**UW PACC**

Psychiatry and Addictions Case Conference

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# MEDICATIONS FOR ACUTE BIPOLAR DEPRESSION IN ADULT PATIENTS


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ECHO

# 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


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.


Patient facing website


Provider facing website

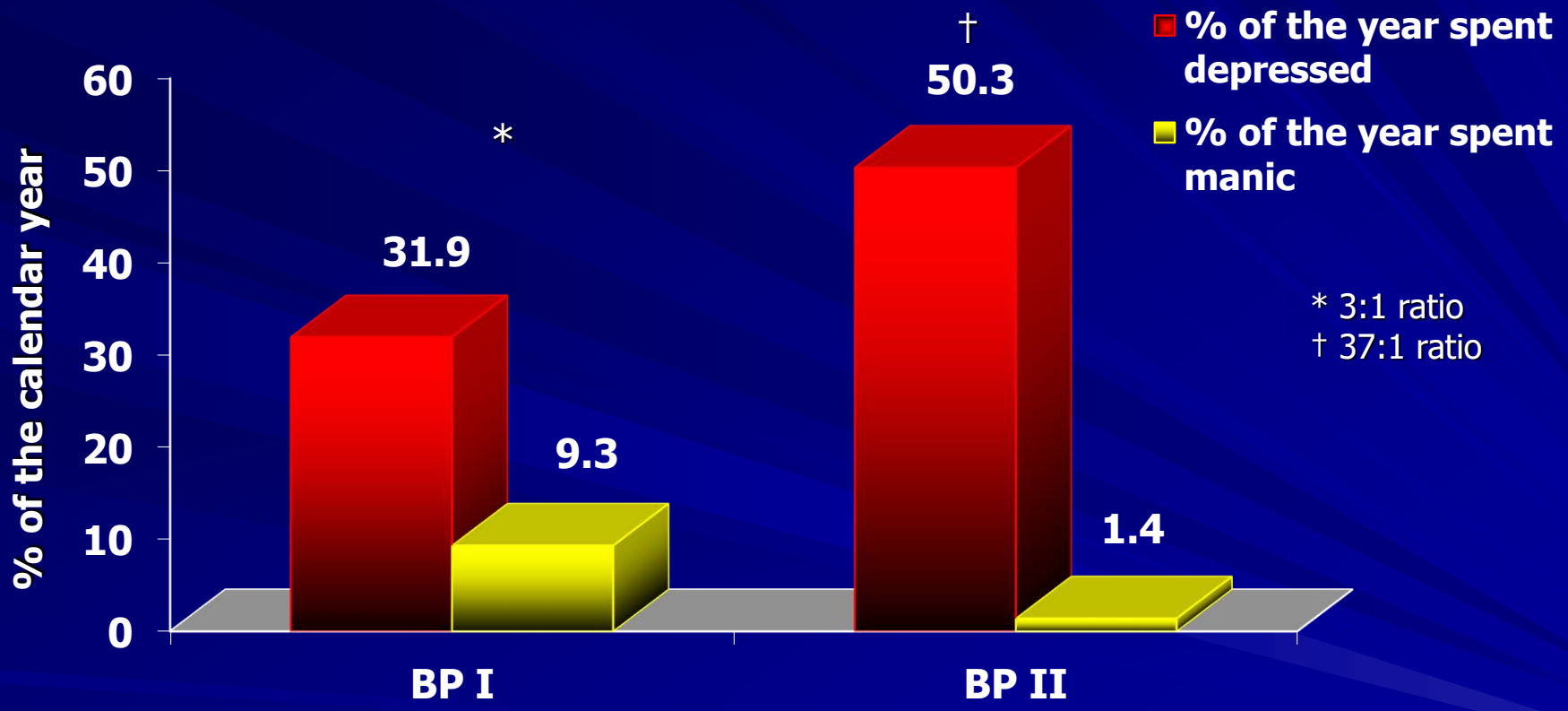
# Interesting articles on gender and antipsychotics:

- 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

Judd LL, et al, *Arch Gen Psychiatry* 2002;59:530-537

Slide Courtesy of Mark Frye

# 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 | |

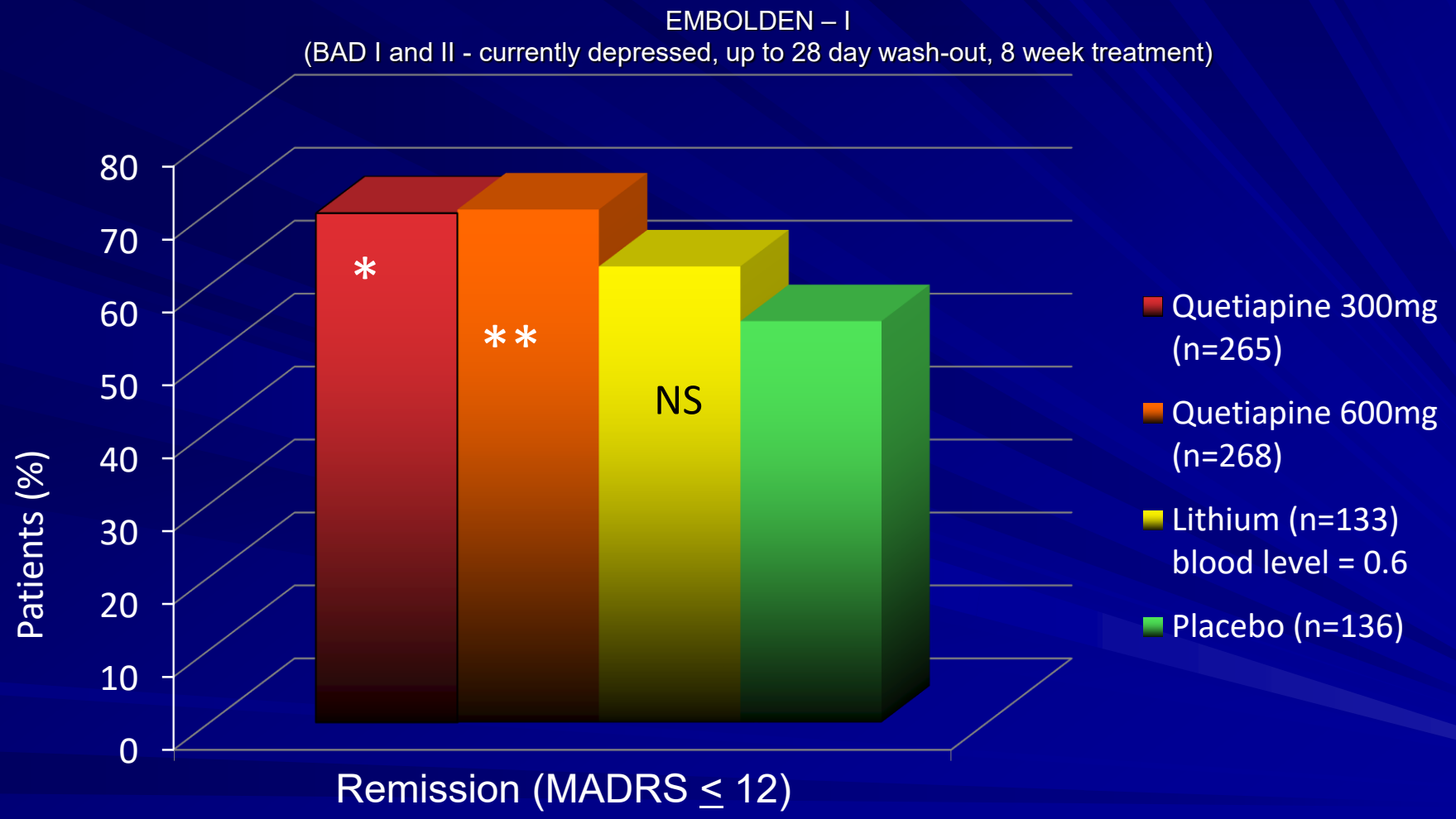
# $

| Med | Daily Dose | Monthly Cost |
|---|---|---|
| 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.

