Neuroscience Education Institute

IN THE MOOD: OPTIMIZING DIAGNOSIS AND TREATMENT OF BIPOLAR DEPRESSION

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Presented at 2021 NEI Congress

Learning Objectives

- Implement best practices for identifying bipolar depression
- Utilize evidence-based strategies to enhance treatment for bipolar depression

Bipolar Depression

Let's start by acknowledging a truth

- We still make mistakes—sometimes it is easy to make the correct diagnosis and other times it is quite difficult

Meet Peter, a Diagnostic Conundrum, Part 1

- Peter is a 25-year-old man with a history of MDD since adolescence; no known history of mania or hypomania
- Recent MDE treated with SSRI but did not get better
- Switched to serotonin norepinephrine reuptake inhibitor (SNRI) but did not get better
- Added bupropion but did not get better
- Now diagnosed with treatment-resistant depression (TRD), and being referred for Rx esketamine nasal spray

Meet Peter, a Diagnostic Conundrum, Part 2

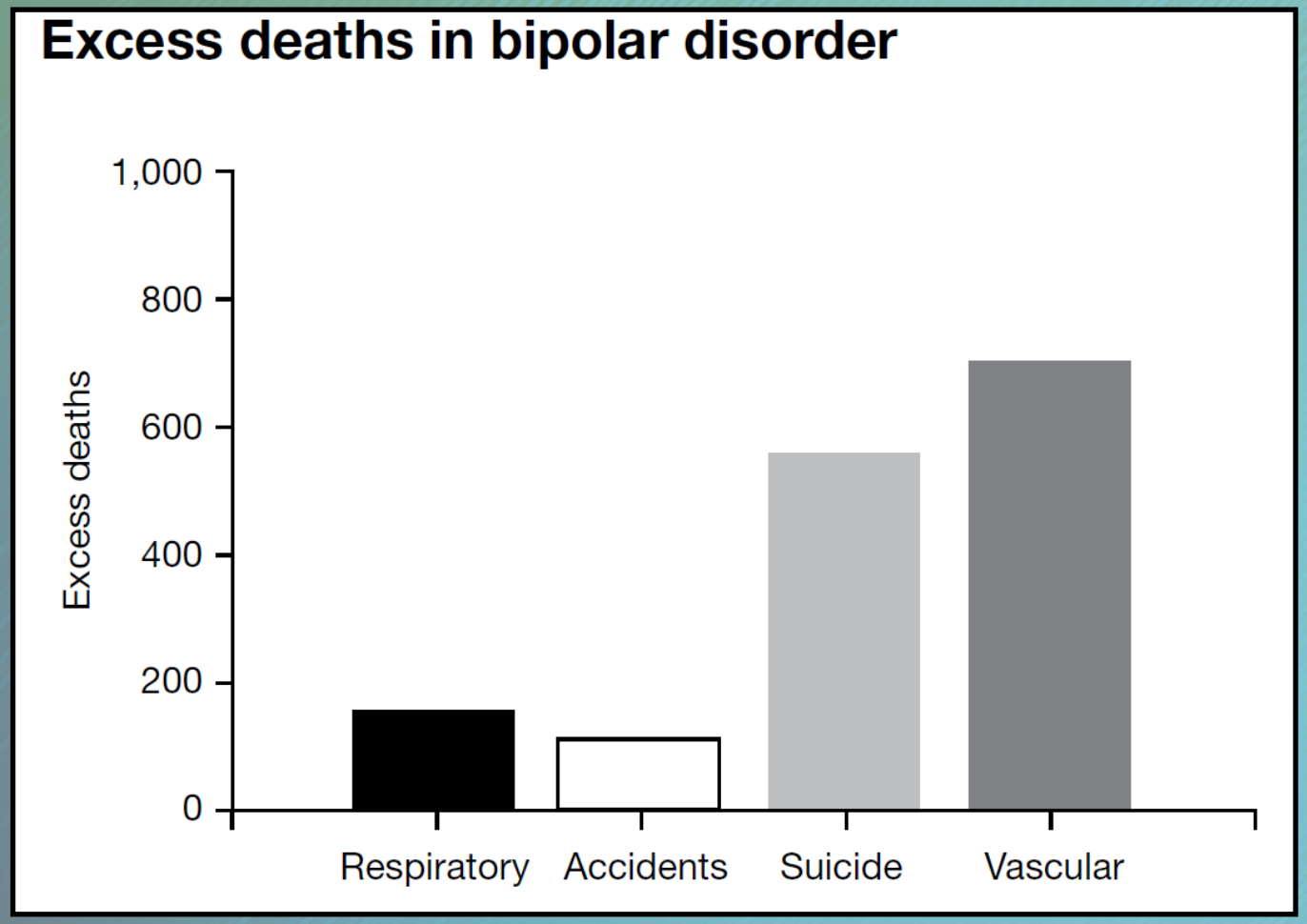
- Second opinion obtained: family history of bipolar disorder now revealed
- Further history uncovered: Peter would go without sleep for a few days (pulled “all-nighters”) before exams and would be full of energy, but this was not consistent from semester to semester and Peter thought this was “not worth mentioning”
    - After a therapeutic alliance was established and Peter felt more comfortable talking about his life, he was able to discuss his gambling sprees and sexual promiscuity, which occurred in discrete periods lasting about a month
- Now diagnosed with bipolar disorder, depressed

What Is Bipolar Depression?

- Bipolar depression is defined by having MDEs *and* manic/hypomanic episodes
  - Bipolar type I is when there is a history of manic episodes
  - Bipolar type II is when there is a history of hypomanic episodes but no manic episodes
- On cross-sectional examination, the symptoms of an MDE are the same for both major depressive disorder and bipolar disorder
  - Easy to misdiagnose bipolar depression for major depressive disorder
- Patients with bipolar disorder often don't have any insight into their symptoms of mania or hypomania and often fail to report them as such
- However, patients with bipolar disorder often have insight into depressive symptoms and come for treatment for that reason

Berk M et al. Med J Aust 2006;184(9):459-62;
Bowden CL. Psychiatr Serv 2001;52(1):51-5;
Muzina DJ et al. Cleve Clin J Med 2007;74(2):89-105.

Is There Excess Mortality?



Cardiovascular risk is double as compared to general population!

Weiner M et al. Ann Clin Psychiatry 2011;23(1):40-7.

What Is the Risk of Suicide?

