MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Long-term Treatment in Bipolar Disorder: Fall 2021 Update

Roy H. Perlis, MD MSc

Center for Quantitative Health
Massachusetts General Hospital
Harvard Medical School

rperlis@partners.org

Disclosures

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

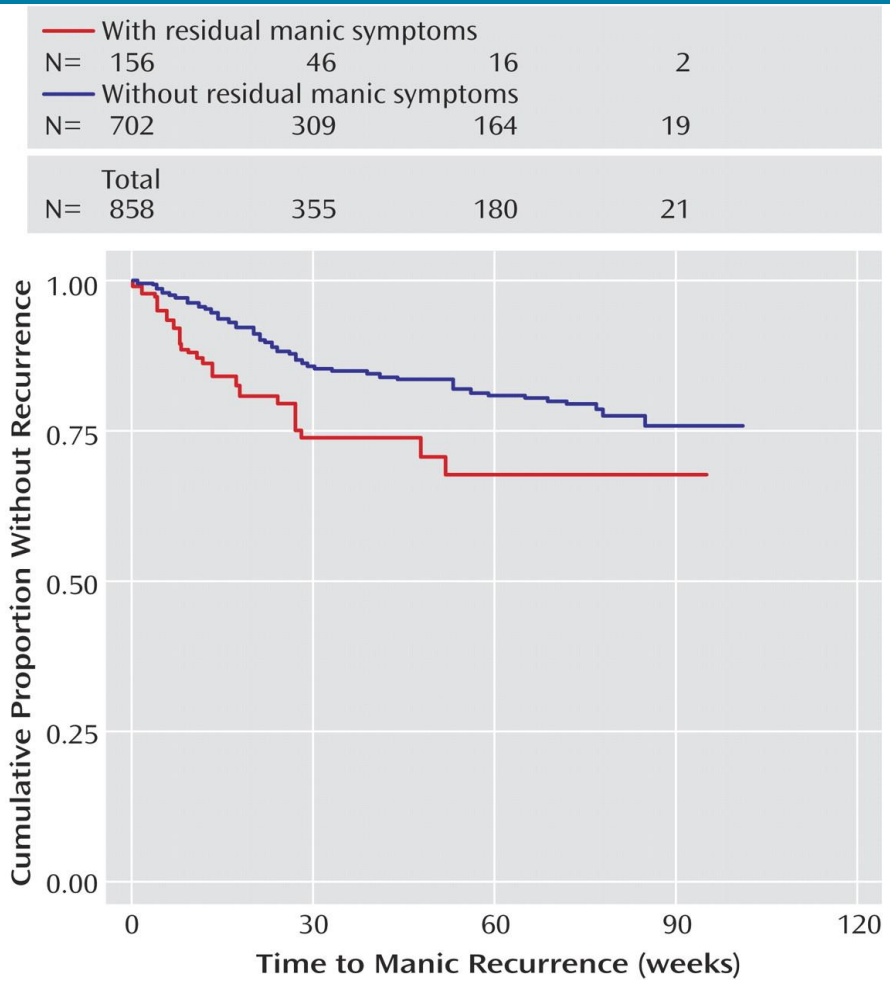
Roy H. Perlis, MD, MSc

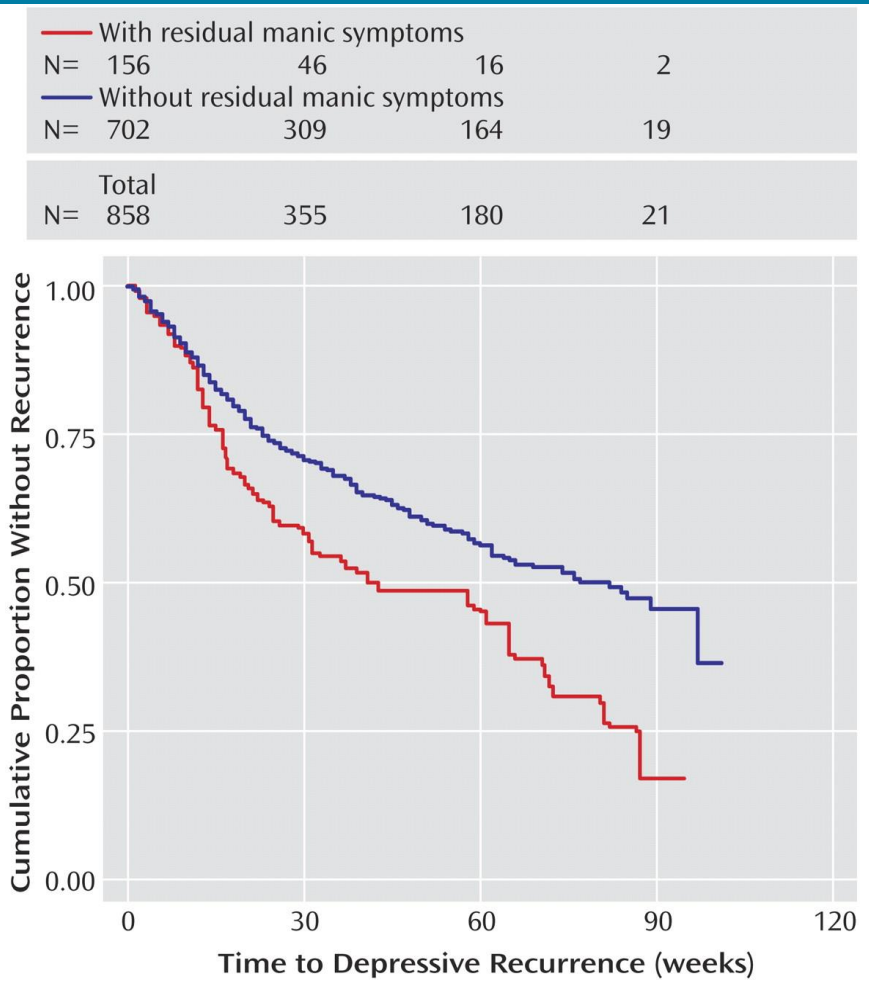
- **Psy Therapeutics (equity) - Founder/SAB member**
- **Outermost Therapeutics (equity) – Founder/SAB member**
- **Belle Artificial Intelligence (equity) – Founder/advisor**
- **Vault Health (consultant fee) - advisor**
- **Genomind (consultant fee) - SAB member**
- **RID Ventures (consultant fee) – advisor**
- **Takeda (consultant fee) – advisor**
- **Burrage Capital (consultant fee) - advisor**

Overview

- Review of efficacy data in maintenance
- Stratified medicine for long-term treatment

About Half of Patients Recur Within Two Years of Index Recovery (Left panel = mania; right panel = depression)





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

Summary of maintenance efficacy

	Level of evidence by phase of treatment				
	Maintenance			Acute	
	Prevention of any mood episode	Prevention of depression	Prevention of mania	Depression	Mania
First-line treatments					
Lithium	●	●	●	◔	●
Quetiapine	●	●	●	●	●
Divalproex	●	◔	◐	◔	●
Lamotrigine	●	●	◔	●	■
Asenapine	◔	◔	◔	n.d	●
Quetiapine + Li/DVP	●	●	●	◕	●
Aripiprazole + Li/DVP	◔	n.d.[a]	◔	◕	◔
Aripiprazole	◔	n.d.[a]	◔	■	●
Aripiprazole OM	◔	n.d.[a]	◔	n.d.	n.d.
Second-line treatments					
Olanzapine	●	●	●	●[b]	●
Risperidone LAI	●	n.d.[a]	●	n.d.	n.d.
Risperidone LAI (adj)	◔	◕	◔	n.d.	n.d.
Carbamazepine	◔	◔	◔	◐	●
Paliperidone (>6 mg)	◔	n.d.[a]	◔	n.d.	●
Lurasidone + Li/DVP	◐[d]	◐[c]	◕	◔	n.d.
Ziprasidone + Li/DVP	◔	n.d.[a]	◔	◧	◧

CANMAT Bipolar Disorders 2018

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…

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.

