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Psychiatry and Addictions Case Conference

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BIPOLAR DEPRESSION PSYCHOPHARMACOLOGY UPDATE

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PLANNER DISCLOSURES

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GENERAL DISCLOSURES

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GENERAL DISCLOSURES

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SPEAKER DISCLOSURES

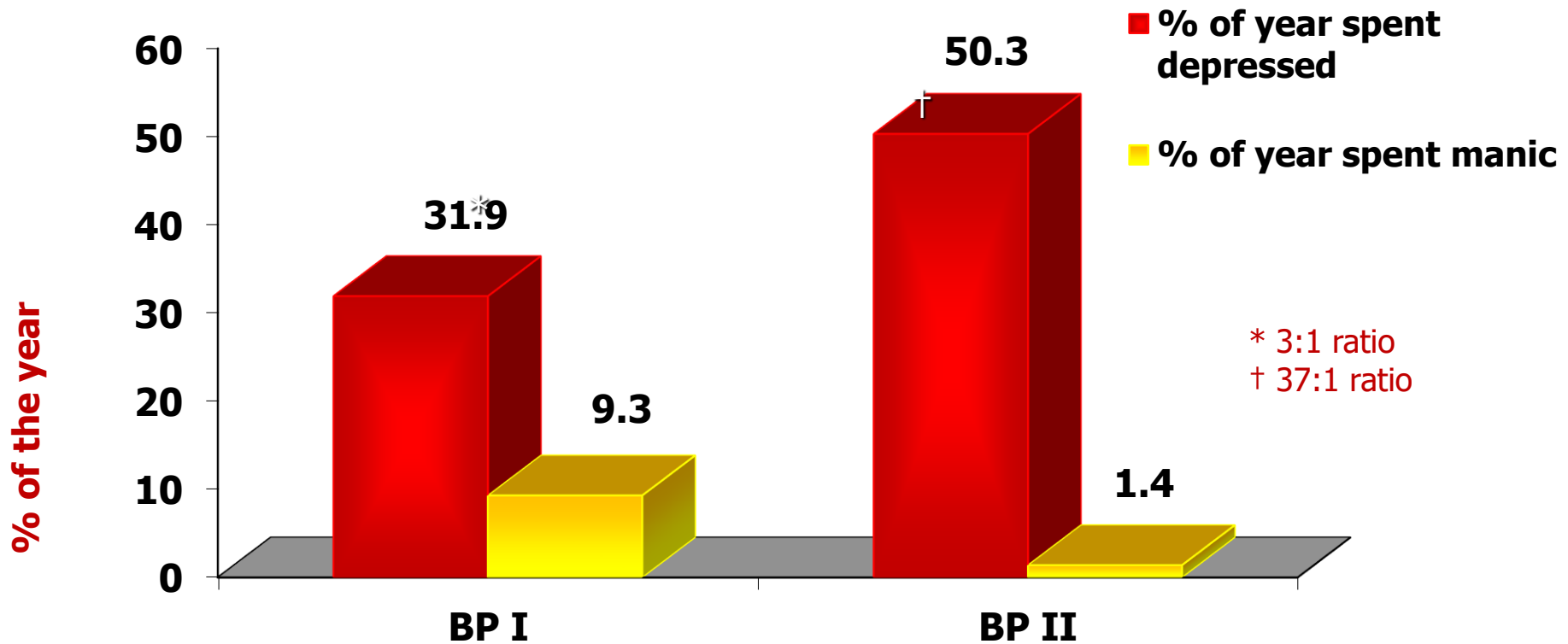
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RATIO OF DEPRESSIVE VS. MANIC TIME



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

EXAMPLE CASE

A 45yo man with a history of Bipolar II, on lamotrigine 200mg daily for a year without a hypomanic episode, presents to the ER with low mood, poor sleep, rumination, anhedonia, and thoughts of jumping off the Aurora Bridge. What medication has the best data for treating an acute, bipolar, depressive episode?

