MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Long-term Treatment in Bipolar Disorder: Fall 2020 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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- **Psy Therapeutics (equity) - Founder/SAB member**
- **Outermost Therapeutics (equity) – Founder/SAB member**
- **Genomind (consultant fee) - SAB member**
- **RID Ventures (consultant fee) – advisor**
- **Takeda (consultant fee) - advisor**

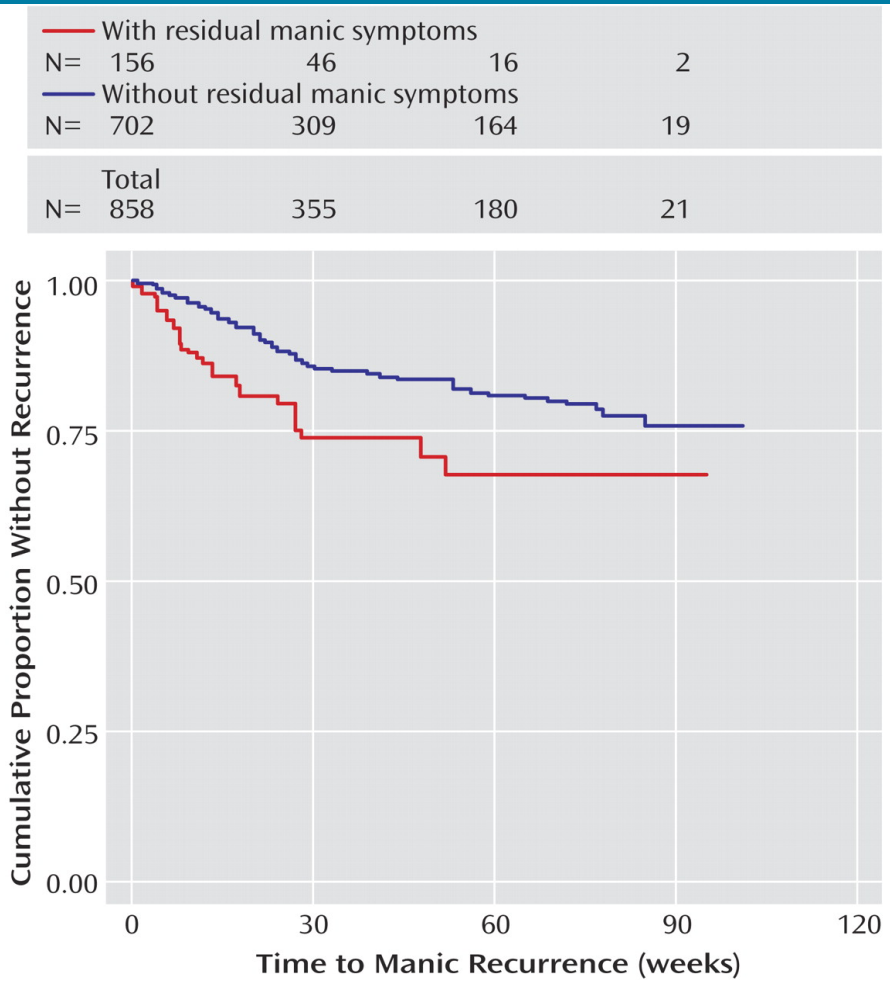
Longer-term treatment

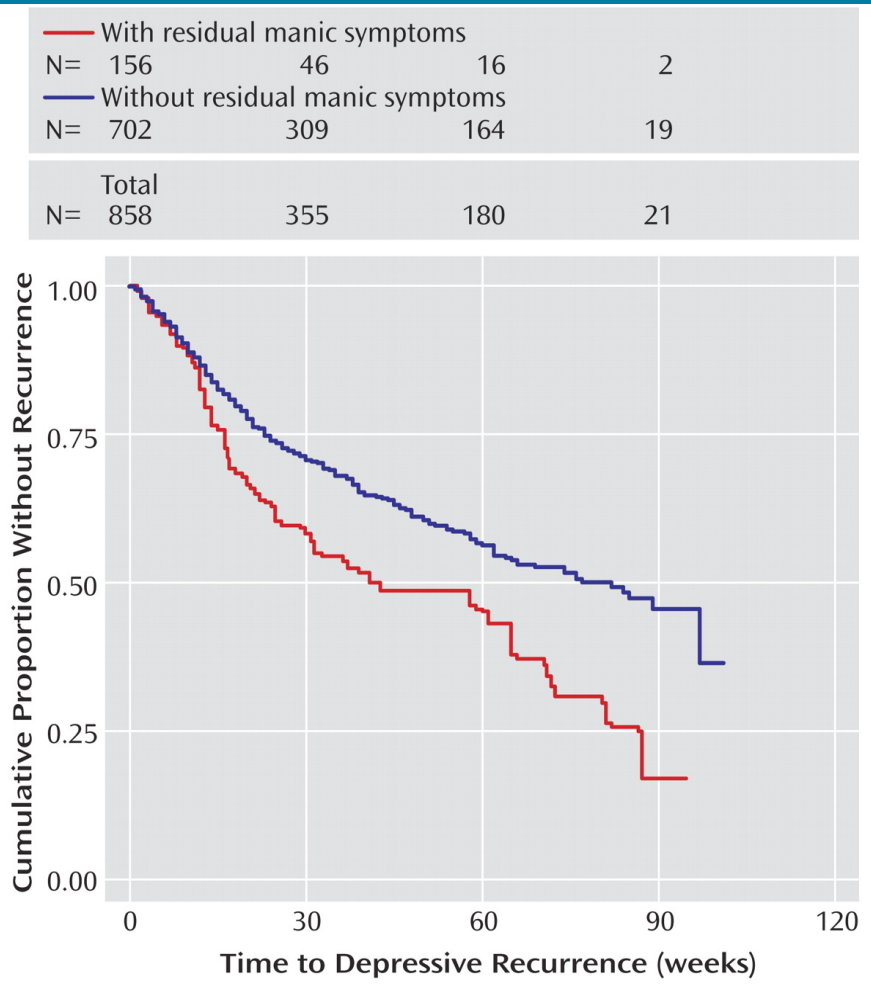
- A marathon, not a sprint

Overview

- Prevention of recurrence
  - Pharmacotherapy
  - Psychosocial therapies
- Special populations

About Half of Patients Recur Within Two Years of Index Recovery





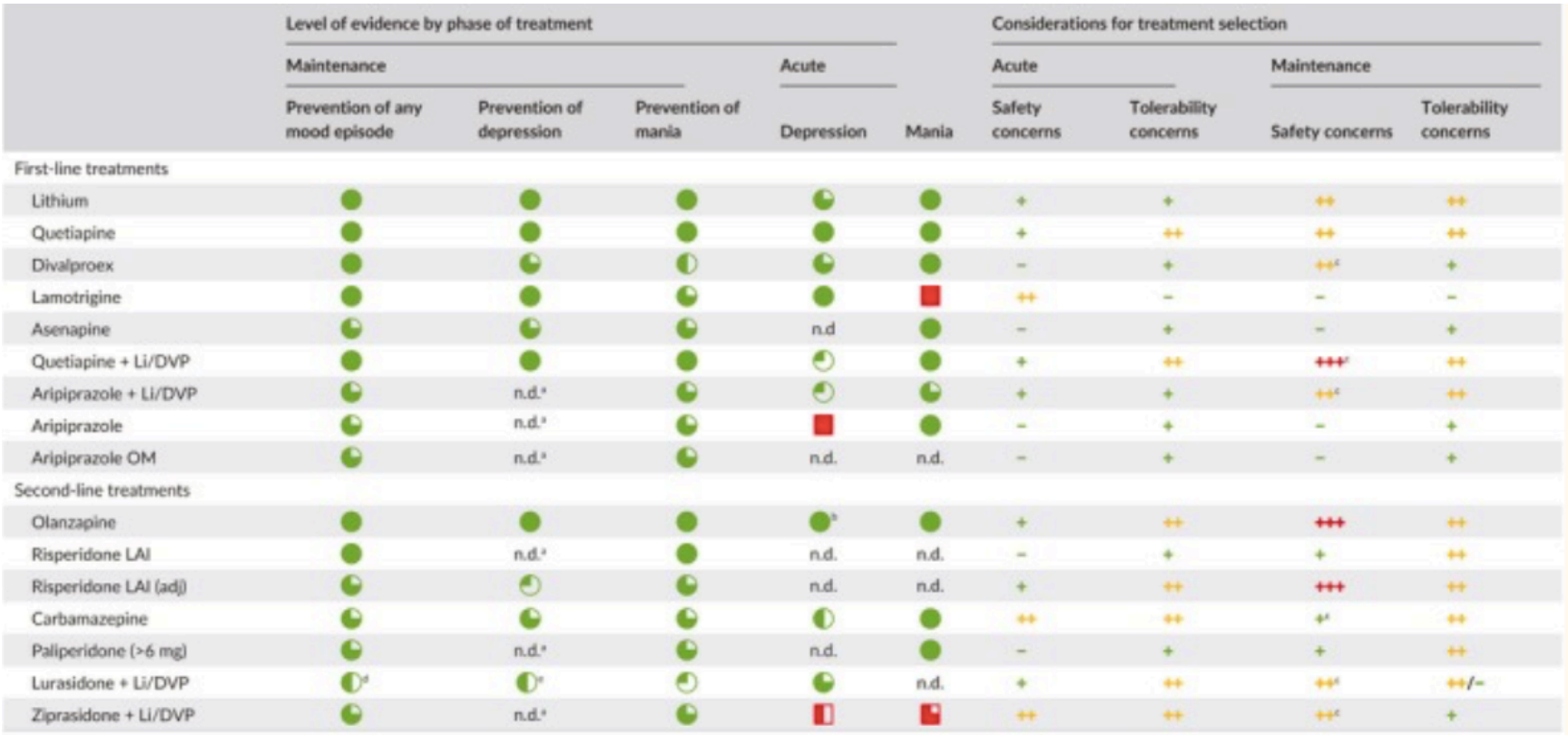
Perlis et al., *Am J Psychiatry* 2006; 163: 217-224

CANMAT 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]	◐[e]	◕	◔	n.d.
Ziprasidone + Li/DVP	◔	n.d.[a]	◔	◧	◧