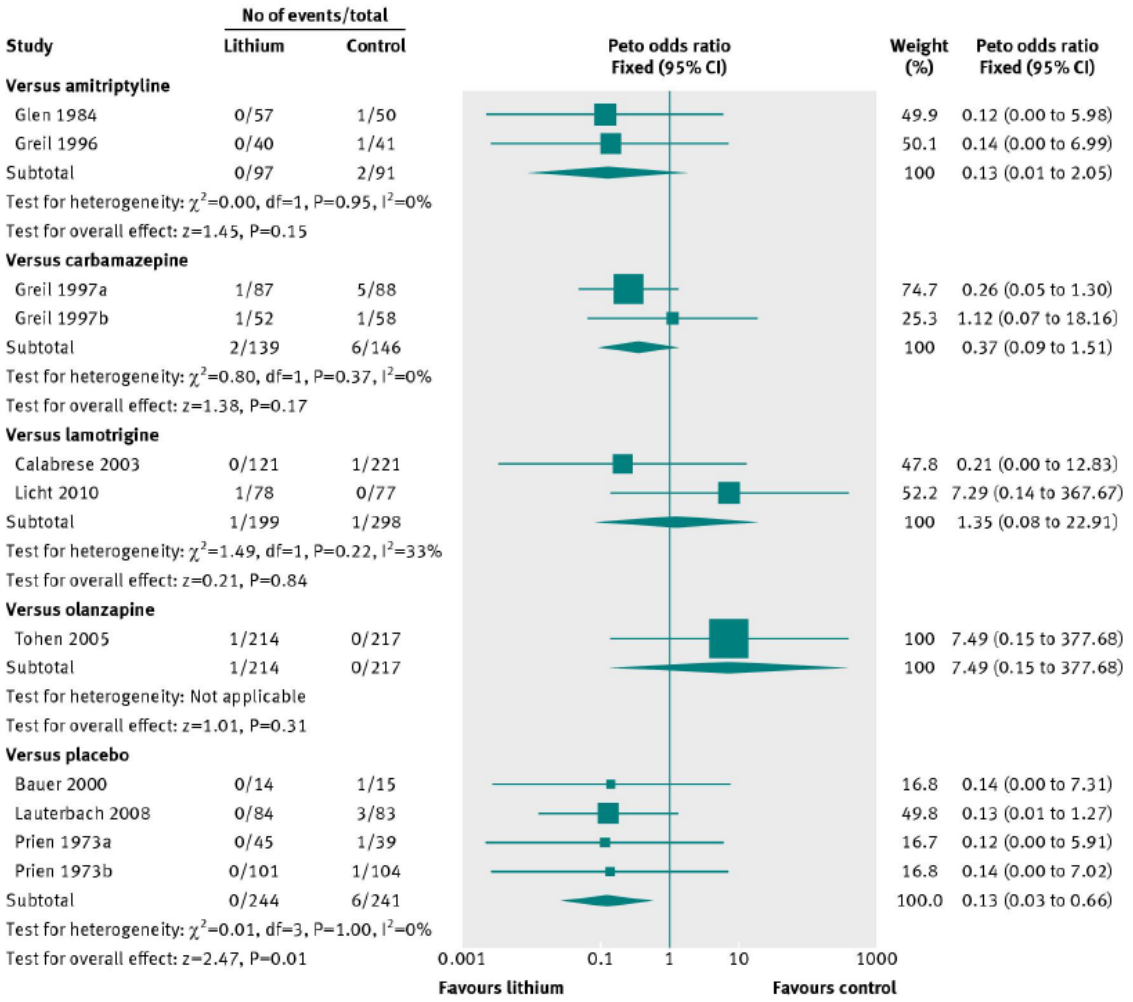
Bai J Clin Psychopharm 2020

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%

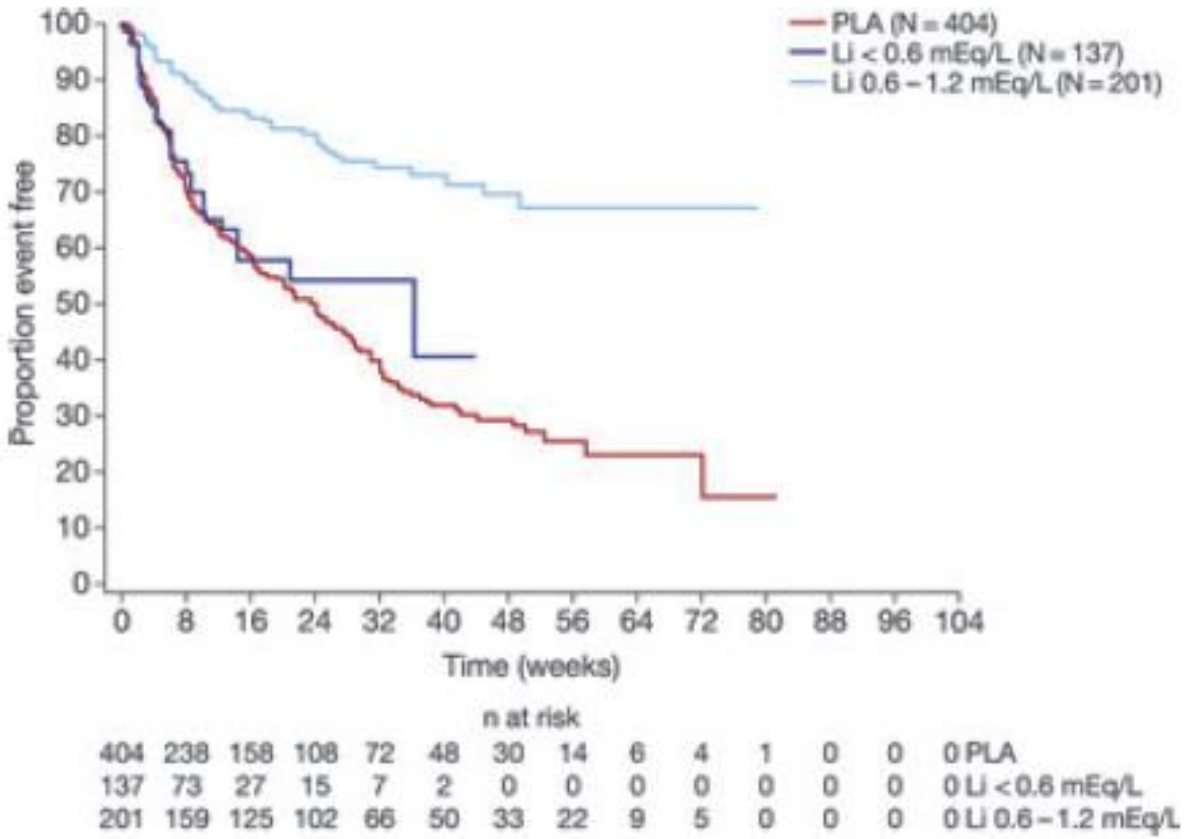


Study	No of events/total: Lithium	Control	Peto odds ratio Fixed (95% CI)	Weight (%)	Peto odds ratio Fixed (95% CI)
Versus amitriptyline					
Glen 1984	0/57	1/50		49.9	0.12 (0.00 to 5.98)
Greil 1996	0/40	1/41		50.1	0.14 (0.00 to 6.99)
Subtotal	0/97	2/91		100	0.13 (0.01 to 2.05)
Test for heterogeneity: χ^2=0.00, df=1, P=0.95, I^2=0%					
Test for overall effect: z=1.45, P=0.15					
Versus carbamazepine					
Greil 1997a	1/87	5/88		74.7	0.26 (0.05 to 1.30)
Greil 1997b	1/52	1/58		25.3	1.12 (0.07 to 18.16)
Subtotal	2/139	6/146		100	0.37 (0.09 to 1.51)
Test for heterogeneity: χ^2=0.80, df=1, P=0.37, I^2=0%					
Test for overall effect: z=1.38, P=0.17					
Versus lamotrigine					
Calabrese 2003	0/121	1/221		47.8	0.21 (0.00 to 12.83)
Licht 2010	1/78	0/77		52.2	7.29 (0.14 to 367.67)
Subtotal	1/199	1/298		100	1.35 (0.08 to 22.91)
Test for heterogeneity: χ^2=1.49, df=1, P=0.22, I^2=33%					
Test for overall effect: z=0.21, P=0.84					
Versus olanzapine					
Tohen 2005	1/214	0/217		100	7.49 (0.15 to 377.68)
Subtotal	1/214	0/217		100	7.49 (0.15 to 377.68)
Test for heterogeneity: Not applicable					
Test for overall effect: z=1.01, P=0.31					
Versus placebo					
Bauer 2000	0/14	1/15		16.8	0.14 (0.00 to 7.31)
Lauterbach 2008	0/84	3/83		49.8	0.13 (0.01 to 1.27)
Prien 1973a	0/45	1/39		16.7	0.12 (0.00 to 5.91)
Prien 1973b	0/101	1/104		16.8	0.14 (0.00 to 7.02)
Subtotal	0/244	6/241		100.0	0.13 (0.03 to 0.66)
Test for heterogeneity: χ^2=0.01, df=3, P=1.00, I^2=0%					
Test for overall effect: z=2.47, P=0.01					

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

- 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

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

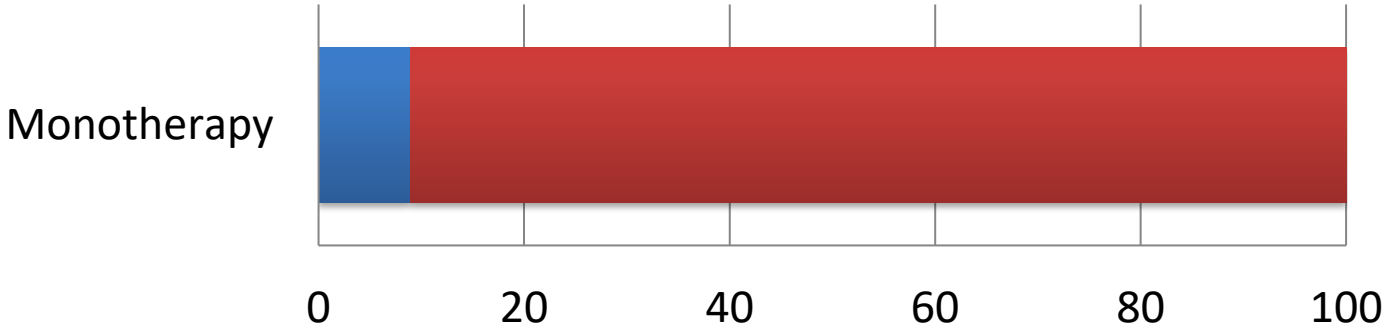
Castro, *Neuropsychopharmacology* 2016

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
- No need for extended release unless gastric discomfort/nausea with standard release

But in the real world, few patients stay on lithium monotherapy

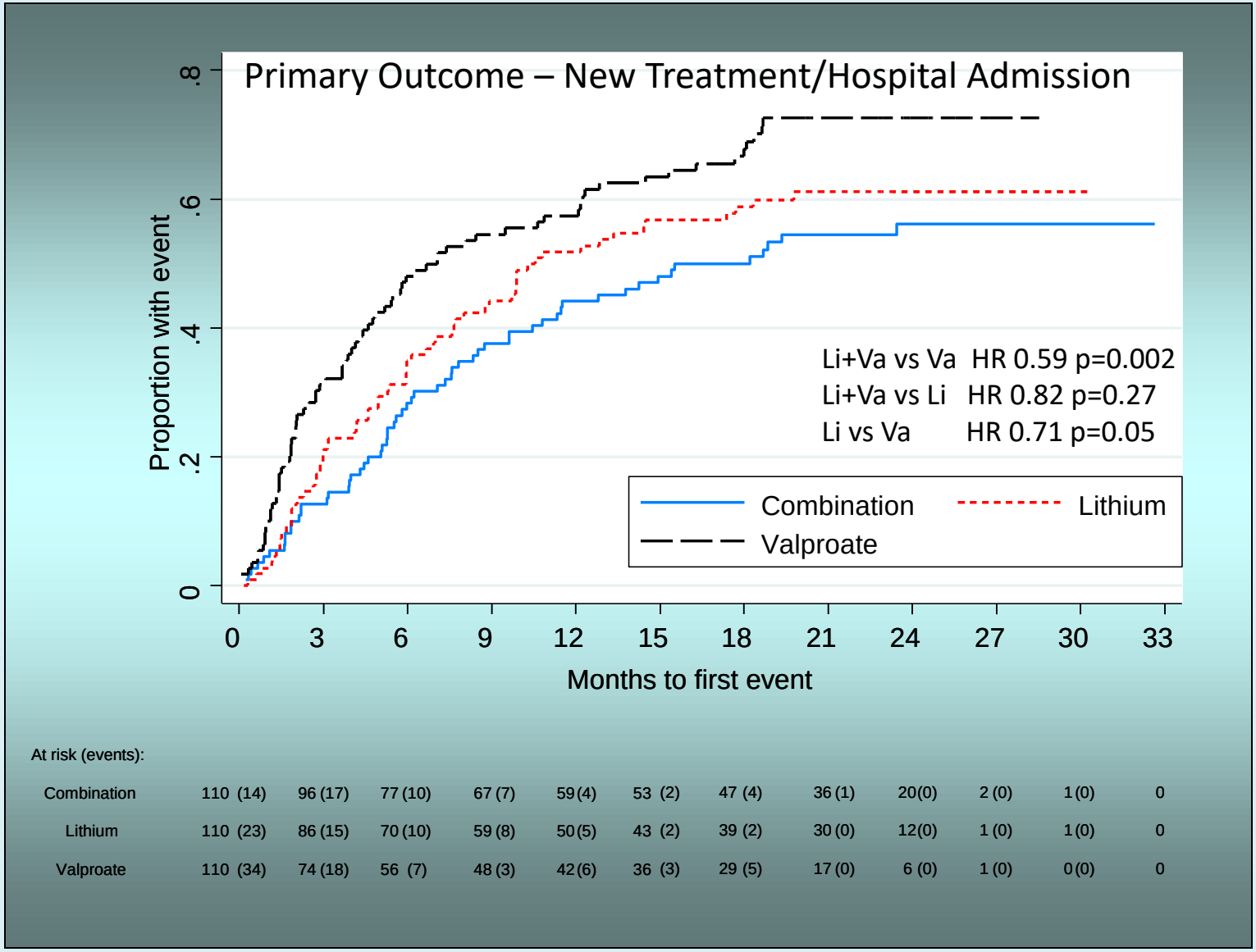
- Danish registry study:
  - 5 years later, only 8.9% still on lithium monotherapy



- 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



At risk (events):