- Twice as likely as those with unipolar depression (MDD)
- Attempts are twice as lethal
- Risk factors
  - Age of onset
  - Number of depressive episodes
  - Comorbid alcohol abuse
  - History of antidepressant-induced mania
  - Family history of suicide/suicidal behavior
  - Impulsivity

Chen YW, Dilsaver SC. Biol Psychiatry 1996;39(10):896-9; Slama F et al. J Clin Psychiatry 2004;65(8):1035-9; Michaelis BH et al. Suicide Life Threat Behav 2004;34(2):172-6; Dalton EJ et al. Bipolar Disord 2003;5(1):58-61; Baldessarini RJ et al. J Clin Psychiatry 2003;64(Suppl 5):44-52.

Is Misdiagnosis Common?

- Up to 69% of persons with bipolar disorder are misdiagnosed initially
- Mean 3.5 diagnoses and 4 clinicians before receiving the right diagnosis
- Comorbidity is common and can be confusing
  - 50%–70% have at least one comorbid condition
  - Examples include anxiety, substance use, obesity, cardiovascular disease (CVD)
- As many as 1 in 5 primary care patients who have clinically significant depressive symptoms and are receiving antidepressant treatment actually have bipolar I or bipolar II disorder

Hirschfeld RM et al. J Am Board Fam Pract 2005;18(4):233-9; Hirschfeld RM, Vornik LA. Am J Manag Care 2005;11(3 Suppl):S85-90; Dilsaver SC. J Affect Disord 2011;129(1-3):79-83; Leboyer M, Kupfer DJ. J Clin Psychiatry 2010;71(12):1689-95; Hirschfeld RM et al. J Clin Psychiatry 2003;64(2):161-74; Baldessarini RJ et al. Bipolar Disord 2007;9(4):386-93.

What Are the Consequences of Misdiagnosis?

- **Incorrect treatment**
- **Incorrect prognosis**
- **Poor outcomes**

Major concern: antidepressant use

- No antidepressant is approved for the treatment of bipolar depression (except for fluoxetine in combination with olanzapine)
- Antidepressant monotherapy can destabilize a person with bipolar depression
  - Induction of mania or hypomania and/or rapid cycling
- Antidepressants do not confer a treatment advantage for acute or enduring response
- However, never say never

Sachs GS et al. N Engl J Med 2007;356(17):1711-22; Valentí M et al. J Clin Psychiatry 2012;73(2):e271-6; Glauser TA et al. Postgrad Med 2013;125(1):144-53; Pacchiarotti I et al. Am J Psychiatry 2013;170(11):1249-62.

What Are Some Clues to Avoid Misdiagnosis?

- Family history
  - Higher rates of psychiatric illness and positive for bipolar disorder
- Course of Illness
  - Onset before age 25 and high number of recurrent episodes
  - Abrupt onset and end of depressive episode
  - Hypersomnia and/or increased appetite
- Treatment response
  - Suboptimal outcome with antidepressants
  - Antidepressant-induced mania or hypomania
- Mania symptoms
- Associated features
  - Chaotic relationships/job environments
  - Substance use

Berk M et al. Med J Aust 2006;184(9):459-62; Bowden CL. Psychiatr Serv 2001;52(1):51-5; Muzina DJ et al. Cleve Clin J Med 2007;74(2):89-105; Manning JS. Prim Care Companion J Clin Psychiatry 2010;12(Suppl 1):17-22.

FDA-Approved Agents for Bipolar Disorder (BD)

- Most FDA-approved agents for BD are approved primarily to treat mania or mixed episodes in BD I or for maintenance therapy and not for depression[a]
- Only four FDA-approved agents are indicated for bipolar depression with various tolerability profiles[a]

Acute Mania[b]	Acute Depression[b]	Long-Term Maintenance[b]
• 1970 Lithium • 1973 Chlorpromazine • 1996 Divalproex, ER (2005) • 2000 Olanzapine* (and Olanzapine/Samidorphan [2021]*) • 2003 Risperidone* • 2004 Quetiapine, XR (2008)*; Ziprasidone; Aripiprazole*; Carbamazepine ERC • 2015 Asenapine* • 2019 Cariprazine	• 2003 Olanzapine + fluoxetine combination • 2004 Quetiapine,# XR (2008)# • 2013 Lurasidone* • 2019 Cariprazine	• 1974 Lithium • 2003 Lamotrigine • 2004 Olanzapine (and Olanzapine/Samidorphan [2021]) • 2005 Aripiprazole* (and LAI monotherapy [2017]) • 2008 Quetiapine, XR* • 2009 Risperidone LAI*; Ziprasidone*

*Adjunctive and monotherapy; #Also approved for bipolar II depression.

[a] Butler M et al. Treatment for Bipolar Disorder in Adults. 2018; [b] APA. DSM-5. Bipolar disorder. 2013.