CANMAT Bipolar Disorders 2018

Efficacy is only half the battle…



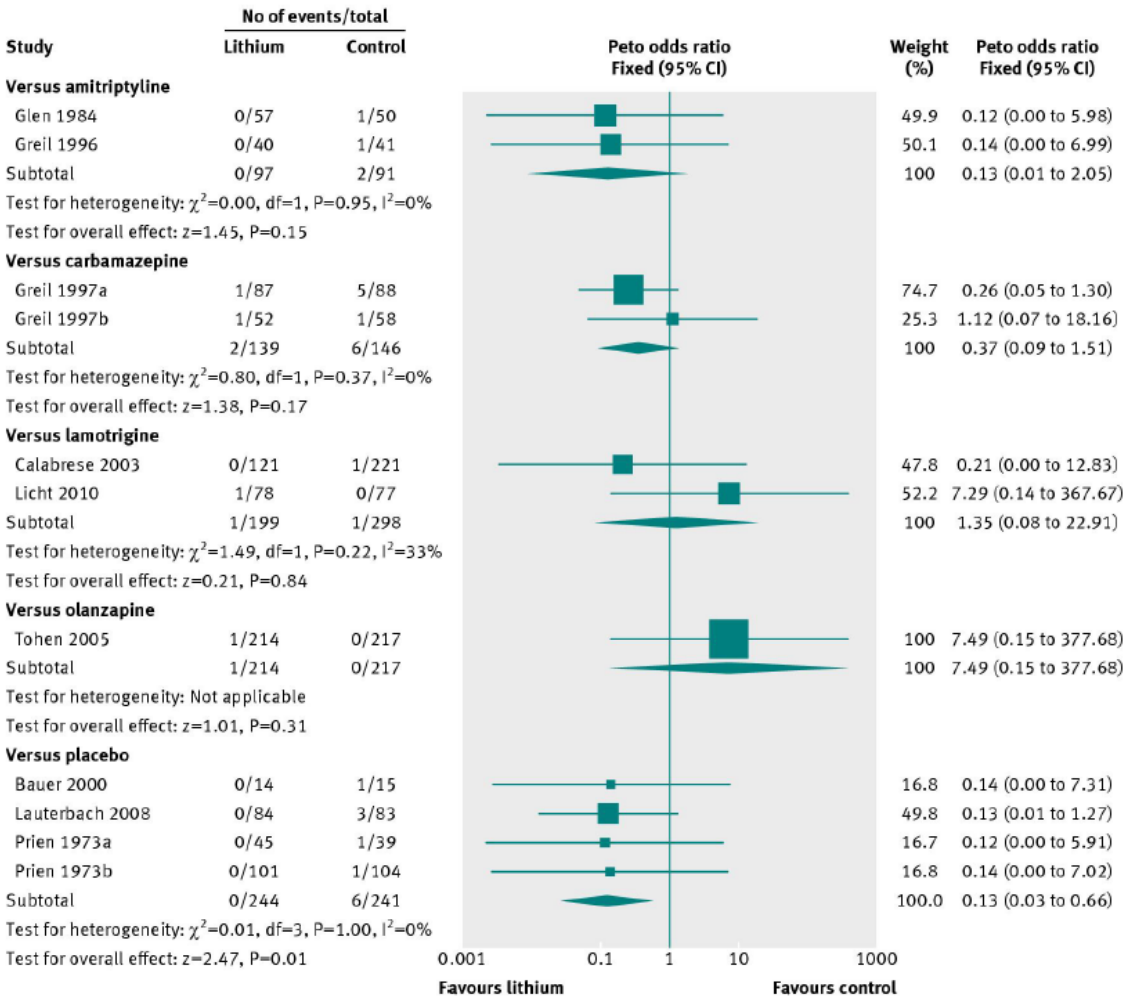
	Level of evidence by phase of treatment					Considerations for treatment selection			
	Maintenance			Acute		Acute		Maintenance	
	Prevention of any mood episode	Prevention of depression	Prevention of mania	Depression	Mania	Safety concerns	Tolerability concerns	Safety concerns	Tolerability concerns
First-line treatments									
Lithium	●	●	●	◔	●	+	+	++	++
Quetiapine	●	●	●	●	●	+	++	++	++
Divalproex	●	◔	◐	◔	●	–	+	++[c]	+
Lamotrigine	●	●	◔	●	■	++	–	–	–
Asenapine	◔	◔	◔	n.d	●	–	+	–	+
Quetiapine + Li/DVP	●	●	●	◔	●	+	++	+++[c]	++
Aripiprazole + Li/DVP	◔	n.d.[a]	◔	◔	◔	+	+	++[c]	++
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	◔	◔	◔	◐	●	++	++	+[c]	++
Paliperidone (>6 mg)	◔	n.d.[a]	◔	n.d.	●	–	+	+	++
Lurasidone + Li/DVP	◐[d]	◐[e]	◔	◔	n.d.	+	++	++[c]	++/–
Ziprasidone + Li/DVP	◔	n.d.[a]	◔	◧	◧	++	++	++[c]	+

CANMAT Bipolar Disorders 2018

- "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

After a 1st manic episode, lithium-treated patients may have greater cognitive improvement

A single-blind, randomised controlled trial on the effects of lithium and quetiapine monotherapy on the trajectory of cognitive functioning in first episode mania: A 12-month follow-up study.

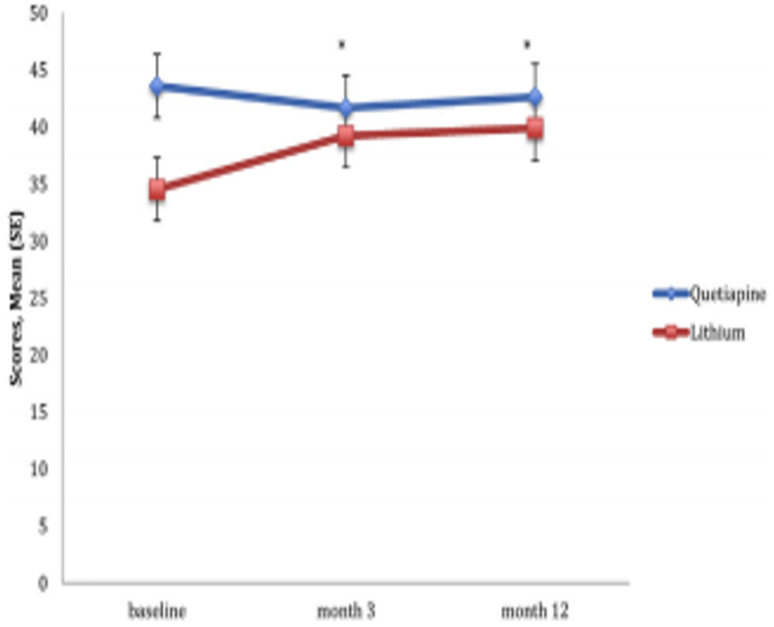
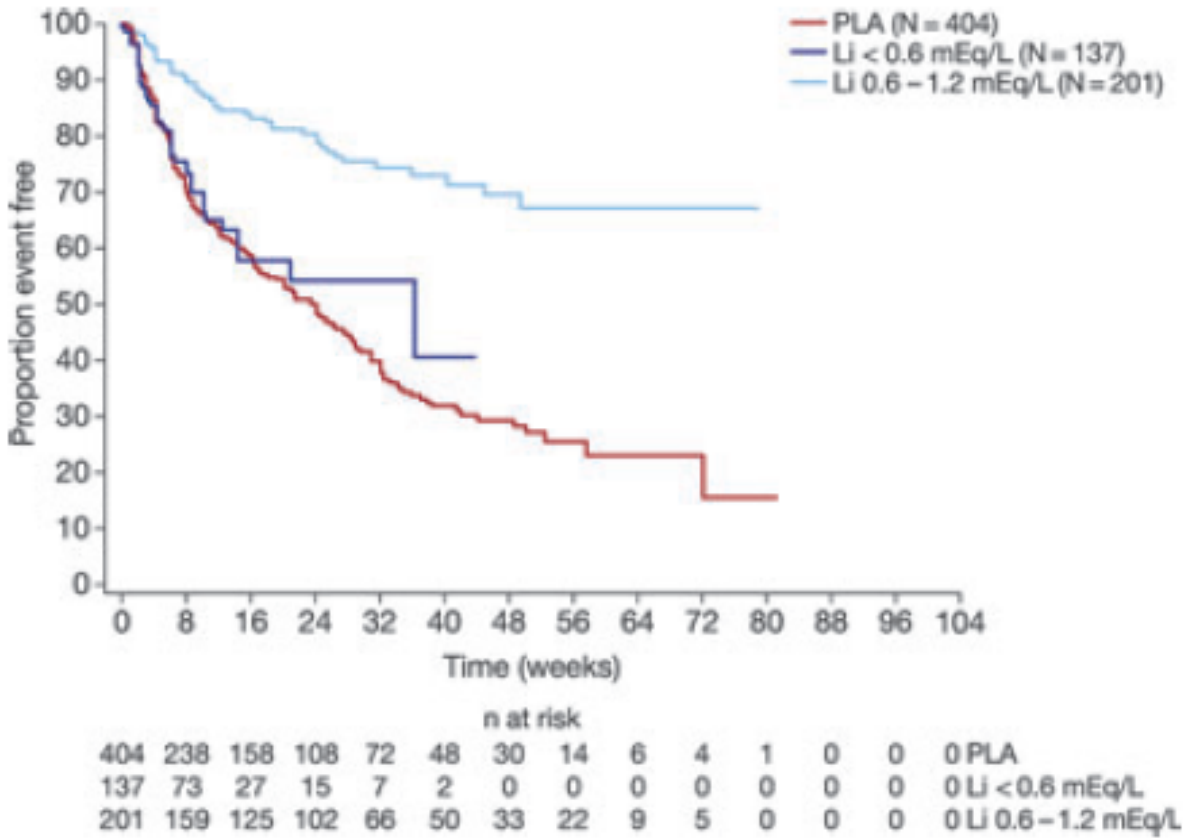


Fig. 2. Mean scores for FAS fluency between treatment groups. *$P < 0.05$, as determined from planned comparisons assessing between group differences in the rate of change from baseline to end points (month 3 or month 12).

Daglas *Eur Psychiatry* 2016; n=16 patients with 1st episode mania

Aim for Li level of 0.6+

- Post hoc analysis of SPaRCle trial – time to recur



Nolen Bipolar Disord 2013

Newer ideas about an old drug

- 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…)
    - Concomitant SSRI/SNRI?
  - Increase risk:
    - Lithium levels exceeding 0.6 mEq/L (risk increases as level increases)
    - Concomitant first-generation antipsychotic?

