Bipolar Disorder & Treatment of Depression

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10th Annual OHSU Primary Care Mental Health Update

March 6, 2026

No conflicts of interest to disclose.

I have never received any payments for any research, speaking engagements, or other services from the pharmaceutical industry.

I will not personally profit from your use of any rating scales or treatment strategies recommended today.

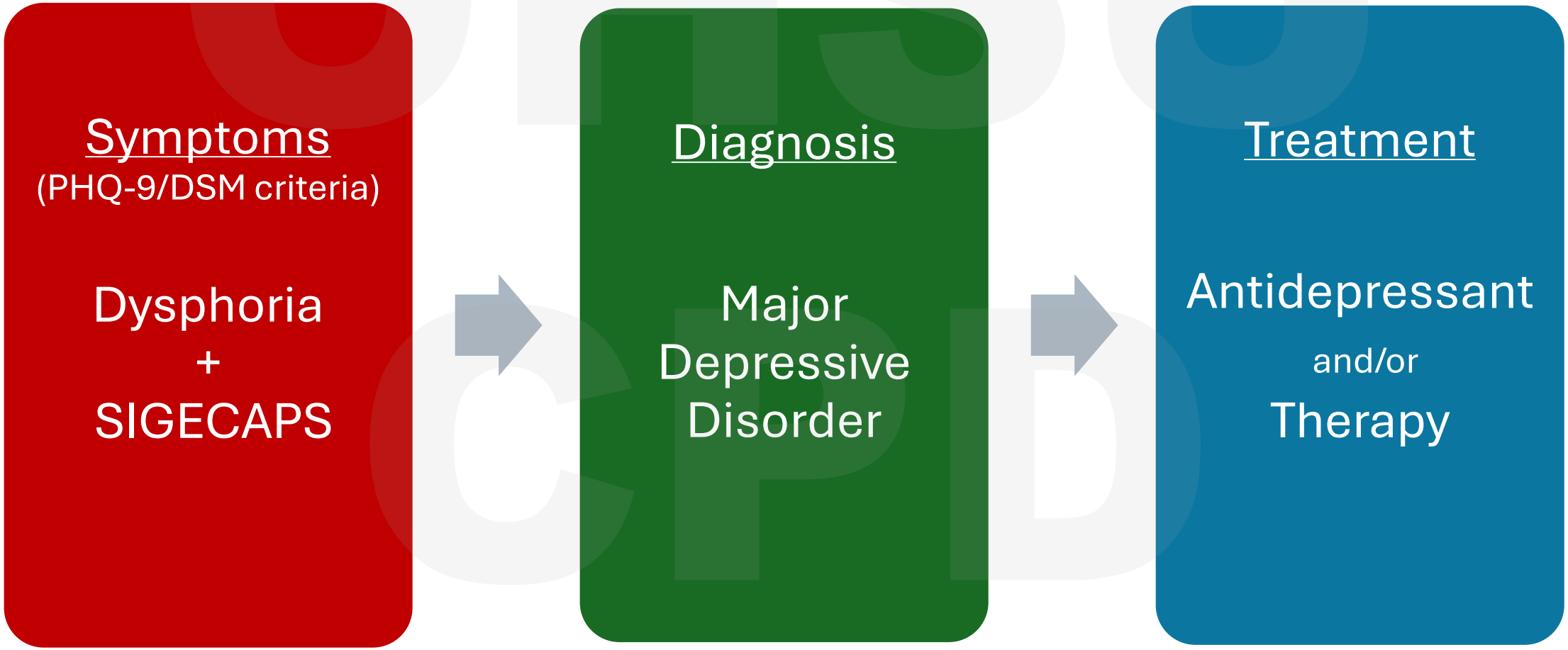
Objectives

Identify clinical challenges in identification of bipolar spectrum disorders and pragmatic clinical tools to facilitate improvements.

Recognize relative risks and benefits of antidepressants when used short-term or long-term in mood disorders across the bipolar spectrum.

Compare efficacy of various medications for long-term treatment of bipolar disorder and the evidence base supporting them.

Overly Reductionistic Approach
Depression Diagnosis and Treatment



Diagnostic Gap: 2000 Survey of those with Bipolar D/o

Hirschfeld, RMA et al. JCP 2003

- Bipolar pts reporting prior misdiagnosis in 2000: 69%
- Mean # of physicians consulted before accurate bipolar dx = 4
- 6-13 years = mean delay between onset & dx of bipolar 1
- Mean number of misdiagnoses received: 3.5
    - 60% - MDD
    - 26% - Anxiety d/o
    - 18% - Schizophrenia
    - 17% - Borderline or Antisocial PD
    - 14% - Substance Use Disorder
    - 11% - Schizoaffective disorder
- Estimated portion of those w\ MDD dx who really have bipolar 1: 25%

Why are detection rates for bipolar disorder so low?

"Undeclared" Bipolarity

- Early in illness course (~3 MDEs on average before 1st mania/hypomania)

Missed diagnosis

- Limited or ineffective screening
- Symptoms well screened for, but . . .
  - Manic/hypomanic sx attributed to another disorder or comorbidity.
  - Hypomania wasn't problematic, so not memorable or thought to be worth mentioning.
  - Pt didn't recall symptoms that occurred during episode, r/t cognitive symptoms.
  - Symptoms endorsed don't meet full DSM criteria for a manic or hypomanic episode

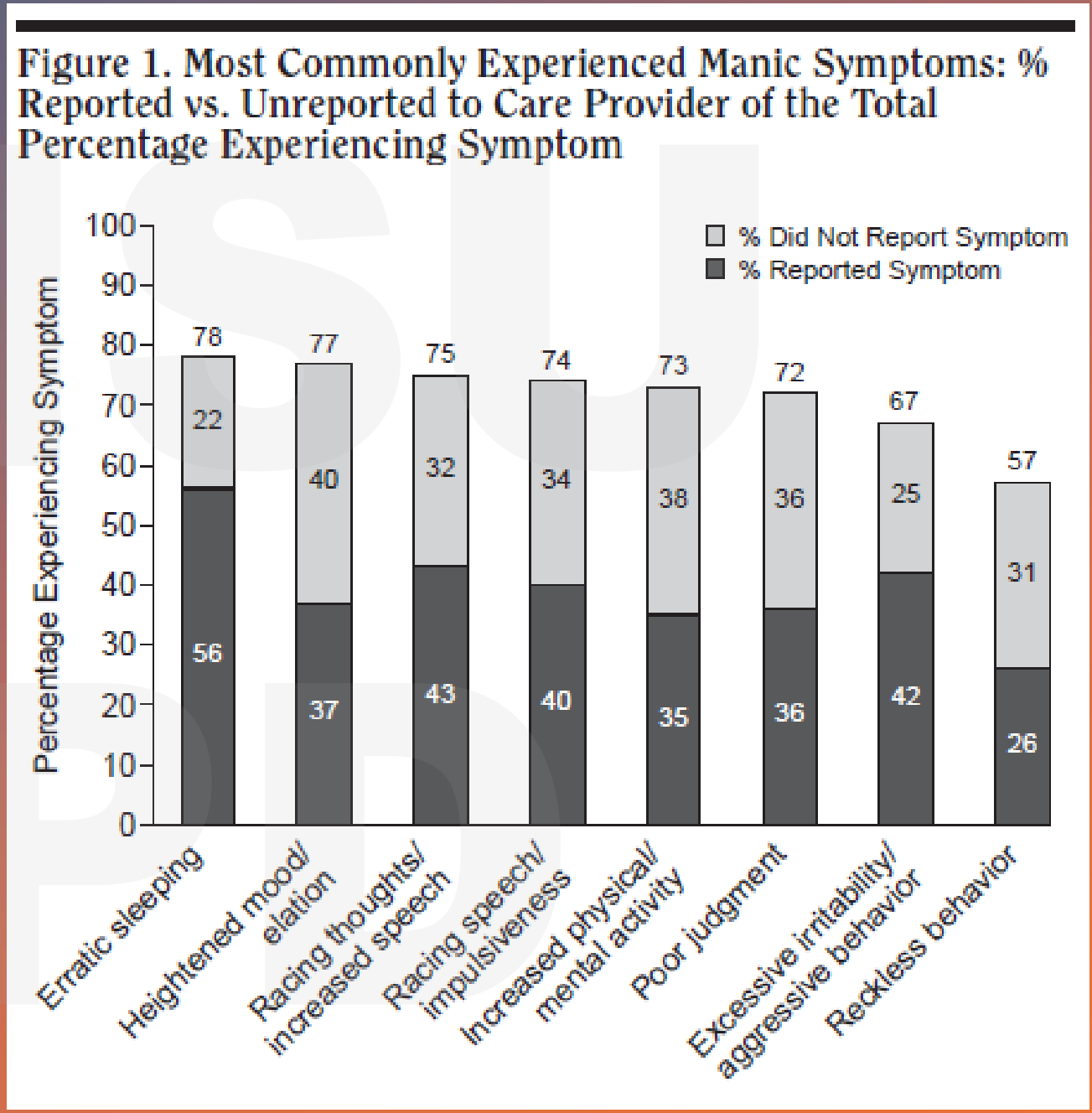
High Comorbidity Rates (avg BP+3 other dx)

- **Anxiety Disorders**: 30% (STEP-BD)
  Panic Disorder: 35% (Nat'l Comorbid. Survey)
- **PTSD:** 16 % (Otto, MW et al. 2004)
- **Borderline Personality Disorder** (20% +bipolar):
  10% in bipolar 1
  20% in bipolar 2 (Zimmerman, M et al. 2013)
- **Substance Use Disorders**:
  61% in bipolar 1
  48% in bipolar 2 (Regier, DA et al. 1990)
- **ADHD**: 13% in adulthood
  43% in adolescence
  73% in childhood (Sandstrom, A et al. 2021)

Patients Under Report Manic Symptoms

Results of the National Depressive and Manic-Depressive Association 2000 Survey of Individuals With Bipolar Disorder.

