



UW PACC

Psychiatry and Addictions Case Conference

UW Medicine | Psychiatry and Behavioral Sciences

MEDICATIONS FOR ACUTE BIPOLAR DEPRESSION IN ADULT PATIENTS

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SPEAKER DISCLOSURES

- ✓ The speaker has no relevant conflicts of interest to disclose; other disclosures have been mitigated.

PLANNER DISCLOSURES

The following series planners have no relevant conflicts of interest to disclose; other disclosures have been mitigated.

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A few words on gender biases evident in bipolar diagnosis and treatment



Approved for a broad range of adults with bipolar depression¹

The first and only approved treatment for depressive episodes associated with bipolar I or II disorder in adults as monotherapy and adjunctive therapy with lithium or valproate²

Clinical studies evaluating adults with a depressive episode associated with bipolar disorder (bipolar depression)^{1,2}

| | Monotherapy | | Adjunctive (with lithium or valproate) | |
|--------------------------|-------------|------------|--|------------|
| | Bipolar I | Bipolar II | Bipolar I | Bipolar II |
| CAPLYTA 42 mg | ✓ | ✓ | ✓ | ✓ |
| Quetiapine/Quetiapine XR | ✓ | ✓ | | |
| Olanzapine/Fluoxetine | ✓ | | | |
| Lurasidone | ✓ | | ✓ | |
| Cariprazine | ✓ | | | |

There are no head-to-head clinical studies comparing the safety and efficacy of these products. This chart is descriptive of the FDA-approved indications in adults with bipolar depression and does not represent all approved indications for each product.

Important Safety Information

Black Box Warnings:

- Elderly patients with dementia-related psychosis treated with antidepressants have an increased risk of death. CAPLYTA is not approved for the treatment of patients with dementia-related psychosis.
- Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adults in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors. The safety and effectiveness of CAPLYTA have not been established in pediatric patients.

CAPLYTA
lumateperone capsules

Review your personal important safety information on page 3 of this brochure.

In the US, women are diagnosed with bipolar disorder twice as often as men. There is no genetic evidence to suggest this ratio should exist.

Marketing directed at prescribers has the potential to reinforce our diagnostic biases.

[Indications](#) | [Prescribing information](#) | [Patient safety information](#) | [For healthcare professionals](#)

LYBALVI
 Lurasidone and citalopram
 Long-acting Long-acting Long-acting Long-acting

[About LYBALVI](#) | [Starting LYBALVI](#) | [Living With Bipolar I](#) | [Frequently Asked Questions](#) | [Co-pay and Resources](#) | [Stay Informed](#)

Indication: LYBALVI® is used in adults to treat manic or mixed episodes that happen with bipolar I disorder, either alone for short-term (acute) or maintenance treatment or in combination with valproate or lithium.



I got help to push back against bipolar I

Individual results may vary.

Patient facing website

[For US Healthcare Professionals](#) | [View Patient Site](#) | [Important Safety Info](#)

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[Efficacy & Safety](#) | [About LYBALVI](#) | [Dosing](#) | [Support & Resources](#) | [Request a Rep](#)

Indications: LYBALVI® is indicated for the treatment of adults with bipolar I disorder for acute treatment of manic or mixed episodes as monotherapy and as an adjunct to lithium or valproate, or as a maintenance monotherapy treatment, or for the treatment of adults with schizophrenia.

POWER TO TREAT
 BIPOLAR I DISORDER AND SCHIZOPHRENIA
 Treat with the proven efficacy of LYBALVI

[See Trial Data >](#)

FASTEST GROWING ORAL ATYPICAL ANTIPSYCHOTIC
 by percent change for both bipolar I disorder and schizophrenia*