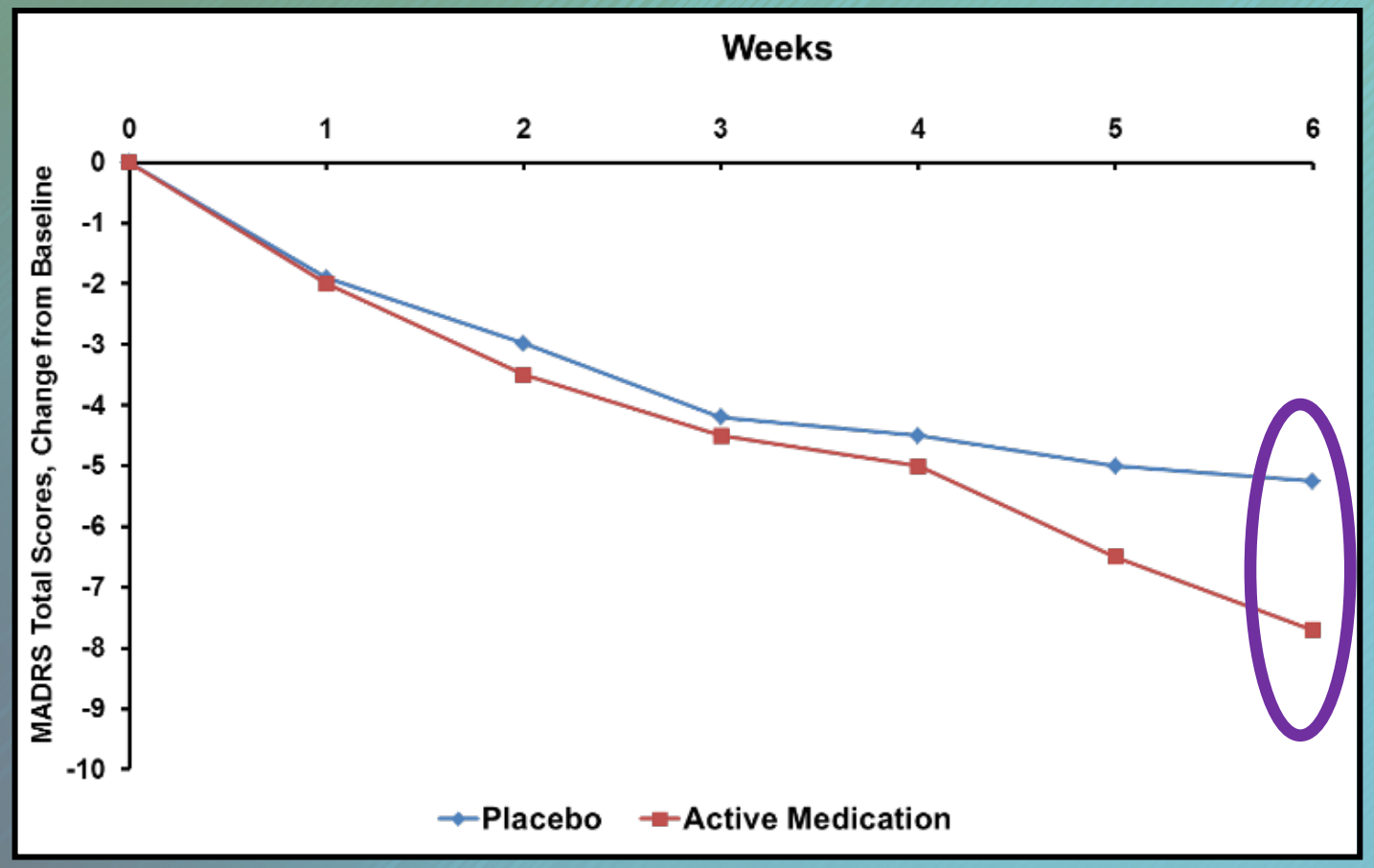
Only 4 Are FDA-Approved for Bipolar Depression

- Olanzapine-fluoxetine combination (was also tested in psychotic bipolar depressed patients)
- Quetiapine immediate- and extended-release (was also tested in bipolar type 2 patients)
- Lurasidone (was also tested in combination with lithium or valproate)
- Cariprazine

- **CAVEAT**:
  - *Lamotrigine is NOT approved for acute bipolar depression; neither are aripiprazole or ziprasidone (these trials failed)*
  - *SSRIs, SNRIs, etc., although approved for MDD, are NOT approved for acute bipolar depression*

Citrome L. Int J Clin Pract 2019;73(10):e13397;
Citrome L et al. J Affect Disord 2014;155:20-7.

Is the Result Clinically Relevant or Not?

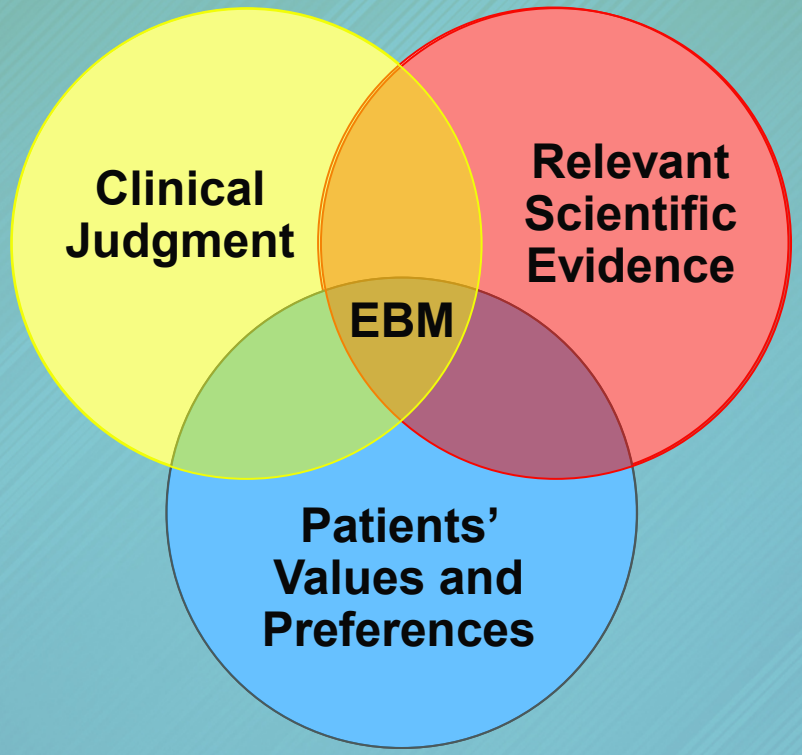


MADRS = Montgomery–Åsberg Depression Rating Scale.

Treatments may decrease MADRS scores when compared with placebo, but *so what*?

Are these differences clinically significant?

What Is Evidence-Based Medicine?