Castro, *Neuropsychopharmacology* 2016

Newer ideas about an old drug

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

= Greater risk with older age, schizoaffective, hypertension, smoking…

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

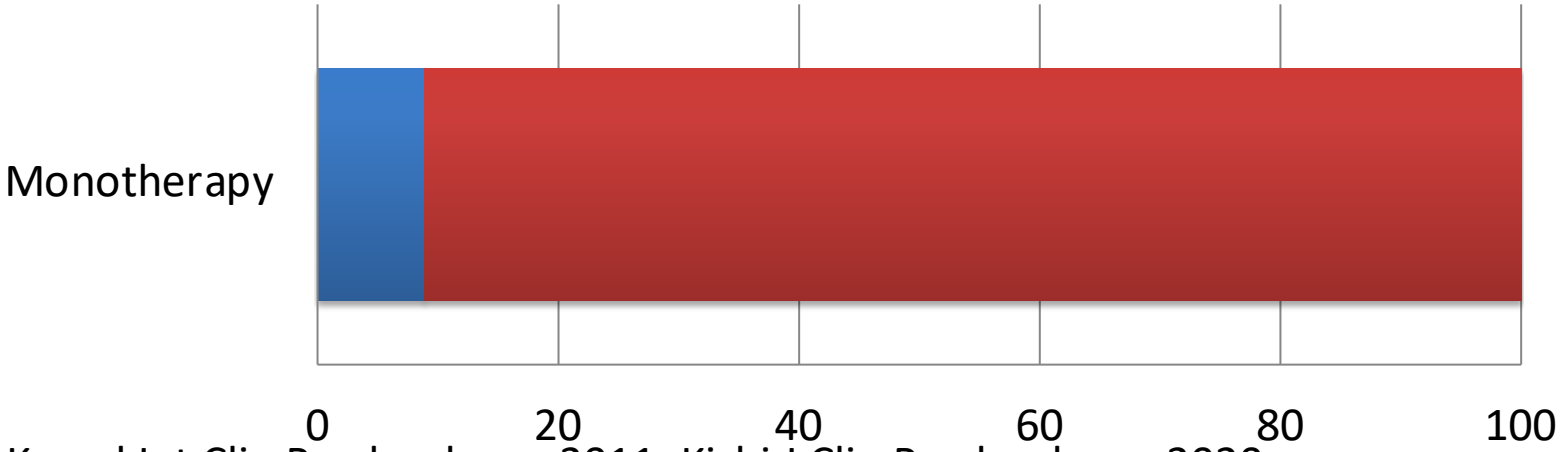
Castro, *Neuropsychopharmacology* 2016

New ideas about an old drug

- *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

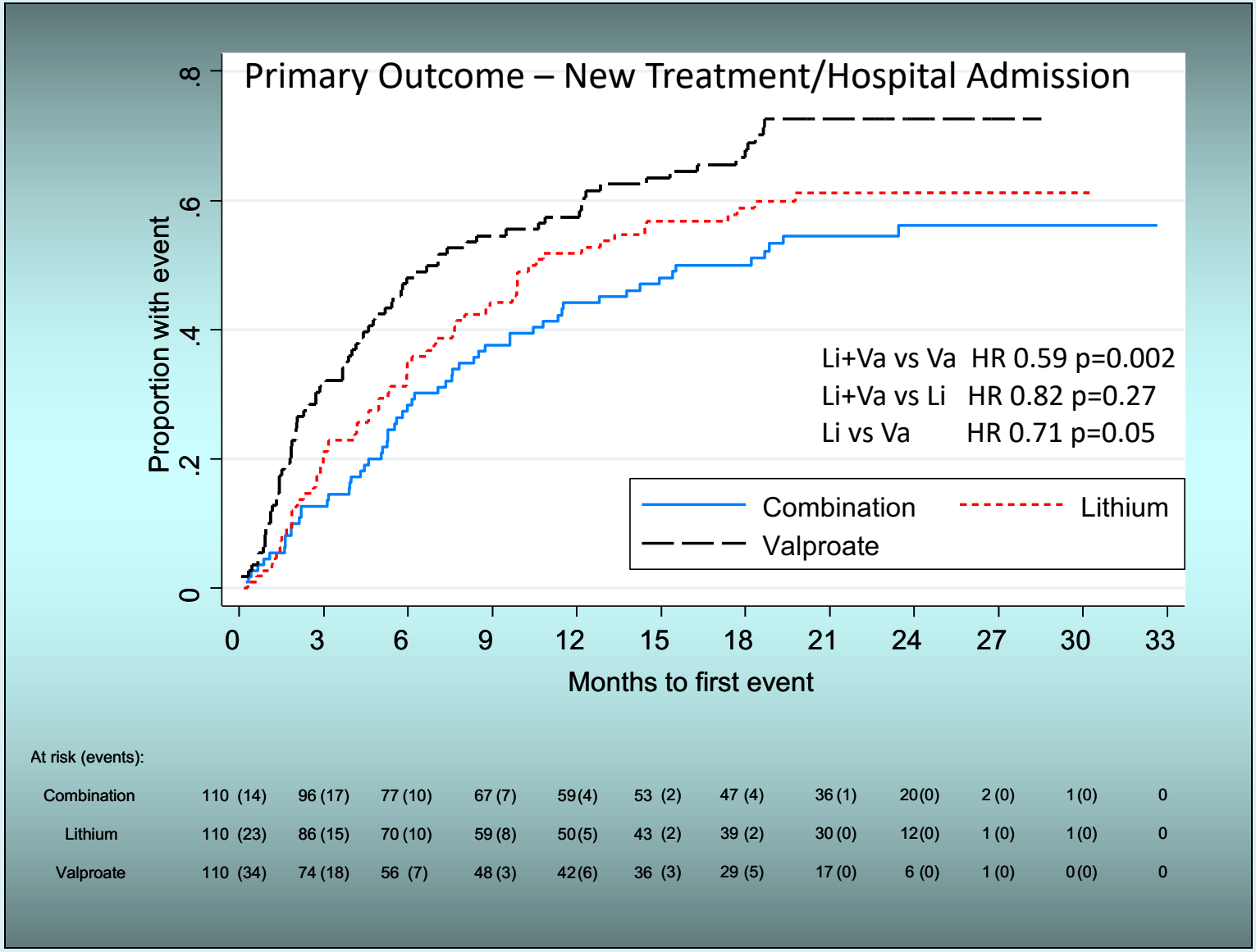
But in the real world, few patients stay on lithium monotherapy

- 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

Li or combination>VPA



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

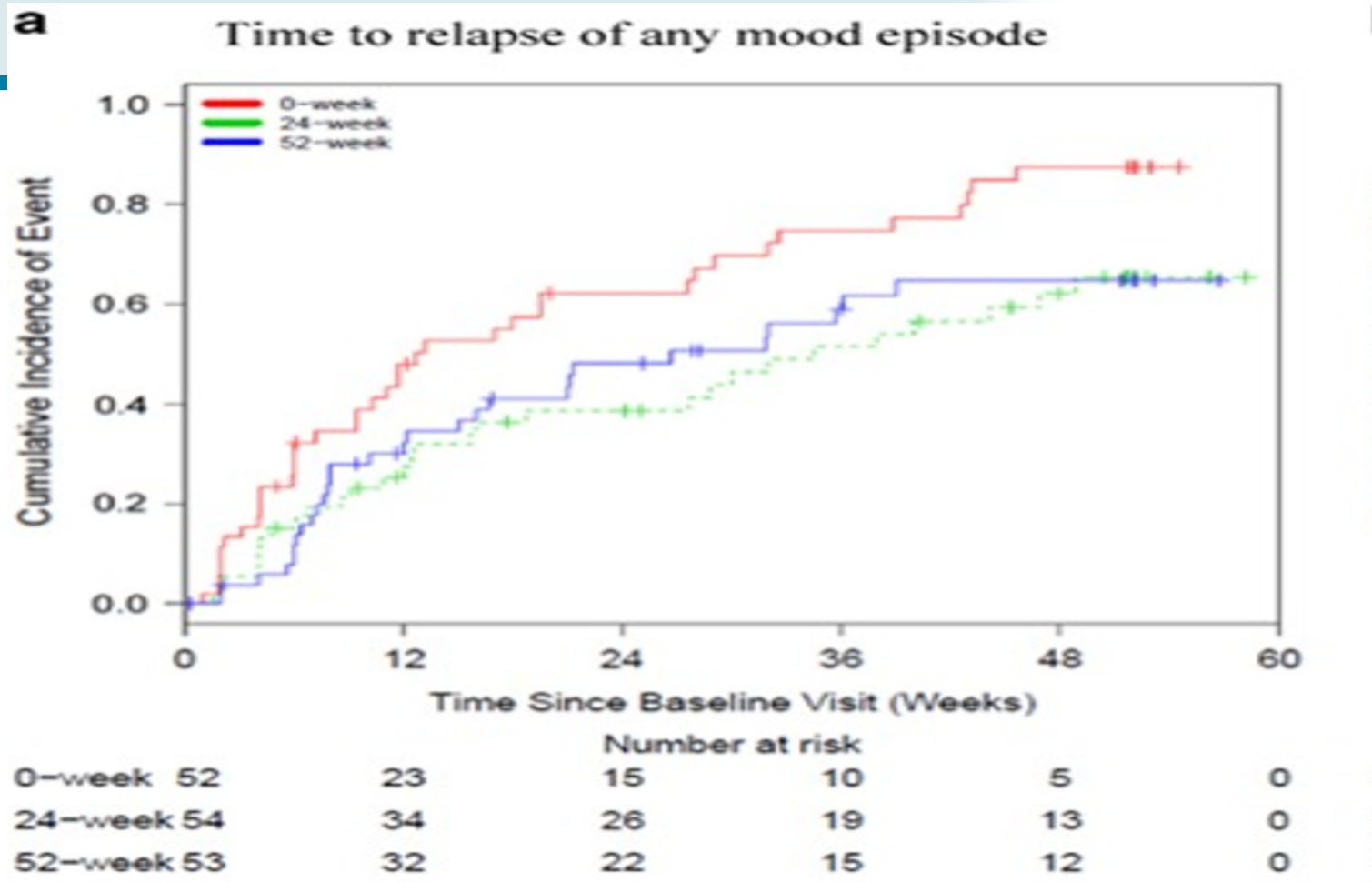
BALANCE Investigators Lancet 2010

How to choose?

- Efficacy, efficacy, efficacy
- Tolerability and patient preference

When treatments are added acutely, beware early discontinuation!

Early vs late discontinuation of add-on atypical antipsychotic



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!)

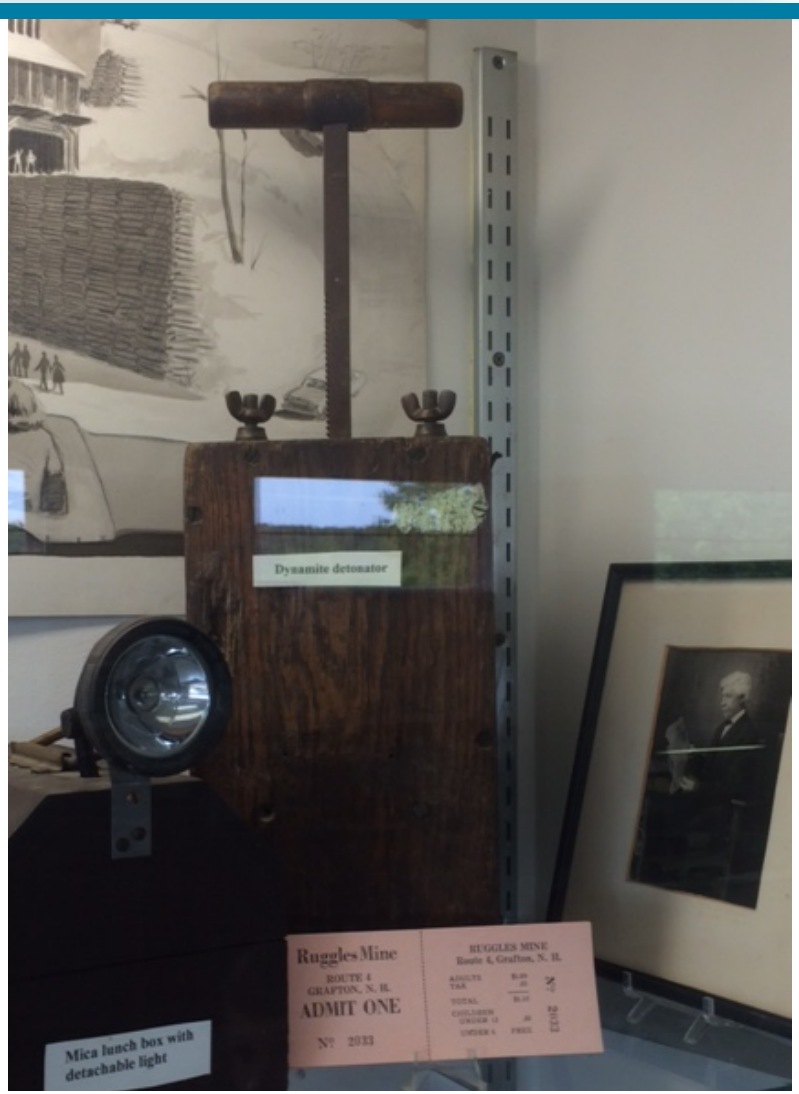
What about bipolar II?
Far less RCT data

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

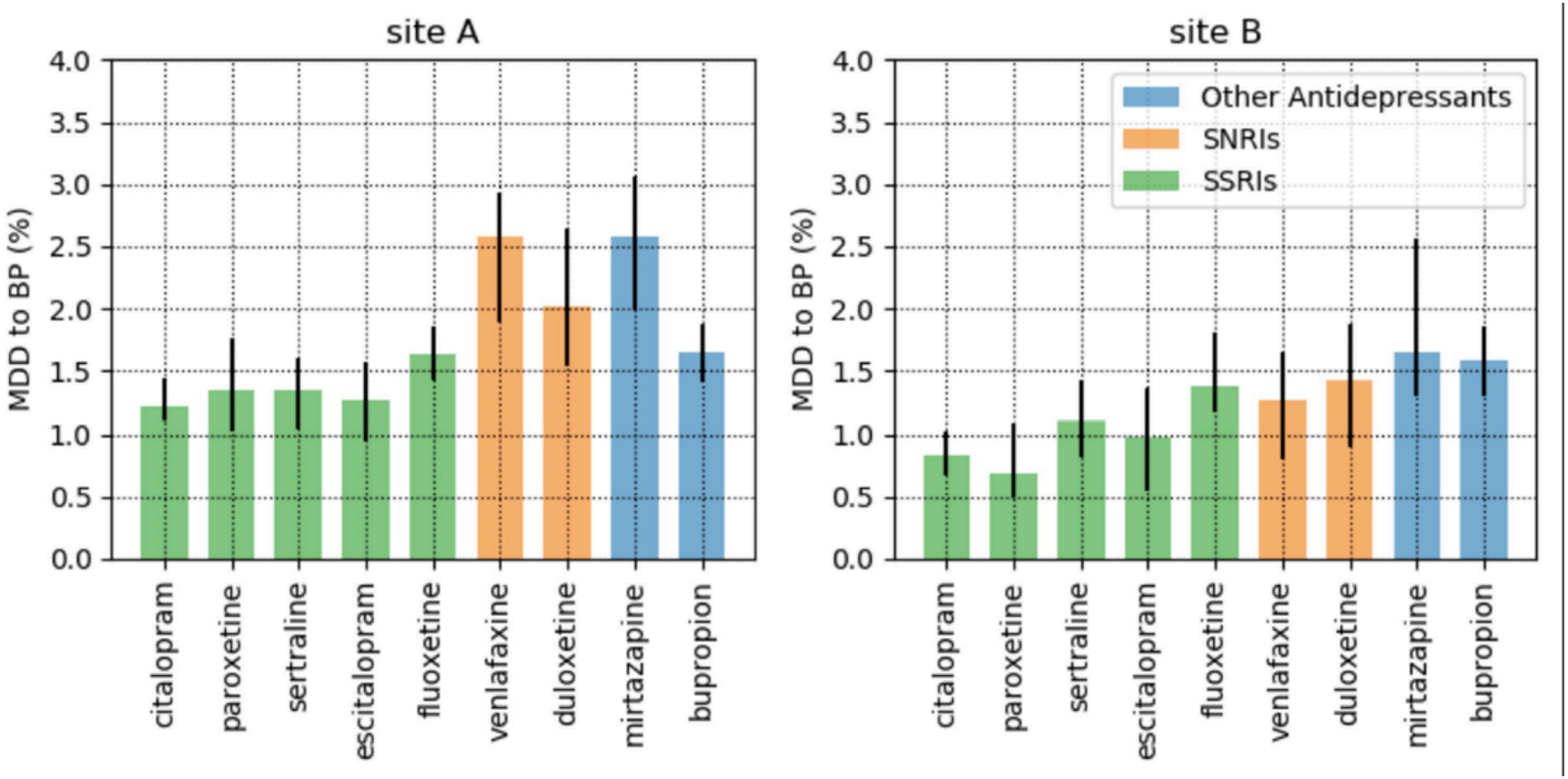
Recommendation	Agent	Evidence level
First-line	Quetiapine	Level 1
	Lithium	Level 2
	Lamotrigine	Level 2
Second-line	Venlafaxine	Level 2
Third-line	Carbamazepine	Level 3
	Divalproex	Level 3
	Escitalopram	Level 3
	Fluoxetine	Level 3
	Other antidepressants	Level 3
	Risperidone[a]	Level 4

CANMAT Bipolar Disorders 2018

And about those antidepressants…



Rates of transition from MDD to BPD, by antidepressant



Pradier, *Neuropsychopharmacology*, in press

TRD is not bipolar disorder

- There continues to be *no good evidence* that bipolar disorder is common among individuals with treatment-resistant depression!