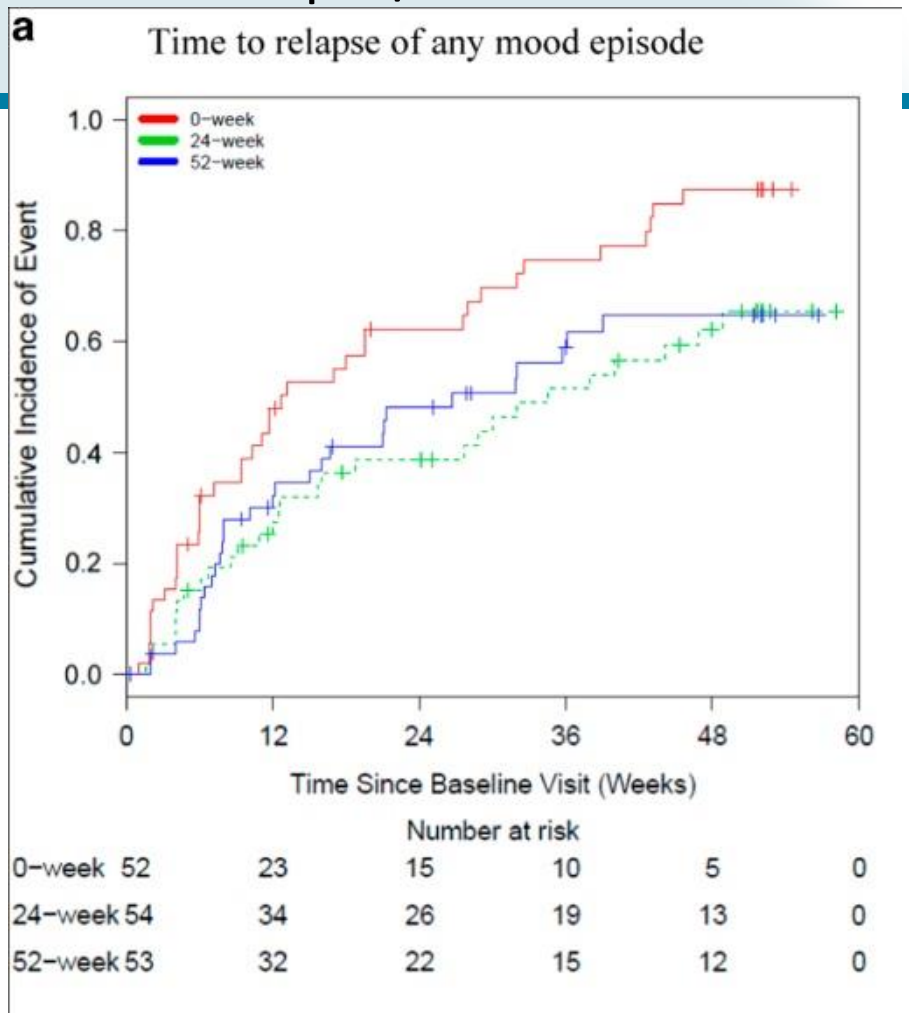
Combination	110 (14)	96 (17)	77 (10)	67 (7)	59 (4)	53 (2)	47 (4)	36 (1)	20 (0)	2 (0)	1 (0)	0
Lithium	110 (23)	86 (15)	70 (10)	59 (8)	50 (5)	43 (2)	39 (2)	30 (0)	12 (0)	1 (0)	1 (0)	0
Valproate	110 (34)	74 (18)	56 (7)	48 (3)	42 (6)	36 (3)	29 (5)	17 (0)	6 (0)	1 (0)	0 (0)	0

BALANCE Investigators Lancet 2010

How to choose?

- Efficacy, efficacy, efficacy
- Tolerability and patient preference

Early discontinuation of add-on atypical antipsychotic = greater relapse/recurrence



Yatham 2016; 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!)

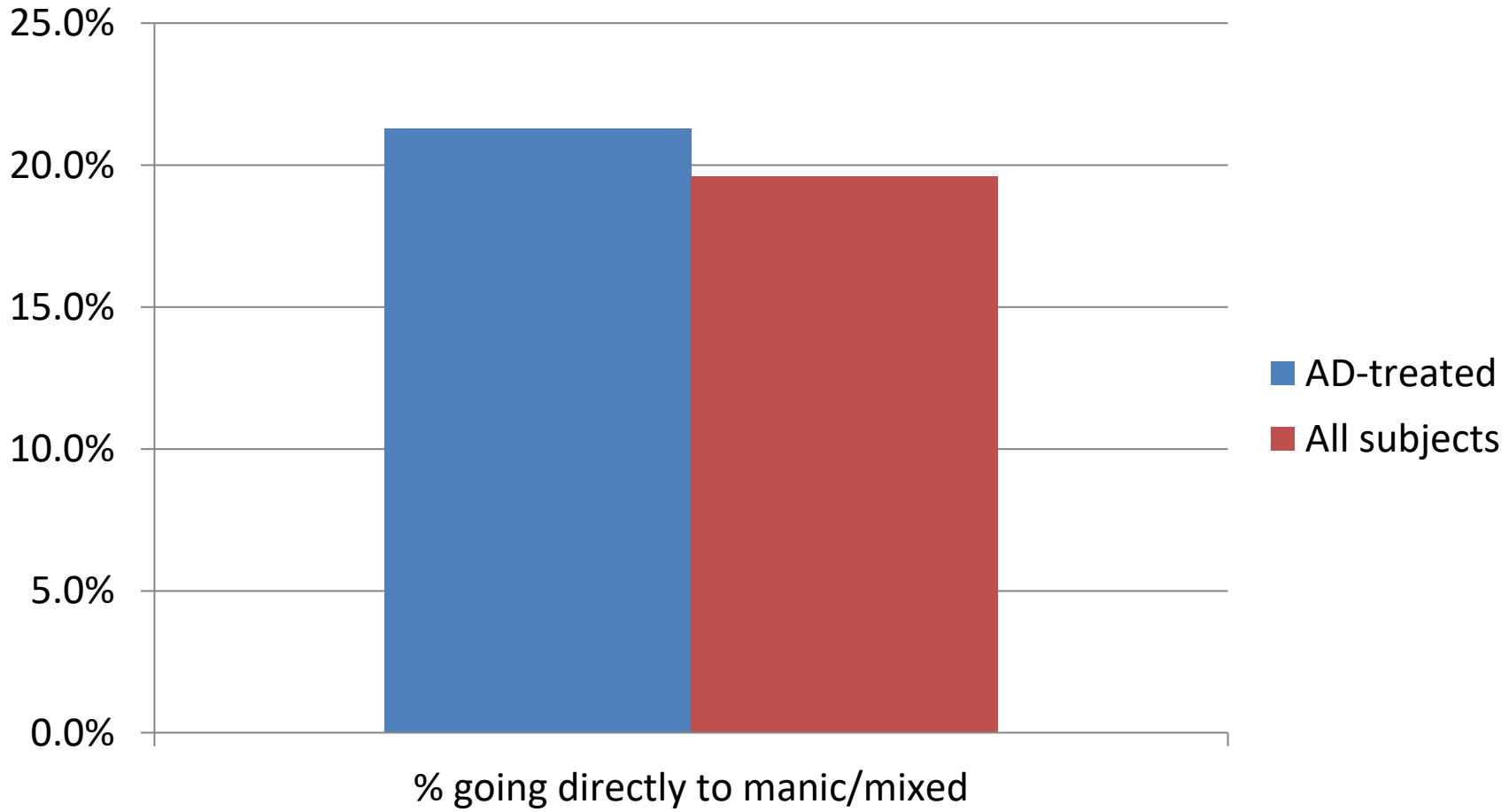
When treatments are added acutely, beware early discontinuation!

- 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.

What about longer-term treatment with antidepressants?

Transition from depression to mania is part of the course of illness!



N~2166 bp 1 or 2; 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

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)

- "Among patients treated with a concurrent mood stabilizer, no acute change in risk of mania was observed during the 3 months after the start of antidepressant treatment (hazard ratio=0.79, 95% CI=0.54, 1.15)…
- … *a decreased risk* was observed during the period 3-9 months after treatment initiation (hazard ratio=0.63, 95% CI=0.42, 0.93)."
- – Viktorin, AJP 2014 (ital. added)

- 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!*

Anxiety comorbidity is common in bipolar disorder…

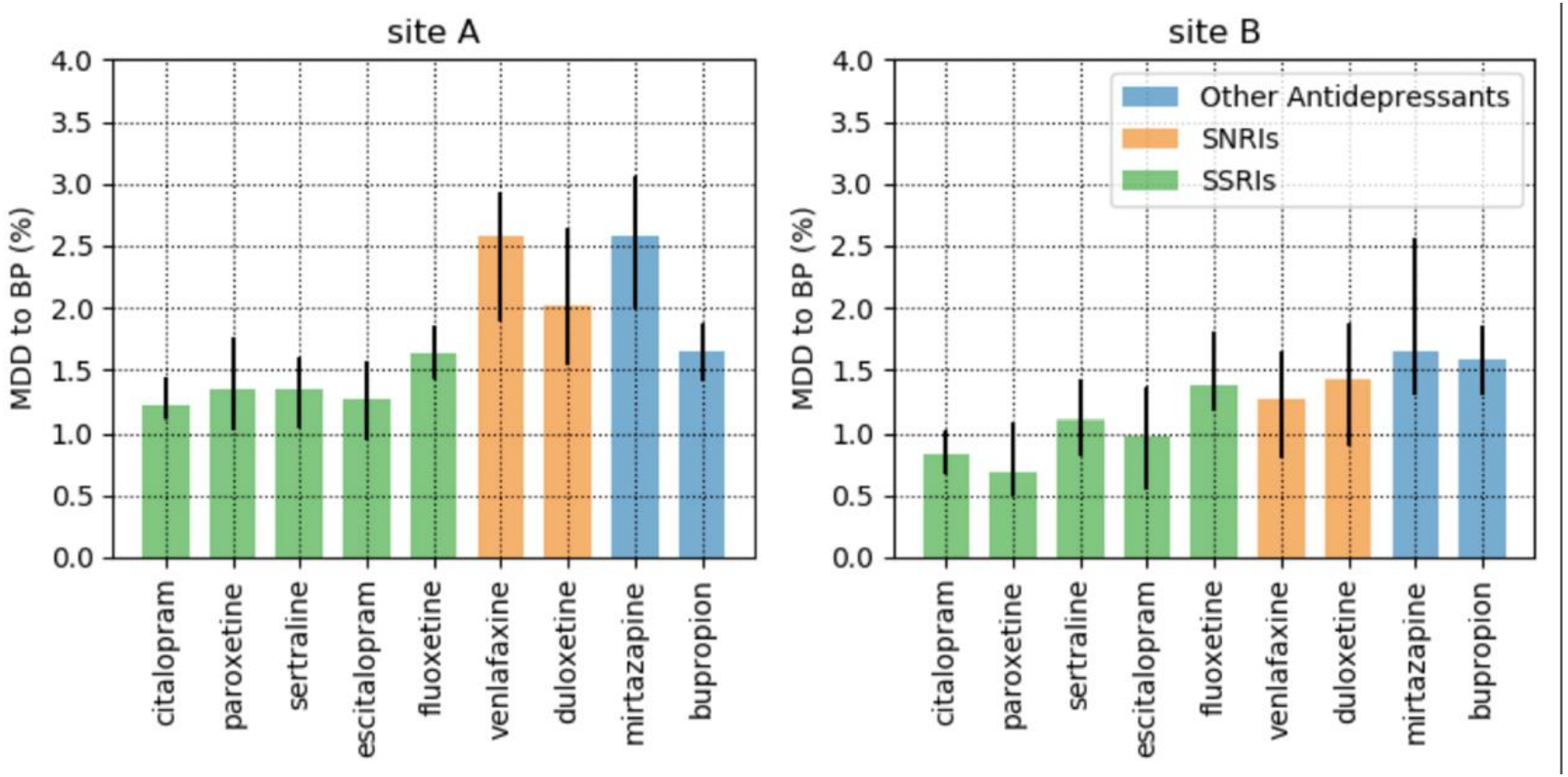
	Studies (n)	Individuals (n)	Rate (95% CI)
Any anxiety disorder	40	14 914	0·453 (0·400–0·506)
Panic disorder	40	14 960	0·193 (0·153–0·234)
Agoraphobia	17	9066	0·117 (0·078–0·156)
Social phobia	31	13 329	0·199 (0·150–0·248)
Generalised anxiety disorder	31	11 196	0·204 (0·147–0·262)
Specific phobia	24	5093	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)

Pavlova Lancet Psych 2015

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)