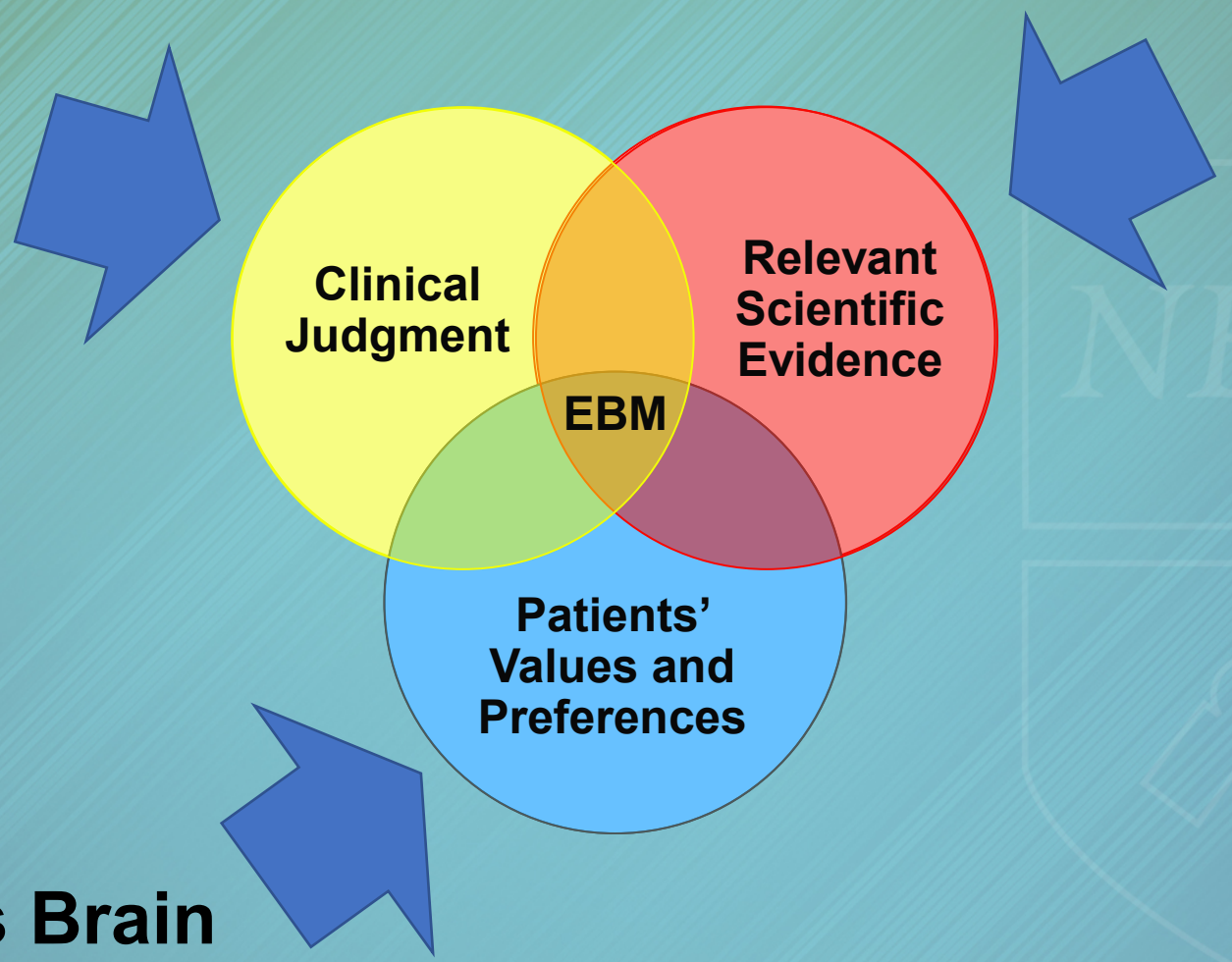


EBM: evidence-based medicine

Sackett DL et al. BMJ 1996;312(7023):71-2; Citrome L. Int J Clin Pract 2019;73(4):e13351.

What is Evidence-Based Medicine?

Your Brain



Keeping Up With New Information and Making Sense of It

Your Patient's Brain

Sackett DL et al. BMJ 1996;312(7023):71-2; Citrome L. Int J Clin Pract 2019;73(4):e13351.

Evidence-Based Medicine/Practice

Your Brain

Keeping Up With New Information and Making Sense of It

It's Not a Cookbook!

Your Patient's Brain

Sackett DL et al. BMJ 1996;312(7023):71-2; Citrome L. Int J Clin Pract 2019;73(4):e13351.

What Is an Effect Size?

- It can be challenging to interpret clinical trial results based on p-value alone
  - A p-value < 0.001 does not mean that the result would be more clinically relevant than if the p-value was < 0.05
- Statistical significance for drug vs placebo does not tell us about the size of the treatment effect
- Effect sizes can be used to evaluate if the statistically significant result is clinically relevant to your practice
- Effect sizes can be described as “point change” on a rating scale (i.e., not “standardized”) or in standard deviation units (i.e., “standardized”)
- Another method is to express effect size in “patient units”

Citrome L. Acta Psychiatr Scand 2010;121(2):94-102.

Measuring Effect Size in Patient Units

Number Needed to Treat (NNT)

How many patients would you need to treat with Intervention A instead of Intervention B before you would expect to encounter one additional positive outcome of interest?

Number Needed to Harm (NNH)

How many patients would you need to treat with Intervention A instead of Intervention B before you would expect to encounter one additional outcome of interest that you would like to AVOID?

Citrome L. Acta Psychiatr Scand 2010;121(2):94-102.

NNT and NNH Are Easy to Calculate

What is the NNT (or NNH) for an outcome for Drug A vs Drug B?

f_A = frequency of outcome for Drug A
f_B = frequency of outcome for Drug B (or placebo)
Attributable Risk (AR) = $f_A - f_B$
NNT= 1/AR

By convention, when not presenting fractions, we round up the NNT to the next *higher* whole number

For example, Drug A results in remission 50% of the time, but Drug B results in remission 20% of the time.

NNT = 1/[0.50-0.20] = 1/0.30 = 3.33 → Round up to 4

Citrome L. Acta Psychiatr Scand 2010;121(2):94-102.

What Is a “Good” NNT?

- It is impossible to have an NNT = 1
- An NNT vs placebo of < 10 is acceptable
- An NNT vs placebo < 5 is even better
- Very few treatments have an NNT vs placebo of 2 or 3
  - One example is medications for acute agitation
  - Another example is the avoidance of a relapse event over a period of 2 years for someone with schizophrenia taking an antipsychotic vs not taking an antipsychotic
- Many treatments have an NNT vs placebo of 7 to 10, especially newer agents where the clinical trials demonstrated higher placebo response rates
  - Cariprazine for bipolar depression
  - Vortioxetine for MDD
  - Brexpiprazole for acute schizophrenia

Citrome L, Ketter TA. Int J Clin Pract 2013;67(5):407-11; Pinson L, Gray GE. Psychiatr Serv 2003;54(2):145-54; Citrome L. Int J Clin Pract 2019;73(10):e13397; Citrome L. Int J Clin Pract 2014;68(1):60-82; Citrome L. Int J Clin Pract 2015;69(9):978-97.

What Is a "Good" NNH?

- An NNH vs placebo of ≥ 10 is acceptable
- An NNH vs placebo ≥ 20 is even better
- Some NNHs may be clinically important, even if they are relatively large (> 100), for example when the outcome is death
- Some NNHs may be clinically irrelevant, even if they are relatively small (< 10), for example when the outcome is a mild dry mouth

- **Bottom line: low values for NNT and high values for NNH are "good"**
  - You will encounter therapeutic response more often than the adverse event

Citrome L, Ketter TA. Int J Clin Pract 2013;67(5):407-11.

What Is Likelihood to Be Helped or Harmed?

- NNT and NNH can be used to quantify benefit versus risk by calculating the ratio of NNH to NNT
- This is called likelihood to be helped or harmed (LHH)
- In general, an LHH > 1 would mean the likelihood to be helped is greater than the likelihood to be harmed, for an LHH < 1, the reverse is true
- For an LHH to be meaningful, the efficacy outcome and adverse outcome must be clinically relevant for the patient being treated

Citrome L, Ketter TA. Int J Clin Pract 2013;67(5):407-11.