- And some evidence that it is not…
  - "indicators of bipolar diathesis including recent maniclike symptoms and family history of bipolar disorder as well as summary measures of bipolar spectrum features were not associated with treatment resistance"

- Beware diagnosis by family history

Perlis Arch Gen Psych 2011

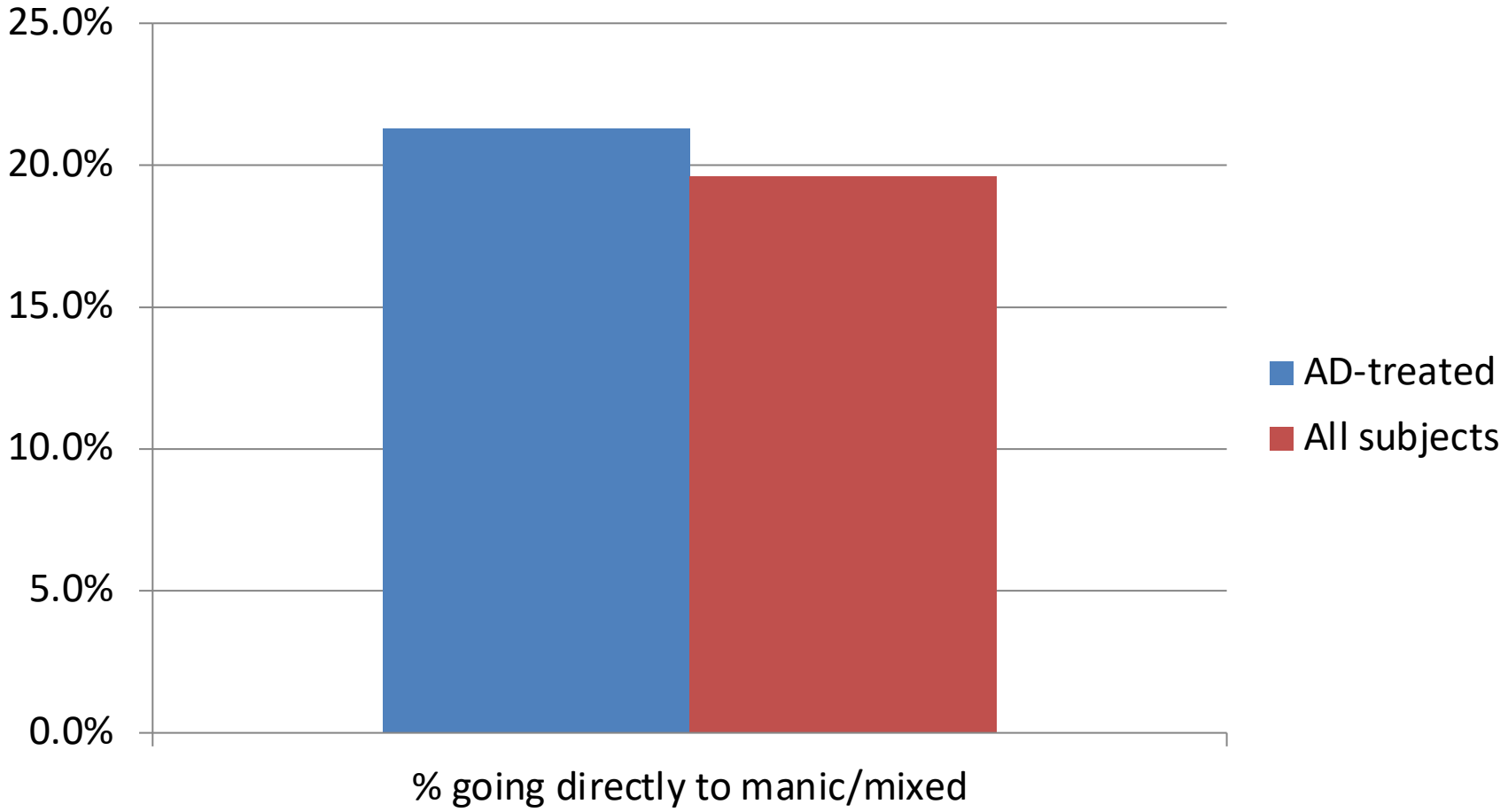
Risk associated with antidepressants in long-term treatment

- 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!*

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

Even the experts are confused

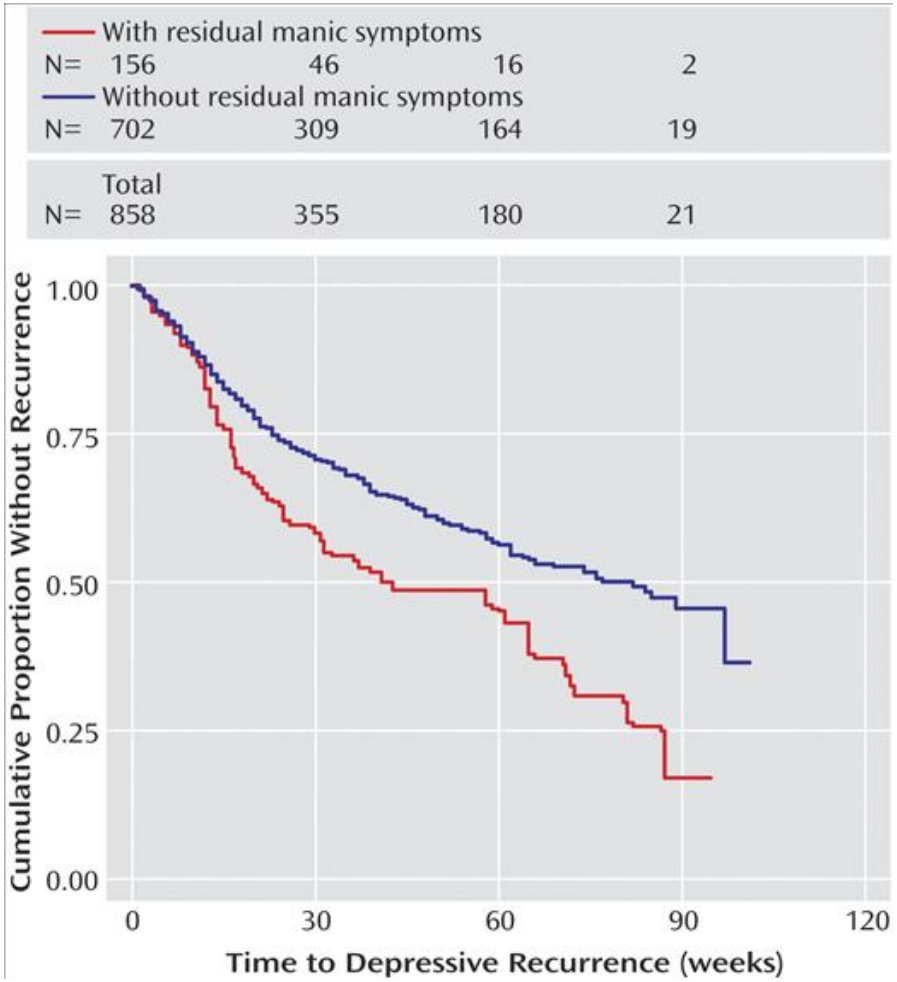
- "Because of limited data, the task force could not make broad statements endorsing antidepressant use but…
- *Individual bipolar patients may benefit from antidepressants.*
- Serotonin reuptake inhibitors and bupropion may have lower rates of manic switch than tricyclic and tetracyclic antidepressants 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

Residual symptoms

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

Residual manic symptoms are associated with recurrence



Perlis AJP 2006

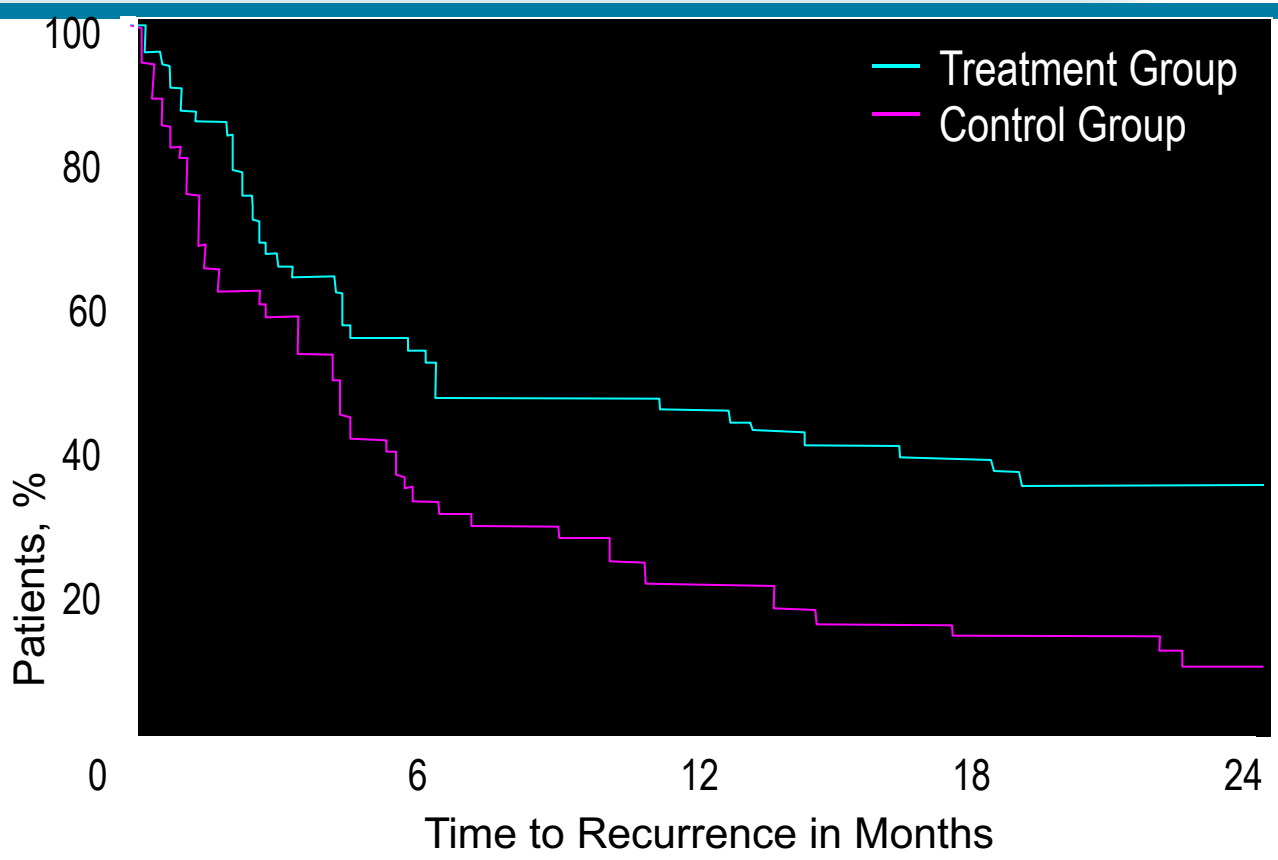
Psychosocial interventions

Effective psychosocial interventions

	Maintenance: Recommendation (Level of Evidence)
Psychoeducation (PE)	First-line (Level 2)
Cognitive behavioural therapy (CBT)	Second-line (Level 2)
Family-focused therapy (FFT)	Second-line (Level 2)
Interpersonal and social rhythm therapy (IPSRT)	Third-line (Level 2)
Peer support	Third-line (Level 2)
Cognitive and functional remediation	Insufficient evidence
Dialectical behavioural therapy (DBT)	Insufficient evidence
Family/caregiver interventions	Insufficient evidence
Mindfulness-based cognitive therapy (MBCT)	Insufficient evidence
Online interventions	Insufficient evidence