ACUTE BIPOLAR DEPRESSION MEDICATION ALGORITHM (CINP, INT J NEUROPSYCHOPHARM, 2016)

- 1 quetiapine**
- 2 lurasidone**
- 3 olanzapine**
- 4 lithium + lamotrigine**
- 5 mood stabilizer + lurasidone, modafinil, or pramiprexole
- 6 Mood stabilizer + Lexapro or Prozac (2nd, 3rd, or not included, depending on which “consensus”)
- 7 valproate
- 8 lamotrigine
- 9 aripiprazole
- 10 lithium

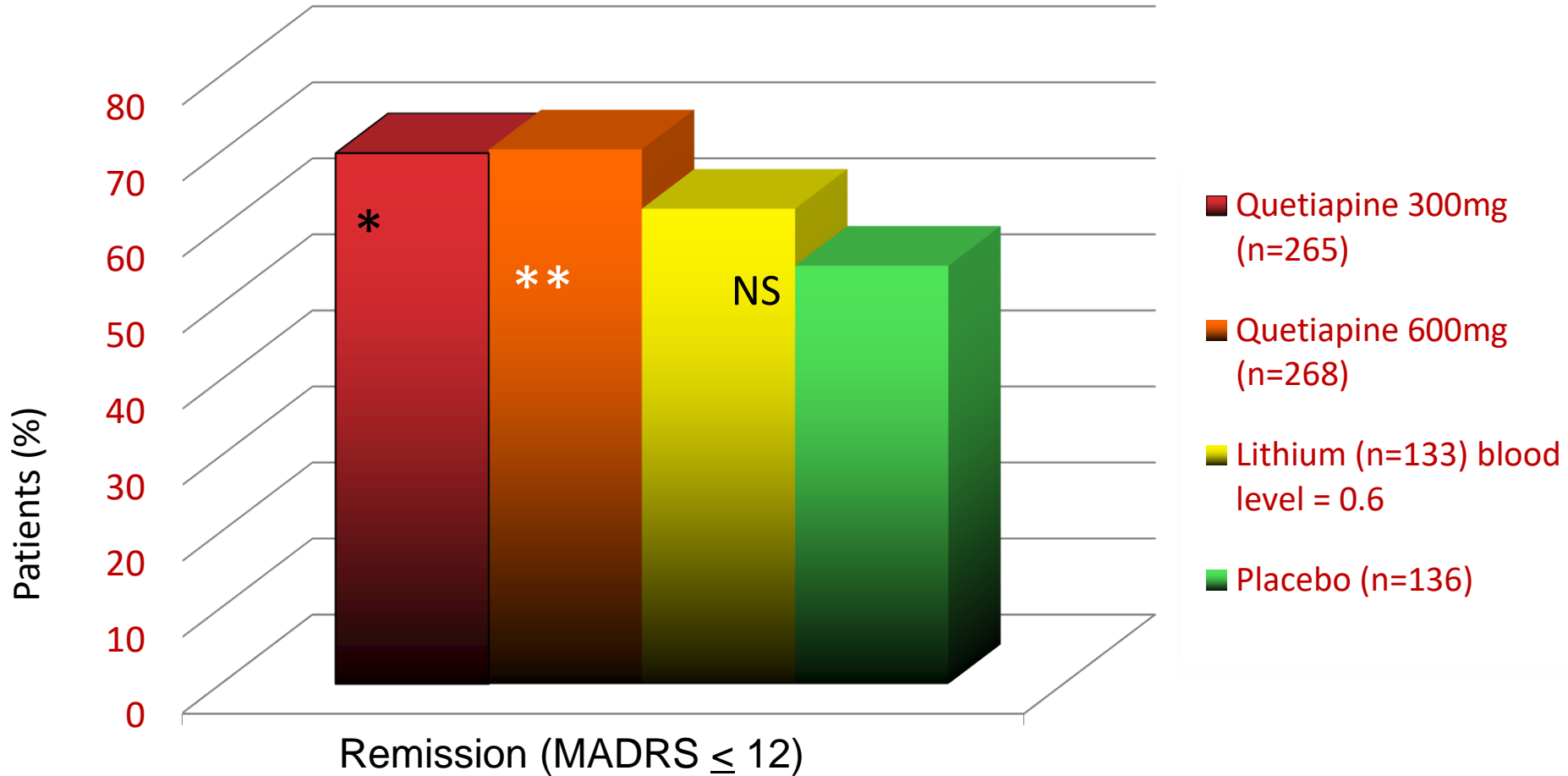
FDA PHARMACOPOEIA FOR BIPOLAR MONOTHERAPY IN ADULTS

	Acute 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		

Example Quetiapine Data

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

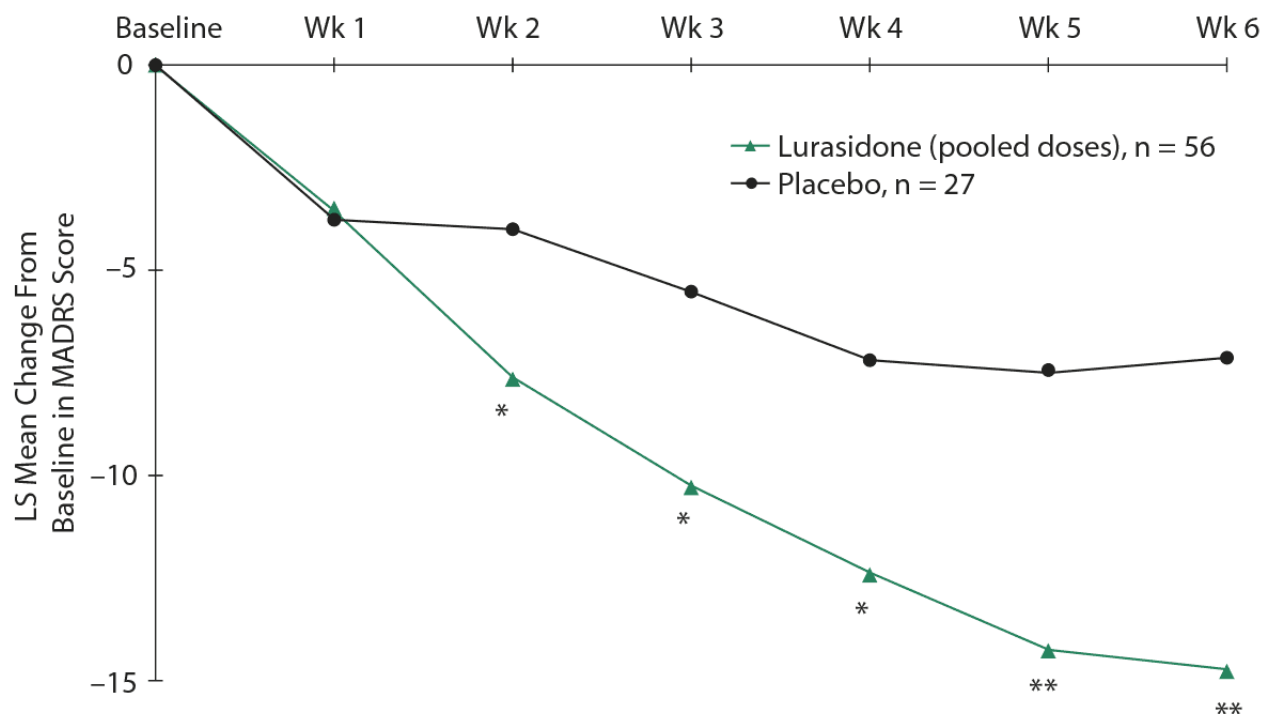
Young AH, et al. *J Clin Psych.* 2010 Feb;71(2):150-62.

EXAMPLE DATA FOR LURASIDONE

SAJATOVIC *ET AL*, J CLIN PSYCH, 2016

BIPOLAR I, OVER AGE 55

Figure 1. Monotherapy With Lurasidone (pooled doses of 20–60 mg/d and 80–120 mg/d)^a vs Placebo: LS Mean Change in MADRS Total Score for the mITT Population^b



^aEffect size for pooled lurasidone dose groups = 0.81.

^bAssessed using a mixed model for repeated measures (MMRM) analysis.

* $P < .05$. ** $P < .01$.

Abbreviations: LS = least squares, MADRS = Montgomery-Åsberg Depression Rating Scale, mITT = modified intent-to-treat.

THE MOST RECENT ADDITION

- Cariprazine (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.
 - Dose 1.5 and 3mg/day
 - For patients with manic symptoms, both doses beat placebo, with the higher dose trending towards a better outcome
 - For patients without manic symptoms, 1.5mg beat placebo, but 3mg did not.