Rates of transition from MDD to BPD, by antidepressant



Pradier, *Neuropsychopharmacology*, 2021

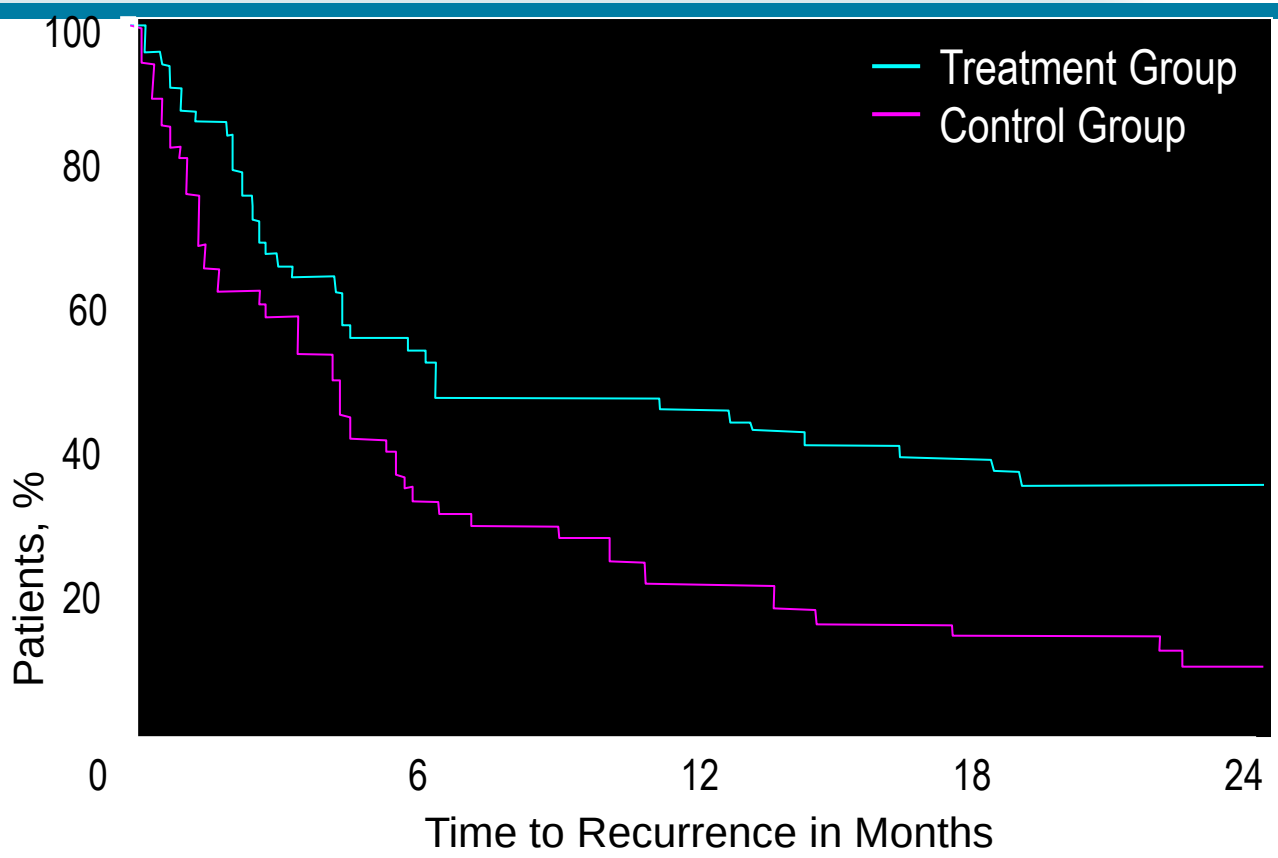
Even the experts are confused

- "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

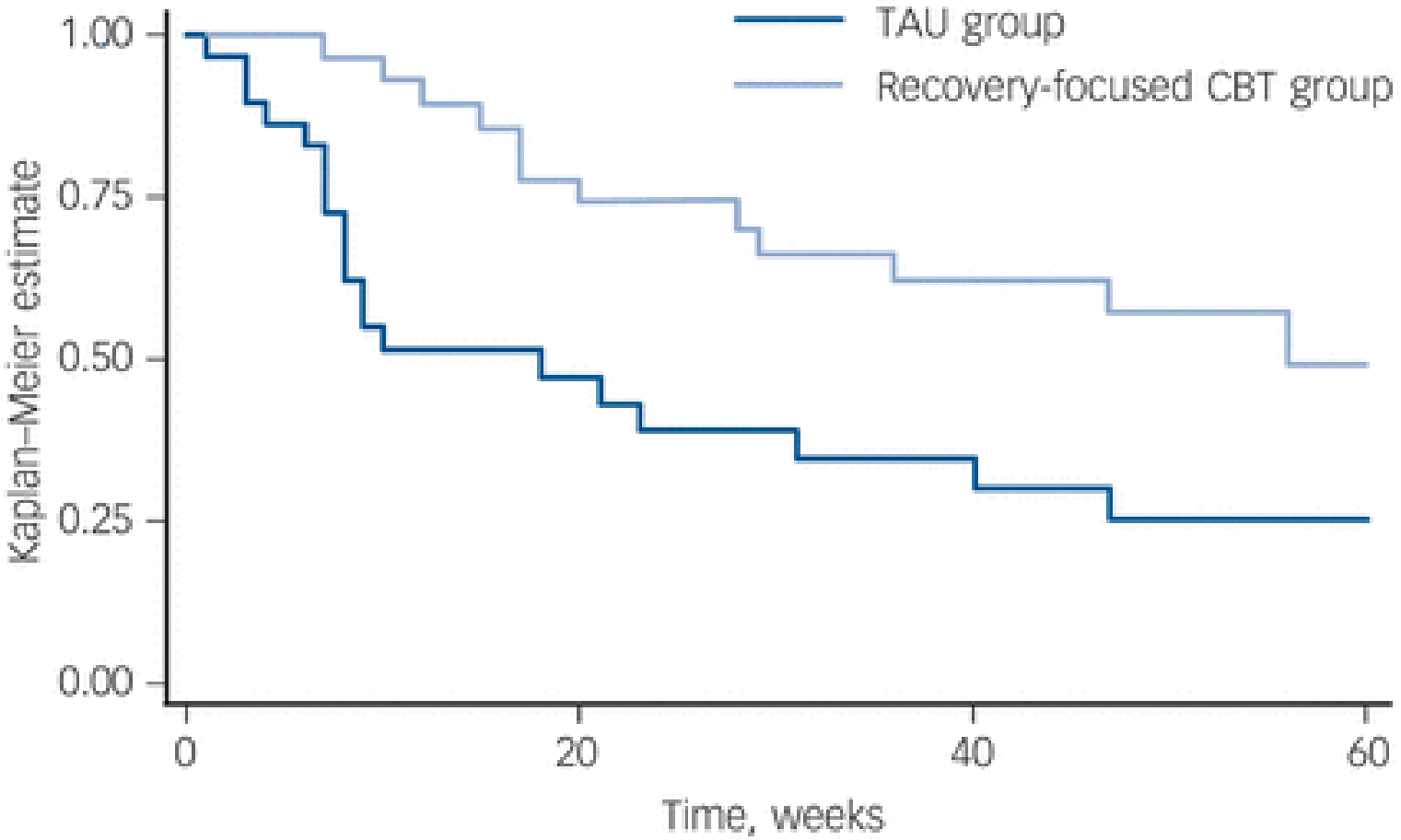
Don’t forget psychosocial interventions

We've known for nearly 2 decades that psychoeducation groups reduce recurrence



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

Recovery-focused CBT in recent-onset bipolar patients decreases recurrence



Jones BJP 2015; n=67 single-blind RCT, CBT vs TAU; benefit in depression>mania

Part 2: Stratified medicine in bipolar disorder

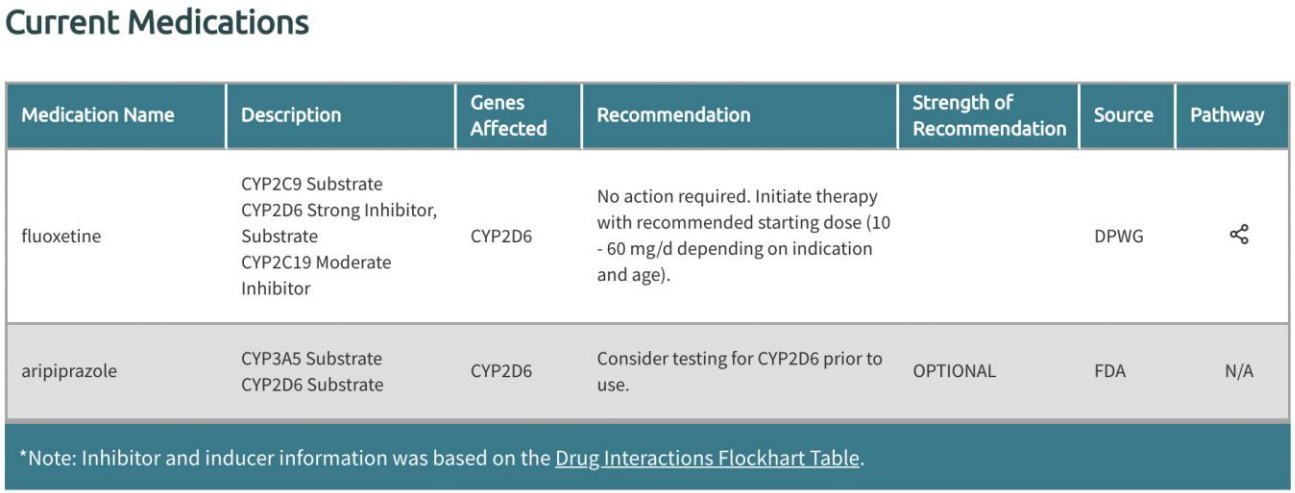
Personalized medicine in bipolar disorder?

- 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
- Most useful consideration in treatment selection among drugs with efficacy: safety and tolerability profile

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, …)



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

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

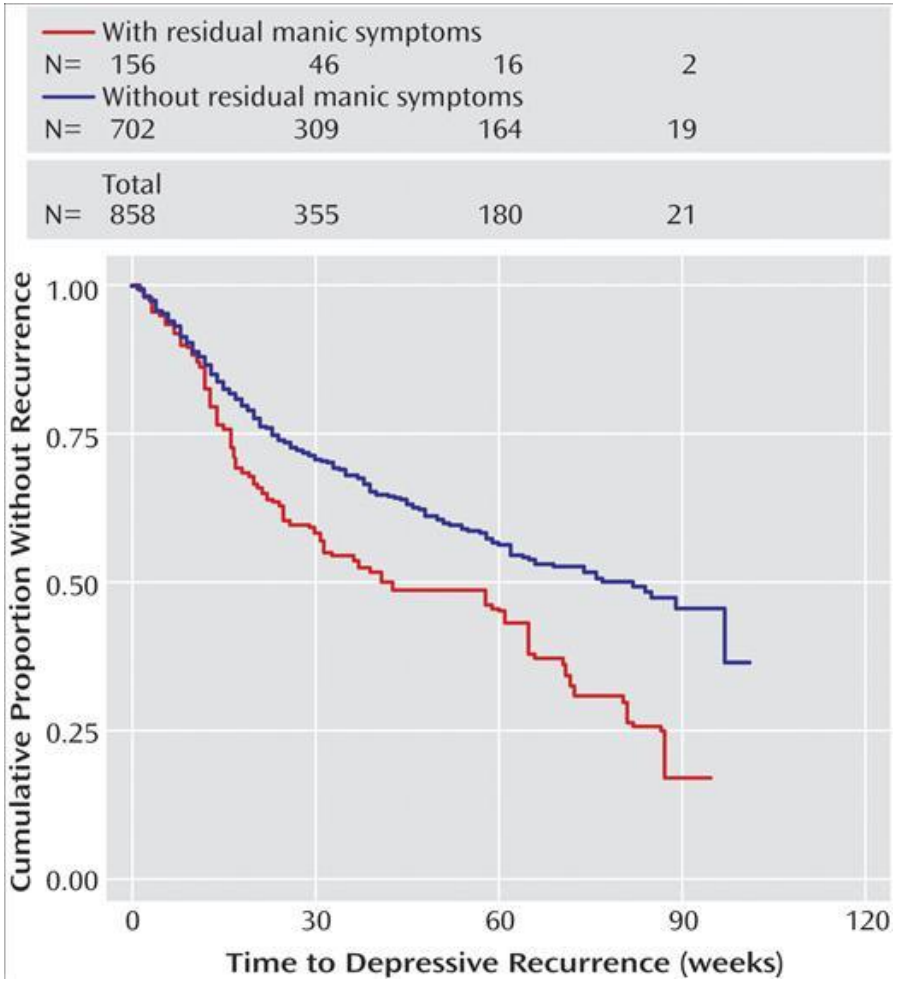
Rely on patient preference and clinical features for treatment selection:

- Patient preference regarding side effects
- Comorbidities
- Residual symptoms

Residual symptoms

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

Residual manic symptoms are associated with recurrence



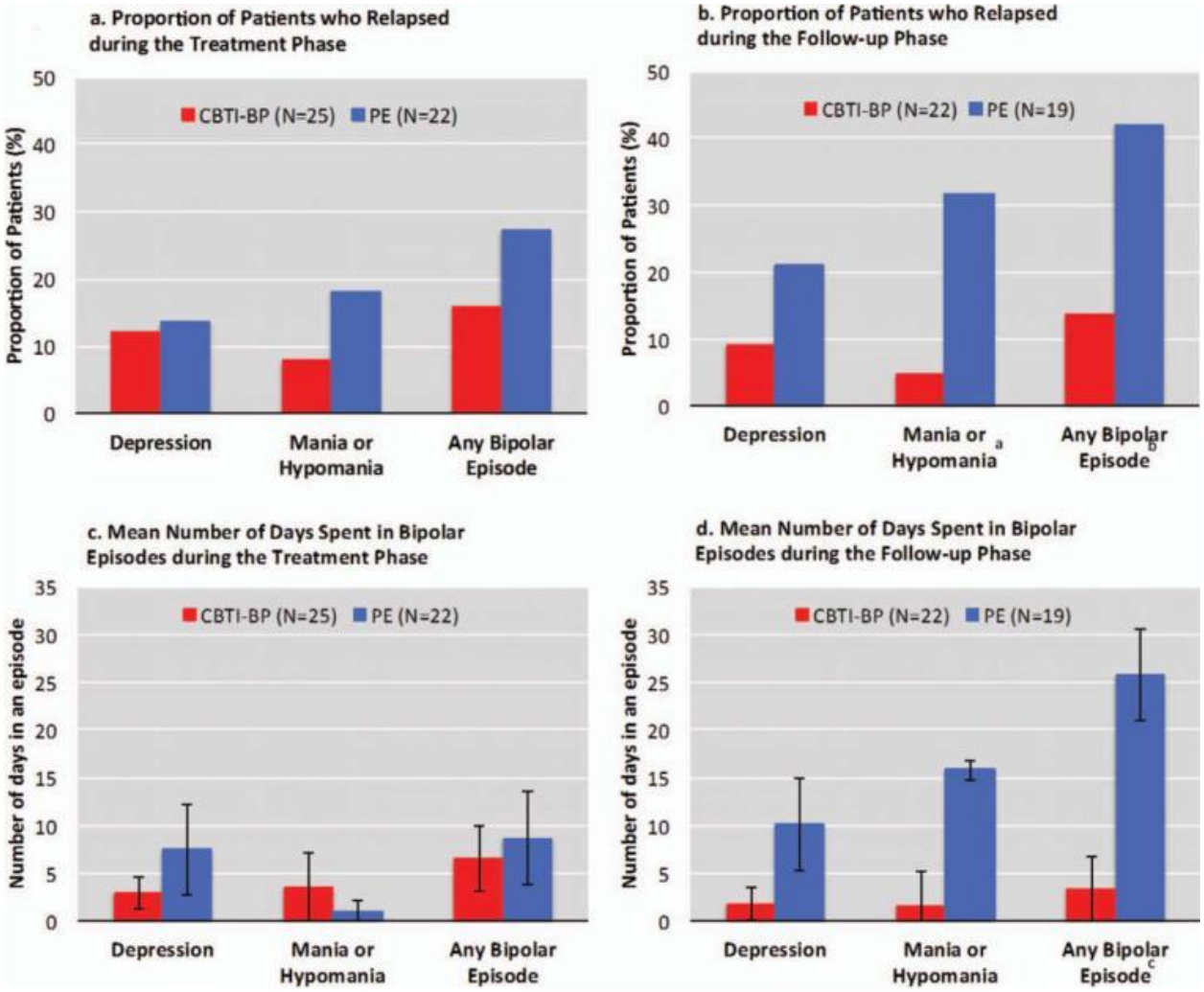
Perlis AJP 2006

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



ONLINE COLOR

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

Blue-blocking glasses may improve sleep quality in bipolar disorder

- Study #1 (n=20)
  - Manic patients, 5 nights
  - Greater sleep efficiency, fewer nights of interrupted sleep
- Study #2 (n=43)
  - Bipolar (not manic)
  - No change in actigraphy or mood ratings
  - … but significant change in Morningness-Eveningness Questionnaire score…

Henriksen J Sleep Res 2020; n=20
Esaki Bipolar Disorder 2020; n=43

Cognition

”I can’t think straight”: persistent cognitive complaints

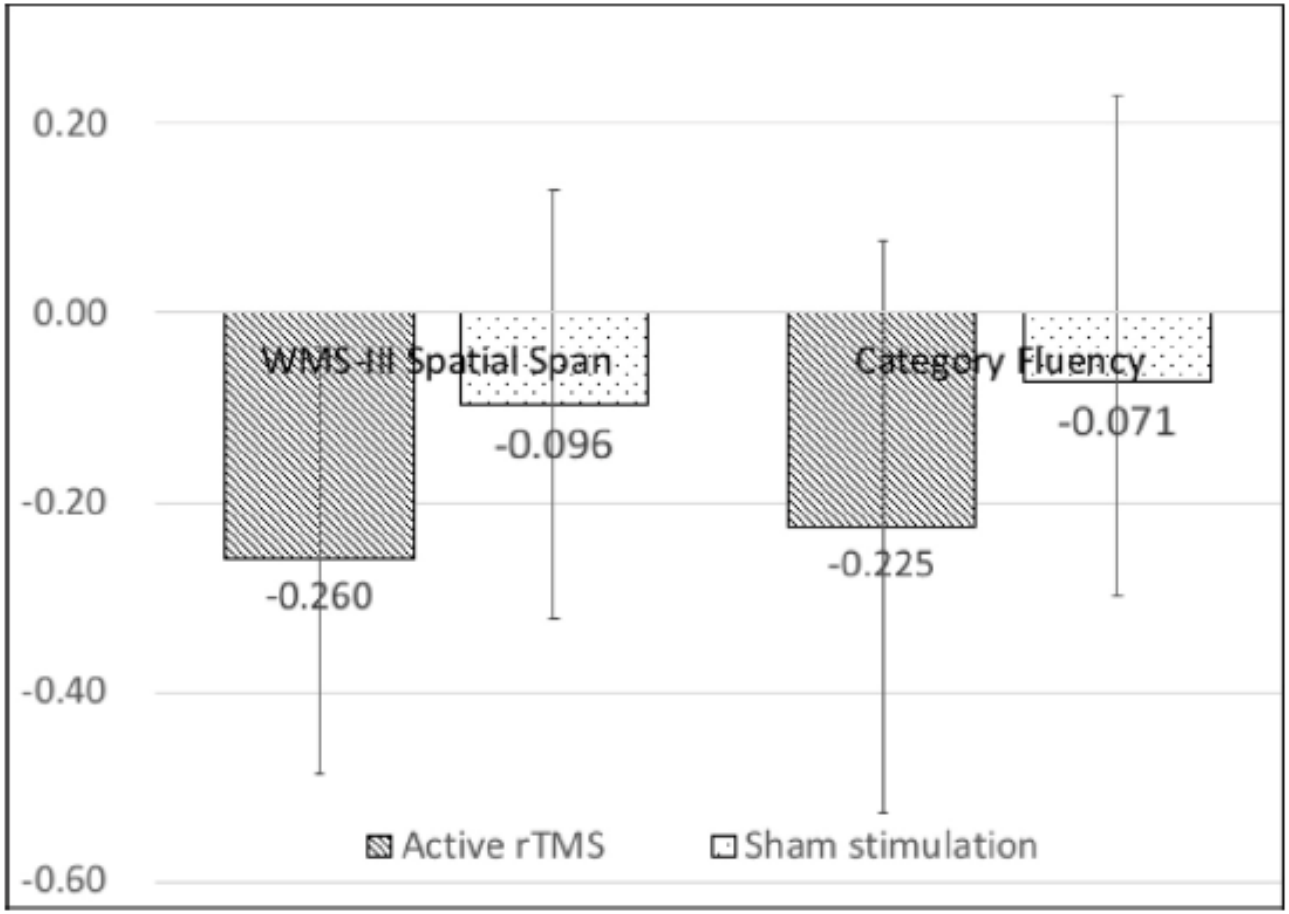
- Multifactorial
  - Medication adverse effects
  - Mood symptoms (including residual symptoms)
  - True comorbidity (ADHD)
  - Chronic features of disease

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; n=325 bipolar 2 disorder
Van Meter J Clin Psychopharm 2021; n=34 bipolar/schizophrenia

Absence of significant benefit of rTMS in euthymic bipolar patients



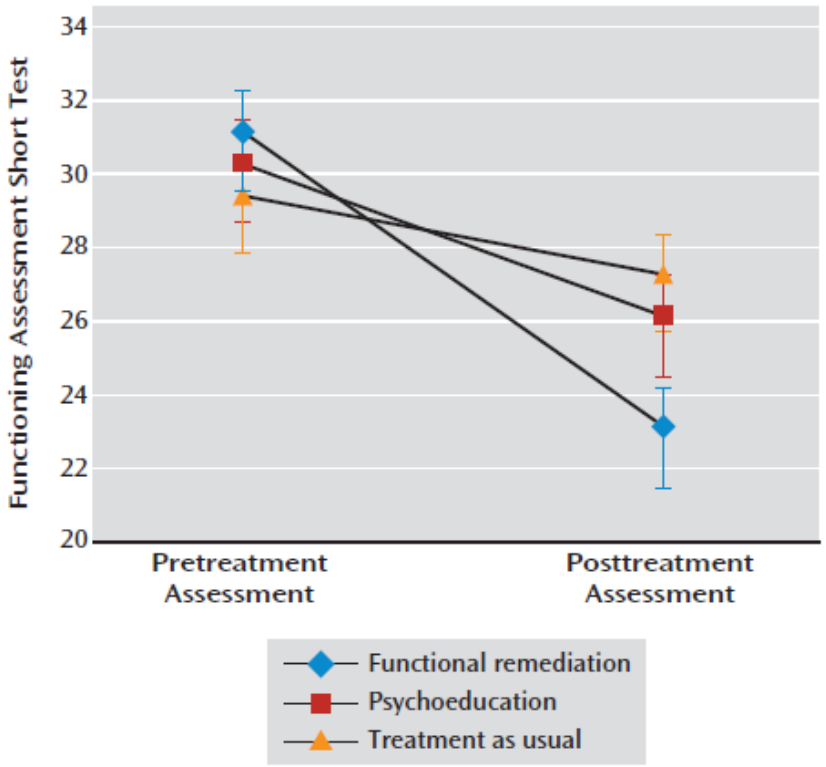
N=52 euthymic bipolar patients; single-blind

Lin-Lin *JAD* 2019 (but does not worsen cognition in depression - Myczkowski *JAD* 2018)

Psychosocial strategies to improve cognition and function

Functional remediation for bipolar disorder

FIGURE 1. Changes in Functional Impairment Scores Before and After Intervention in Patients With Bipolar Disorder[a]



Valls Psychol Med 2021; n=65

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

Torrent AJP 2013; See also Valls Psychol Med 2021

Cognitive remediation in remitted bipolar disorder

- Action-Based Cognitive Remediation (ABCR) x 11 weeks
- No benefit on composite cognitive score (primary); no benefit on functional measure