Hirschfeld, RMA et al. JCP 2003



Higher Odds of Bipolarity

- Early onset of mood disorder
  - Often before 25y/o in bipolar - vs after 30 y/o with MDD
- Higher number of lifetime major depressive episodes
  - >50% w\ bipolar reported >25 prior MDEs - vs just 1-5 MDEs w\MDD
- Poor antidepressant response
  - Antidepressant treatment resistance (e.g. lack of response to 3+ trials)
  - Worsening during antidepressant treatment
    - Worsening of dysphoria or experience of new/worsened mixed symptoms
  - Hypomanic/manic symptoms/episode after starting antidepressant
- FH of bipolar
  - 42% of pts with Bipolar have +FH of bipolar (vs 5-8 % of MDD pts)

Perlis RH, et al. Am J Psychiatry. 2006; 163: 225-231.
Aiken CB et al. The Bipolarity Index. J of Affective Disorders, 2015.

Easy Way to Improve Bipolar Detection

Less than 2 minutes!

88% Sensitivity
80% Specificity
for Bipolar 1

Rapid Mood Screener (RMS)

Patient Name:
Date:

The following questions ask about certain aspects of your current and past medical history.

Please select one response for each question.

	YES	NO
1. Have there been at least 6 different periods of time (at least 2 weeks) when you felt deeply depressed?	☐	☐
2. Did you have problems with depression before the age of 18?	☐	☐
3. Have you ever had to stop or change your antidepressant because it made you highly irritable or hyper?	☐	☐
4. Have you ever had a period of at least 1 week during which you were more talkative than normal with thoughts racing in your head?	☐	☐
5. Have you ever had a period of at least 1 week during which you felt any of the following: unusually happy; unusually outgoing; or unusually energetic?	☐	☐
6. Have you ever had a period of at least 1 week during which you needed much less sleep than usual?	☐	☐

Scoring:

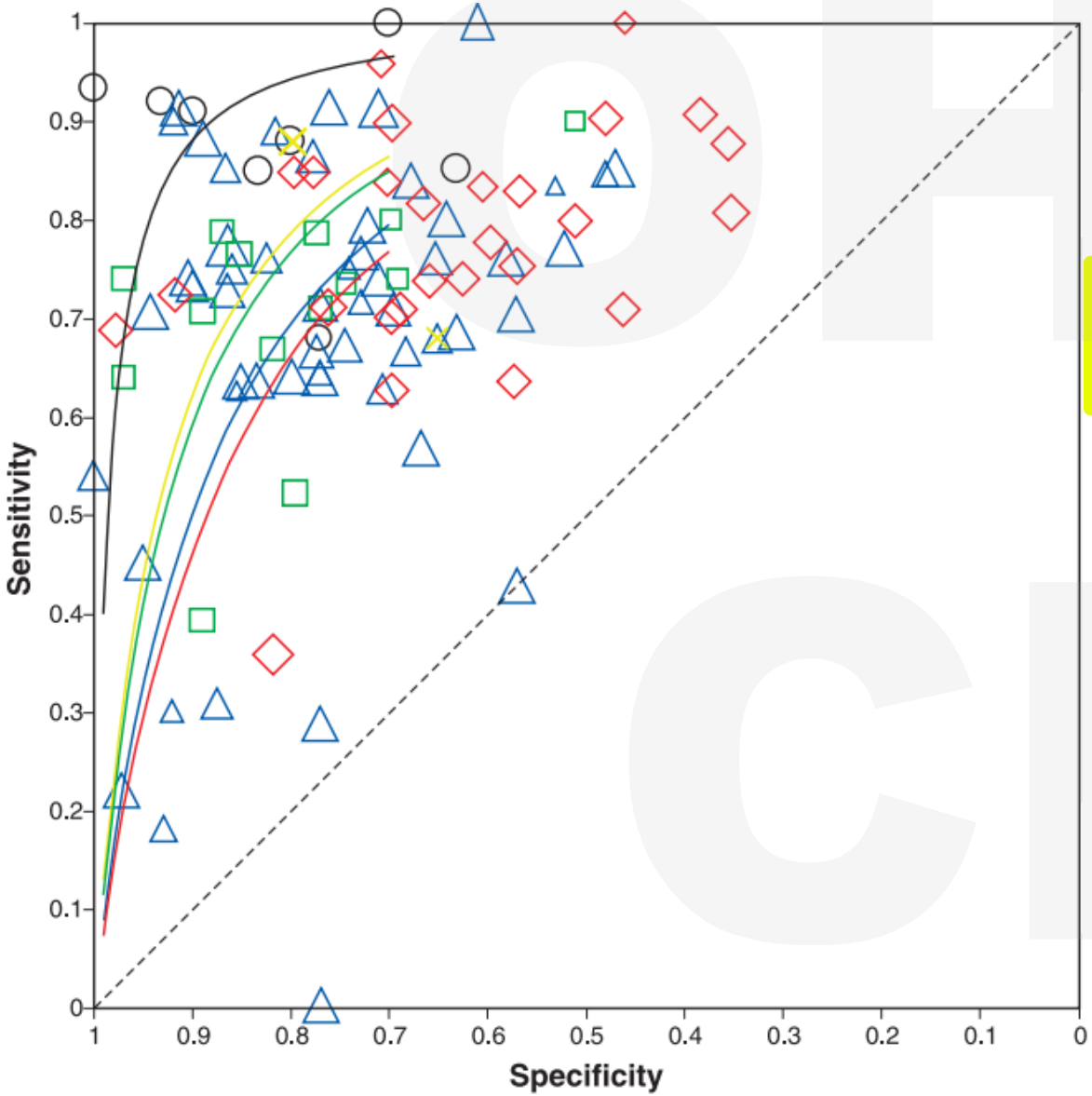
In order to screen positive for possible bipolar disorder, the following criteria must be met:

- "YES" to 4 or more of the 6 items results.

Diagnostic Performance

for Detecting Any Type of Bipolar Disorder

Meta-Analysis
Sayyah M et al. Braz J Psych 2022



Bipolarity index (BI)

Rapid Mood Screener (RMS)

Bipolar Spectrum Diagnostic Scale (BSDS)

Mood Disorder Questionnaire (MDQ)

Hypomania Checklist-32 (HCL-32)

Bipolar Spectrum Diagnostic Scale
(Patient Version)

- Narrative about bipolar pt lived experience.
- Each check mark is one point then at bottom 0-6 pts from how well pt says story fits them
- Scores range from 0-25 (cut-off recs 12-16)

- Using a cut off score of 13:
  - Sensitivity of 75%
  - Specificity of 93%

- Limited utility in pts with very poor insight
- Collateral version is also available

Ghaemi, SN et al. J of Affective Disorders, 2005

Some individuals notice that their mood and/or energy levels shift drastically from time to time ☐. These individuals notice that, at times, their mood and/or energy level is very low, and at other times, very high ☐. During their "low" phases, these individuals often feel a lack of energy; a need to stay in bed or get extra sleep; and little or no motivation to do things they need to do ☐. They often put on weight during these periods ☐. During their low phases, these individuals often feel "blue", sad all the time, or depressed ☐. Sometimes, during these low phases, they feel hopeless or even suicidal ☐. Their ability to function at work or socially is impaired ☐. Typically, these low phases last for a few weeks, but sometimes they last only a few days ☐.

Individuals with this type of pattern may experience a period of "normal" mood in between mood swings, during which their mood and energy level feels "right" and their ability to function is not disturbed ☐. They may then notice a marked shift or "switch" in the way they feel ☐. Their energy increases above what is normal for them, and they often get many things done they would not ordinarily be able to do ☐. Sometimes, during these "high" periods, these individuals feel as if they have too much energy or feel "hyper" ☐. Some individuals, during these high periods, may feel irritable, "on edge", or aggressive ☐. Some individuals, during these high periods, take on too many activities at once ☐. During these high periods, some individuals may spend money in ways that cause them trouble ☐. They may be more talkative, outgoing, or sexual during these periods ☐. Sometimes, their behavior during these high periods seems strange or annoying to others ☐. Sometimes, these individuals get into difficulty with co-workers or the police, during these high periods ☐. Sometimes, they increase their alcohol or non-prescription drug use during these high periods ☐.

Now that you have read this passage, please check one of the following four boxes (consider your whole life when you answer, including recent times):

☐ This story fits me very well, or almost perfectly	6
☐ This story fits me fairly well	4
☐ This story fits me to some degree, but not in most respects	2
☐ This story does not really describe me at all	0

The Bipolarity Index

Scored 0-100, > 50 = Positive

Sensitivity: 0.91

Specificity: 0.90

5 Areas of History +/- Collateral:

- Episode Characteristics
- Age of Onset
- Course of Illness, Features
- Response to Treatment
- Family History

CB Aiken, Weisler, & Sachs. J Affective Disorders, 2015.

The Bipolarity Index

Directions: Circle the bulleted items that are positive in the patient's history. Score each of the five sections by circling the highest number (0-20) for which there is at least one positive item. The final score is the sum of all five sections.