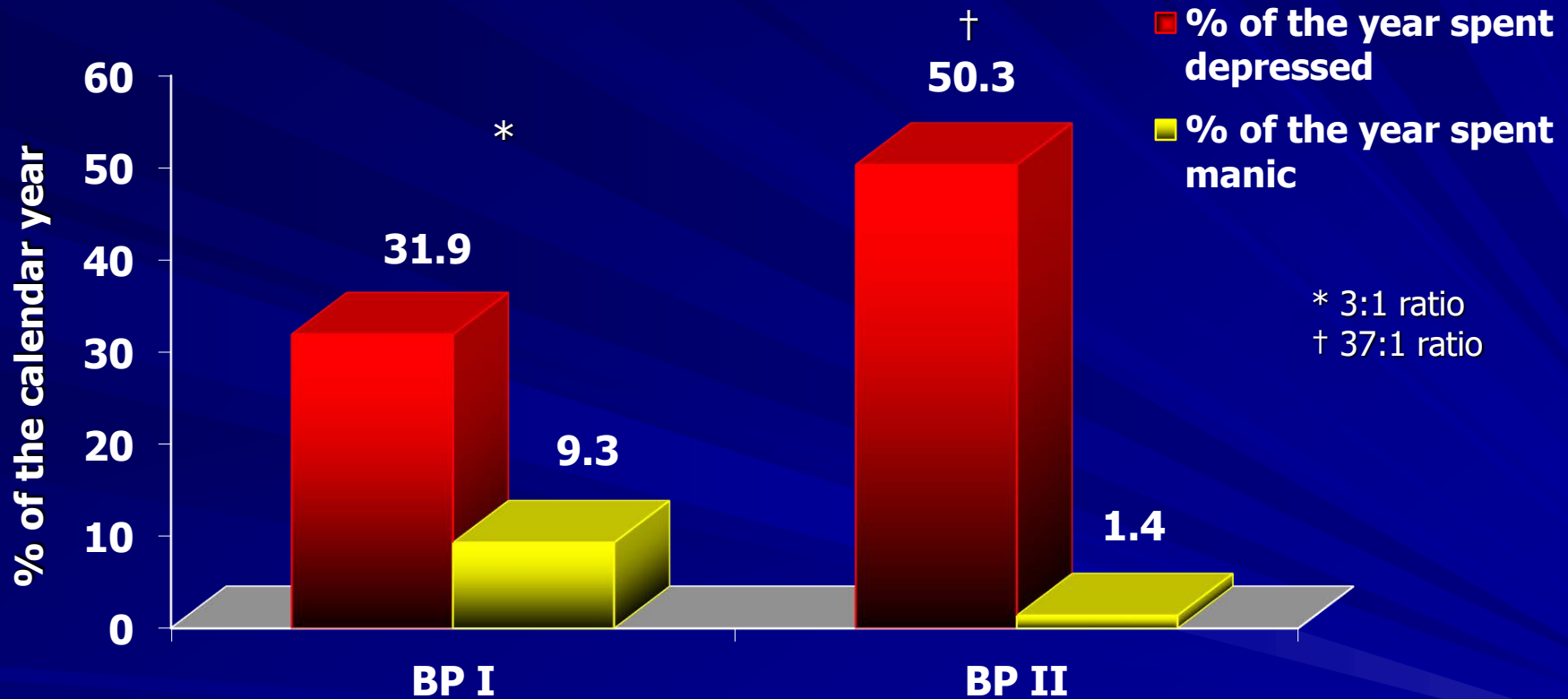
*Percent Change Based on IQVIA Monthly Prescription Data for the month of February 2020 compared to the month of October 2017 (date of LYBALVI launch). Analysis includes market leaders of oral atypical antipsychotic products that have an indication consistent with an FDA-approved indication for LYBALVI. Some categories may not include all products due to unavailability of prescribing and dispensing data.

Provider facing website

Interesting articles on gender and antipsychotics:

- In a Norwegian study, twice as many women as men described the side effect burden of antipsychotics as severe. (Iverson, Prog. Neuro-Psychopharmacol. Biol. Psychiatry. 2018)
- Long term exposure to prolactin-increasing, but not prolactin-sparing, antipsychotics was associated with increased odds for breast cancer in a Finnish study of women with schizophrenia. Taipale et al, Lancet Psychiatry, 2021
- There aren't many studies that research antipsychotic prescribing biases in transgender or gender nonbinary patients. Here is an interesting recent one, though...
 - Carrillo et al, Ment Health Clin, 2024 Aug 7 [Comparison of inpatient psychiatric medication management in gender diverse youth with cisgender peers - PMC \(washington.edu\)](#)

Ratio of Depressive vs. Manic Time



- NIMH Collaborative Depression Study
- 10 years follow-up: BP II had greater chronicity and comorbidity

FDA Pharmacopoeia for Bipolar Monotherapy in Adults

| | Manic or Mixed | Bipolar Maintenance | Bipolar Depression |
|----------------------------|----------------|---------------------|--------------------|
| Aripiprazole | 2004 | 2005 | |
| Asenapine | 2009 | | |
| Carbamazepine (ER) | 2004 | | |
| Cariprazine | 2017 | | 2019 |
| Chlorpromazine | 1999 | | |
| Lamotrigine | | 2003 | |
| Lithium | 1975 | 1978 | |
| Olanzapine | 2000 | 2003 | |
| Lurasidone | | | 2013 |
| Olanzapine/Fluoxetine | | | 2003 |
| Quetiapine (original & XR) | 2004, 2008 | 2008 | 2004, 2008 |
| Risperidone | 2003 | | |
| Valproate (original & ER) | 1994, 2005 | | |
| Ziprasidone | 2004 | | |
| Lumateperone | | | 2021 |
| Olanzapine/Samidorphan | 2021 | 2021 | |

