How do we differentiate bipolar depression from major depressive disorder?

How can bipolar depression be managed?

What are the risks of mistreating bipolar disorder?

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Is There A Changing Paradigm In The Management Of Bipolar Depression?

An Evidence-based Approach To Help Define Treatment Options

Provided by Vindico Medical Education

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What is Bipolar Depression?

- Bipolar depression is defined by having major depressive episodes (MDEs) *and* manic/hypomanic episodes – usually with recurrence
  - 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 a 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

Berk M, Berk L, Moss K, Dodd S, Malhi GS. *Med J Aust.* 2006;184(9):459-462.
Bowden CL. *Psychiatr Serv*. 2001;52(1):51-55.
Muzina DJ, Colangelo E, Manning JS, Calabrese JR. *Cleve Clin J Med*. 2007;74(2):89-105.

Misdiagnosis of Bipolar Disorder and Bipolar Depression is 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 1 comorbid psychiatric or mental condition**
  - **Examples include anxiety, substance use, obesity, 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, Cass AR, Holt DCL, Carlson CA. *J Am Board Fam Pract*. 2005;18(4):233-239.
Hirschfeld RM, Vornik LA. *Am J Manag Care*. 2005;11(3 suppl):S85-S90.
Dilsaver SC. *J Affect Disord*. 2011;129(1-3):79-83.
Leboyer M, Kupfer DJ. *J Clin Psychiatry*. 2010;71(12):1689-1695.
Hirschfeld RM, Lewis L, Vornik LA. *J Clin Psychiatry*. 2003;64(2):161-174.
Baldessarini RJ, Tondo L, Baethge CF, Lepri B, Bratti IM. *Bipolar Disord*. 2007;9:386-393.

Clues to Avoid Misdiagnosis
Increase your index of suspicion if…

- **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**
  - **Recurrence rates higher in bipolar disorder**
- **Treatment response**
  - **Suboptimal outcome with antidepressants**
  - **Antidepressant-induced mania or hypomania**
- **Mania symptoms**
- **Associated features**
  - **Chaotic relationships/job environments**
  - **Substance use**

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Bowden CL. *Psychiatr Serv*. 2001;52(1):51-55.
Muzina DJ, Colangelo E, Manning JS, Calabrese JR. *Cleve Clin J Med*. 2007;74(2):89-105.
Manning JS. Prim Care Companion *J Clin Psychiatry*. 2010;12(suppl 1):17-22.

Consequences of Misdiagnosis

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**
  - **More definable in subgroups: Type I disease, ≥ recurrences in last year, mixed features, substance abuse, previous reaction to antidepressant**
- **Antidepressants do not confer a benefit for acute or enduring response**
- **However, never say never**

Sachs GS, Nierenberg AA, Calabrese JR, et al. *N Engl J Med*. 2007;356(17):1711-1722.
Valentí M, Pacchiarotti I, Bonnín CM, et al. *J Clin Psychiatry*. 2012;73(2):e271-276.
Glauser TA, Cerenzia W, Wiley S, Howson A, Thase M. *Postgrad Med*. 2013;125(1):144-153.
Pacchiarotti I, Bond DJ, Baldessarini RJ, Nolen WA, et al. *Am J Psychiatry*. 2013;170(11):1249-1262.

FDA-approved Medications for Bipolar Depression

- **Olanzapine (atypical antipsychotic) and fluoxetine (antidepressant)[1]**
  - **Approved as combination therapy – in 2003**
  - **Most clinically relevant adverse effects – weight gain/metabolic problems**
- **Quetiapine (atypical antipsychotic])[2]**
  - **Approved as monotherapy – IR in 2006, XR in 2008**
  - **Most clinically relevant adverse effects – somnolence/sedation**
  - **Also some risk of weight gain/metabolic problems**
- **Lurasidone (atypical antipsychotic)[3,4]**
  - **Approved as monotherapy or adjunct to lithium/valproate – in 2013**
  - **Most clinically relevant adverse effects – akathisia, nausea**
  - **Lower risks of weight gain/metabolic problems, somnolence/sedation**

[1]Tohen M, et al. *Arch Gen Psychiatry*. 2003;60:1079-88; [2]Calabrese JR, et al. *Am J Psychiatry*. 2005;162:1351-60; [3]Loebel A, et al. *Am J Psychiatry*. 2014;171:160-8; [4]Loebel A, et al. *Am J Psychiatry*. 2014;171:169-77.