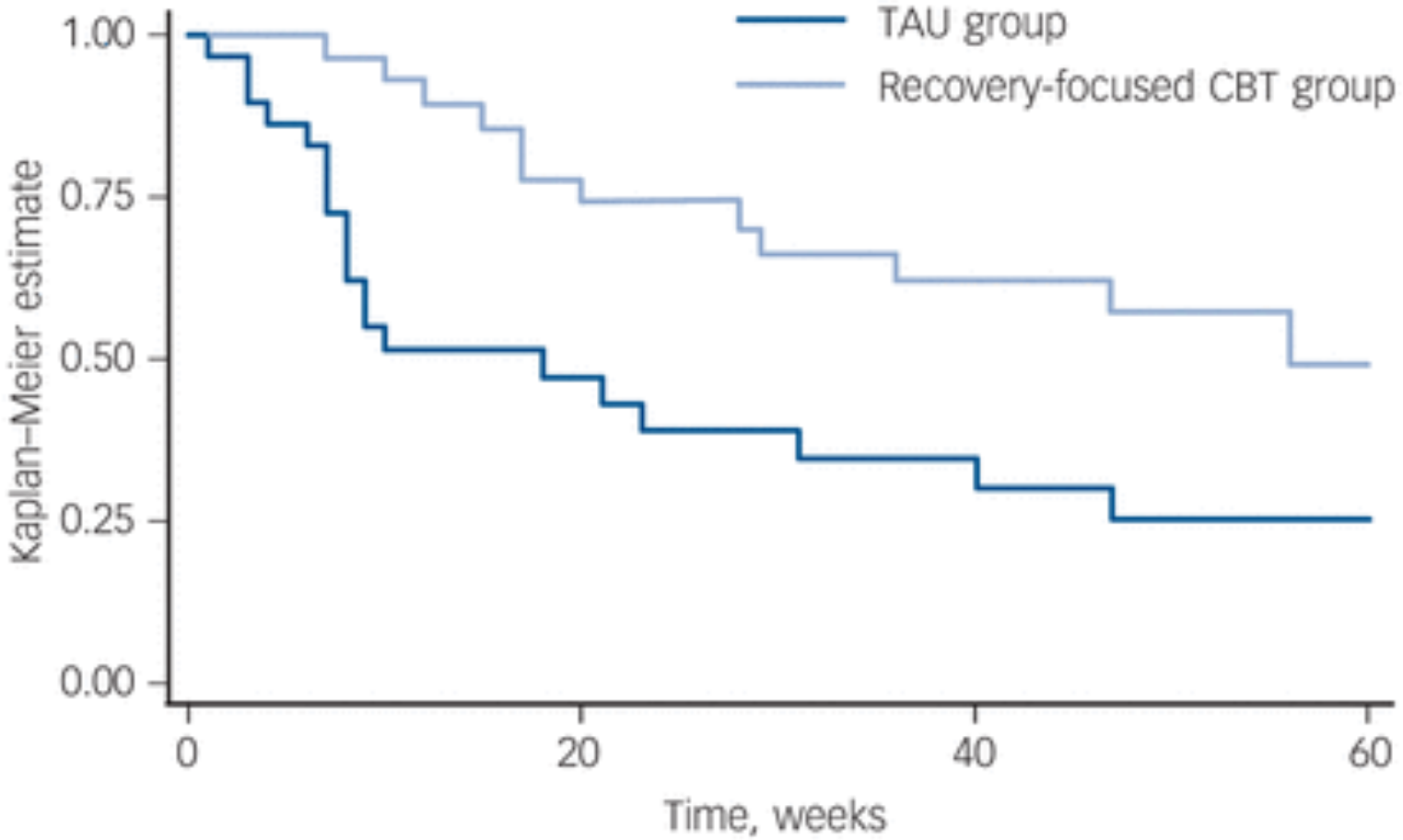
CANMAT Bipolar Disord 2018

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



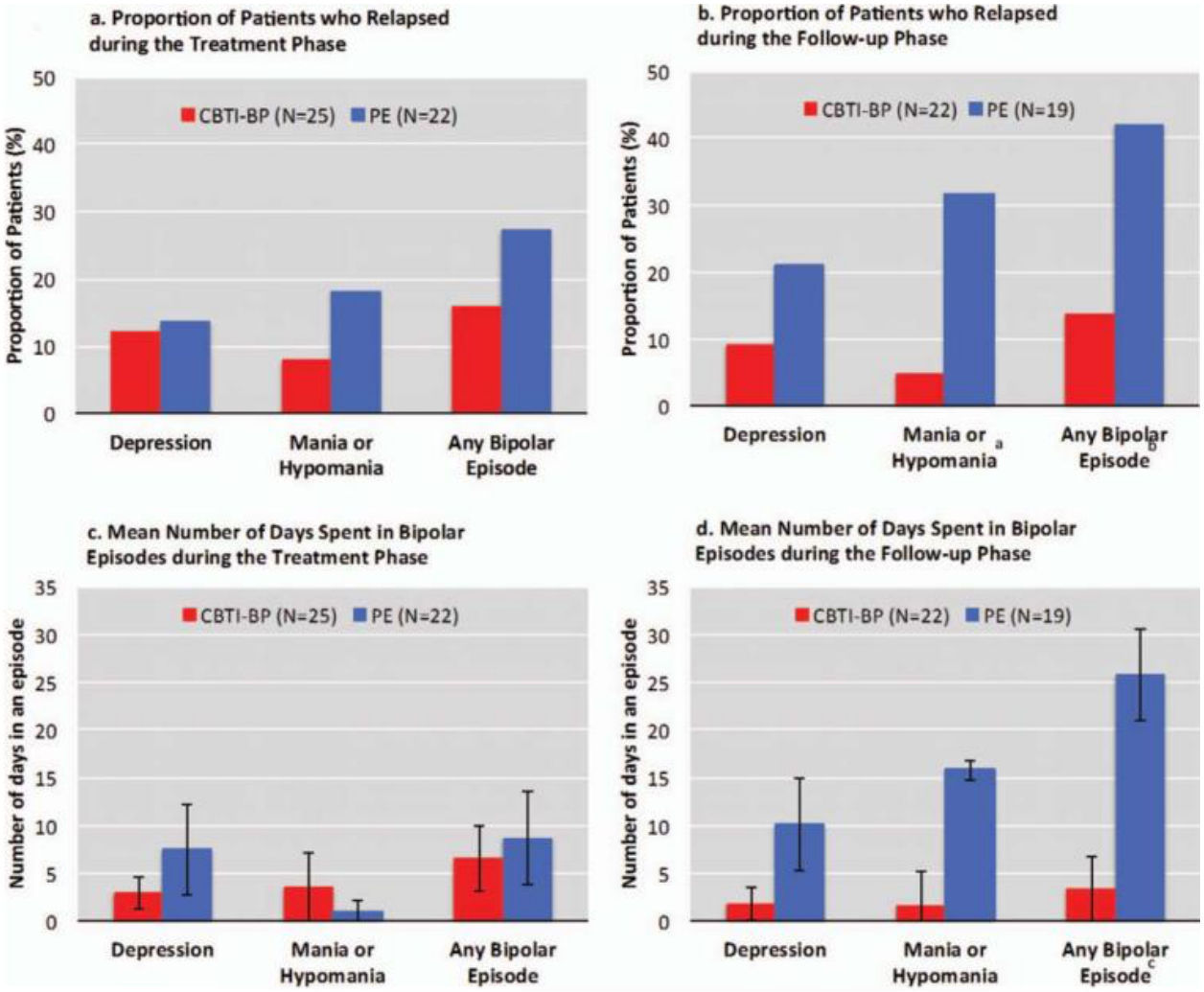
Colom, et al. *Arch Gen Psychiatry.* 2003; 60(4):402-407.

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

CBT for insomnia in bipolar disorder

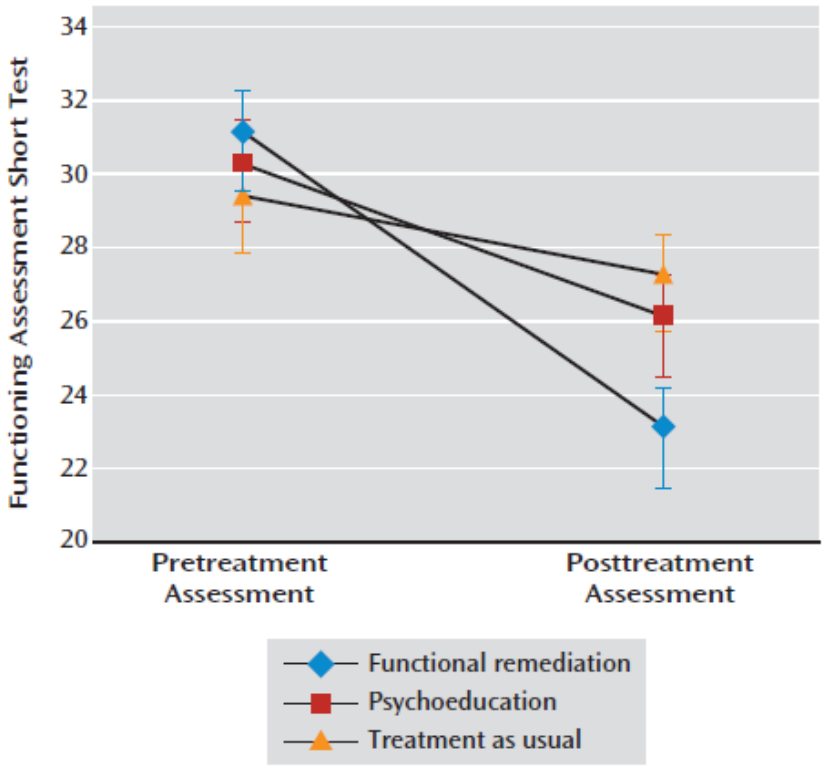


ONLINE COLOR

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

Functional remediation for bipolar disorder

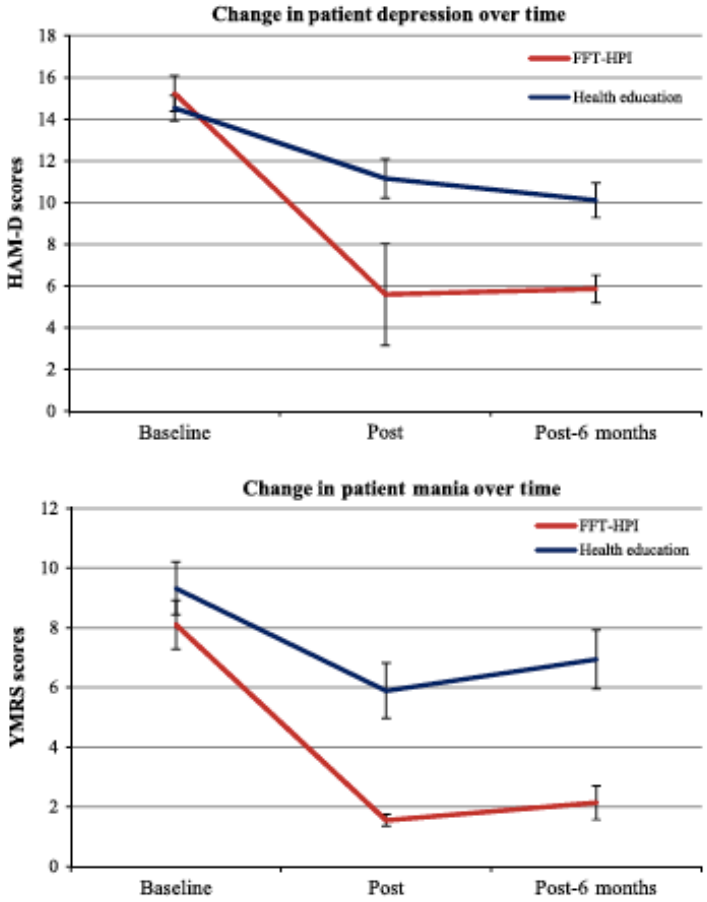
FIGURE 1. Changes in Functional Impairment Scores Before and After Intervention in Patients With Bipolar Disorder[a]