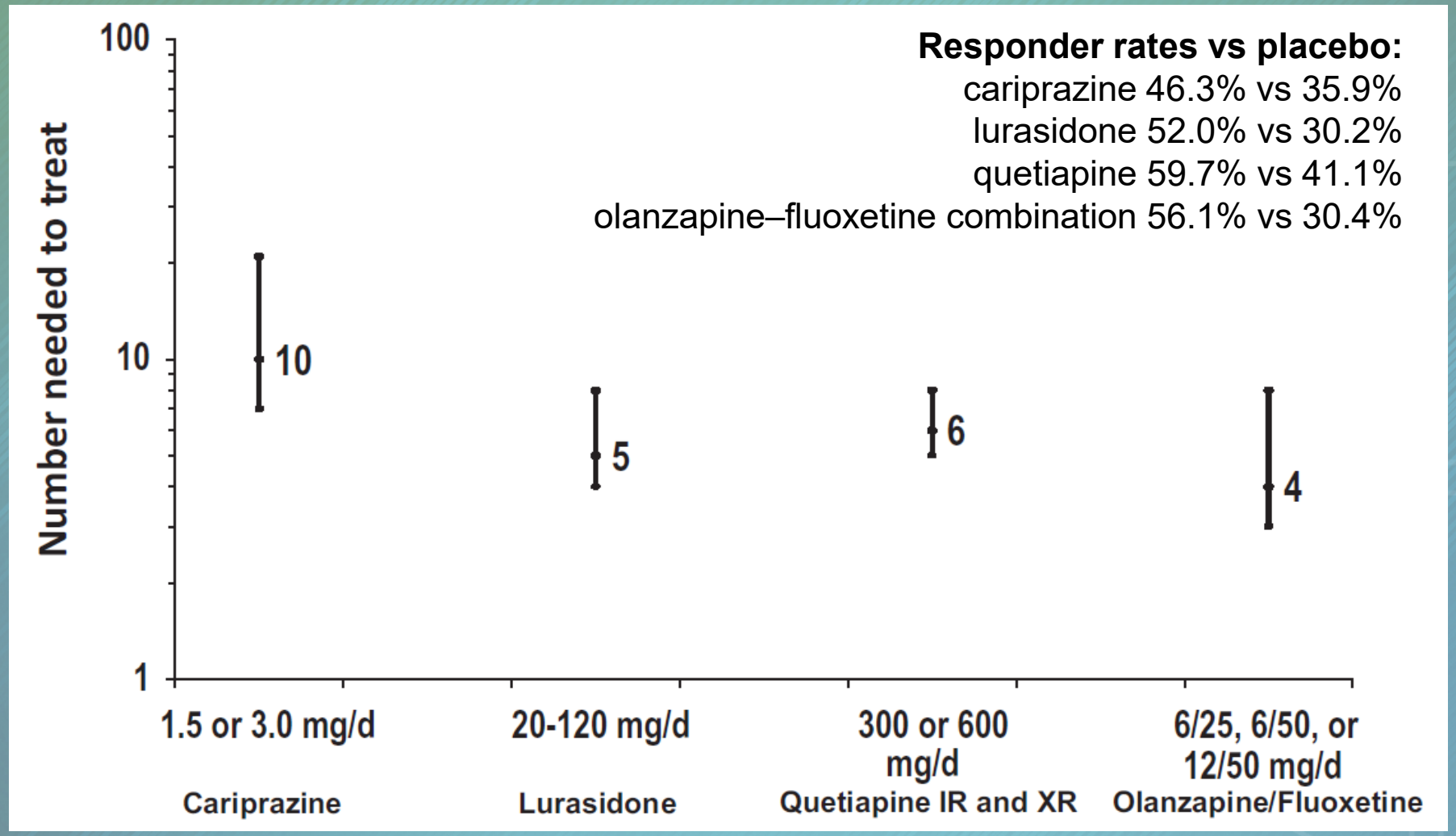
Outcomes of Interest vs Placebo

- **NNT**—want these as small as possible, and especially < 10
  - MADRS Responders
    - ≥ 50% reduction from baseline to endpoint
  - MADRS Remitters
    - Total score ≤ 12 or ≤ 10 at endpoint
- **NNH**—want these to be as large as possible, and especially > 10
  - ≥ 7% Weight Gain
  - AE Sedation/Somnolence
  - AE Akathisia
  - Any AE that would be of interest to the patient and clinician

AE=adverse event

Citrome L et al. J Affect Disord 2014;155:20-7.

MADRS Responders (≥ 50% reduction)