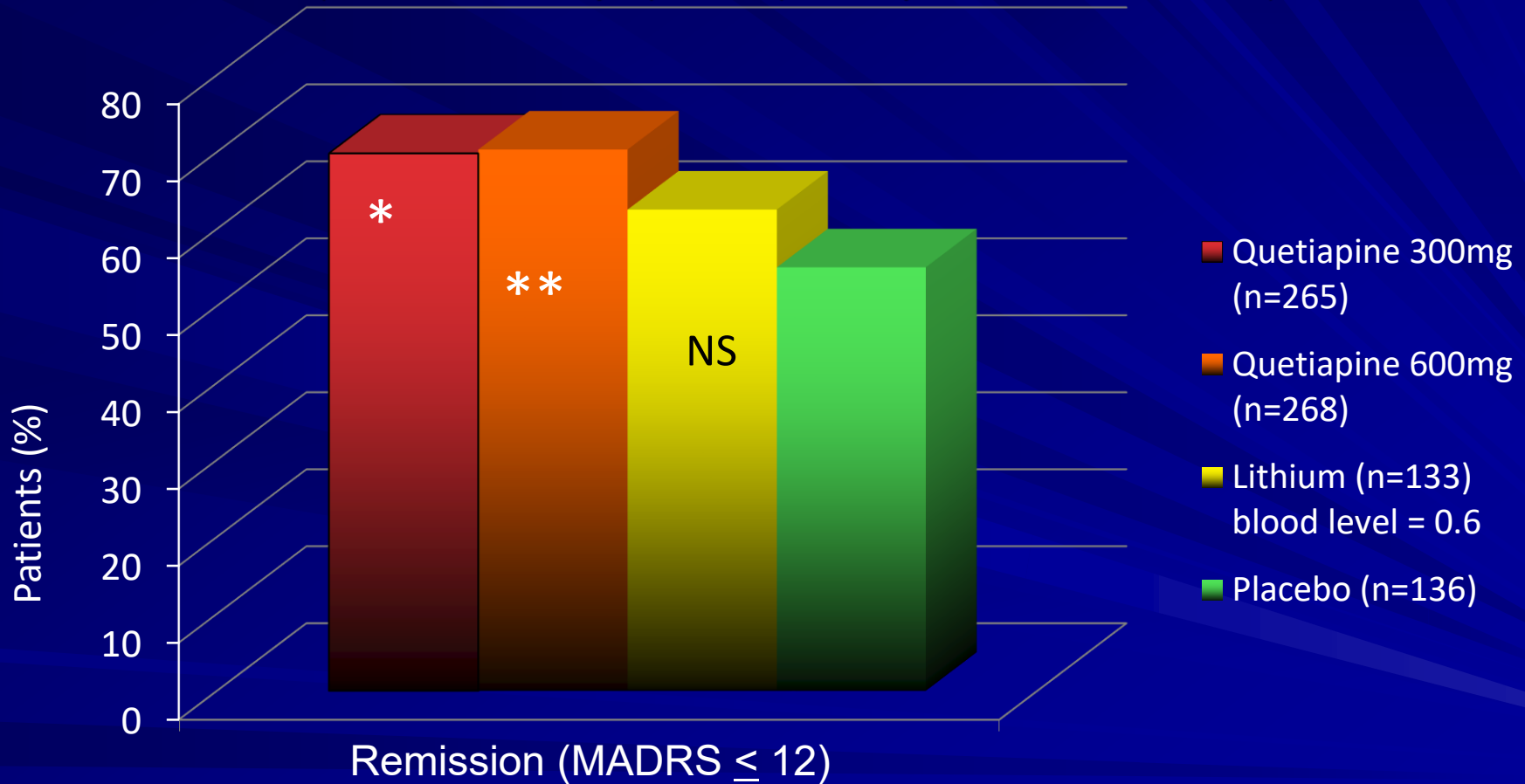
\$

| <u>Med</u> | <u>Daily Dose</u> | <u>Monthly Cost</u> |
|--------------|-------------------|---------------------|
| olanzapine | 10mg | generic |
| quetiapine* | 600mg | generic |
| lurasidone* | 80mg | generic |
| cariprazine | 6mg | \$1500 |
| lumateperone | 42mg | \$1700 |

* These two meds are often at the top of published treatment algorithms for acute bipolar depression.