I. Episode Characteristics	
20	• Acute manic or mixed episode with prominent euphoria, grandiosity or expansiveness and no significant medical or other secondary etiology.
15	• Acute mixed episode or dysphoric or irritable mania with no significant medical or other secondary etiology.
10	• Hypomanic episode with no significant medical or other secondary etiology; or • Cyclothymia with no significant medical or other secondary etiology; or • A manic episode within 12 weeks of starting an antidepressant.
5	• A hypomanic episode within 12 weeks of starting an antidepressant • Episodes with characteristic symptoms of hypomania, but symptoms, duration, or intensity are subthreshold for hypomania; or • A single MDE with psychotic or atypical features (atypical is ≥2 of the following: hypersomnia, hyperphagia or leaden paralysis of limbs); or • Any postpartum depression.
2	• Recurrent unipolar major depressive disorder (≥3 episode); or • History of any kind of psychotic disorder (i.e., presence of delusions, hallucinations, ideas of reference or magical thinking).
0	• No history of significant mood elevation, recurrent depression or psychosis.
II. Age of Onset (first affective episode or syndrome)	
20	• 15 to 19 years.
15	• Before age 15 or between age 20 and 30.
10	• 30 to 45 years.
5	• After age 45.
0	• No history of affective illness (no episodes, cyclothymia, dysthymia or bipolar-NOS).
III. Course of Illness & Associated Features	
20	• Recurrent, distinct manic episodes separated by at least 2 months of full recovery.
15	• Recurrent, distinct manic episodes with incomplete inter-episode recovery; or • Recurrent, distinct hypomanic episodes with full inter-episode recovery.
10	• Any substance use disorder (excluding nicotine/caffeine); or • Psychotic features only during acute mood episodes; or • Incarceration or repeated legal offenses related to manic behavior (e.g. shoplifting, reckless driving or bankruptcy).
5	• Recurrent unipolar MDD with ≥3 or more major depressive episodes; or • Recurrent, distinct hypomanic episodes without full inter-episode recovery; or • Borderline personality disorder, anxiety disorder (including PTSD and OCD), eating disorder; or history of ADHD with onset before puberty; or • Engagement in gambling or other risky behaviors with the potential to pose a problem for patient, family or friends; or • Behavioral evidence of perimenstrual exacerbation of mood symptoms.
2	• Baseline hyperthymic personality when not manic or depressed; or • Marriage 3 or more times (including remarriage to the same individual); or • In two or more years, has started a new job and changed jobs after less than a year; or • Has more than two advanced degrees.
0	• None of the above.
IV. Response to Treatment	
20	• Full recovery within 4 weeks of therapeutic treatment with a mood stabilizer.
15	• Full recovery within 12 weeks of therapeutic treatment with a mood stabilizer or relapse within 12 weeks of discontinuing treatment; or • Affective switch to mania (pure or mixed) within 12 weeks of starting a new antidepressant or increasing dose.
10	• Worsening dysphoria or mixed symptoms during antidepressant treatment subthreshold for mania (exclude worsening that is limited to known antidepressant side effects such as akathisia, anxiety or sedation); or • Partial response to one or two mood stabilizers within 12 weeks of therapeutic treatment; or • Antidepressant-induced new or worsening rapid-cycling course.
5	• Treatment resistance: lack of response to complete trials of 3 or more antidepressants; or • Affective switch to mania or hypomania with antidepressant withdrawal.
2	• Immediate, near-complete response to antidepressant withdrawal within 1 week or less.
0	• None of the above, or no treatment.
V. Family History	
20	• At least one first-degree relative with clear bipolar disorder.
15	• At least one second-degree relative with clear bipolar disorder; or • At least one first-degree relative with recurrent unipolar MDD and behavioral evidence suggesting bipolar disorder.
10	• First-degree relative with recurrent unipolar MDD or schizoaffective disorder; or • Any relative with clear bipolar disorder or recurrent unipolar MDD and behavioral evidence suggesting bipolar disorder.
5	• First-degree relative with clear substance use disorder (excluding nicotine/caffeine); or • Any relative with possible bipolar disorder.
2	• First-degree relative with possible recurrent unipolar MDD; or • First-degree relative with anxiety disorder (including PTSD and OCD), eating disorder or ADD/ADHD.
0	• None of the above or no family history of psychiatric disorders.
	← Total score (0 – 100). Add the highest number in each section. A score ≥50 indicates a high probability of bipolar disorder.

Bipolarity Index and self-report measures by d

Diagnosis	Percent (%)	Bipolarity Index mean ± SD
Bipolar I	17.50	79 ± 12
Bipolar II	22.10	60 ± 11
Cyclothymic disorder[a]	1.30	56 ± 11
BP-NOS[b]	2.70	51 ± 13
Major depression, recurrent	30.20	37 ± 11
Major depression, ≤ 2 episodes	14.42	27 ± 10
Dysthymic disorder[a]	0.32	24 ± 5
Substance use disorder[a]	0.59	18 ± 9
ADHD[a]	4.38	12 ± 9
Personality disorder[a]	0.11	12 ± 3
Adjustment disorder[a]	0.76	5 ± 7
Other disorder[a]	5.62	13 ± 11

[a] Without a comorbid mood disorder.
[b] Antidepressant-induced mania or hypom

Mood Disorder Spectrum

100% Unipolar

"A little bipolar?"

100% Bipolar

No Signs of Bipolarity

Low –> Moderate Signs of Bipolarity

Sufficient Signs of Bipolarity Seen for High Confidence in Dx

Dx = MDD

Antidepressant Monotherapy Benefits > Risks

Dx = Unspecified Mood D/o
Unspecified Bipolar/Related D/o
Cyclothymia
MDD with mixed features

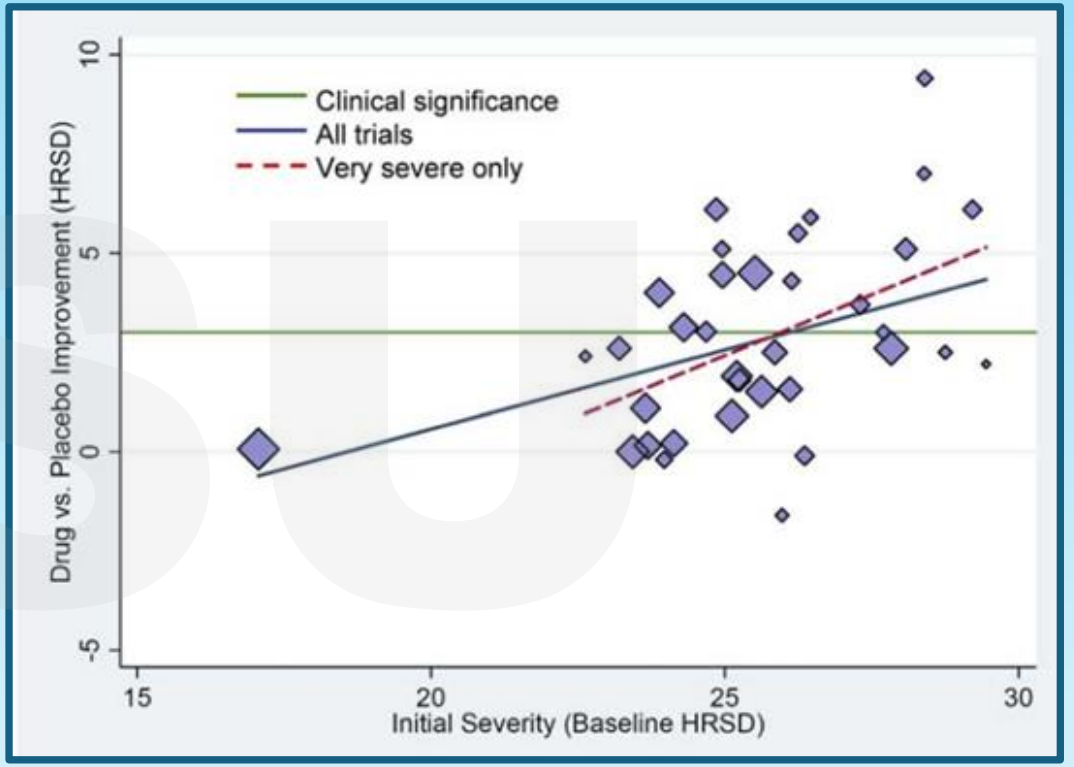
Risk: benefit of Antidepressant Monotherapy or Adjunctive Tx??

Dx = Bipolar 1 or Bipolar 2

Antidepressants:
Risks > Benefits
(limited studies for many situations)

Unipolar Depression Severity & Antidepressant Efficacy

Depression Severity by HDRS score	CGI-Severity correlate (Muller, MJ et al 2003)	PHQ-9 equivalent to HDRS score range severity (Sun, Y et al .BMC Psych, 2020)	Depression Severity by PHQ-9 score
Not ill HDRS 0-7	"Not at all" or "Marginally" ill	PHQ 0-7	None/Min. PHQ 0-4
			Mild PHQ 5-9
Mild HDRS 8-16	"Mildly" or "Moderately" ill	PHQ 8-14	Moderate PHQ 10-14
Moderate HDRS 17-23	"Moderately" or "Markedly" ill	PHQ 15-20	Moderately Severe PHQ 15-19
Severe HDRS >23	**"Markedly," "Severely," or "Extremely Severely" ill**	PHQ >20	**Severe PHQ 20-27**



Metanalysis of 35 RCTs (Kirsch I et al 2008)

Depression Severity by APA Research. Cmte Def.	Baseline HDRS Score	HDRS change over Pcbo	Effect Size Diff. Vs. Pcbo
Mild = HDRS <25	AD 22.6 Pcb 23.6	-0.8	+5% NOT Significant
Moderate = 25-27	AD 25.6 Pcb 25.4	-3.1	+12% Signif. (>11.5%)
Severe = HDRS >27	AD 28.8 Pcb 28.2	-4.8	+16% Significant

Antidepressants in Bipolar Disorder

Benefits?

Risks.

STEP-BD: Adj. Paroxetine or Bupropion + Li/VPA for Bipolar Depression

Sachs, GS et al. NEJM, 2007

- DBPC-RCT x 26 weeks, n=366 bipolar pts taking Li / VPA were randomized into paroxetine 10-40mg/d, bupropion 150-375mg/d, and placebo groups
- Benefits?
  - No significant differences seen in depression recovery rates vs placebo
- Risks?
  - No significant differences seen in rates of treatment emergent mania
  - **Suicidal ideation higher:** **Adj. Antidepressant - 25%**
    vs Placebo - 14%
  - Rates of SI by phase of bipolar (DSM-IV):

49% depressed	9% manic/hypomanic
47% mixed episode	7% euthymic

Elevated Suicide Risk in Bipolar Disorder that Increased by 6x with Antidepressants

- Just 1-3% of people have a bipolar d/o, but
  3-14% of all deaths by suicide occur in those with a bipolar disorder
- Suicide rate is ~20x higher than in the general population
  - Lifetime risk of **suicide attempt** with bipolar d/o: **25-50%**
  - Lifetime risk of **death by suicide** with bipolar d/o: **6-15%**
- Danish National Health Data study by Kessing et al. 2005:
  - n = 13,186 who purchased lithium in Denmark from 1995-1999
  - Purchase of antidepressants: 6x increase in the risk of suicide
    - This risk was **not** reduced by lithium prescription purchase rates

AHRQ Publication No. 18-EHC012-EFTondo et al. 2003; Baldessarini & Tondo 2003; Yerevanian 2007; Cipriani 2005; Goodwin 2003

Adjunctive Antidepressants added to Li/VPA

Short-term RCTs (6-10 wks.) for Acute Bipolar Depression

- **Benefits: Minimal at best**
  - **No significant differences from placebo groups for Response or Remission**
  - Only small differences in MADRS scores in some RCTs & in meta-analyses pooling data.
- **Risks:**
  - **Increased Suicidality**
  - **Mania/Hypomania Emerging with Antidepressant Treatment:**

Lower risk of Tx Emergent Mania:

SSRI/bupropion w\ Li/VPA/OLZ

SSRIs	7-16 %
Bupropion	5-14 %

No sig. diff. in YMRS >13 in many short PC-RCTs.
Less strict criteria for show higher rates of ranges listed.