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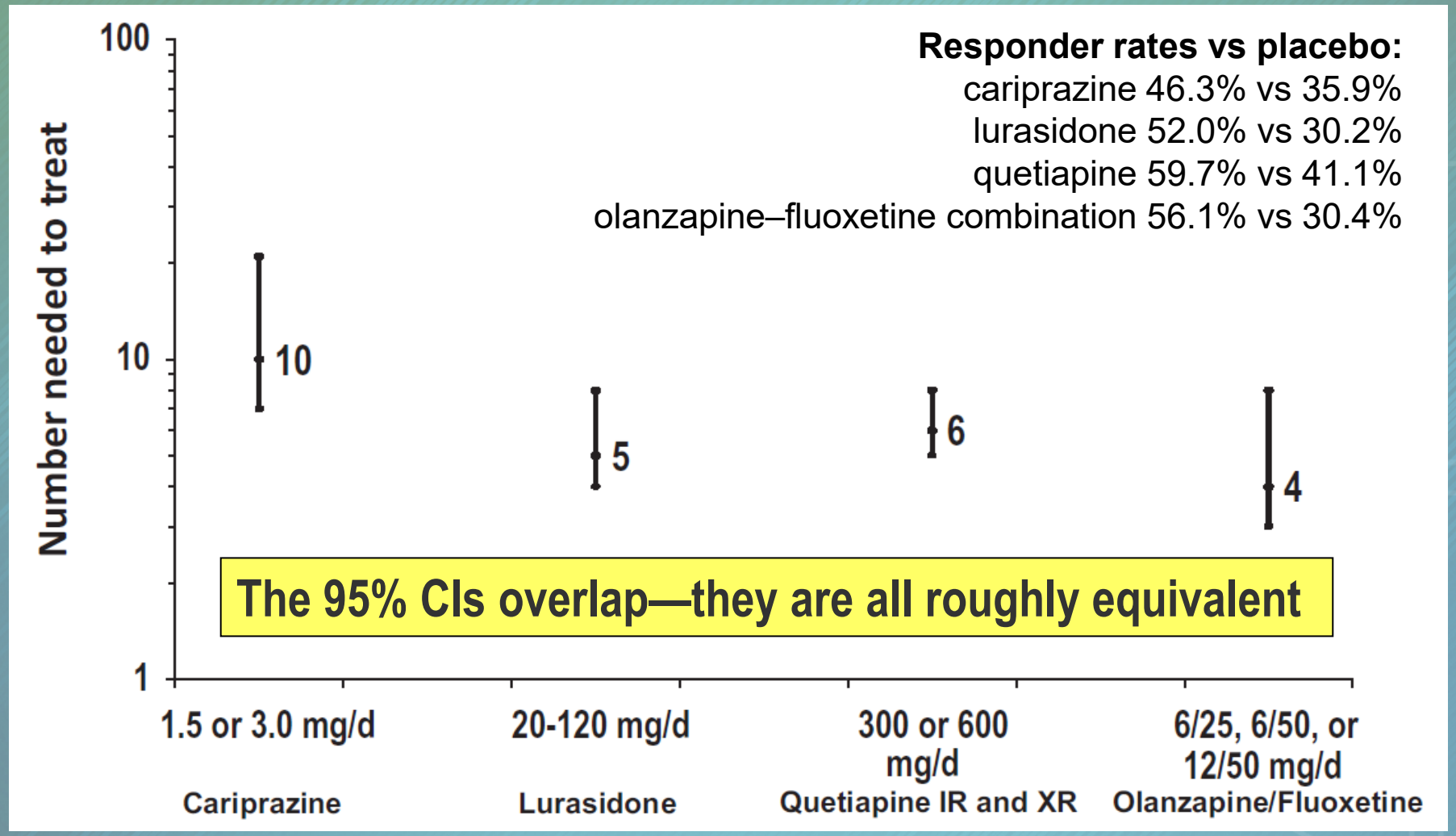
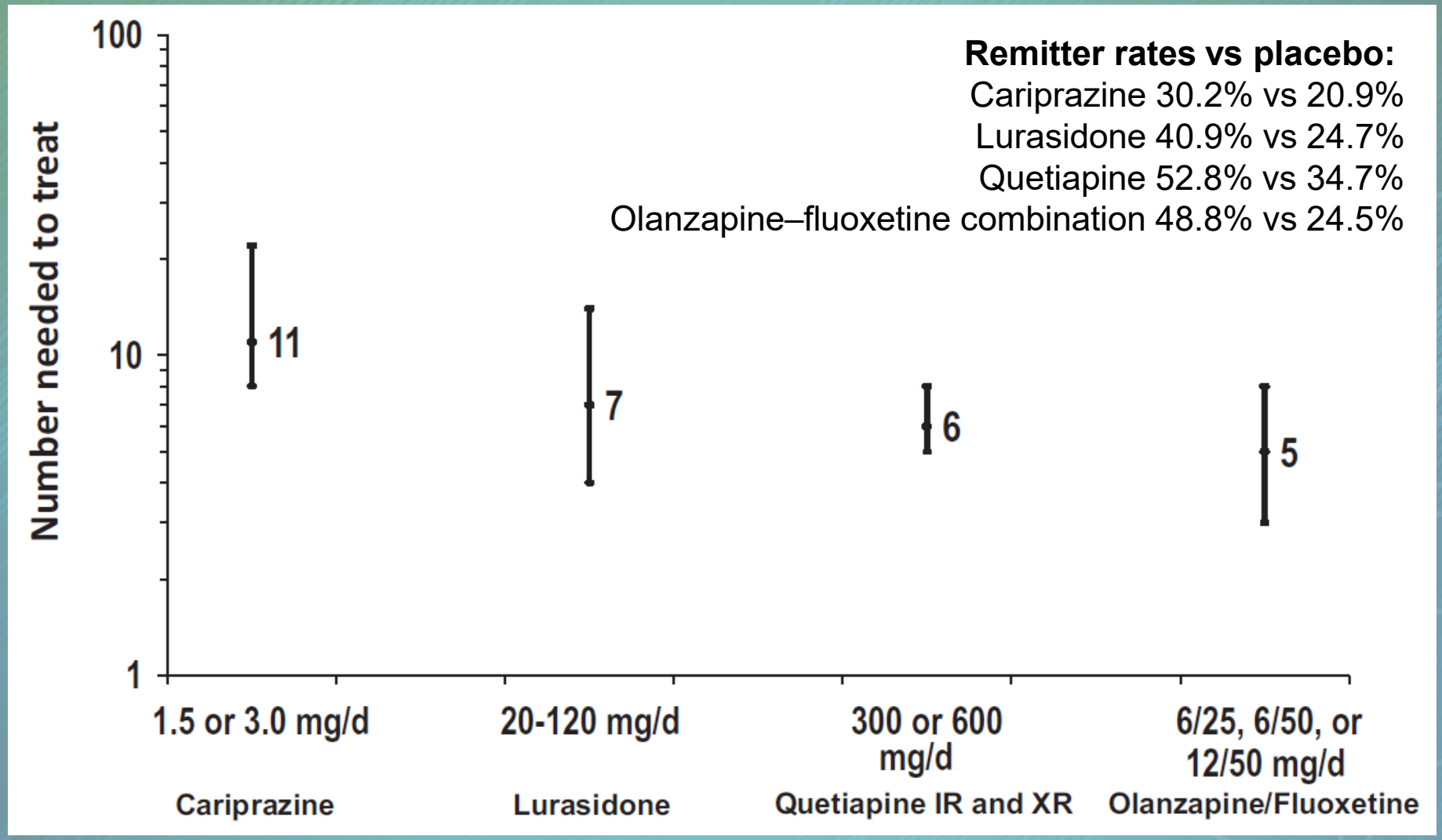
MADRS Responders (≥ 50% reduction)



Citrome L. Int J Clin Pract 2019;73(10):e13397.