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

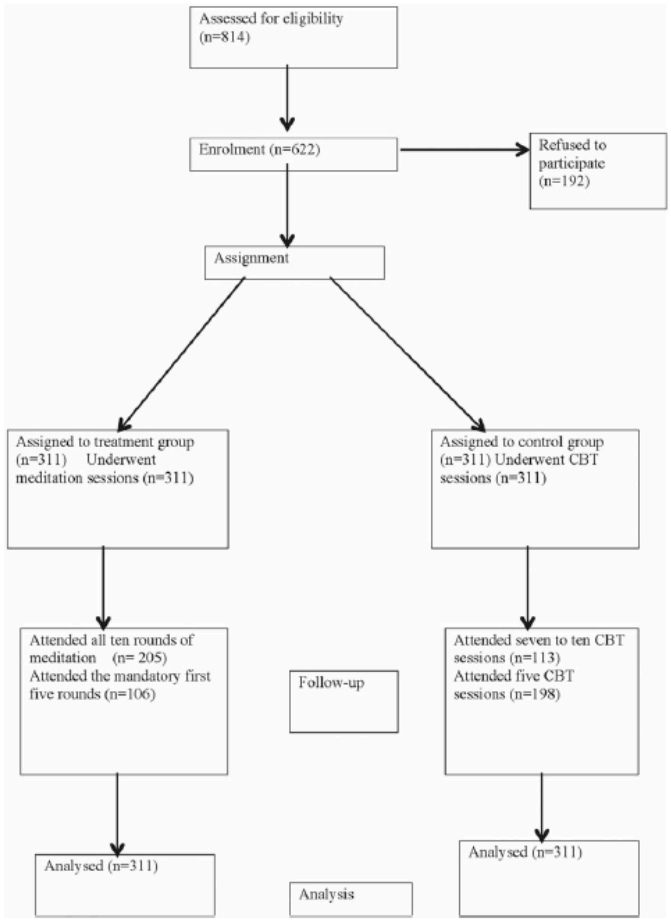
Torrent AJP 2013; See also Bonnin 2017

Family-focused therapy for caregivers alone works too!



N=46 caregivers x 12-15 weeks, plus 6month f/u – benefits for caregiver *AND PATIENT*

Biggest bipolar RCT of the year! (bipolar II)



1. Sitting still and contemplating on something that brings joy—5 min,
2. Isometric contraction of the muscles of the body followed by supine rest or simply lying down—3 min,
3. Slowly coming up from the left side and standing at ease and balancing the weight on both feet, called centering—3 min,
4. Then, bending the body both sides in a slow and relaxed fashion and the returning to the centre position (could be done one or two times)—3 min,
5. Standing in the centre position and contemplating by focusing on the place, which is in between the eyebrows—4 min,
6. Relaxation in the standing position and focusing on nature or universe or God—2 min,
7. Slow forward and backward bending of the body and the returning to centre position—3 min,
8. Slowly coming down in the supine posture (lying motionless on one's back) with instructions to relax different parts of the body in a sequence, also called deep relaxation technique—7 min.

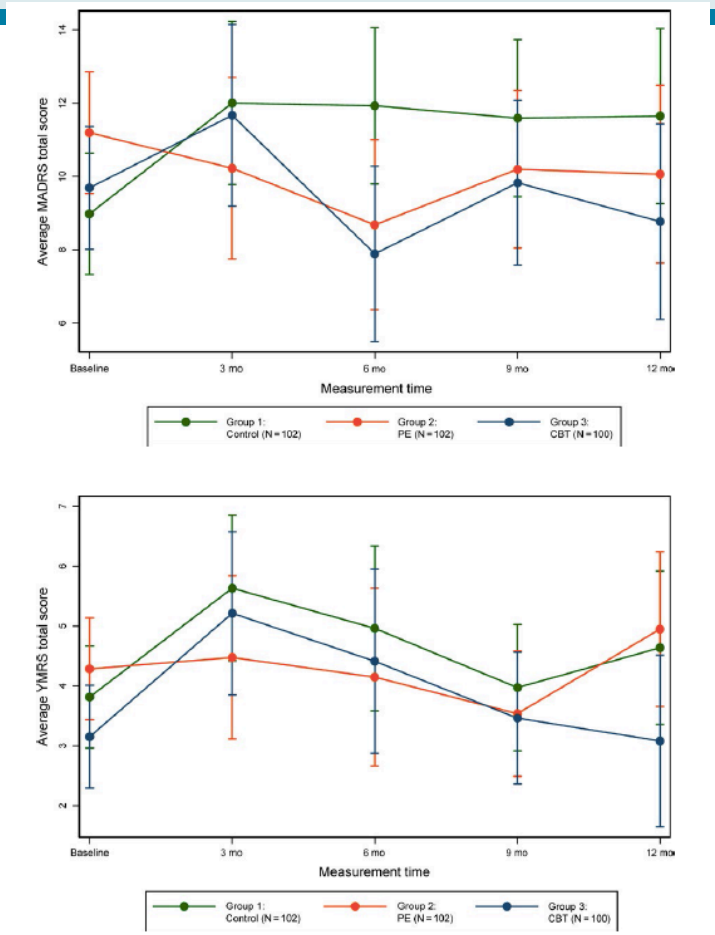
N=622 (1:1 CBT+meditation vs CBT control) – 8 African and Asian cities – 10x4d 1/2h sessions
mean difference BDRS = −9.71, $p \leq 0.01$; Cohen's d = 0.68

Does internet-based therapy work?

- Not necessarily.

Lobban 2016; n=96

Benefit for depressive symptoms from online psychoed but not necessarily CBT modules ("Moodswings 2.0")

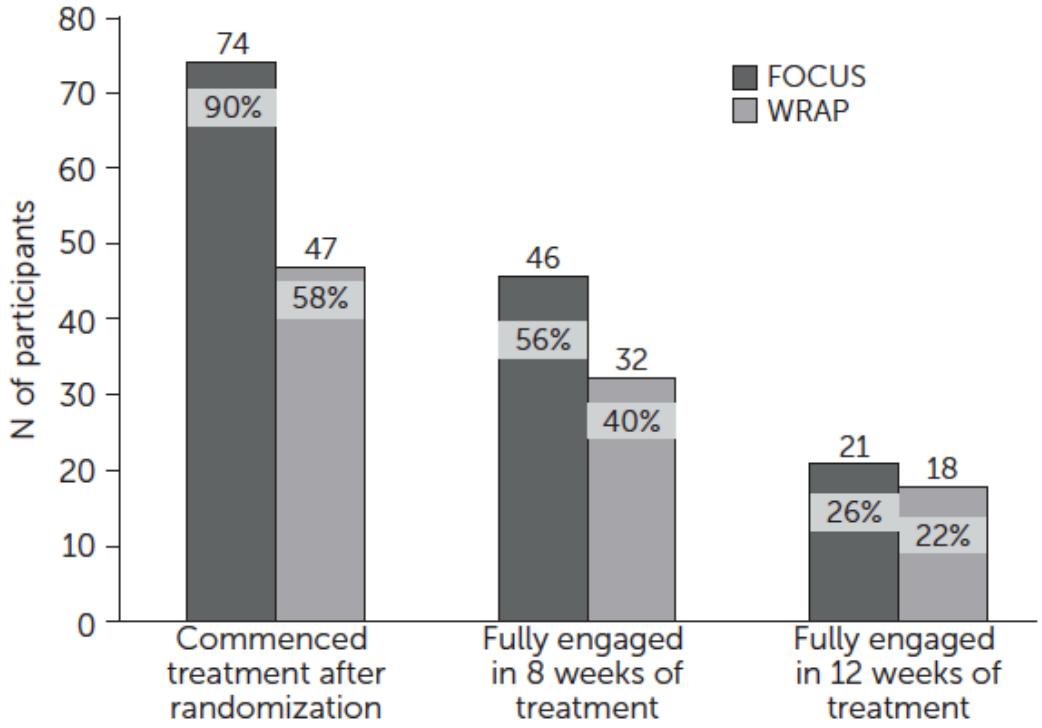


N~304: peer support forum + psychoed modules + CBT tools; Gliddon Bipolar Disorders 2018

Apps? (*Hi-roller*, circa 2003)

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

Finding the right apps for bipolar patients

- https://apps.digitalpsych.org

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?


SIMPLE DISCOVERY
LEADS TO GREAT NEW TASTE SENSATION IN CEREAL
When we tried sugar *coating* our big, crisp flakes of corn, they tasted fine. But not until we *toasted in* the secret sugar frosting did we really get excited. Out of our ovens popped a sparkling new flavor. Ever tried the new cereal with the *toasted-in* sugar flavor? Quite a find . . . in sparkling go-ahead energy, too.
Kellogg's SUGAR FROSTED FLAKES
Kellogg's
SUGAR
FROSTED
FLAKES

Special considerations

- Treatment resistance/Rapid cycling
- Smoking/Substance use
- Anxiety
- Adherence
- Weight gain

- Personalization

Treatment resistance

- No consistent/standardized definition exists!

Role of ECT in mood disorder maintenance remains unclear

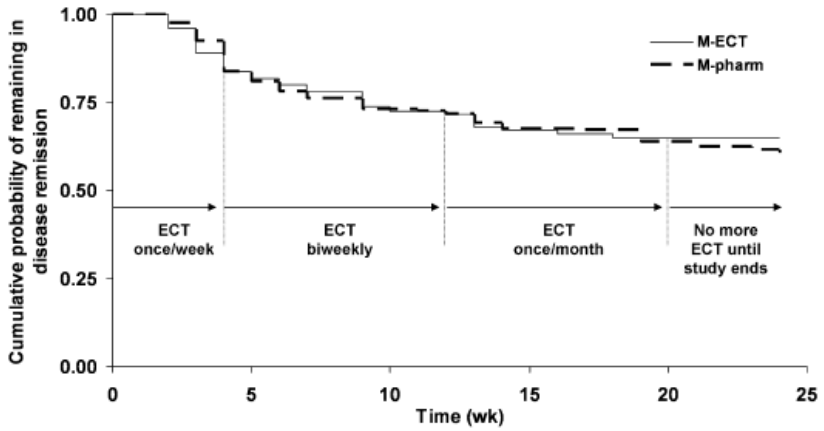


FIGURE 1. Proportion of patients remaining in remission during the maintenance phase in the CORE trial. Reprinted with permission from Kellner et al.[15] Log-rank test comparing distributions of time to relapse for M-ECT versus M-pharm: $\chi^2 = 0.30$; $P = 0.59$.

TABLE 4. CANMAT Recommendations for ECT in Bipolar Disorders

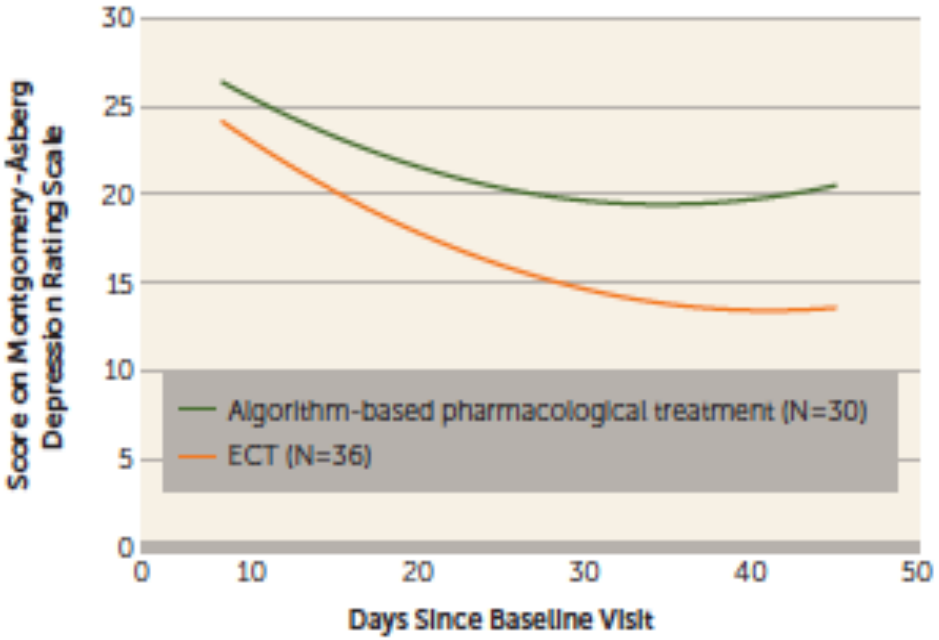
Diagnosis	Recommendations for ECT
Acute mania	Second line
Acute bipolar I depression	Third line
Maintenance therapy of bipolar disorder	Third line (adjunctively)
Maintenance therapy of bipolar II disorder	Third line