WHAT ABOUT SYMBYAX FOR ACUTE BP DEPRESSION?

- Symbyax is FDA approved for bipolar depression and demonstrates good efficacy as a monotherapy in meta-analyses. (Vieta *et al.*, J Clin Psychopharmacol. 2010 Oct;30(5):579-90).
- Symbyax vs. Olanzapine is complicated. In the original, 8-week, drug company trial, Symbyax beat olanzapine, and both beat placebo, but the drop out rate and unequal arms confuse the intent-to-treat data (Placebo drop out 232/377, olanzapine 191 of 370, Symbyax 31 of 86).
- Olanzapine monotherapy now has a new placebo-controlled trial to support use (Tohen, Br J Psych, 201(2012), though 46% of patients on long-term olanzapine have weight gain >7% of their body weight.

WHAT ABOUT OTHER ANTIPSYCHOTICS FOR BP DEPRESSION?

- Both placebo-controlled trials of Abilify monotherapy (5-30mg) for acute bipolar depression were negative. (Cruz, Int J Neuropsychopharmacol. 2010 Feb;13(1))
- Mood stabilizer + risperidone or paroxetine or risperdal/paroxetine or placebo did not separate and had only a modest effect for acute bipolar depression. (Shelton, J Clin Psych. 2004 65(12))
- A 298 patient Ziprasidone trial (dose 40-160mg) was negative (Sachs, J Clin Psych, 72(2011)).

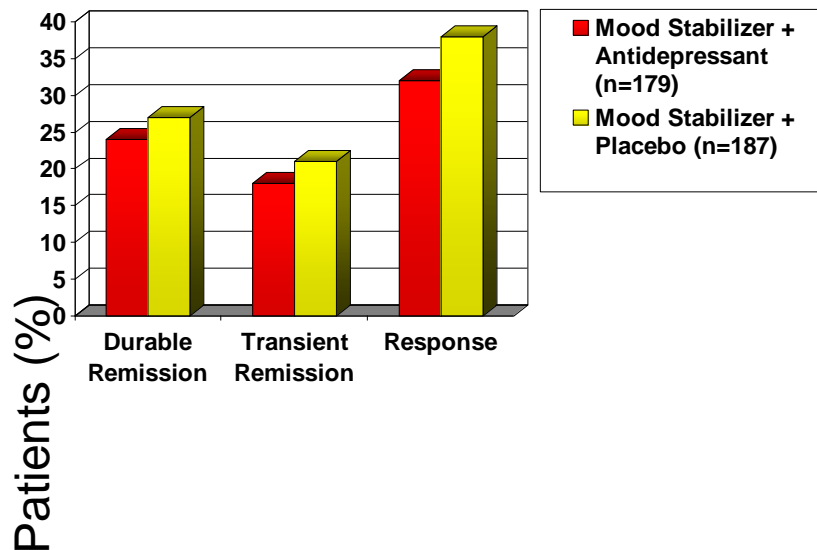
\$

Med	Daily Dose	Monthly Cost
Olanzapine	10mg	generic
Quetiapine	600mg	generic
Latuda	80mg	\$1200
Vraylar	6mg	\$1200

Comparing Our Side Effect Data (from fda.gov package inserts)

Drug	New glucose >126	New LDL >160	Gain >7% body weight	% with Parkinsonism	% with akathisia
olanzapine (48 weeks)	12.8%	39.8%	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)

EXAMPLE ANTIDEPRESSANT BIPOLAR DEPRESSION STUDY



- 26 week study of Bipolar I and Bipolar II
- bupropion or paroxetine
- lithium or valproate
- “Durable” = 8 wks euthymic
- “Transient” = 1-8 weeks euthymic
- “Response” = $\geq 50\%$ improvement without mania

Sachs GS, et al. *N Engl J Med* 2007;356.