MADRS Remitters (score ≤ 10 for cariprazine or ≤ 12 others)



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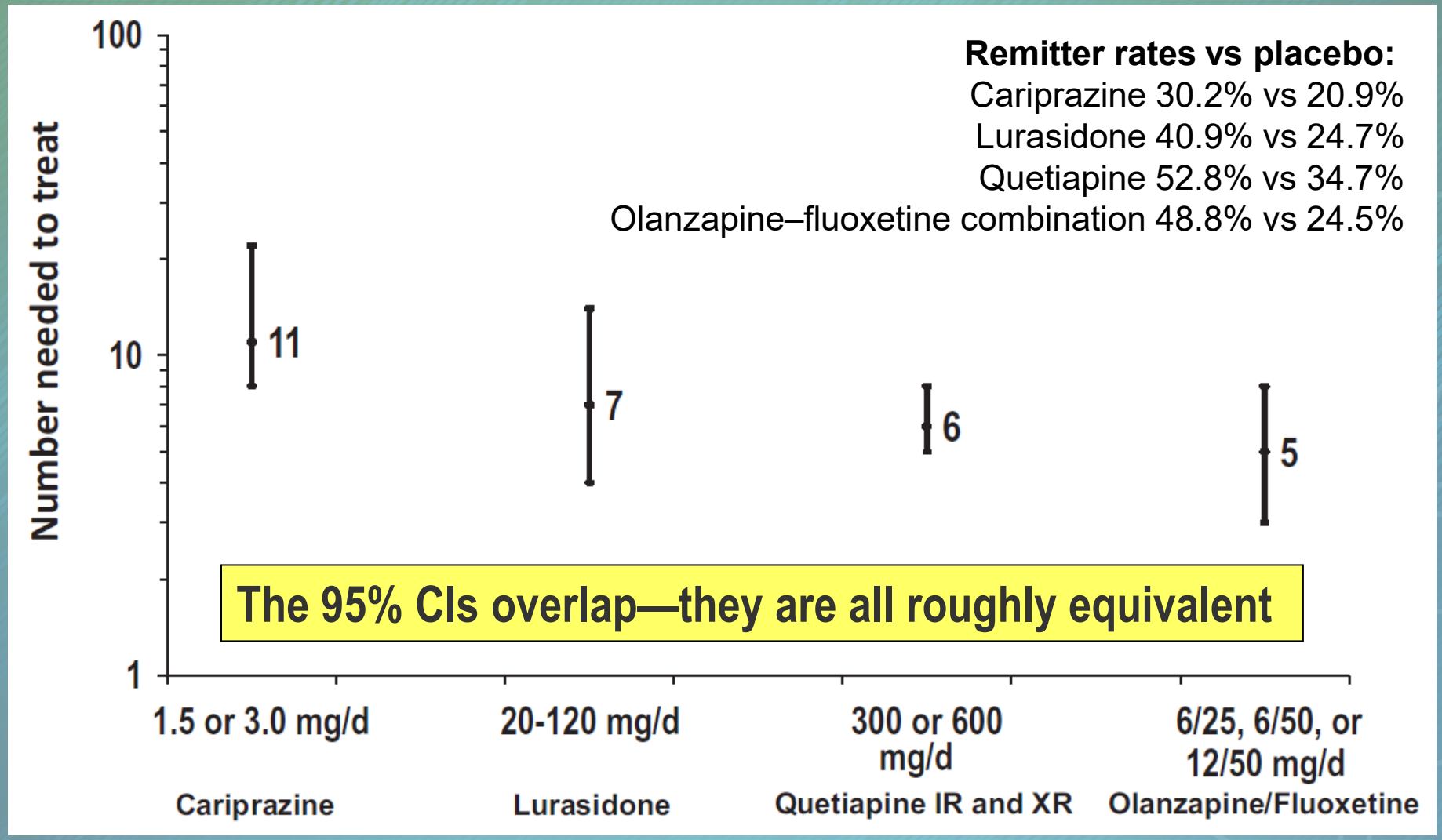

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However, NNH vs Placebo Differs!

	Lurasidone 20-60 mg/d	Lurasidone 80-120 mg/d	OFC 6/25, 6/50, 12/50 mg/d	Quetiapine IR/XR 300 or 600 mg/d	Cariprazine 1.5 mg/d	Cariprazine 3.0 mg/d
Weight gain ≥7%	29	5550	6	16	50	50
Extrapyramidal symptoms	40	16	N/A	N/A	50	25
Somnolence	130	14	13	3	34	50
Akathisia	18	12	N/A	N/A	36	13
Nausea	39	11	N/A	N/A	29	21
D/C due to adverse events	642	-151	-37	10	298	31

Effect size: NNH <10 **Higher risk**; NNH: 10-19 **Intermediate risk**; NNH ≥20 **Lower risk***

OFC: olanzapine/fluoxetine combination; D/C: discontinuation; N/A: not available
*A negative value for NNH occurs when the rate of the harm is lower for drug than for placebo

Citrome L et al. Presented at ASCP Virtual; 2020. Abstract F30; Citrome L et al. CNS Spectr 2021;26(2):146; Citrome L. J Clin Psychopharmacol 2020;40(4):334-8.

Let's Use Our Brains! Some Thoughts

- Considerations include the **time to onset** of the AE vs. time to onset of a therapeutic response, as well as the severity and duration of the AE
- The AE in question may be easily manageable if it is non-serious and short-lived
- Despite their tolerability challenges, olanzapine–fluoxetine combination and quetiapine monotherapy may still have utility in **high urgency** situations, particularly in persons who have demonstrated good outcomes with these interventions in the past, where a pressing clinical need for efficacy mitigates their tolerability shortcomings

Citrome L et al. J Affect Disord 2014;155:20-7.

Let's Use Our Brains! More Considerations

- In addition, despite their efficacy challenges, the older unapproved treatments, specifically lamotrigine and antidepressants, may have utility in **low-urgency** situations, in which a compelling need for tolerability might mitigate their efficacy shortcomings
- Limitations: study populations (BD I with or without BD II, with or without psychosis), use with adjunctive lithium or valproate (results not shown here), and durations (6 vs. 8 weeks) differed in the clinical trials for cariprazine, lurasidone, quetiapine, and olanzapine–fluoxetine combination

Citrome L et al. J Affect Disord 2014;155:20-7;
Citrome L. Int J Clin Pract 2019;73(10):e13397.

Let's Use Our Brains! Still More Considerations

- However, success will depend on making an accurate diagnosis
  - Treatment for MDEs associated with bipolar disorder differs from treatment for MDEs associated with MDD
- Patients who are incorrectly treated will have persistent symptoms, but **never say never**
  - If your individual patient did better *on* Drug X, and worse *off* Drug X, give Drug X

Evidence-Based or Not? You Decide!

Ms. A, age 20, presents with a Major Depressive Episode

Assessment/intervention	Is this evidence-based?	Why or why not?
Ms. A is depressed, so prescribe an SSRI	?	?