Higher risk of Tx Emergent Mania:

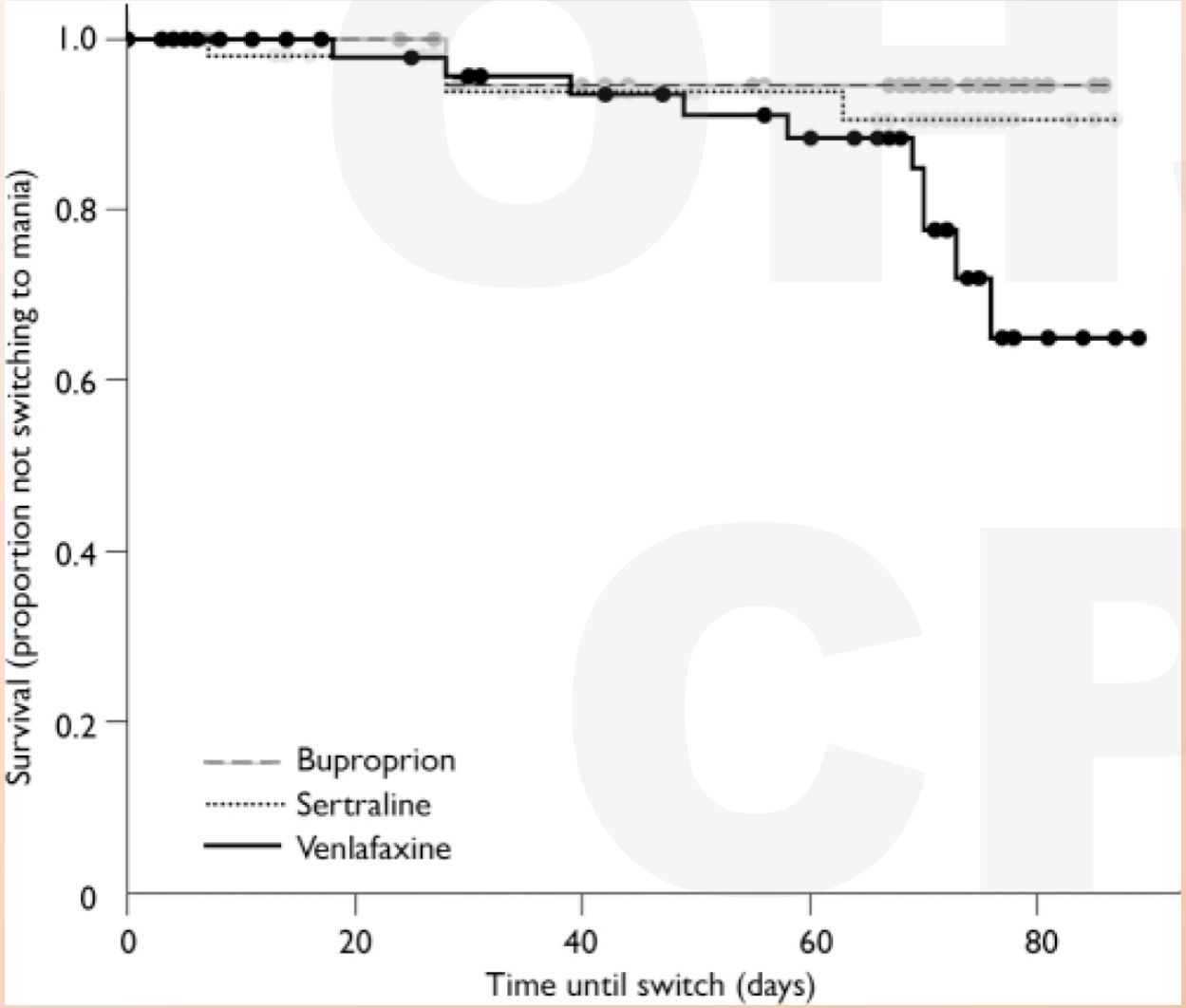
5HT + NE MOA Antidepressants w\ Li/VPA

TCAs	25-43 %
MAOIs	21-?? %
SNRIs	15-31 %
Tetracyclics (mirtazapine?)	8x higher risk of mania in MDD RCTs with mianserin, maprotiline vs SSRI

Rohde, C et al. Am J Psychiatry 2024; Sidor, MM et al. JCP 2011; Silverstone, T et al Acta Psy Scand. 2001.

Antidepressant-Associated **MANIA** Increases Over Time

Post, RM et al 2006 --- Mania by YMRS >13



- 10 wks, n=174 w\ BP1, BP2, BP NOS, depressed & on 1+ MS/antimanic AP
- Avg pt on 1.4: Lithium (64 pts), valproate (93), carbamazepine (16), lamotrigine (8), FGAs (8), SGAs (30)
- Similar response (49–53%) & remission (34–41%) rates in 3 groups.
- **Switches into mania at 10 wks using criteria of YMRS > 13:**

venlafaxine	15%
sertraline	7%
bupropion	5%

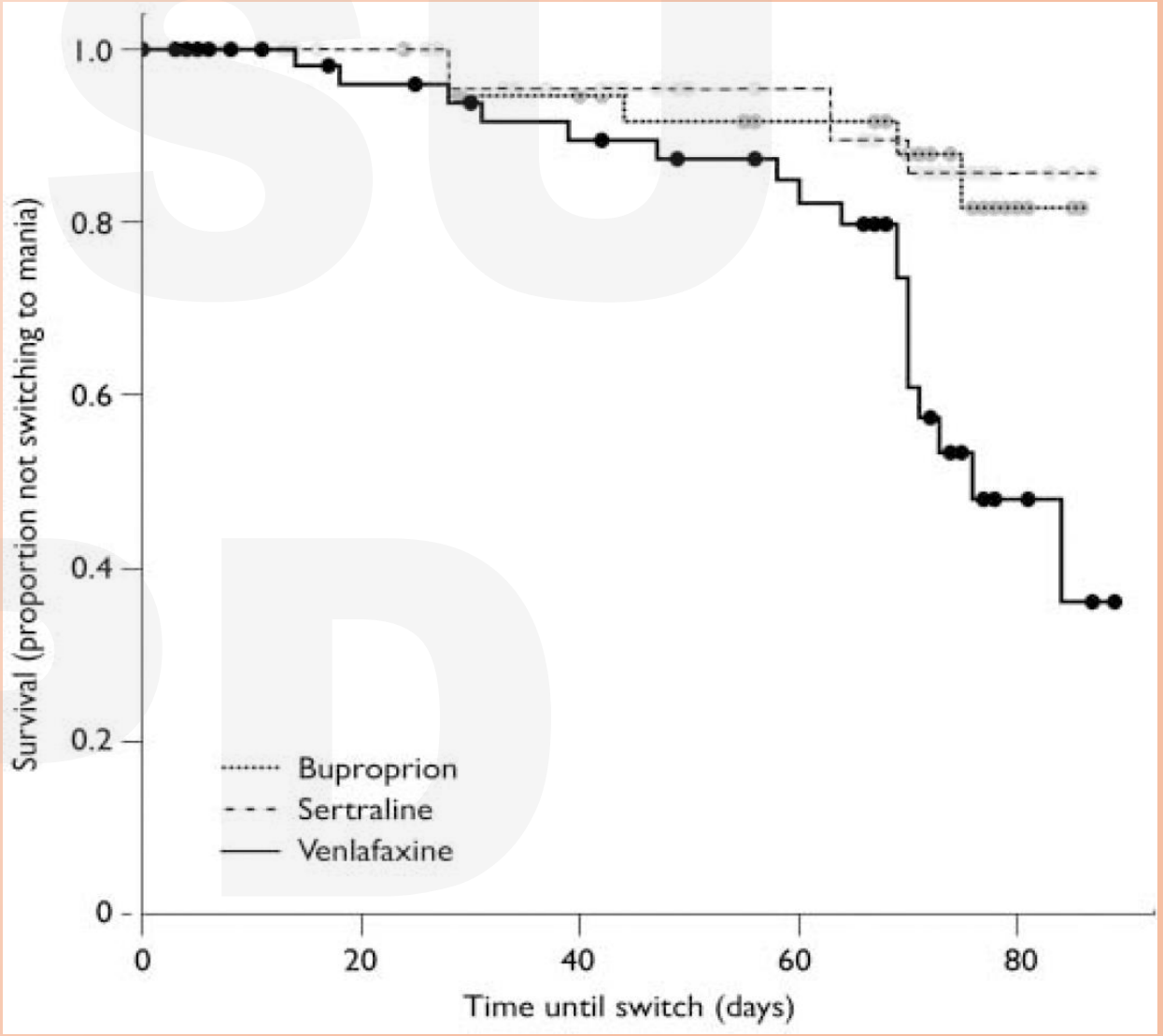
Antidepressant-Asso. **DESTABILIZATION** Increases Over Time

Post, RM et al 2006 --- 2pt Incr. on CGI-BD Mania severity item

- 10 wks, n=174 w\ BP1, BP2, BP NOS, depressed & on 1+ MS/antimanic AP
- Avg pt on 1.4: Lithium (64 pts), valproate (93), carbamazepine (16), lamotrigine (8), FGAs (8), SGAs (30)

- **Manic/mixed sx emergence over 10 wks using broader criteria (CGI-BD mania severity 2 pt change, e.g. "not ill" to "mildly ill"-or-"minimally" to "moderately"):**

venlafaxine	**31%**
sertraline	**16%**
bupropion	**14%**



Long-term Adj. Antidepressants + Li/VPA: Any Benefits?