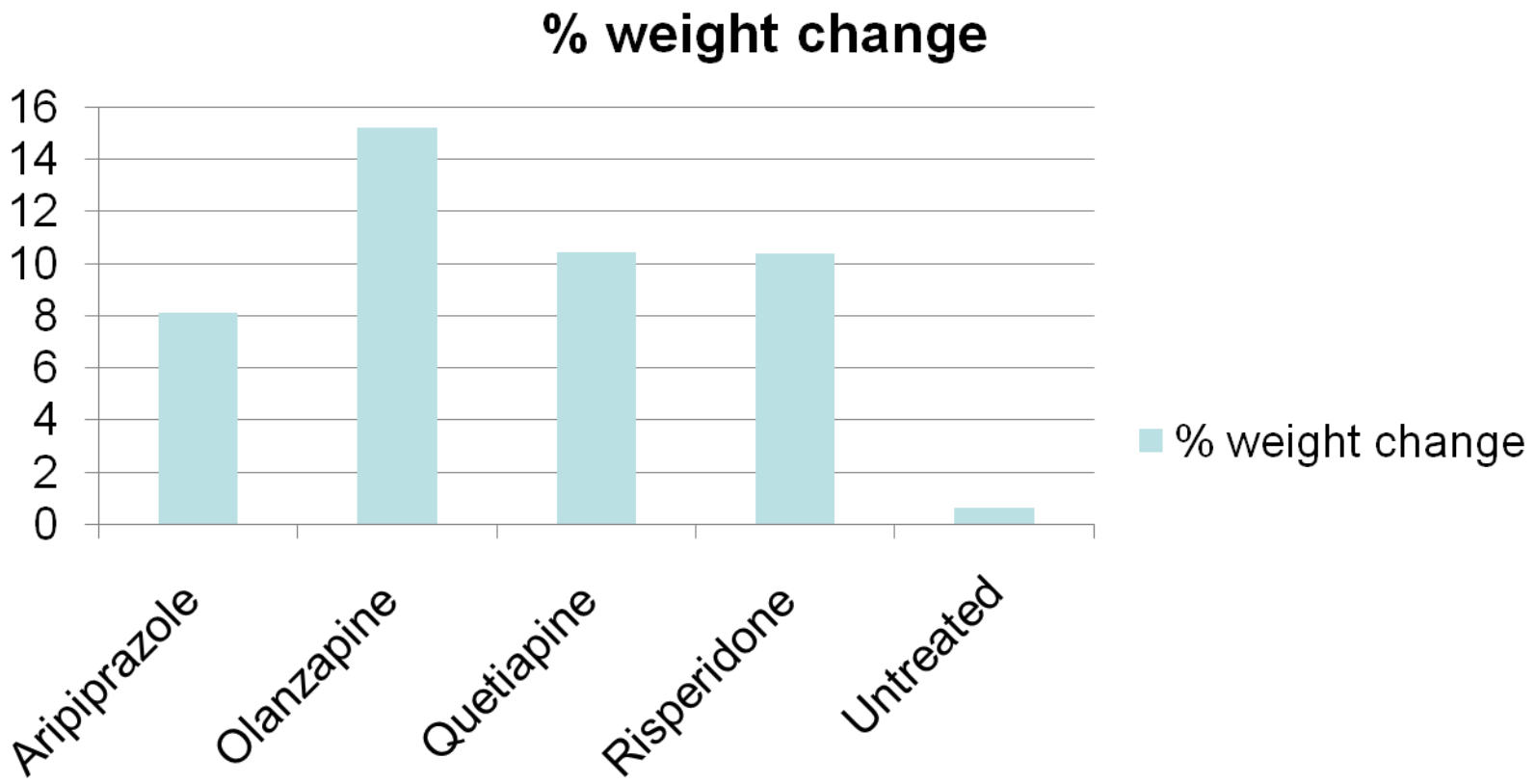
- BUT – secondary measures:
  - executive function measure (d = 0.65)
  - subjective cognitive functioning (d = 0.80)

- (and adding aerobic exercise did not improve outcomes)

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

Weight gain/metabolic adverse effects

12-week weight change in treatment-naïve children and adolescents



Correll JAMA 2009

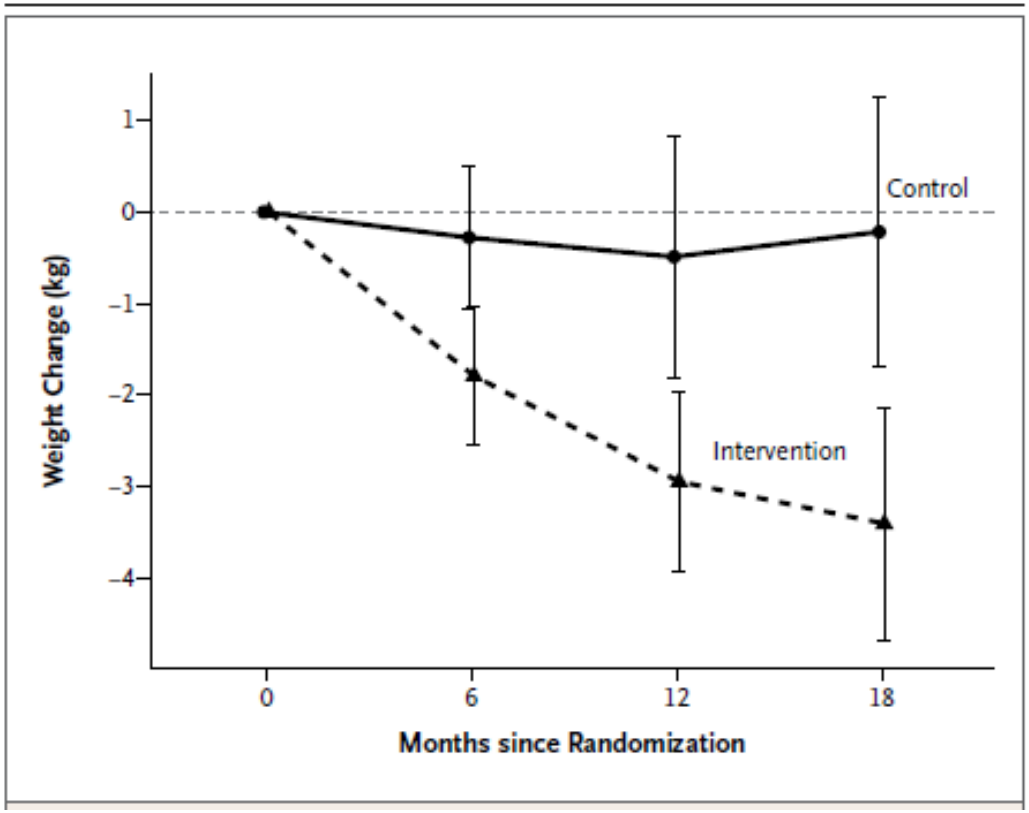
Managing Adverse Effects: weight gain

- Provide education about diet and exercise
- Provide referral to a nutritionist

- Older strategies:
  - Metformin (250tid or 500bid)^
  - Topiramate titrated to point of appetite suppression (100-150mg)*
  - Zonisamide titrated to point of appetite suppression (100-200mg)*
  - Bupropion (SR or XL) 100mg-300mg*
- Newer general weight loss strategies:
  - Sibutramine
  - Orlistat (beware GI symptoms)
  - Lorcaserin
  - Naltrexone-bupropion
  - Semaglutide
  - Liraglutide

From TMAP (http://www.mhmr.state.tx.us/centraloffice/medicaldirector/TMAPtoc.html
And https://www.niddk.nih.gov/health-information/weight-management/prescription-medications-treat-overweight-obesity)

Weight loss programs work in serious mental illness

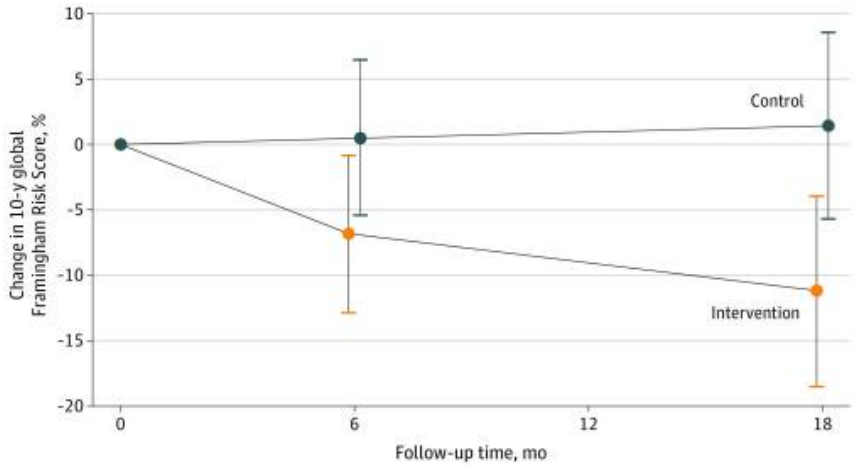


Mean 18-mo weight loss 3.2kg in intervention group (22% bipolar; ~82% on atypical antipsychotic)

Daumit NEJM 2013; see also Kilbourne JCP 2013, Bartels AJP 2015

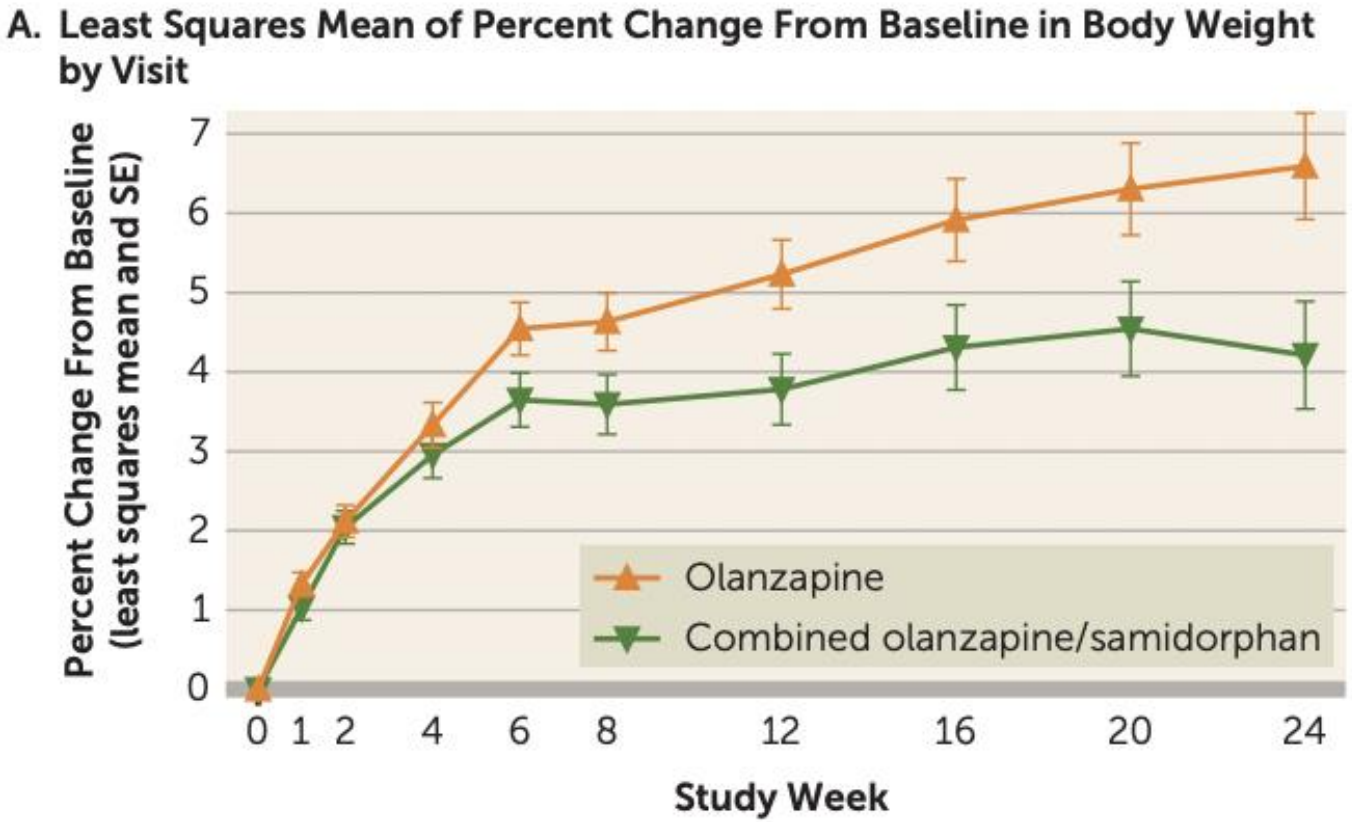
Psychosocial interventions to decrease cardiovascular risk in SMI