Citrome L, Arbuck D. Current Psychiatry 2021 May;20(5):34-8,46.

Evidence-Based or Not? You Decide!

Ms. A, age 20, presents with a Major Depressive Episode

Assessment/intervention	Is this evidence-based?	Why or why not?
Ms. A is depressed, so prescribe an SSRI	**No**	The MDE may be because of bipolar disorder and not major depressive disorder. **Additional information is needed** to make an accurate diagnosis; otherwise, an incorrect treatment may be provided, and that treatment may worsen the underlying condition. There is *no information about individual circumstances* that would make treatment with a SSRI an EBM-based approach.

Citrome L, Arbuck D. Current Psychiatry 2021 May;20(5):34-8,46.

Evidence-Based or Not? You Decide!

Ms. A, age 20, presents with a Major Depressive Episode

Assessment/intervention	Is this evidence-based?	Why or why not?
Three years ago, Ms. A had a hypomanic episode that spontaneously resolved. Two years ago, she had an MDE that was treated successfully with an SSRI without any emergence of hypomania, so prescribe an SSRI	?	?

Citrome L, Arbuck D. Current Psychiatry 2021 May;20(5):34-8,46.

Evidence-Based or Not? You Decide!

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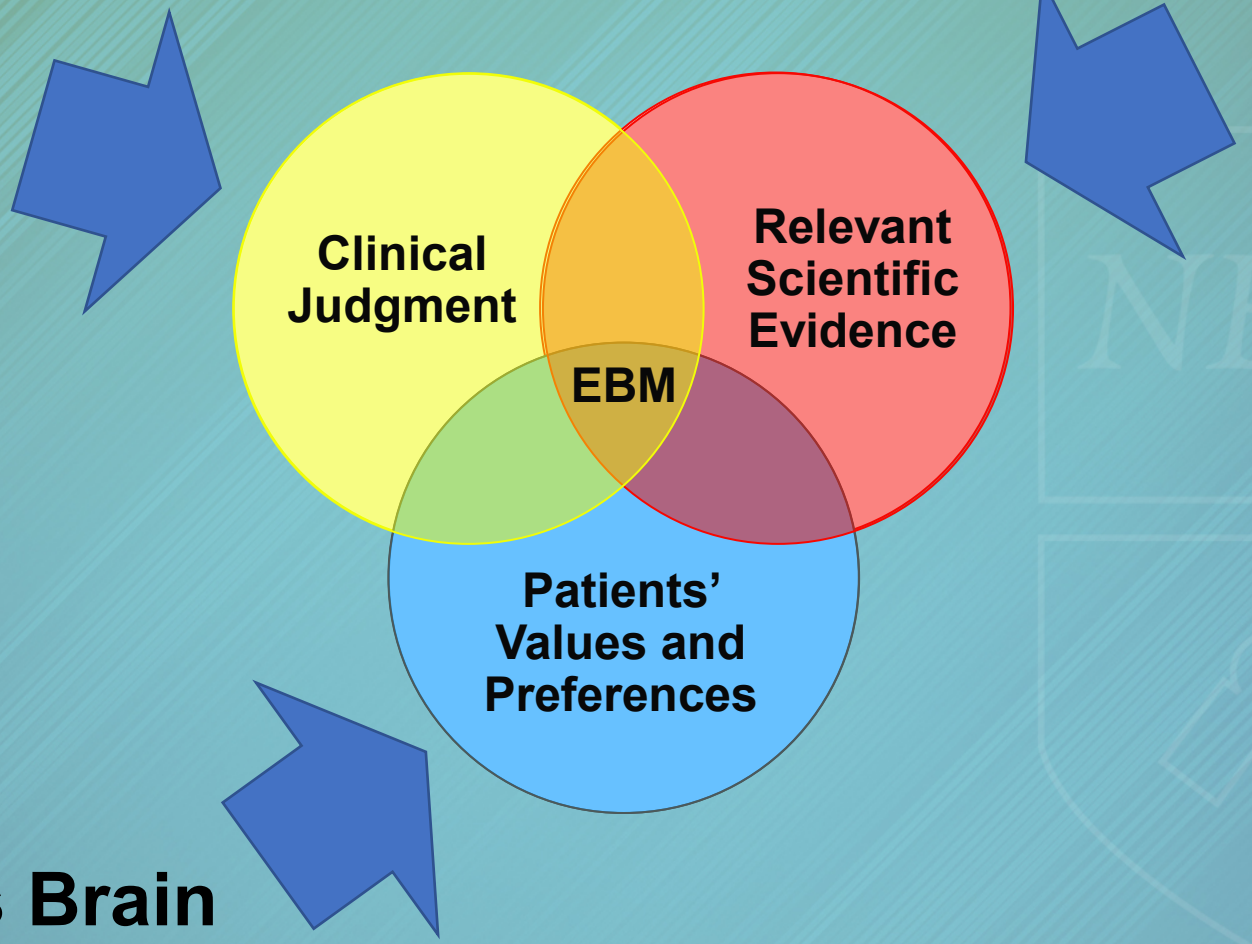
Assessment/intervention	Is this evidence-based?	Why or why not?
Three years ago, Ms. A had a hypomanic episode that spontaneously resolved. Two years ago, she had an MDE that was treated successfully with an SSRI without any emergence of hypomania, so prescribe an SSRI	**Yes**	More information is now available. Diagnosis is likely bipolar II, but Ms. A did do well with SSRI monotherapy in the past. Although this appears to be a non-EBM choice, **individual patient values and preferences, together with clinical judgement**, make this treatment consistent with EBM as originally conceptualized. If it emerges that Ms. A has had a manic episode, SSRI monotherapy would be a suboptimal choice and the available evidence should steer the clinician to *avoid* SSRI monotherapy.

Citrome L, Arbuck D. Current Psychiatry 2021 May;20(5):34-8,46.

Summary

Your Brain



Keeping Up With New Information and Making Sense of it

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Posttest Question 1

Which of the following attributes makes you consider that the patient has bipolar depression rather than unipolar depression?

1. Insomnia
2. Decreased appetite
3. Increased appetite
4. Duration of major depressive episode > 6 months

Posttest Question 2

FDA-approved treatments for bipolar depression include:

1. Aripiprazole
2. Lamotrigine
3. Lurasidone
4. All of the above

Posttest Question 3

The ideal treatment would have which of the following characteristics?

1. High NNT, low NNH, LHH < 1
2. High NNT, high NNH, LHH > 1
3. Low NNT, low NHH, LHH > 1
4. Low NNT, high NNH, LHH > 1