Few long term (52-wk) placebo-controlled RCTs adj. have been completed on adjunctive antidepressants in bipolar disorder:

1. Yatham 2016 – n=344 BP1 – **Agomelatine** (melatonin agonist with 5HT2A blockade) + Li/VPA
   - **No benefits** (No differences in MADRS scores.)

2. CAPE-BD 2021 – n=119 BP1/BP2 – **Citalopram** + Li/VPA
   - **No benefits** for treatment or prevention of depression

3. BEAM-BD 2023 - n=177 BP1 – **Escitalopram or Bupropion** + Li/VPA,
   - **No benefits** for prevention of depression (in group that started in remission)

NO LONG-TERM BENEFITS of Adj. Antidepressants +Li/VPA

Ghaemi, SN et al. BJP 2016; Ghaemi SN, et al. JCP 2021; McGirr, A et al FOCUS 2021; Yatham, LN et al. NEJM 2023.

Long-term Adj. Antidepressants +Li/VPA: the Risks.

1. Yatham 2016 – n=344 BP1 – Agomelatine (melatonin agonist with 5HT2A blockade) + Li/VPA
   - **More pts with manic/hypomanic sx w\ adj. agomelatine** (13 pts, 7.6%) vs placebo (7 pts, 4.1%) in extension phase but not acute phase
2. CAPE-BD 2021 – n=119 BP1/BP2 – Citalopram + Li/VPA
   - **YMRS increased more with adj. citalopram in the rapid cycling subgroup**
   - NS in the overall group, both in acute and extension phases.

1+2: Metanalysis that pooled data from above 2 trials (McGirr, A et al. 2021)

- **NNH = 19 for mania with adj. antidepressant use over Li/VPA alone** (SMR of 1.774)
- Mania: 17% of the AD +Li /VPA group vs 10% of the placebo +Li /VPA group (24 of 231)

3. BEAM-BD 2023 - n=177 BP1 – Escitalopram/Bupropion + Li/VPA,
   - **Mania 2x as freq. with antidepressant (12% vs 6% when AD dc at 8 wks) –** NS, underpowered

- **HIGHER RISK for Mania/Hypomania/Mixed Episodes & NO BENEFITS**

→ No role for adj. antidepressant use > 8 wks ever in bipolar d/o

Ghaemi, SN et al. BJP 2016; Ghaemi SN, et al. JCP 2021; McGirr, A et al FOCUS 2021; Yatham, LN et al. NEJM 2023.

Olanzapine vs OFC for Bipolar Depression

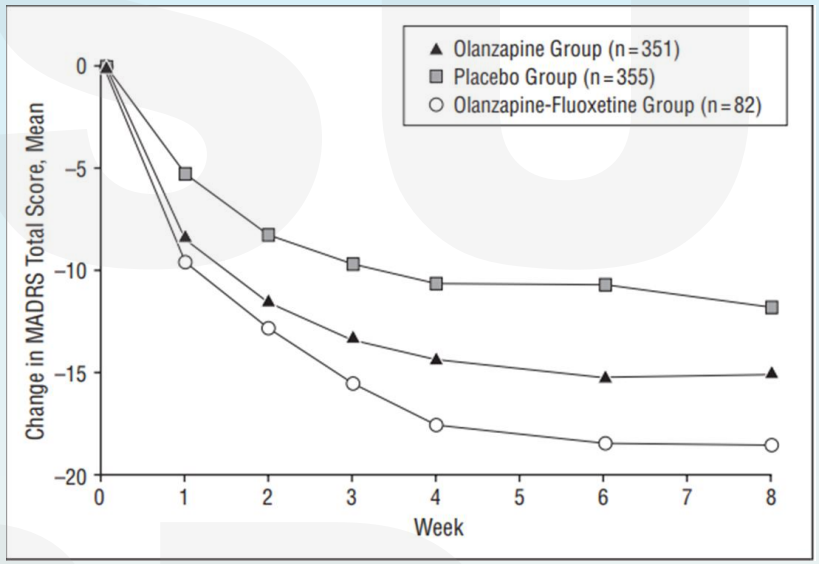
Short-Term: 8 wk Double-blind, placebo-controlled RCT, n = 833 (~1/3 rapid cycling)

n=377 on placebo, n=370 on olanzapine 5-20 mg/d. (avg 10mg/d.) , n=86 OFC (avg olanz 7.5mg-fluox 40mg/d.)

- Benefits: OFC > olanz > placebo

	OFC	olanz	placebo
Response Rates	56%	39%	30%
Remission Rates	49%	32%	25%

- Risks:
  - No diff. in tx emergent mania: 5.7-6.7%
  - Weight gain (+>7% of baseline wt.):
    0.3% placebo
    18.7% olanzapine
    19.5% OFC



Long-term: 24 wk open label extension w\ a "switched" group in data reported

Depressive relapse for pts starting in remission : 24% on OFC vs 11% on olanz over 24 weeks (50% of "switched")

Pts not remitted at start: MADRS score reduced 6 pts on OFC vs 12 pts on olanz (6 pts in "switched" group)

Depression remission occurred in 63-67% in all groups

Tohen, M et al. Efficacy of Olanzapine and Olanzapine-Fluoxetine Combination in the Treatment of Bipolar I Depression, Arch Gen Psych, 2003.

Corya, SA et al. A 24-week open-label extension study of OFC and olanzapine monotherapy in the tx of bipolar depression. JCP, 2006.

Tx Emergent Manic Sx on Antidepressants + Antipsychotics

Review of the Limited Long term RTC data: Sidor, MM et al. JCP 2011

- Sidor 2011: **Reviewed RTCs adding on antidepressants to an antipsychotic**
  - Tohen et al 2003 **n = 34** BP1 pts: 8 on fluoxetine, 8 olanzapine, 9 OFC, 9 placebo
  - Shelton et al 2004 **n = 20** BP1/BP2 pts on Risperidone & MS + paroxetine/placebo
- **Switch rates (more liberal criteria of YMRS > 7):**
  - Overall rate was 6x higher, but NS (RR =3.05; 95% CI, 0.62–15.11; *P* = .17)
    - **4% for placebo**
    - **24% for antidepressants**
  - Most of these cases were from the olanzapine/fluoxetine study by Tohen et al. which showed switch (YMRS>7) rates of:
    - **33% placebo**
    - **13% olanzapine monotherapy**
    - **47% fluoxetine monotherapy**
    - **47% olanzapine-fluoxetine combo**

Unipolar Depression's

"ANTIDEPRESSANTS"

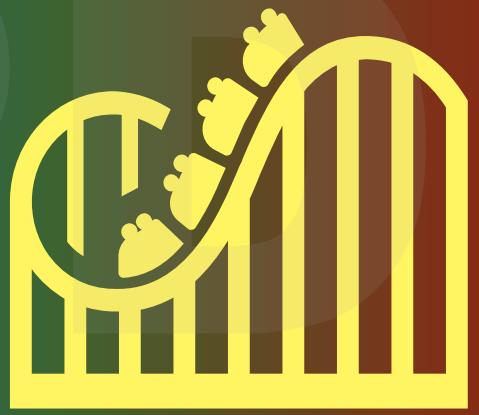
Bipolar Disorder's

= "MOOD DESTABILIZERS"

Unipolar

Unspecified Mood D/o
Other Bipolar Related D/o

Bipolar 1 & 2



Dose-Response Modeling
Chapel, S et al 2016

Data from Lurasidone Mono & Adj Tx RCTs by Loebel A, et al. AJP, 2014 (x2)

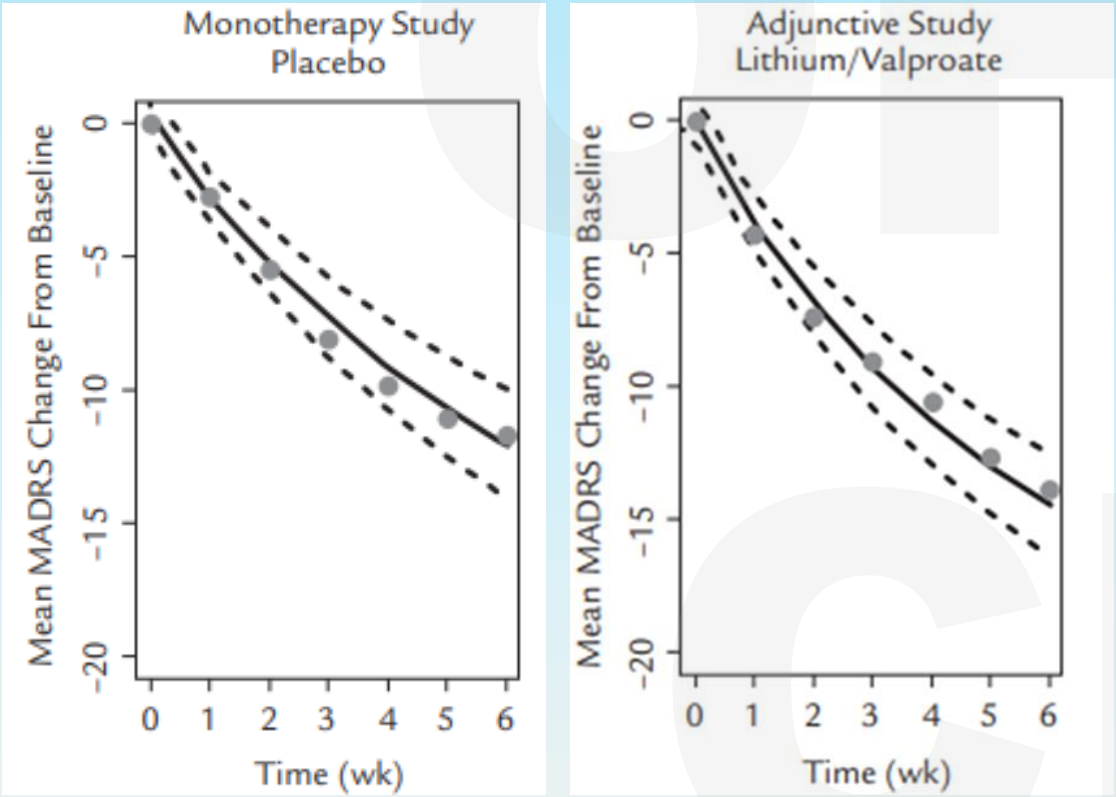


Figure 4. Predictive distribution of the observed means, featuring a 90% prediction interval overlaid by observed mean scores. MADRS = Montgomery-Åsberg Depression Rating Scale.