Quetiapine separates from placebo as a monotherapy for acute bipolar depression.

EMBOLDEN – I
(BAD I and II - currently depressed, up to 28 day wash-out, 8 week treatment)



* $p < .05$; ** $p < .01$ vs. placebo; NS = not significant vs. placebo

Young AH, et al. *J Clin Psych.* 2010 Feb;71(2):150-62.

Lurasidone

- Must be taken with a 350 calorie meal.
- Akathisia rate increases with escalating doses (4% at 40mg and 23% at 120mg)
- Effective dose may be lower than what is used in schizophrenia.

NNT for remission of bipolar-I depression:

■ “6” when used at 20-60mg/day
monotherapy

■ “7” when used at 80-120mg/day
monotherapy

■ “7” when used as adjunct to Li or VPA

Data from Citrome et al., J Affective Disorders, 2013

Cariprazine (Vraylar) Efficacy Data

- McIntyre *et al.*, CNS Spectrums, Oct 2019
 - Post hoc analysis of 3 placebo-controlled trials of Bipolar I patients in a current depressive episode. 58% had concurrent manic symptoms.
 - For patients with manic symptoms, both 1.5 and 3mg/day beat placebo, with the higher dose trending towards a better outcome
 - For patients without manic symptoms, 1.5mg beat placebo, but 3mg did not.
- Another good article is Early *et al.*, Am J Psych 176:6, June 2019

Lumateperone (Caplyta)

- Be aware that “first-in-class” and “truly innovative” does not always equate to “works better.” *
- Moderate D2 binding, very strong 5-HT2A antagonism, effects on GluN2B. This GLU action is unusual for antipsychotics and might contribute to efficacy or might just cause sedation. *
- Has approval for schizophrenia, BAD-I and BAD-II depression. There is no evidence that it is better for bipolar depression than the generic antipsychotics with an FDA indication for bipolar depression. We also don't truly know if depression in BAD-I is biologically different than depression in BAD-II.

* These are the pessimistic comments of the jaded, old, psychiatrist who is giving this presentation.

Lumateperone (Caplyta)

- Side effect profile is not wholly worked out since most of the data is from short-term studies:
 - Low D2 binding yields EPS rates similar to placebo (~3%) in pharma-sponsored trials (Dugram, Schizophren Bulletin, 2020)
 - Somnolence ~8% vs placebo ~1% (Calabrese, Am J Psych, 2021)
 - Dizziness 10%

H1 Side Effects

| Med | H1 (Ki) | More Sedating | More Weight Gain |
|-----------------|---------|--|--|
| ■ clozapine | 1 |  |  |
| ■ olanzapine | 2 | | |
| ■ quetiapine | 7 | | |
| ■ cariprazine | 8 | | |
| ■ iloperidone | 12 | | |
| ■ brexpiprazole | 19 | | |
| ■ risperidone | 20 | | |
| ■ aripiprazole | 28 | | |
| ■ ziprasidone | 63 | | |
| ■ lurasidone | none | Less Sedating | Less Weight Gain |

general trends

Lumateperone does not bind H1 but 8-24% of patients experience sedation

Data from fda.gov package inserts

| Drug | New glucose >126 | New LDL >160 | Gain >7% body wt. | % with Parkinsonism | % with akathisia |
|-------------------------|--------------------------|-------------------------|-----------------------------|----------------------------|----------------------------|
| olanzapine (48 weeks) * | 12.8% | 39% | 64% | 12% (10mg) 14% (15mg) | 19% (10mg) 27% (15mg) |
| quetiapine (short term) | 2.6% | 6% | 8% | 1.9% (300mg) 2% (600mg) | 0% (300mg) 0% (600mg) |
| cariprazine (6 weeks) | none | none | 8% | 9% (1-3mg) 14% (9-12mg) | 15% (1-3mg) 20%(9-12mg) |
| lurasidone (8 weeks) | none | none | 2.4% | 9% (40mg) 17% (120mg) | 11% (40mg) 22%(120mg) |
| lumateperone (6 weeks) | none (8% 1yr non-RCT) | none (4% 1yr nonRCT) | none (-3.2kg 1yr nonRCT) | 4% | 1.3% |

* Olanzapine does not have an FDA indication for bipolar depression

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Where are the SSRIs?