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)

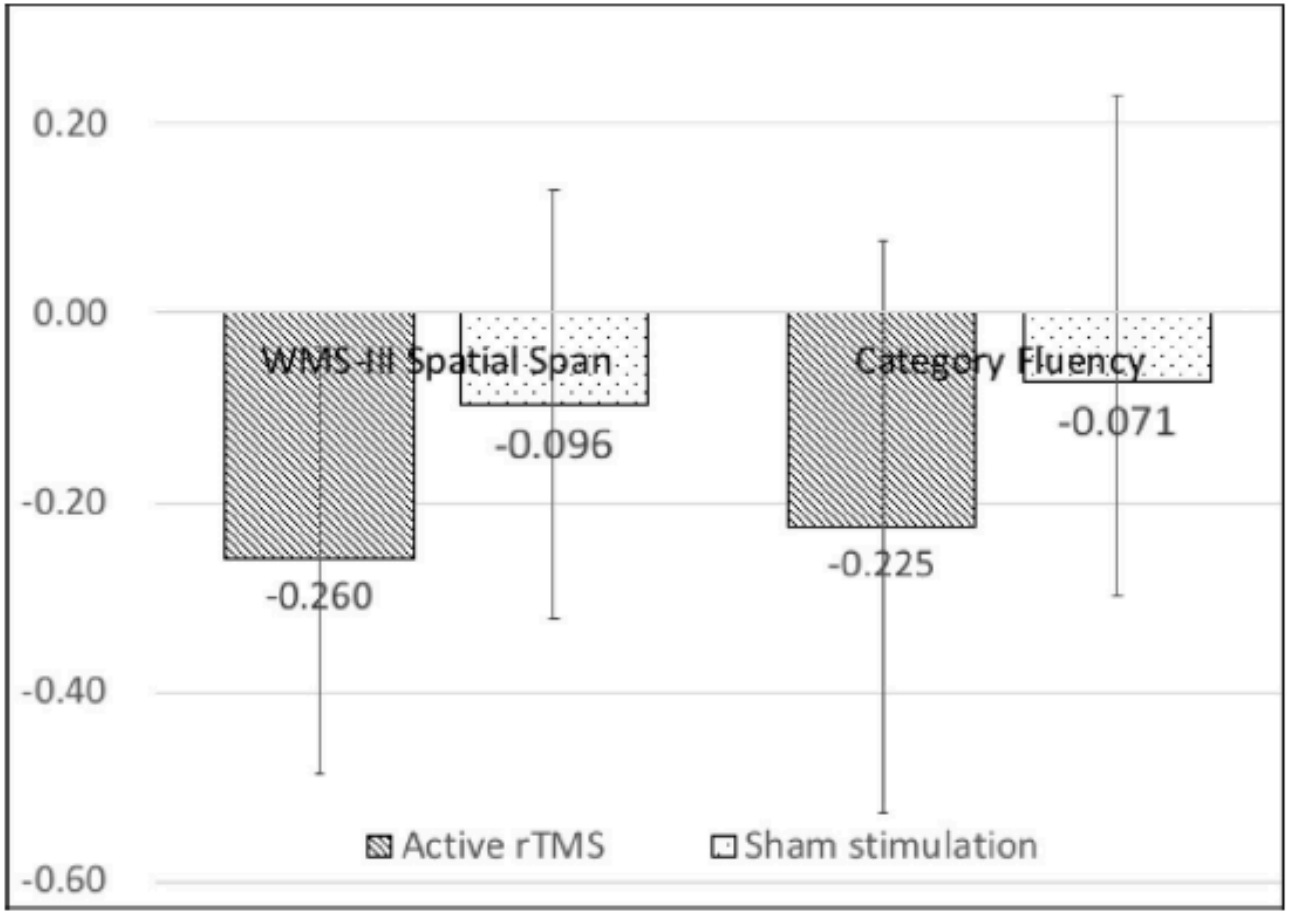
- N=26 assessed at 6 mo
- MATRICS Consensus Cognitive Battery composite score *improved* by 4.1 points in both groups (P = .04) from baseline to 6 months

- 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

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)

Rapid Cycling

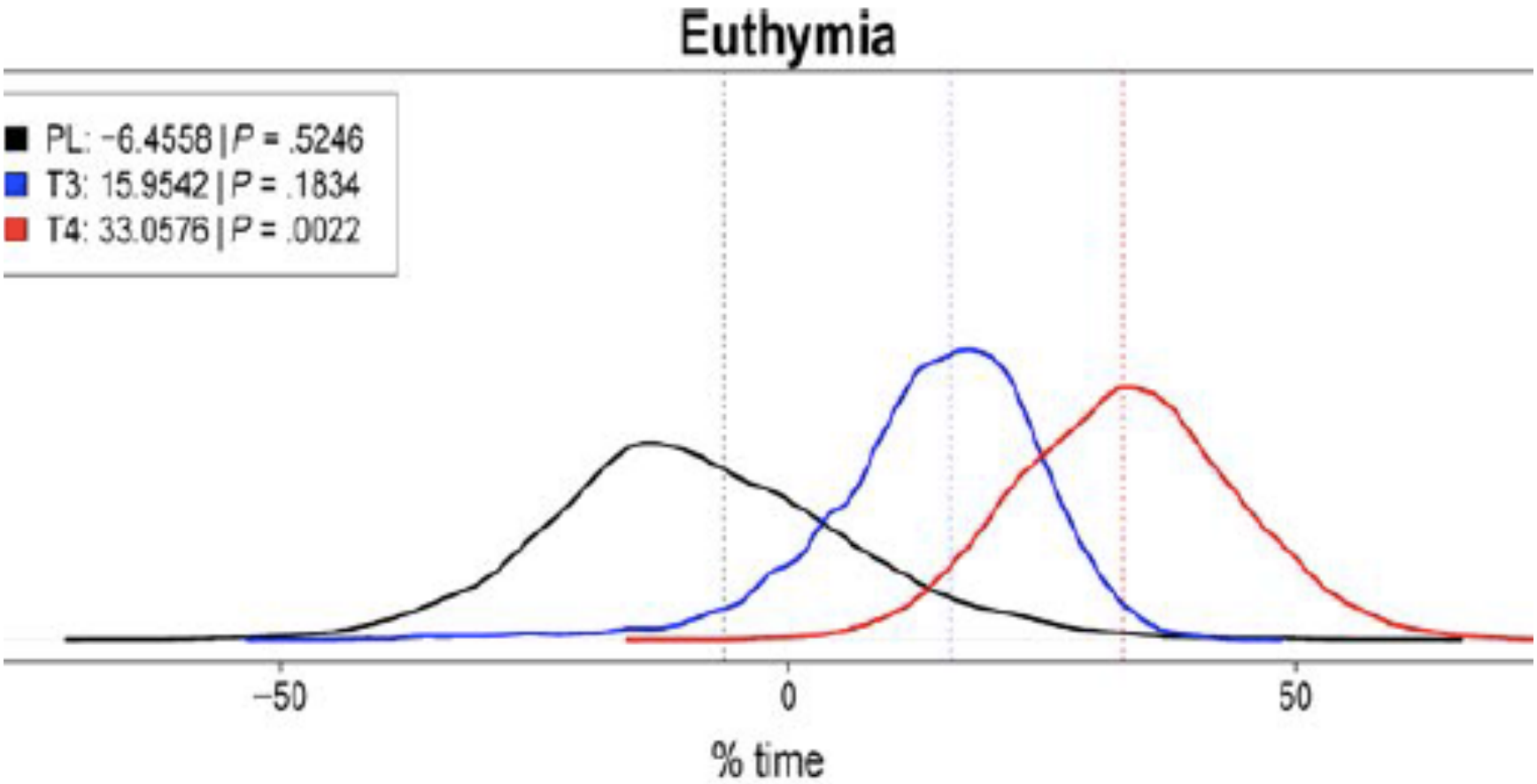
- 6 RCT'S in rapid cycling
- 19 other post-hoc analyses of trials with rapid cycling patients

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

Substance use

- Opioids, opioids, opioids…
  - "A mood disorder clinician without a buprenorphine waiver is practicing with one arm tied behind his/her back."
- Vaping (especially cannabis)

- Old view – 'treat addiction first' – is outdated. Must be prepared to treat bipolar disorder and substance use disorders simultaneously.

https://www.asam.org/resources/practice-resources/buprenorphine-waiver-management

Smoking cessation

- Bipolar patients have elevated cardiovascular mortality risk (Osby Archives 2001, among many others) – likely exacerbated by atypical antipsychotics and other medications, as well as tobacco use.
- Varenicline appears to be efficacious and safe for smoking cessation (Chengappa JCP 2014)
- And… effective in maintenance of abstinence (at 1 year of treatment, and 6 months after rx discontinuation) (Evins JAMA 2014)

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)

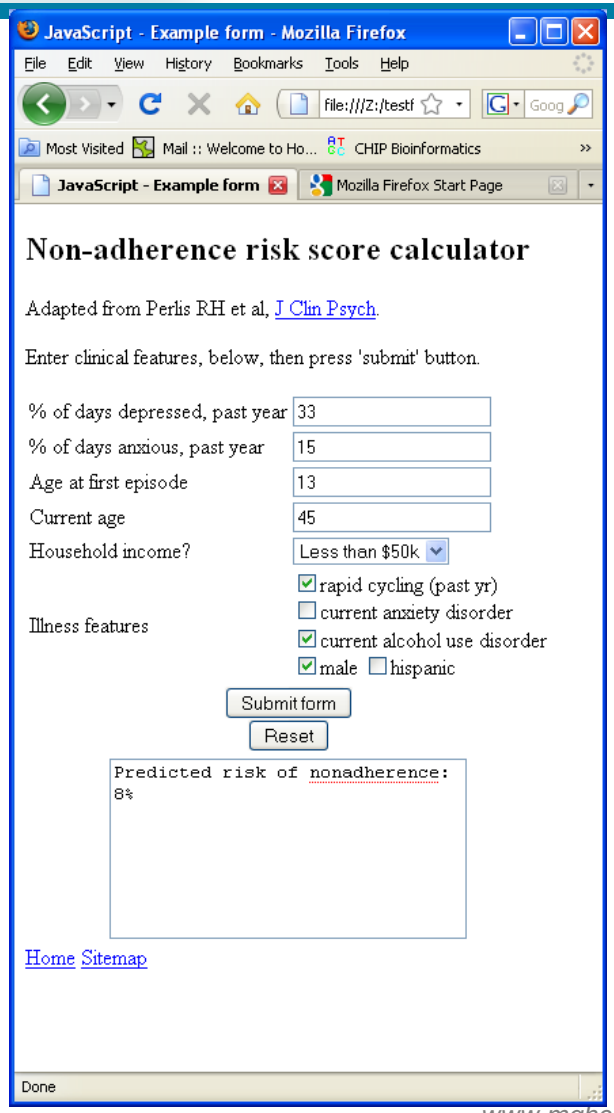
Adherence in bipolar disorder

24% poorly adherent on at least 1 in 5 visits

Poorer adherence at 3 months=
Poorer function at 12 months

Perlis JCP 2010

(See also Levin 2017:
"The median proportion of days with missed bipolar medication doses was 53.6%.")