MADRS scores (0-60 range):

- Average starting MADRS score: 30.5, 30.6
- Response = 50% decrease in score
- Remission = MADRS <13.

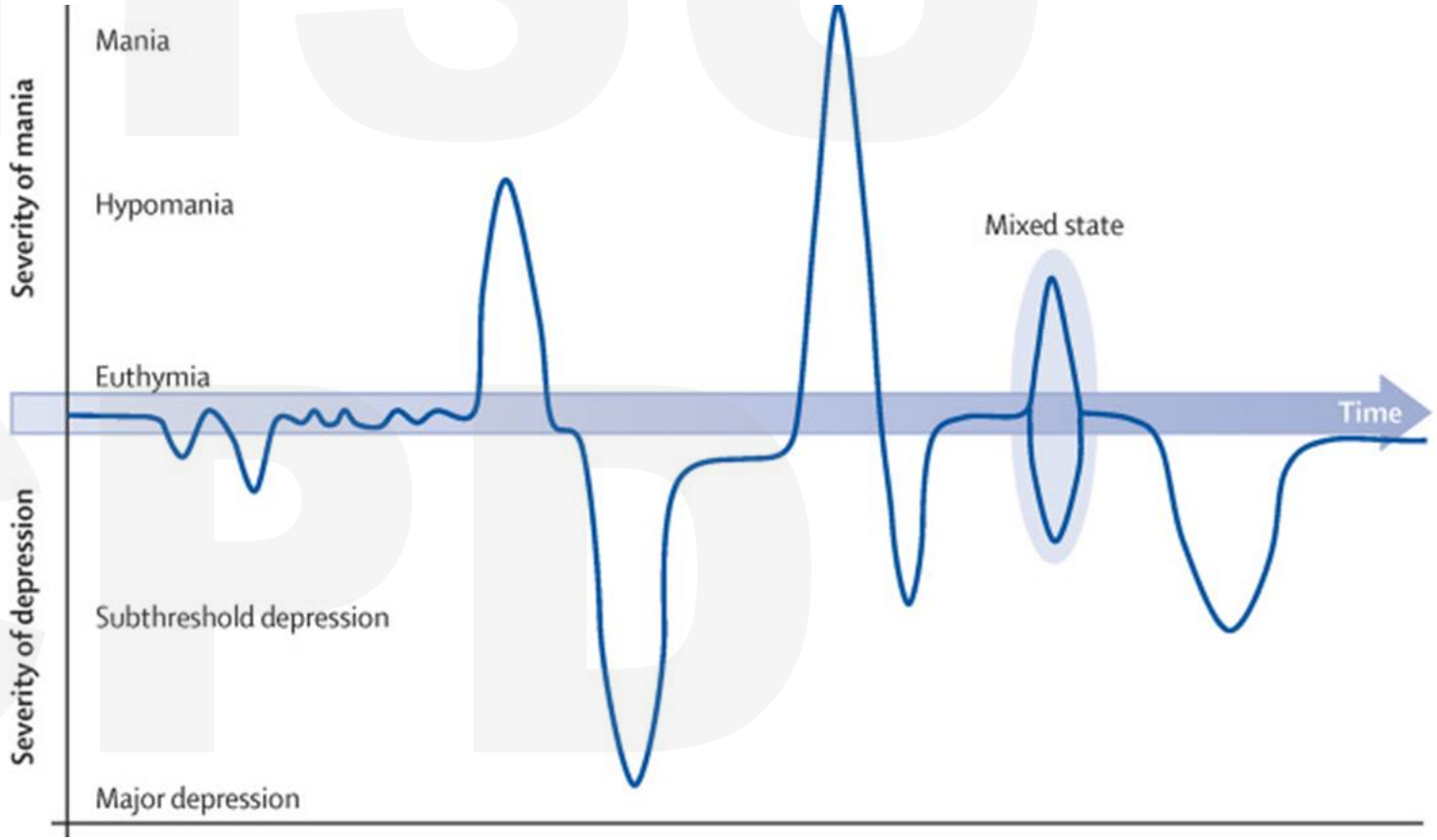
Placebo group score changes fit an exponential asymptotic model totaling 13-14 pts at 6 wks.

- 50% of score reduction seen at 2.5 wks
- 95% of score reduction seen at 12 wks

Drug effects showed linear dose-response.

- Scores reduced 3.5 points on avg. with 20mg dose; 6.5 pts with 120mg dose.
- 95% of max net drug effect was seen at 2 wks

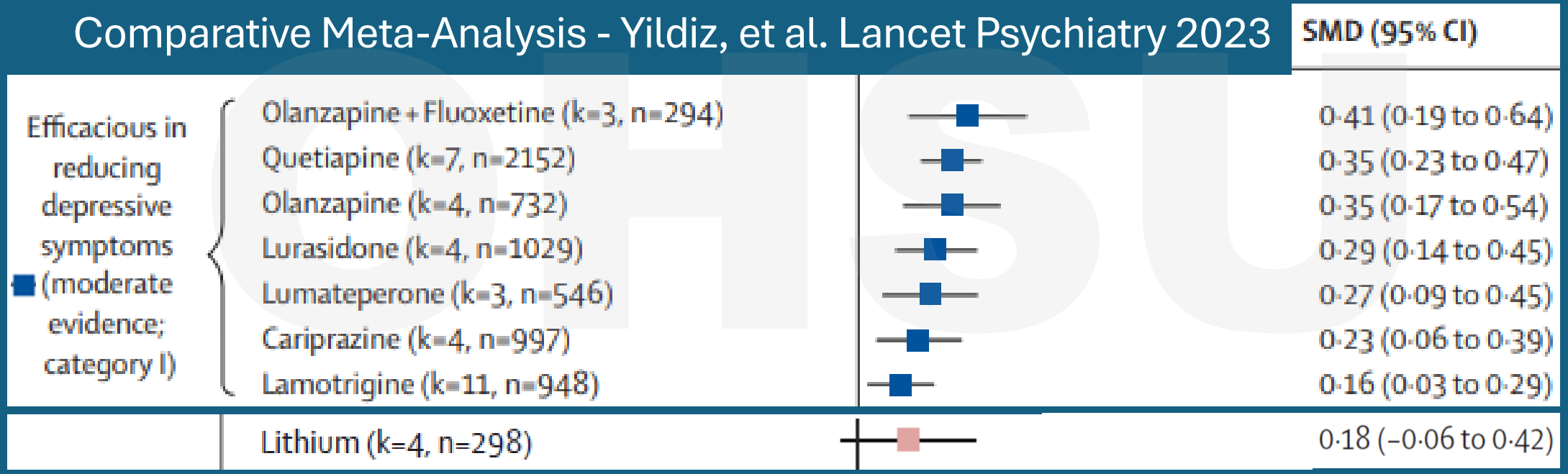
effect? Drug Effect?
Or Just Bipolar Disorder Cycling?



Graph from Grande, I et al. Lancet 2016

Acute Bipolar Depression Drug Efficacy

Comparative Meta-Analysis - Yildiz, et al. Lancet Psychiatry 2023



Metanalysis of RCTs on Antipsychotics for Acute Bipolar Depression

Li, S et al.
Eur Psych, 2024

Antipsychotic	Odds Ratio for Response
Quetiapine	**2.08** (1.69-2.56)
Lurasidone	**2.00** (1.11-2.94)
Lumateperone	**1.75** (1.11-2.94)
Olanzapine	**1.54** (1.19-2.13)
Cariprazine	**1.45** (1.14-1.85)

Lithium – the “Hard Evidence” in Bipolar Tx

Meta-analysis of RCTs, Fountoulakis KN, et al 2022

- **Efficacy in Acute Bipolar Depression ???**
  - Considered “unclear” due to limitations in methods of studies completed
  - Positive data seen in older trials
    - 9 RCTs from1960s &1970s, and one from1995
  - Only 1 RCT this century with modern methodology (EMBOLDEN I)

EMBOLDEN I: Quetiapine vs. Lithium for BP Depression

Fountoulakis KN, et al. 2022

- 8-week dbpc-RTC
- 136 pts on lithium, 265 pts on quetiapine, and 133 pts on placebo.
- Results: positive for quetiapine, but negative for lithium
- **The mean lithium serum level of pts in the study was 0.61**
  - **34.9% pt pts on lithium had levels below 0.6**
- Levels of 0.8-1.2 have been recommended by experts for depressed phase tx
  - Young et al., 2010 reported a post-hoc analysis of Li > 0.8 subgroup gave negative results and noted lithium level did not correlate with change in MADRS.
  - But, Li level >0.8 subgroup almost certainly lacked sufficient power to draw reliable conclusions about lithium's efficacy.
  - Also, trial used flexible dosing, so patients with more severe illness would have been more likely to be treated with higher doses aiming for higher levels.