Per Good Rx app 2026

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




* $p < .05$; ** $p < .01$ 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 depresison. We also don’t truly know if depression in BAD-I is biologically different that depression in BAD-II.

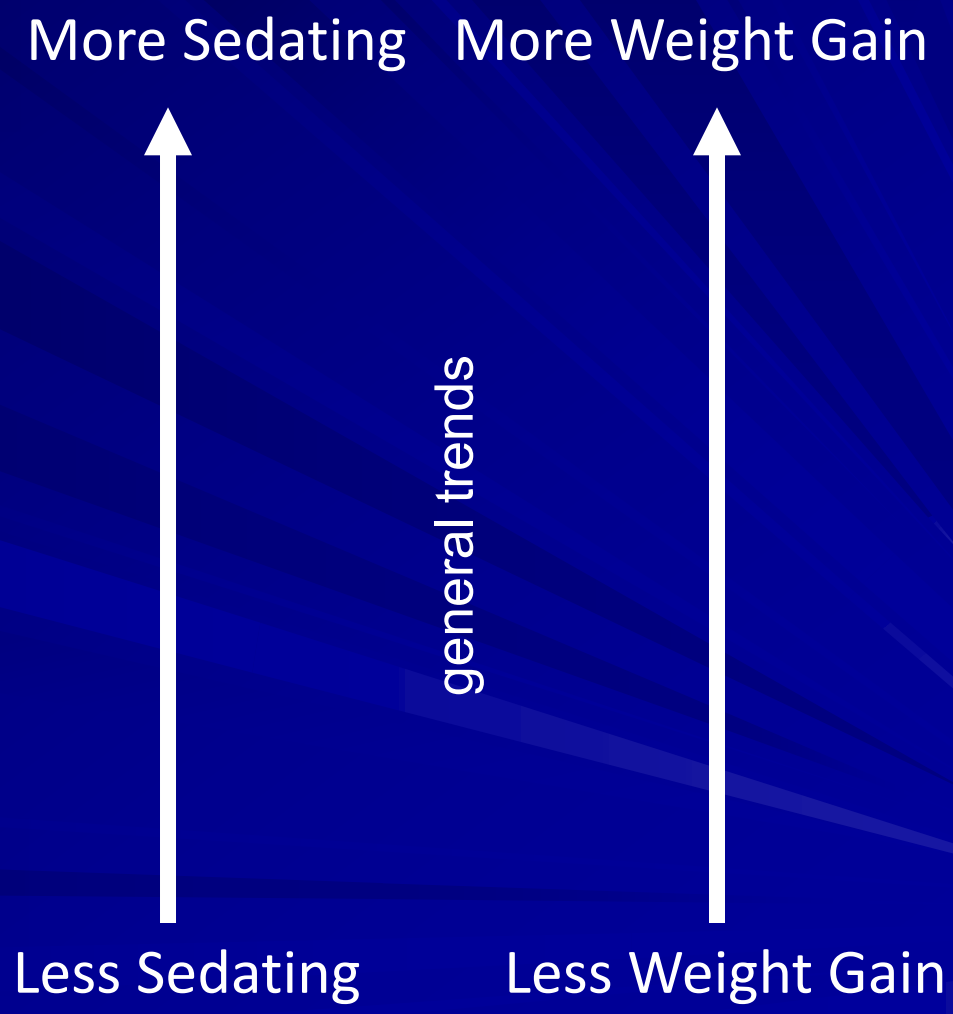
* These are the pessimistic comments of the jaded, old, psychiatrist who is giving this presentation.