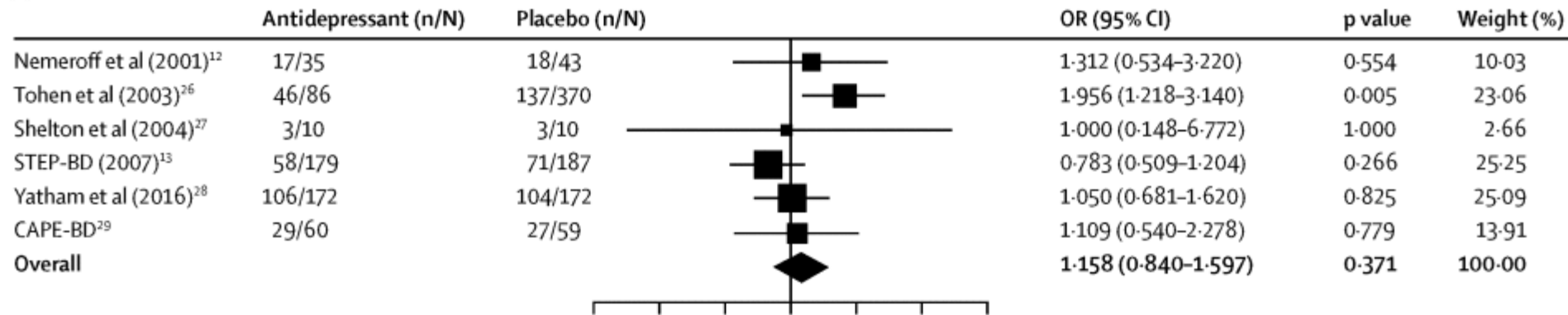
Antidepressant Controversy

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

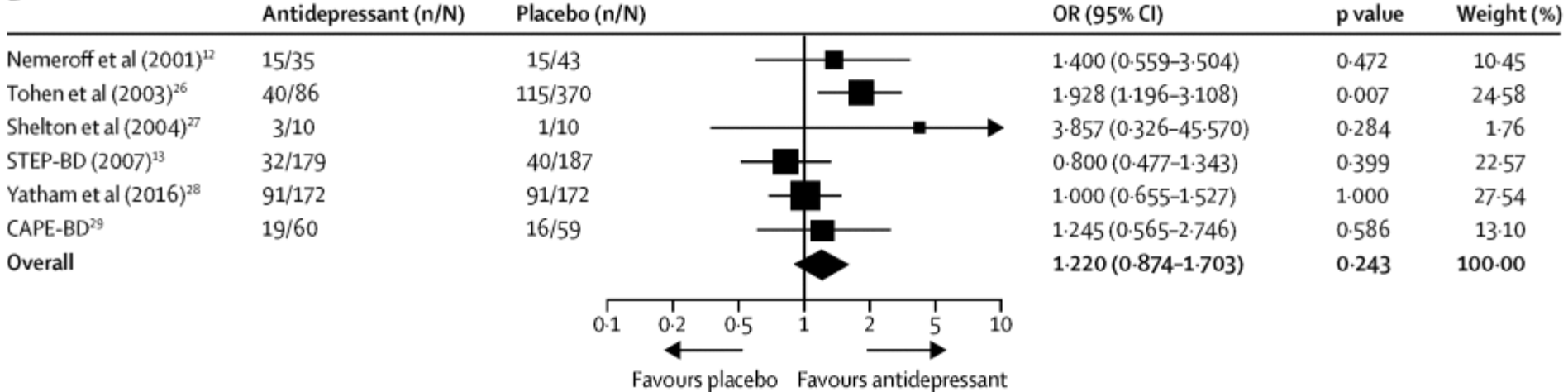
A = Response (50% reduction in rating scale score)

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

A



B



SHOULD WE TREAT BAD-I AND BAD-II DEPRESSIVE EPISODES DIFFERENTLY?

- Altschuler et al., Am J Psych, March 2017
 - 16 week, double-blind, 142 patients with BAD-II depression, divided lithium monotherapy (goal level 0.8-1.2), sertraline monotherapy (minimum 100mg), or combo.
 - Outcomes:
 - Switch to hypomania or mania: 17.9% overall, all hypomanias (no manias), and no statistical difference between groups (even amongst rapid-cyclers)
 - The discontinuation rate of the combo group (70%) was significantly higher than either monotherapy group (sertraline 42%, lithium 55%); predictors of discontinuation overall were younger age at onset of depression and lower CGI score.