Current Guidelines for Acute Bipolar Depression

VA-DoD 2023

Bipolar Depression Tx Guidelines

Strong rec for:

quetiapine

Weak recs for:

Monotherapy: **cariprazine**
lumateperone
lurasidone
olanzapine

Combos: lamotrigine + lithium/quetiapine
adj. short-term light therapy
adj. rTMS if tx resistant to meds

No recs for or against:

antidepressants
lamotrigine
(es)ketamine

ISBD/CANMAT 2023

Bipolar Depression Tx Guidelines

First Line (Hierarchically Ranked):

quetiapine
lurasidone
lithium
lamotrigine
cariprazine
lurasidone (adj. +Li/VPA)

Second Line (Hierarchically Ranked):

divalproex
SSRIs/bupropion (adj. +Li/VPA)
ECT
olanzapine-fluoxetine
lumateperone

Third Line (In no particular order):

Monotx: **olanzapine**, carbamazepine
Adj: rTMS, light tx, SNRI/MAOI, IV ketamine,
+8 more drug/supplement options

Current Guidelines for Acute Bipolar Depression

VA-DoD 2023

Bipolar Depression Tx Guidelines

Strong rec for:

quetiapine

Weak recs for:

Monotherapy:

cariprazine
lumateperone
lurasidone
olanzapine

Combos: lamotrigine + lithium/quetiapine
adj. short-term light therapy
adj. rTMS if tx resistant to meds

No recs for or against:

antidepressants
lamotrigine
(es)ketamine

ISBD/CANMAT 2023

Bipolar Depression Tx Guidelines

First Line (Hierarchically Ranked):

quetiapine
lurasidone
lithium
lamotrigine
cariprazine
lurasidone (adj. +Li/VPA)

Second Line (Hierarchically Ranked):

divalproex
SSRIs/bupropion (adj. +Li/VPA)
ECT
olanzapine-fluoxetine
lumateperone

Third Line (In no particular order):

Monotx: **olanzapine**, carbamazepine
Adj: rTMS, light tx, SNRI/MAOI, IV ketamine,
+8 more drug/supplement options

Minimizing Bipolar Cycling is Essential

- **2-year recurrence rate of bipolar mood episodes is ~50% for pts receiving treatment**
- Increasing number of bipolar episodes is associated with shortening of the inter-episode interval and further tx resistance
- **Does hypomania (YMRS ~12) matter, or subsyndromal sx (e.g. YMRS >7, mixed fx)?**
  - Mixed symptoms are associated with higher rates of SI (in bipolar & MDD)
  - Bipolar pts spend more time in subsyndromal episodes than episodes meeting full criteria for a manic, hypomanic, or depressed episode
- **Psychosocial interventions with focus on avoiding triggers reduce mood episodes**

Triggers of mania/hypomania:

Disrupted circadian rhythms, Childbirth
Brain stimulation, Goal attainment events
Antidepressants, Stimulants, Steroids
Energy drinks, St. John's Wort, Acetyl-l-carnitine

Triggers of depression:

First-gen. Antipsychotics
Negative life events

Pikalov A et al. 2017; da Costa et al., 2016; Rodrigues Cordeiro, C et al 2023; Yatham et al. 2018; Proudfoot et al. 2011; Bostock et al., 2015; Johnson, 2005; Johnson et al., 2008

Current Guidelines for Bipolar Maintenance

VA-DoD 2023 Bipolar Maintenance
For Prevention of Depression

Strong rec for:
Monotherapy: **Lamotrigine**

Weak recs for:
Monotherapy: **Lithium** or **Quetiapine**
if not Li/QTP, then **Olanzapine**

Combos: Li/VPA + olanzapine
Li/VPA + lurasidone
Li/VPA + quetiapine

No recs for or against: Other APs/MSs (incl. VPA) or combos for depression ppx.

For Mania Prevention:
Monotx: Li, QTP, OLZ, paliperidone, or risperidone.
Adj. tx: (ARI, OLZ, QTP, or ZIP) + (Li/VPA)

ISBD/CANMAT 2023
For Bipolar Maintenance

First Line (In Hierarchical Rank):
Lithium
Quetiapine
Divalproex
Lamotrigine
Asenapine
Quetiapine +Li/DVP
Aripiprazole +Li/DVP
Aripiprazole (PO, then LAI)

Second Line (In Hierarchical Rank):
Olanzapine
Risperidone LAI, then Risper. LAI (adj)
Carbamazepine
Paliperidone (>6 mg)
Lurasidone +Li/DVP
Ziprasidone +Li/DVP

Current Guidelines for Bipolar Maintenance

VA-DoD 2023 Bipolar Maintenance For Prevention of Depression

Strong rec for:
Monotherapy: **Lamotrigine** (not for ppx of mania)

Weak recs for:
Monotherapy: **Lithium** or **Quetiapine**
if not Li/QTP, then **Olanzapine**

Combos: Li/VPA + olanzapine
Li/VPA + lurasidone
Li/VPA + quetiapine

No recs for or against: Other APs/MSs (incl. VPA) or combos for depression ppx.

For Mania Prevention:
Monotx: Li, QTP, OLZ, paliperidone, or risperidone.
Adj. tx: (ARI, OLZ, QTP, or ZIP) + (Li/VPA)

ISBD/CANMAT 2023 For Bipolar Maintenance

First Line (In Hierarchical Rank):
Lithium
Quetiapine
Divalproex
Lamotrigine
Asenapine
Quetiapine +Li/DVP
Aripiprazole +Li/DVP
Aripiprazole (PO, then LAI)

Second Line (In Hierarchical Rank):
Olanzapine
Risperidone LAI, then Risper. LAI (adj)
Carbamazepine
Paliperidone (>6 mg)
Lurasidone +Li/DVP
Ziprasidone +Li/DVP

Lithium – Evidence for Bipolar Maintenance

Meta-analysis of RCTs, Fountoulakis KN, et al 2022

- Prophylaxis against **recurrence of mania** is **clearly supported**

- Prophylaxis against **depressive relapse** is **unclear** (study limitations)
  - 21 RTC on Li monotherapy – older trials suggest benefits but methodology not ideal
  - just 4 relatively recent/modern trials:
    - 1 with enriched population of quetiapine responders – showed both lithium and quetiapine **prevented both mania/hypomania and depression recurrences**
    - 2 with enriched population of lamotrigine responders – showed lithium **only prevented mania/hypomania** while lamotrigine prevented depressive relapse
    - 1 failed trial (3 groups that didn't separate at all)

Long term Efficacy in Bipolar Disorder:

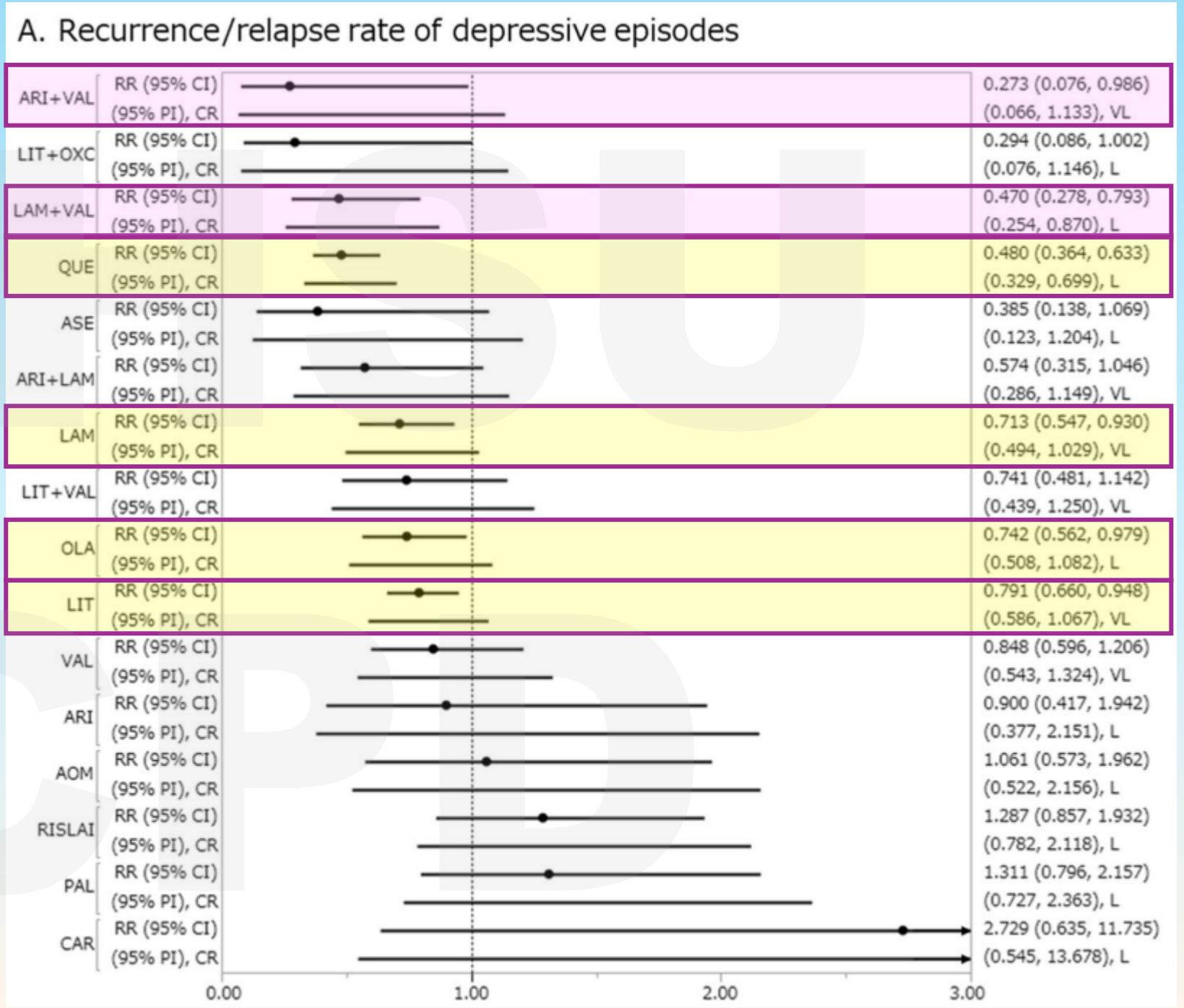
Metanalysis of RCTs, Kishi T et al, 2021

Depression Prevention

QUE = quetiapine
LAM = lamotrigine
OLA = olanzapine
LIT = lithium

ASE = asenapine
AOM = aripiprazole once/mo. LAI
ARI = aripiprazole
CAR = carbamazepine
OXC = oxcarbazepine
PAL = paliperidone
RISLAI = risperidone LAI
VAL = valproate

Confidence level estimates indicated to the right (L: low, M: moderate, VL: very low).



