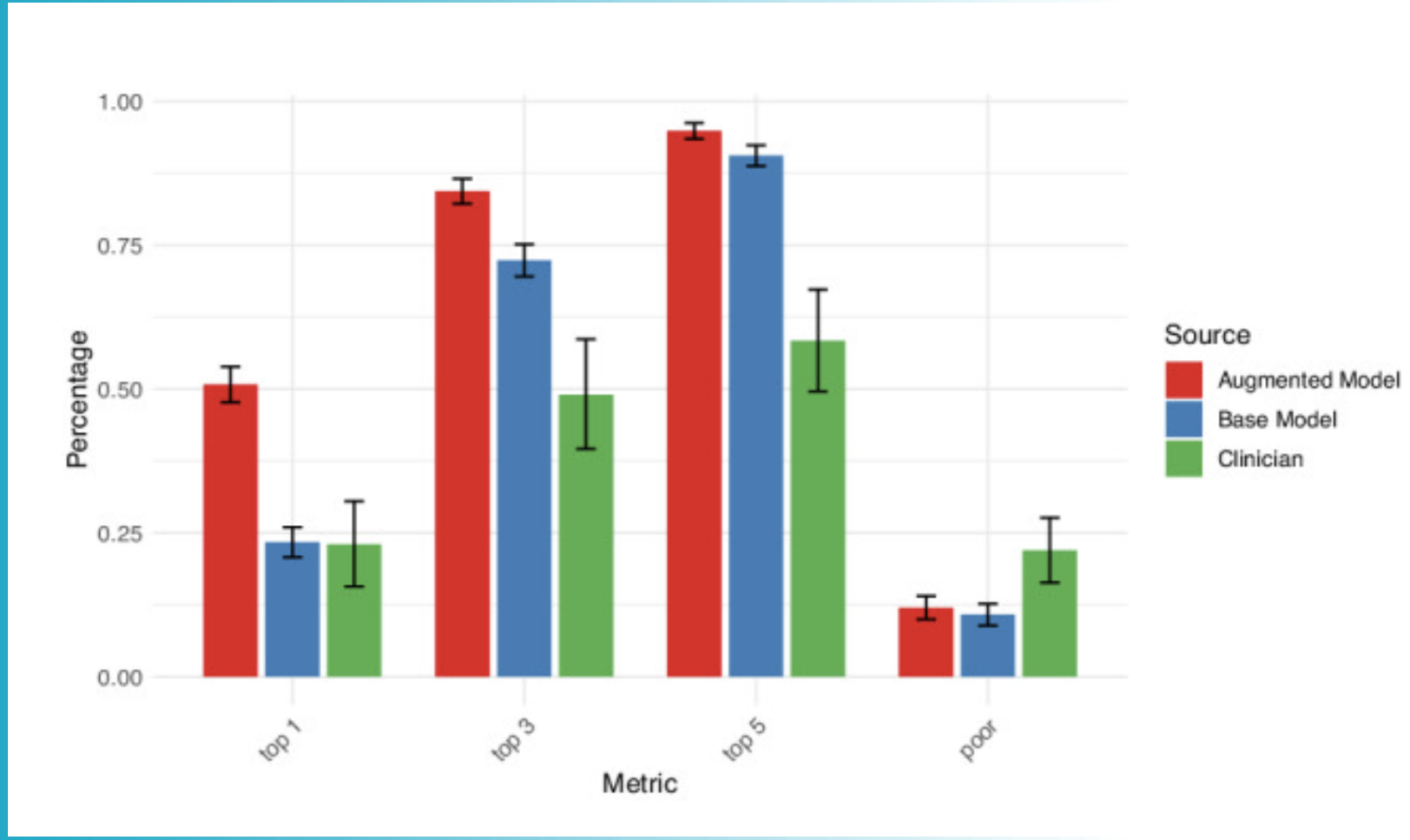


Patients with at least 1 relative with BD (n = 660) compared to those without any family history of mood disorders (n = 404).

Polygenic scores are associated with mood disorder onset independent of familial high risk for BD and early psychopathology

Freeman, JNO, April 2025

Can AI do better at choosing meds?



Perlis. *Neuropsychopharmacology.* August 2024

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Long-Term Treatment in Bipolar Disorder: Fall 2025 Update

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