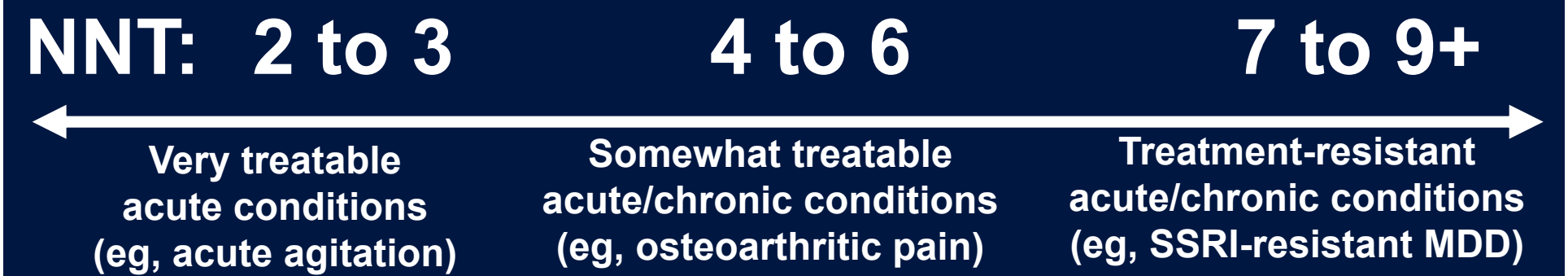
Metrics of Evidence-based Medicine

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 1 additional positive outcome of interest?

What Is an Acceptable NNT for Drug vs Placebo?

A "good" NNT is usually a single digit and the lower the number the better, but how high an NNT is still acceptable?



SSRI, selective serotonin reuptake inhibitor; MDD, major depressive disorder.

Citrome L, Ketter TA. *Int J Clin Pract*. 2013;67(5):407-411.

What Is a Clinically Important NNT?

- A small NNT of 2 would be a hugely important difference
- Single-digit NNTs are important enough to notice in day-to-day clinical practice
- A large NNT of 100 or more means that there is little difference between choosing drug A or drug B for the outcome measured
- Some NNTs may be clinically important, even if they are relatively large, for example when the outcome is death
- Some NNTs may be clinically irrelevant, even if they are relatively small, for example when the outcome is a mild dry mouth

Citrome L. *Acta Psychiatr Scand.* 2008;117(6):412-9.

Metrics of Evidence-Based Medicine

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 1 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 1 additional outcome of interest that you would like to AVOID?

Numbers Needed to Treat in Bipolar Disorder and Depression

	Mania (Mono)	Mania (Adjunct)	Depression (Mono)	Depression (Adjunct/ Combo)	Maintenance (Mono)	Maintenance (Adjunct)
Atypical Antipsychotics						
Olanzapine	**5**	**5**	12 (unapproved)		**3**	
Risperidone Oral, LAI	**4**	**6**			**4** (LAI)	**5** (LAI)
Quetiapine IR, XR	**6**	**8**	**6**		**4** (unapproved)	**4** (unapproved)
Ziprasidone	**7**		148 (unapproved)	??? (unapproved)		**8**
Aripiprazole	**5**	**7**	44 (unapproved)		**6**	**10**
Asenapine	**8**	**14**				
Lurasidone			**5**	**7**		
Combination						
Olanzapine + Fluoxetine				**4**		