- 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 w

24-week study of olanzapine+samidorphan vs olanzapine alone in schizophrenia

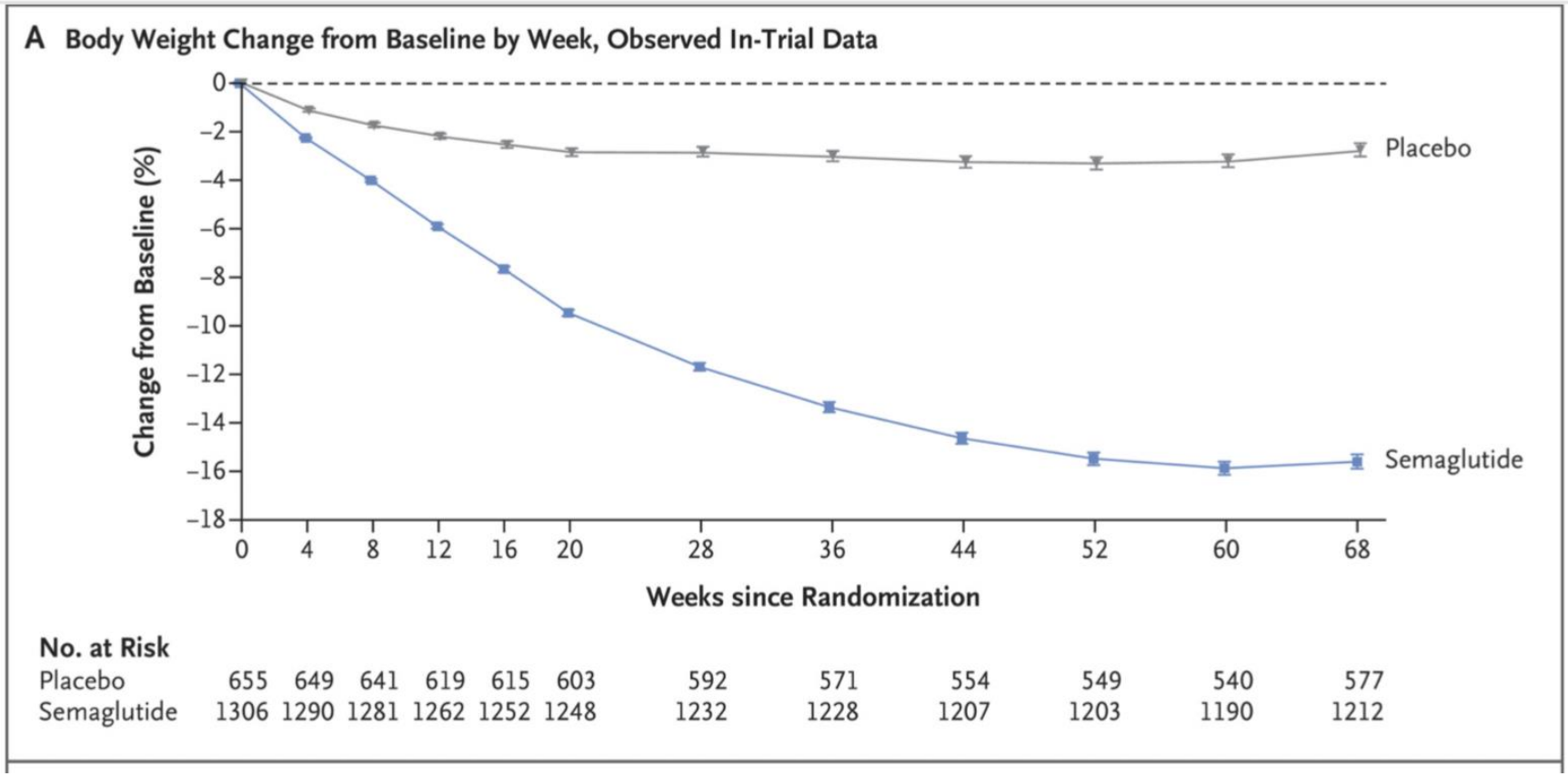


Correll AJP 2020; n=561

weight gain 7%+ in **27.5% vs 42.7%**

No meaningful differences in efficacy/tolerability

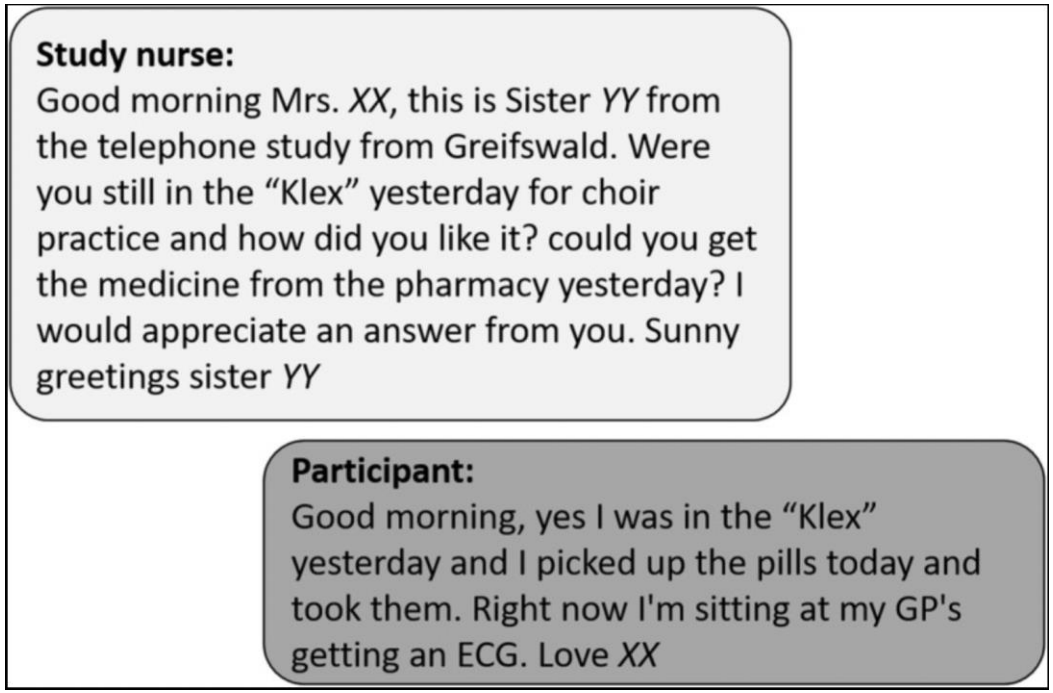
Semaglutide for overweight or obesity



Wilding NEJM 2021; 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%)

What about apps? (*Hi-roller*, circa 2003)

Texting did not improve QOL outcomes in bipolar disorder and schizophrenia



Stenzel BMC Psychiatry 2021; n=118

… but note, may improve adherence: Menon *J Psych Res* 2018; Biederman *J Clin Psychopharm* 2019

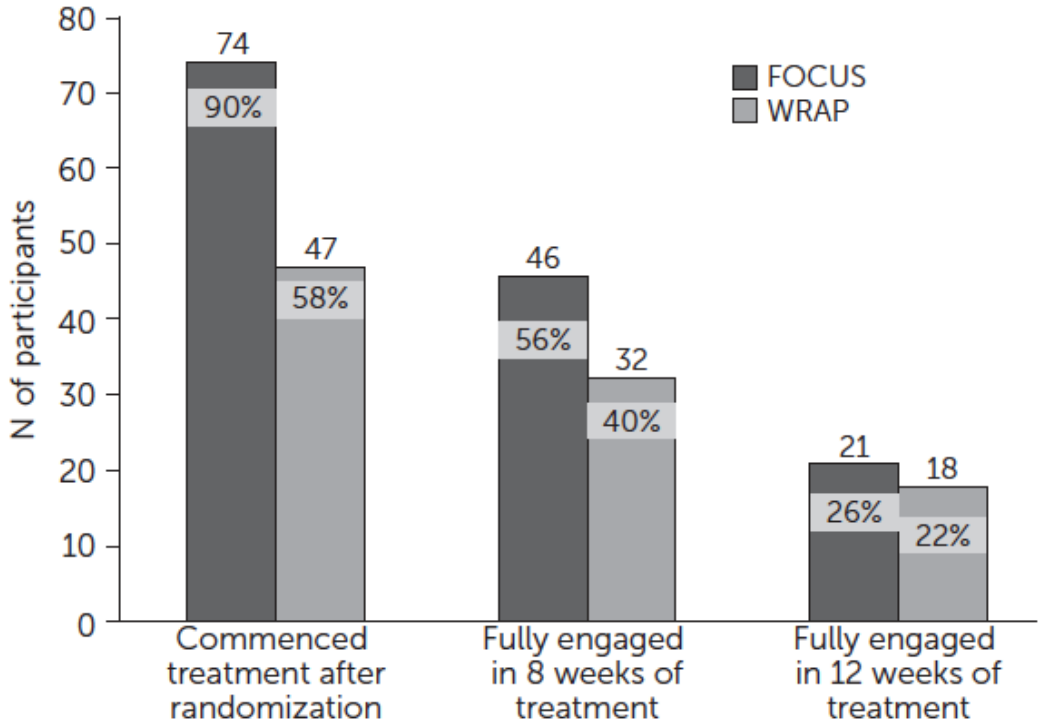
Mood tracking apps did not improve mood but…

- 9 months of smartphone-based mood tracking or TAU
- No difference in depressive or manic symptoms
- Improved self-reported QOL/stress

Faurholt-Jepsen, Psychol Med 2020; n=129

Smartphone app (FOCUS) did as well or better than clinic-based group therapy (WRAP) x 3mo

FIGURE 1. Percentage of patients fully engaged in Wellness Recovery Action Plan (WRAP) and FOCUS, by stage of intervention



N=163 with SMI; similar benefit in depressive sx; retained at 6mo

Ben-Zeev *Psych Services* 2018

Apps

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

BUT…

- 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?

Special considerations

- Treatment resistance/Rapid cycling
- Bipolar 2
- Covid-19

Treatment resistance

- No consistent/standardized definition exists!

Role of ECT in mood disorder maintenance remains unclear

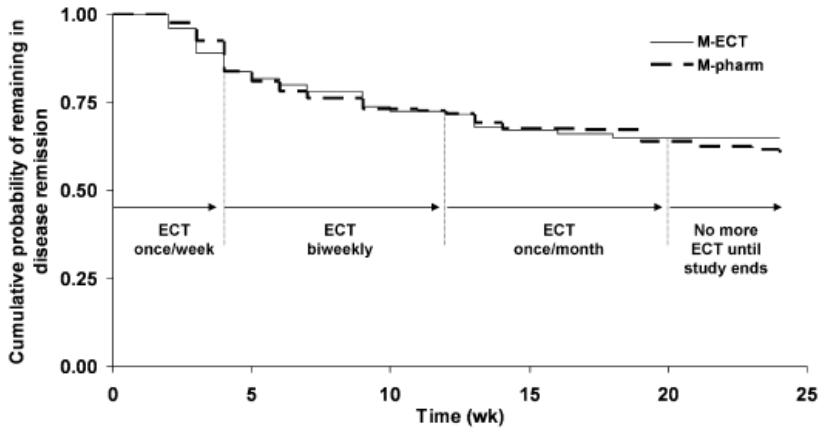


FIGURE 1. Proportion of patients remaining in remission during the maintenance phase in the CORE trial. Reprinted with permission from Kellner et al.[15] Log-rank test comparing distributions of time to relapse for M-ECT versus M-pharm: $\chi^2 = 0.30$; $P = 0.59$.