# 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) |
|---|---|
| clozapine | 1 |
| olanzapine | 2 |
| quetiapine | 7 |
| cariprazine | 8 |
| iloperidone | 12 |
| brexpiprazole | 19 |
| risperidone | 20 |
| aripiprazole | 28 |
| ziprasidone | 63 |
| lurasidone | none |




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)<br>14% (15mg) | 19% (10mg)<br>27% (15mg) |
| quetiapine (short term) | 2.6% | 6% | 8% | 1.9% (300mg)<br>2% (600mg) | 0% (300mg)<br>0% (600mg) |
| cariprazine (6 weeks) | none | none | 8% | 9% (1-3mg)<br>14% (9-12mg) | 15% (1-3mg)<br>20%(9-12mg) |
| lurasidone (8 weeks) | none | none | 2.4% | 9% (40mg)<br>17% (120mg) | 11% (40mg)<br>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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| Lumateperone | | | 2021 |

**Where are the SSRIs?**

Slide adapted from Mark Frye.

# Metanalysis of Antidepressants in Bipolar Depression

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

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

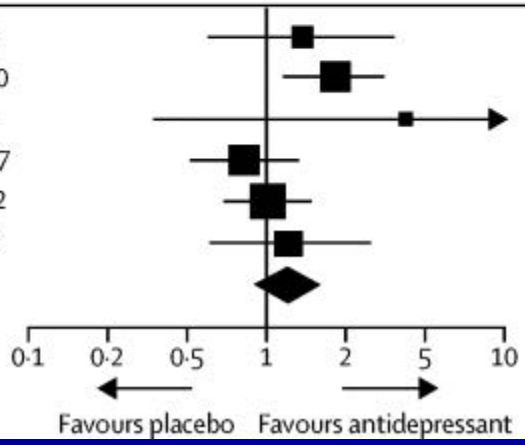
B = Remission (MADRS <12, HDRS < 7)

**A**

| | Antidepressant (n/N) | Placebo (n/N) | OR (95% CI) | p value | Weight (%) |
|---|---|---|---|---|---|
| Nemeroff et al (2001)[12] | 17/35 | 18/43 | 1·312 (0·534–3·220) | 0·554 | 10·03 |
| Tohen et al (2003)[26] | 46/86 | 137/370 | 1·956 (1·218–3·140) | 0·005 | 23·06 |
| Shelton et al (2004)[27] | 3/10 | 3/10 | 1·000 (0·148–6·772) | 1·000 | 2·66 |
| STEP-BD (2007)[13] | 58/179 | 71/187 | 0·783 (0·509–1·204) | 0·266 | 25·25 |
| Yatham et al (2016)[28] | 106/172 | 104/172 | 1·050 (0·681–1·620) | 0·825 | 25·09 |
| CAPE-BD[29] | 29/60 | 27/59 | 1·109 (0·540–2·278) | 0·779 | 13·91 |
| **Overall** | | | **1·158 (0·840–1·597)** | **0·371** | **100·00** |

**B**

| | Antidepressant (n/N) | Placebo (n/N) | OR (95% CI) | p value | Weight (%) |
|---|---|---|---|---|---|
| Nemeroff et al (2001)[12] | 15/35 | 15/43 | 1·400 (0·559–3·504) | 0·472 | 10·45 |
| Tohen et al (2003)[26] | 40/86 | 115/370 | 1·928 (1·196–3·108) | 0·007 | 24·58 |
| Shelton et al (2004)[27] | 3/10 | 1/10 | 3·857 (0·326–45·570) | 0·284 | 1·76 |
| STEP-BD (2007)[13] | 32/179 | 40/187 | 0·800 (0·477–1·343) | 0·399 | 22·57 |
| Yatham et al (2016)[28] | 91/172 | 91/172 | 1·000 (0·655–1·527) | 1·000 | 27·54 |
| CAPE-BD[29] | 19/60 | 16/59 | 1·245 (0·565–2·746) | 0·586 | 13·10 |
| **Overall** | | | **1·220 (0·874–1·703)** | **0·243** | **100·00** |



# 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 1. 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