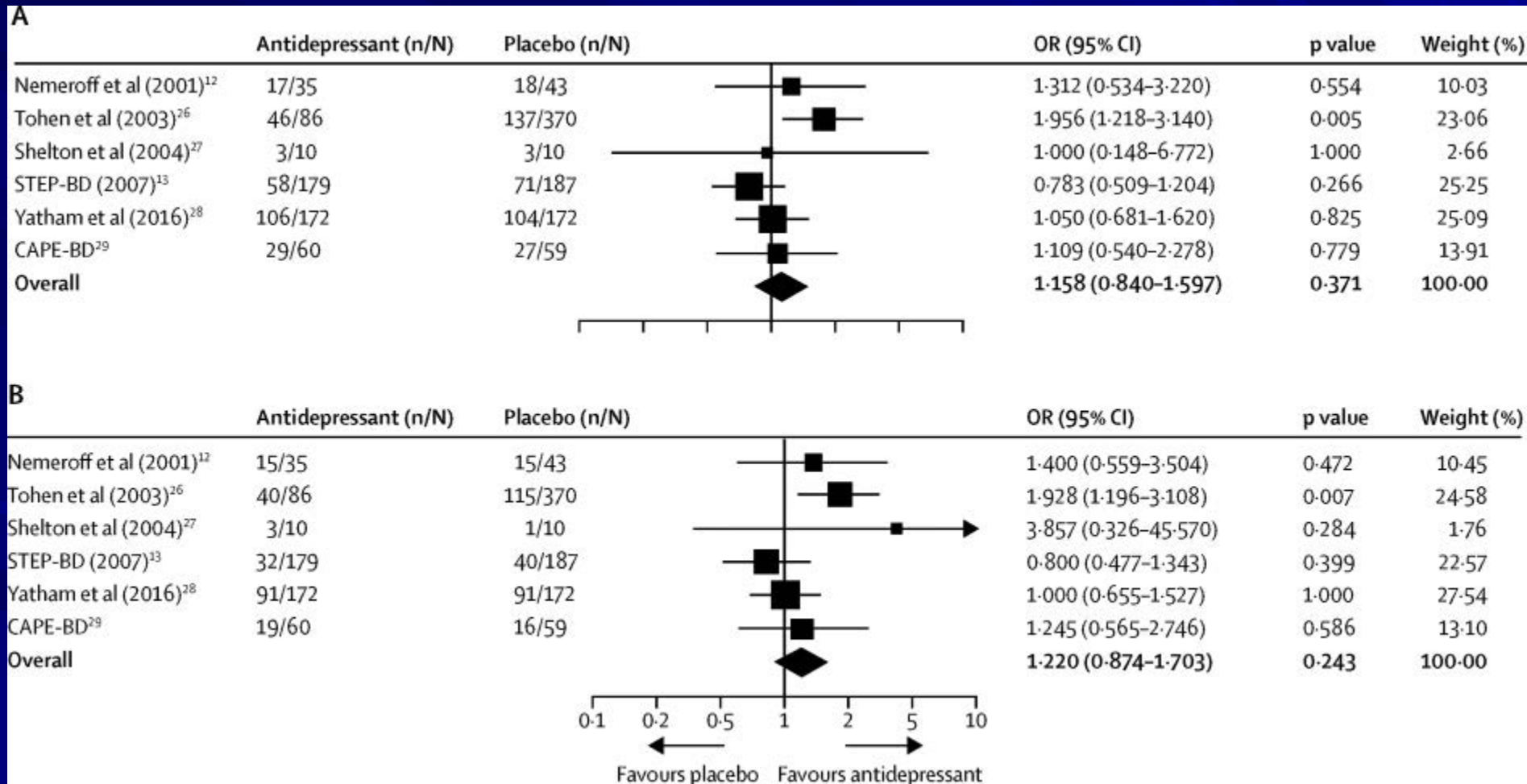
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|----------------------------|------------|------|------------|
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| Lumateperone | | | 2021 |

Metanalysis of Antidepressants in Bipolar Depression

(McGirr *et al*, Lancet Psychiatry, 2016)

A = Response (50% reduction in rating scale score)

B = Remission (MADRS <12, HDRS < 7)



What if we separate out Bipolar II?

- This is an ongoing debate with some data to suggest there are differences in medication response rates and some data to suggest there is no difference.
- Ghaemi, J Clin Psych, Jan 2021
 - Re-examined the CAPE-BD study from 2014 and separated out Bipolar II and Bipolar I. This was RCT of citalopram + mood stabilizer vs placebo + mood stabilizer for acute depression and depression prevention.
 - Patients with Bipolar II did no better than patients with Bipolar I.
 - There was no clinically meaningful efficacy compared to placebo and maintenance treatment with citalopram worsened manic symptoms, especially in patients with a rapid-cycling course.

Some other interventions with at least one, positive, RCT for bipolar depression

- Lithium + lamotrigine
- Depakote
- ECT
- TMS
- Ketamine