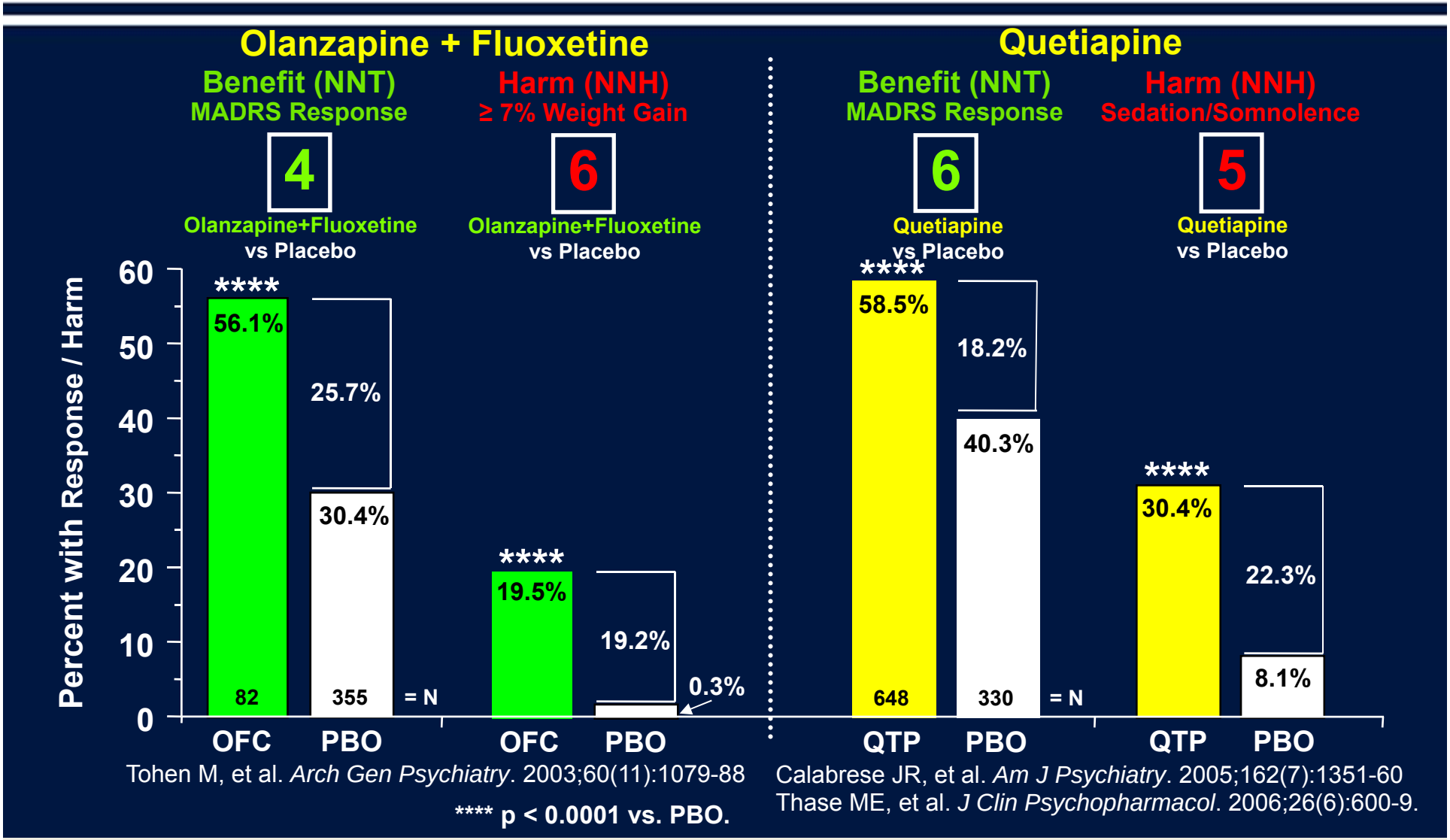
Most FDA-approved bipolar disorder treatments have single-digit NNTs.