Mobile applications and messaging may help…

- Text messages re medication adherence (RCT; n=132):
  - Improvement in adherence @3mo
  - Persistent benefit @6mo
  - Menon *J Psych Res* 2018; see also Biederman *J Clin Psychopharm* 2019 re ADHD

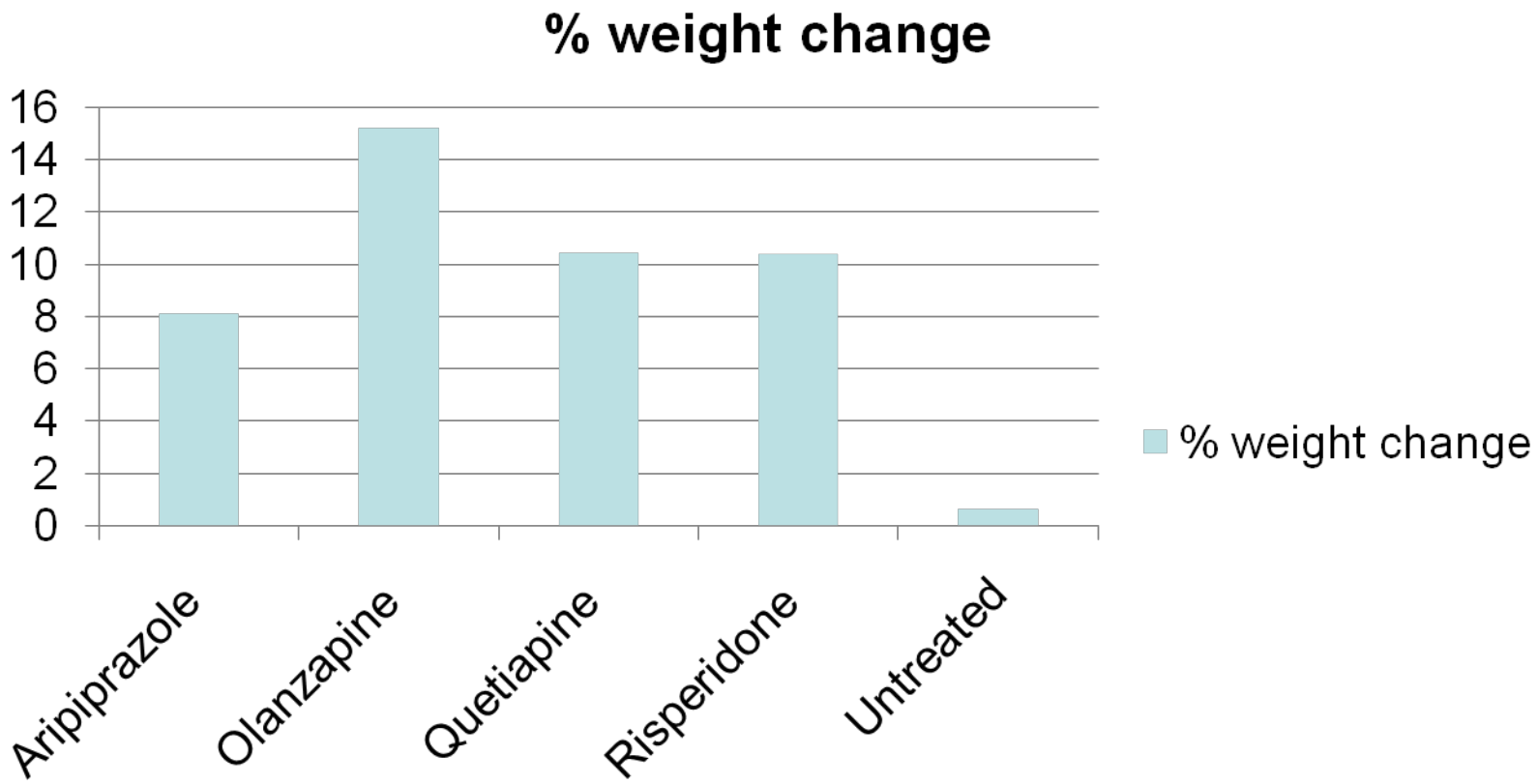
BUT consider injectables where adherence is poor

- 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)

Weight gain/metabolic adverse effects

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



Correll JAMA 2009

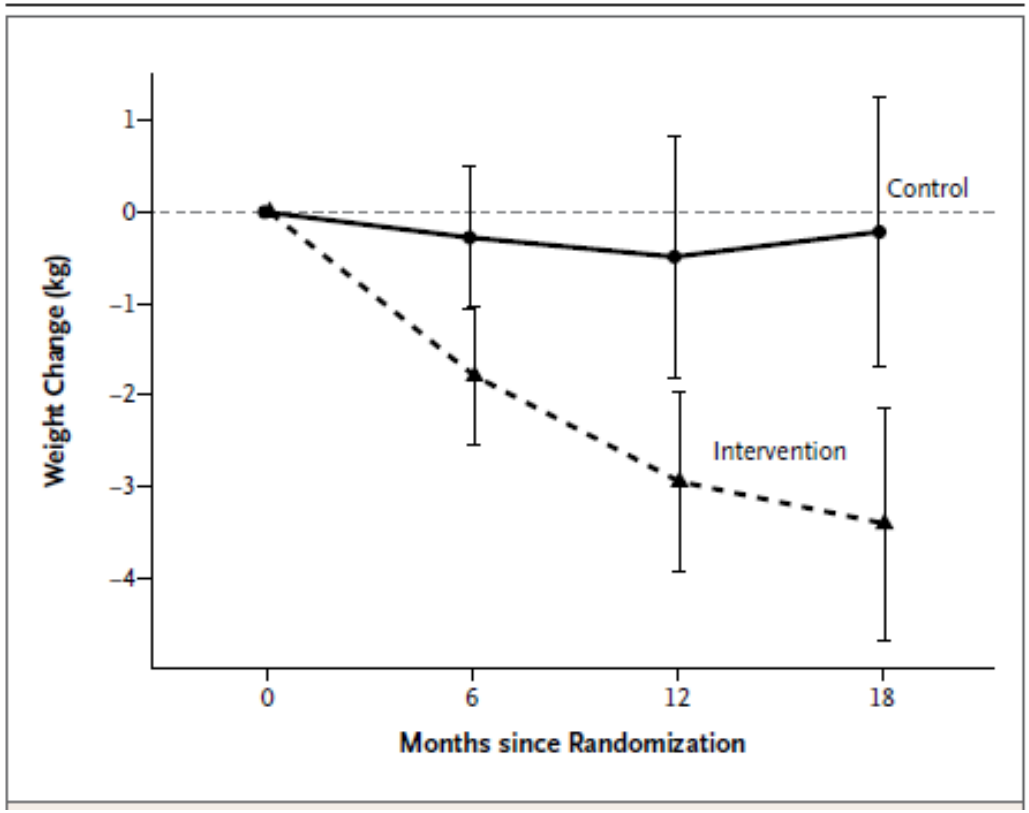
Managing Adverse Effects: weight gain

- 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
  - 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

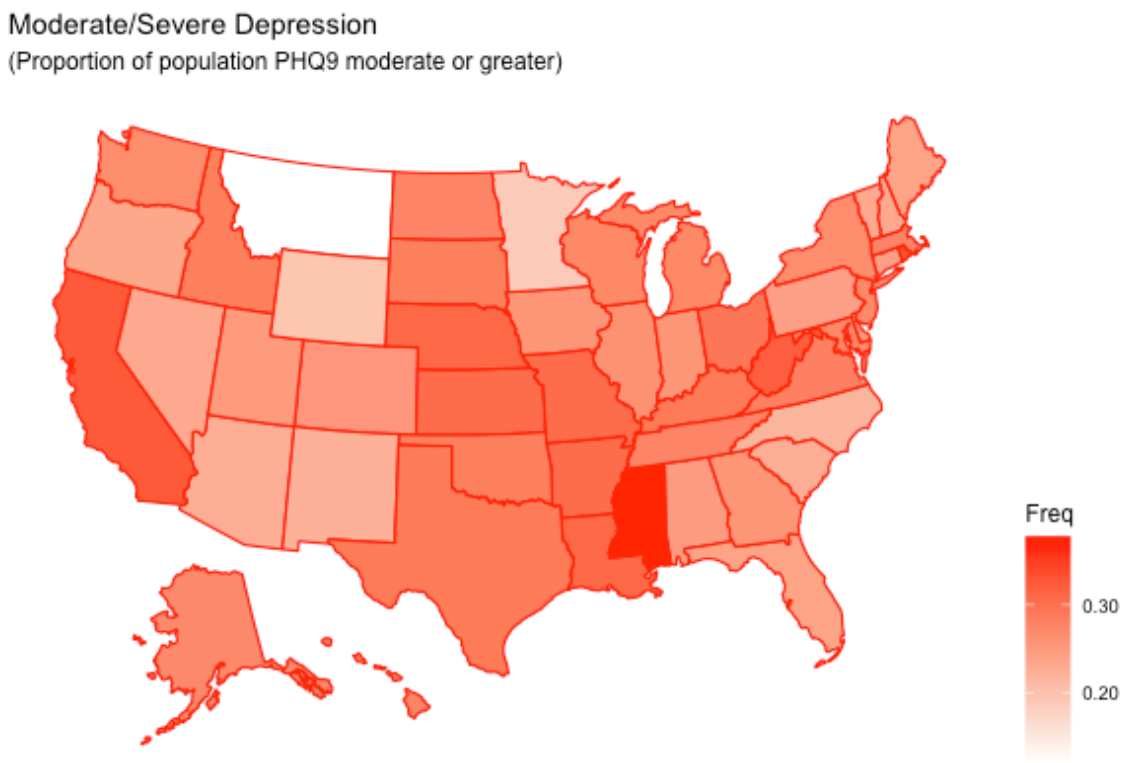


Mean 18-mo weight loss 3.2kg in intervention group (22% bipolar; ~82% on atypical antipsychotic)

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

Latest and greatest

Prevalence of moderate or greater major depression (May 2020)

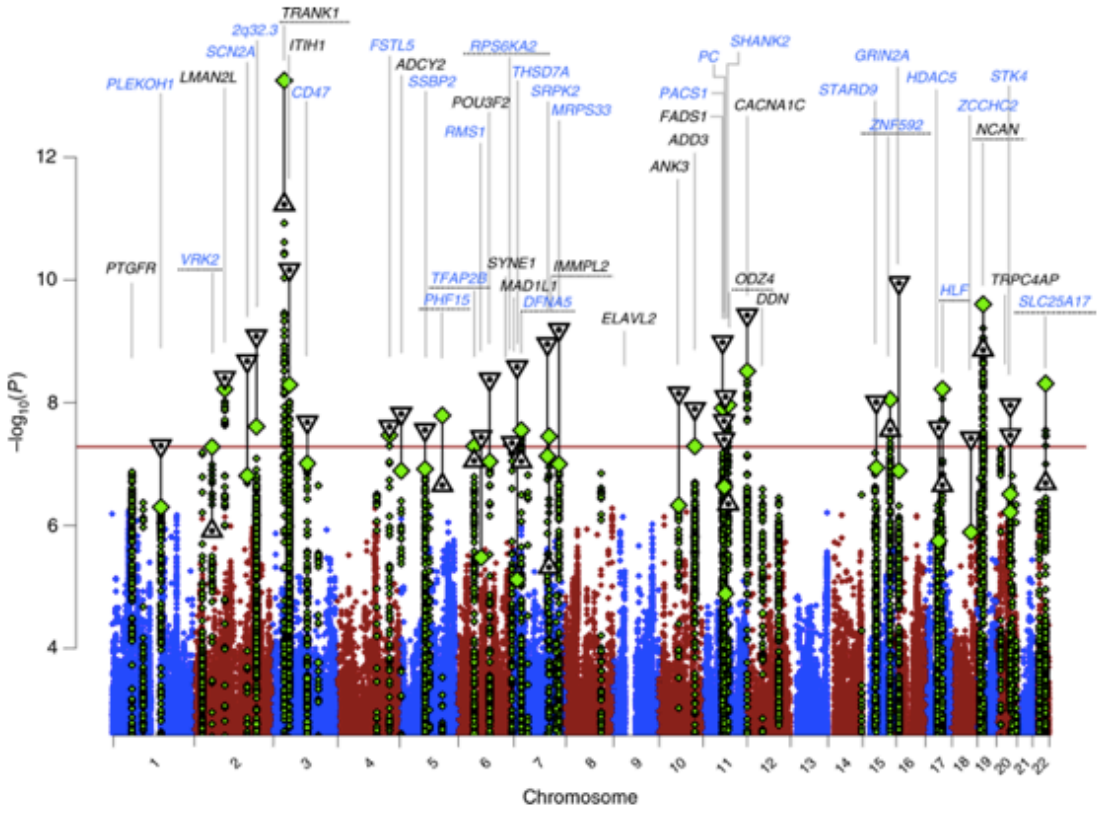


Mood disorder comorbidity may be associated with poorer outcome among individuals hospitalized with COVID-19

covidstates.org

~30 regions of genome associated with bipolar disorder

Fig. 1: Manhattan plot for our primary genome-wide association analysis of 20,352 cases and 31,358 controls.



Stahl Nat Gen 2019

Personalized medicine in bipolar disorder?

- Still no *actionable* common genetic variants identified
  - NEJM report of a predictor of lithium response did not replicate in multiple other cohorts (Chen NEJM 2014)
- 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/
- Most useful consideration in treatment selection among drugs with efficacy: safety and tolerability profile

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Long-term Treatment in Bipolar Disorder: Fall 2020 Update

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