Long term Efficacy in Bipolar Disorder:

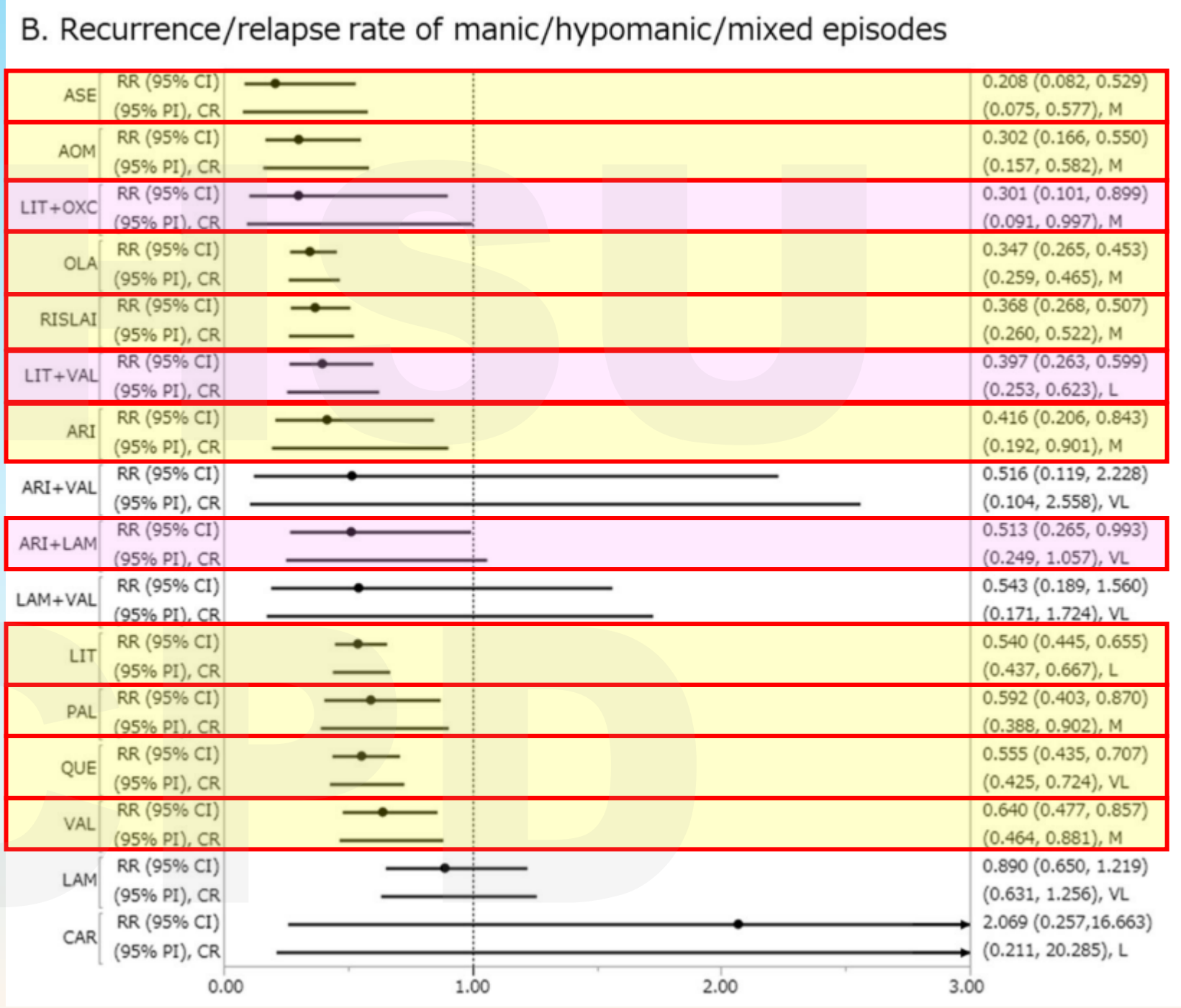
Metanalysis of RCTs, Kishi T et al, 2021

Mania Prevention

ASE = asenapine
AOM = aripiprazole once/mo. LAI
OLA = olanzapine
RISLAI = risperidone LAI
ARI = aripiprazole
LIT = lithium
PAL = paliperidone
QUE = quetiapine
VAL = valproate

LAM = lamotrigine
CAR = carbamazepine
OXC = oxcarbazepine

Confidence level estimates indicated to the right (L: low, M: moderate, VL: very low).



Long term Efficacy in Bipolar Disorder

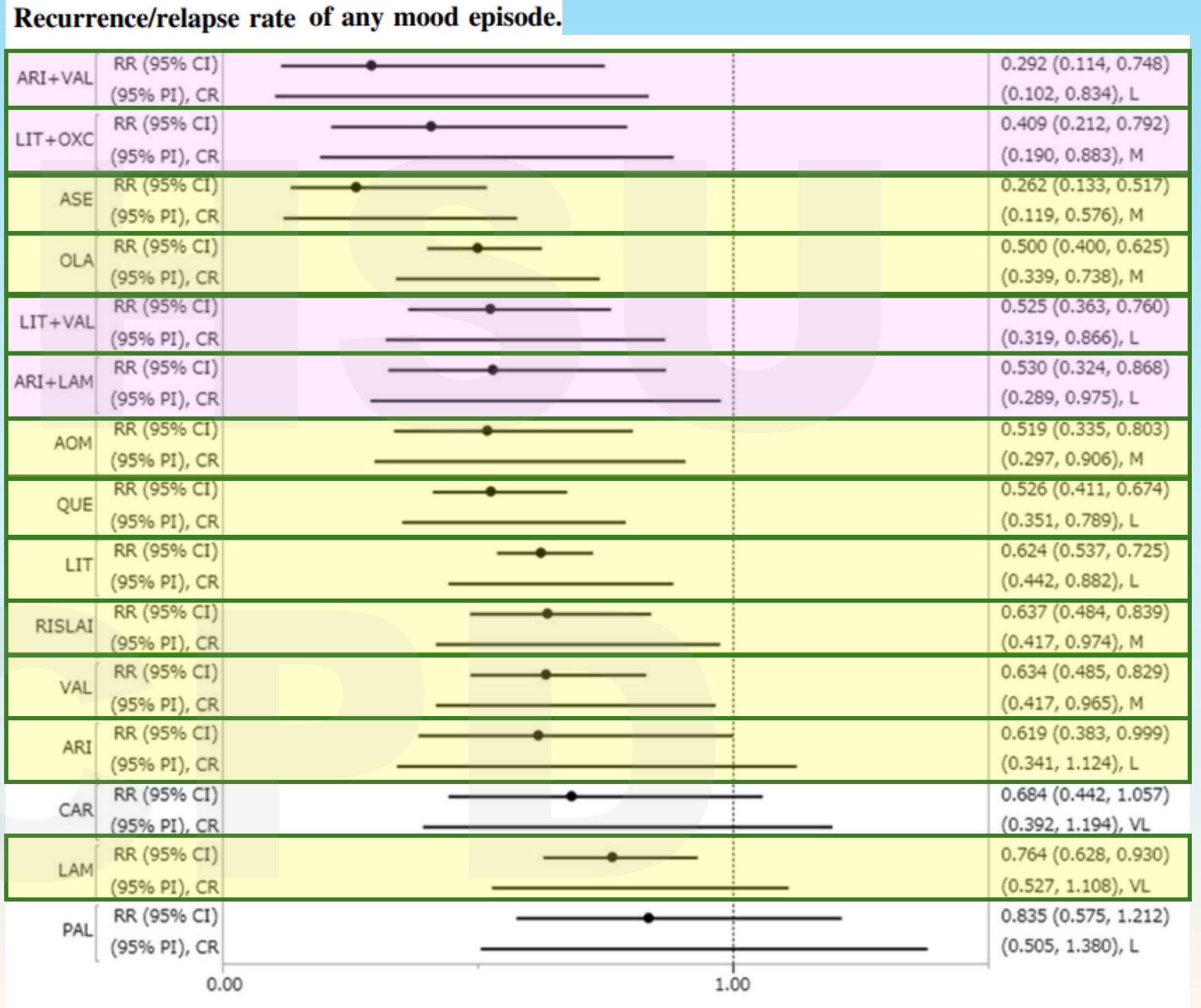
Metanalysis of RCTs, Kishi T et al, 2021

Prevention of Recurrence of Any Mood Episode

ASE = asenapine
OLA = olanzapine
AOM = aripiprazole once/mo. LAI
QUE = quetiapine
LIT = lithium
RISLAI = risperidone LAI
VAL = valproate
ARI = aripiprazole
LAM = lamotrigine

CAR = carbamazepine
PAL = paliperidone
OXC = oxcarbazepine

Confidence level estimates indicated to the right (L: low, M: moderate, VL: very low).



Antipsychotic Monotherapy vs in Combo with Li/VPA x 6 Months

Systematic Review & Meta-Analysis by Kishi, T et al. Bipolar Disorders, 2021

- **Meta-analysis of 8 RCTs of antipsychotic + lithium/VPA** (pooled n=1,456)
  versus antipsychotic + placebo (pooled n=1,476)
  - 3 studies on aripiprazole, 2 quetiapine, 1 lurasidone, 1 olanzapine, 1 ziprasidone
  - Mean study duration = 58.25 ± 33.63 weeks

- Pooled data for **antipsychotic + Li/VPA showed significantly lower mood episodes recurrence rates** than antipsychotic monotherapy
  - Any mood episode — RR 0.51 (CI 0.39–0.86)
  - Manic/hypomanic/mixed episodes — RR 0.42 (CI 0.30–0.59)
  - Depressive episodes — RR 0.39 (CI 0.28–0.54)

- Also showed significantly **lower all-cause discontinuation rates for** treatment with combination of **antipsychotic + Li/VPA** vs. antipsychotic alone. RR 0.67 (CI 0.50–0.89)

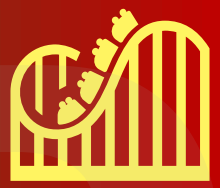
Summary:

1) How much bipolarity suspected?

Unipolar → Bipolar Features → Bipolar type 1 or 2

Tools: Rapid Mood Screener, Bipolarity Index, Bipolar Spectrum Dx Scale

2) "ANTIDEPRESSANT" or "MOOD DESTABILIZER"?



3) Focus on long-term stabilization of bipolar disorder via tx with:

Depression PPx: lamotrigine, lithium, quetiapine, olanzapine

Mania/Mixed episode PPx: lithium, quetiapine, olanzapine, aripiprazole, asenapine, valproate, risperidone

Combo of Li/VPA + atypical antipsychotic is more effective than antipsychotic alone