TABLE 4. CANMAT Recommendations for ECT in Bipolar Disorders

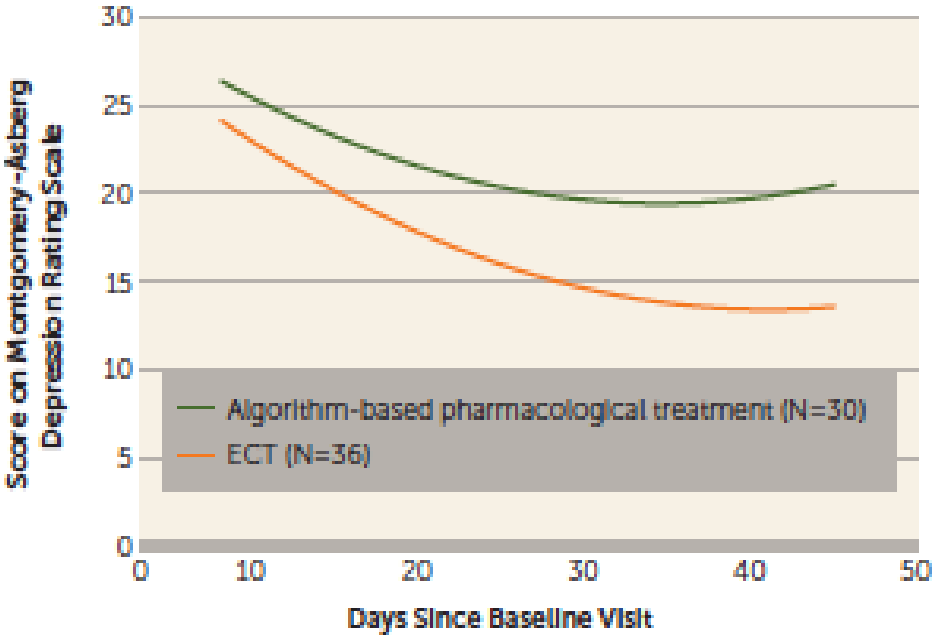
Diagnosis	Recommendations for ECT
Acute mania	Second line
Acute bipolar I depression	Third line
Maintenance therapy of bipolar disorder	Third line (adjunctively)
Maintenance therapy of bipolar II disorder	Third line

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).

Schoeyen AJP 2015 (n=66 in ITT analysis; blinded raters only) - >50% bipolar II; Minimal difference in cognitive measures between groups (Kessler JCP 2014)

Unilateral ECT can still contribute to memory change (6mo f/u)

- N=26 assessed at 6 mo
- MATRICS Consensus Cognitive Battery composite score *improved* by 4.1 points in both groups (P = .04) from baseline to 6 months

- BUT Autobiographical Memory Interview-Short Form consistency scores were *worsened* in both groups
  - (72.3% of baseline in pharm vs 64.3% ECT; P = .09).

- SO – **overall cognition likely improves, but memory is still impacted**.

Bjoerke-Bertheussen Bipolar Disorders 2018

Consider clozapine and 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)

- Eg, Paliperidone (Fu JCP 2015); aripiprazole once-monthly (Calabrese JCP 2017); risperidone long-acting (Vieta Neuropsychopharm 2012)

Rapid Cycling

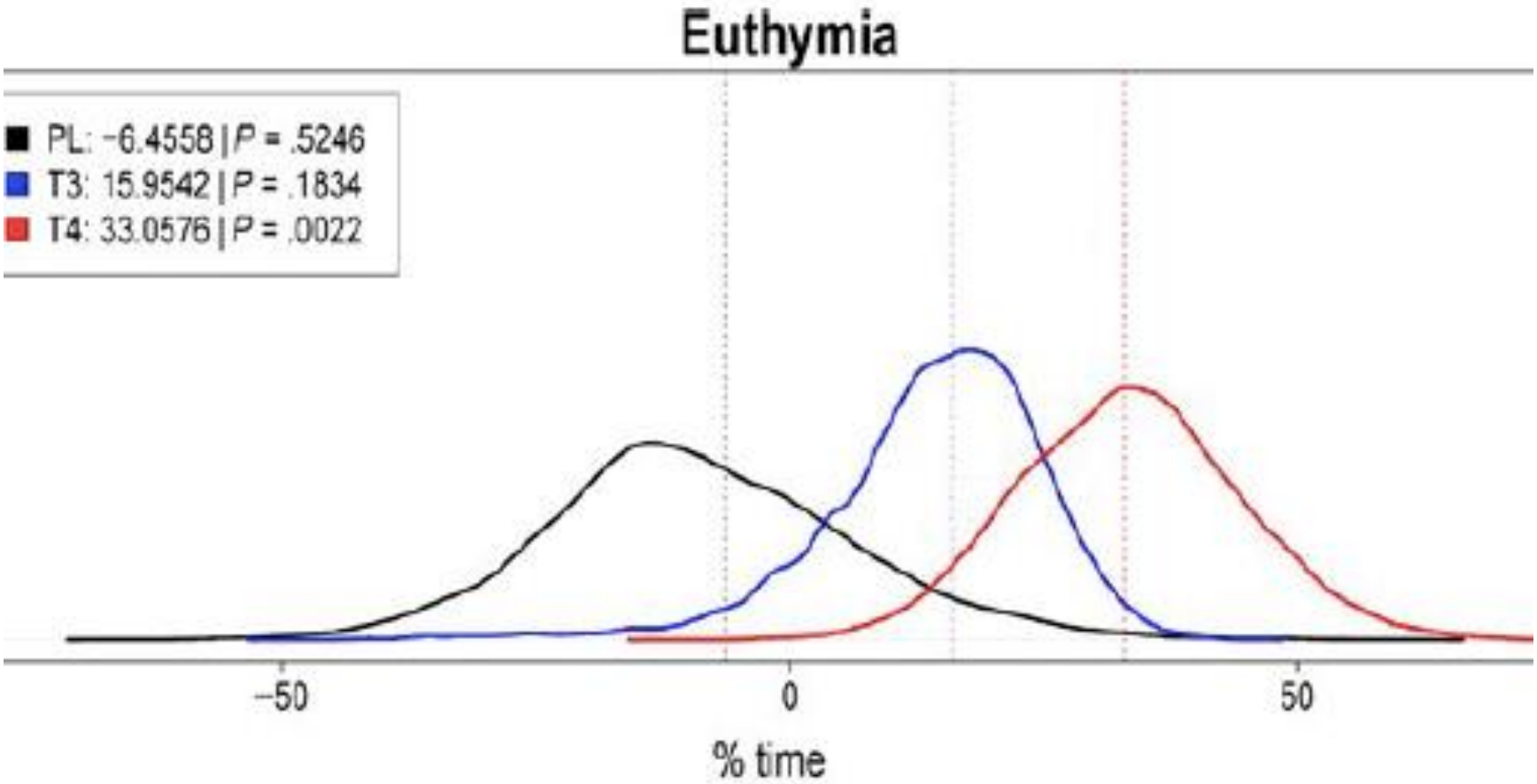
- 6 RCT'S in rapid cycling
- 19 other post-hoc analyses of trials with rapid cycling patients

1. rapid cycling patients perform worse in the follow-up period
2. lithium efficacy comparable to anticonvulsants
3. aripiprazole and olanzapine appear promising for the maintenance of response of rapid cyclers
4. there might be an association between antidepressant use and the presence of rapid cycling.

- "…there is no clear consensus with respect to its optimal pharmacological management."

Fountoulakis *Bipolar Disord* 2013

Something new about something old: L-T4 for rapid cycling



N=32 treatment-resistant rapid cycling bipolar patients; L-T4 vs T3 vs pbo (L-T4 increased until FT4I 4.5-7.5 or TSH<0.1) – 4+ months

Walshaw *Bipolar Disorders* 2018

What about bipolar II?
Far less RCT data

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

CANMAT Bipolar Disorders 2018

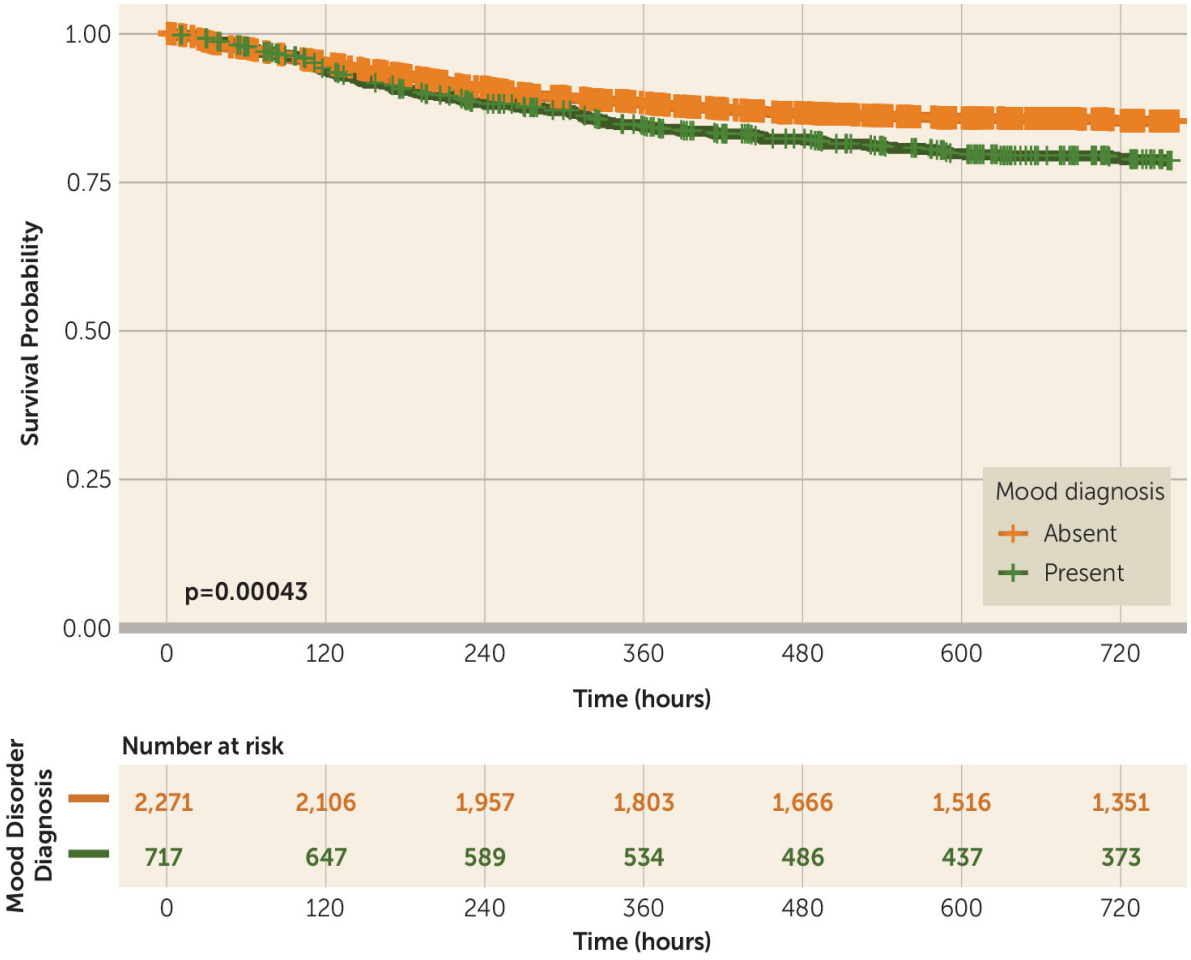
Lack of consensus regarding management of bipolar 2 disorder

- 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

Latest and greatest

Mood disorders are associated with poorer outcome among individuals hospitalized with COVID-19



Castro AJP 2021

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Long-term Treatment in Bipolar Disorder: Fall 2020 Update

Roy H. Perlis, MD MSc

Center for Experimental Drugs and Diagnostics
Massachusetts General Hospital
Harvard Medical School

rperlis@partners.org