Yellow boldface indicates NNTs for approved treatments. **LAI** = Long Acting Injectable formulation.

Ketter TA (ed). Handbook of Diagnosis and Treatment of Bipolar Disorder, Am Psychiat Pub, Inc., Washington, DC, 2010.

Older Approved Bipolar Depression Rx Benefits & Harms

Numbers Needed to Treat & Harm, Response & Adverse Effect Rates



Tohen M, et al. *Arch Gen Psychiatry*. 2003;60(11):1079-88

Calabrese JR, et al. *Am J Psychiatry*. 2005;162(7):1351-60

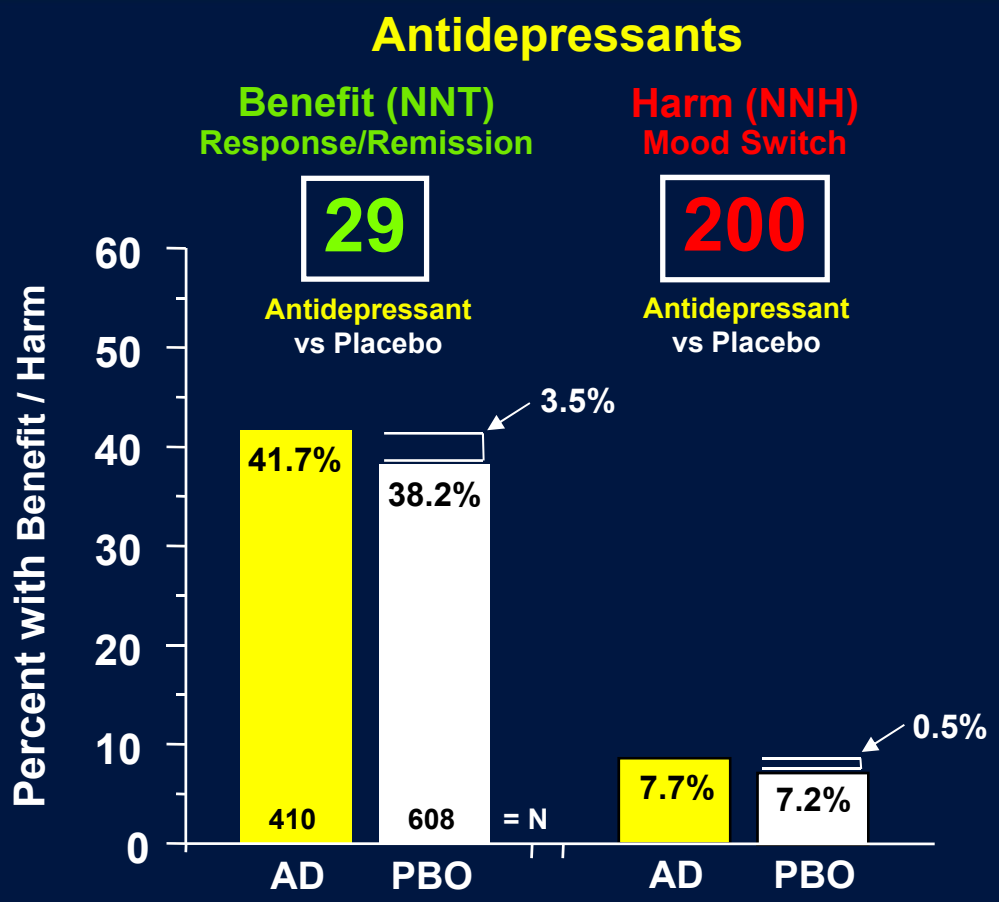
Thase ME, et al. *J Clin Psychopharmacol*. 2006;26(6):600-9.

**** p < 0.0001 vs. PBO.

Older approved treatments similarly likely to yield benefit and harm compared with placebo.

Unapproved Bipolar Depression Rx Benefits & Harms

Numbers Needed to Treat & Harm, Response & Adverse Effect Rates

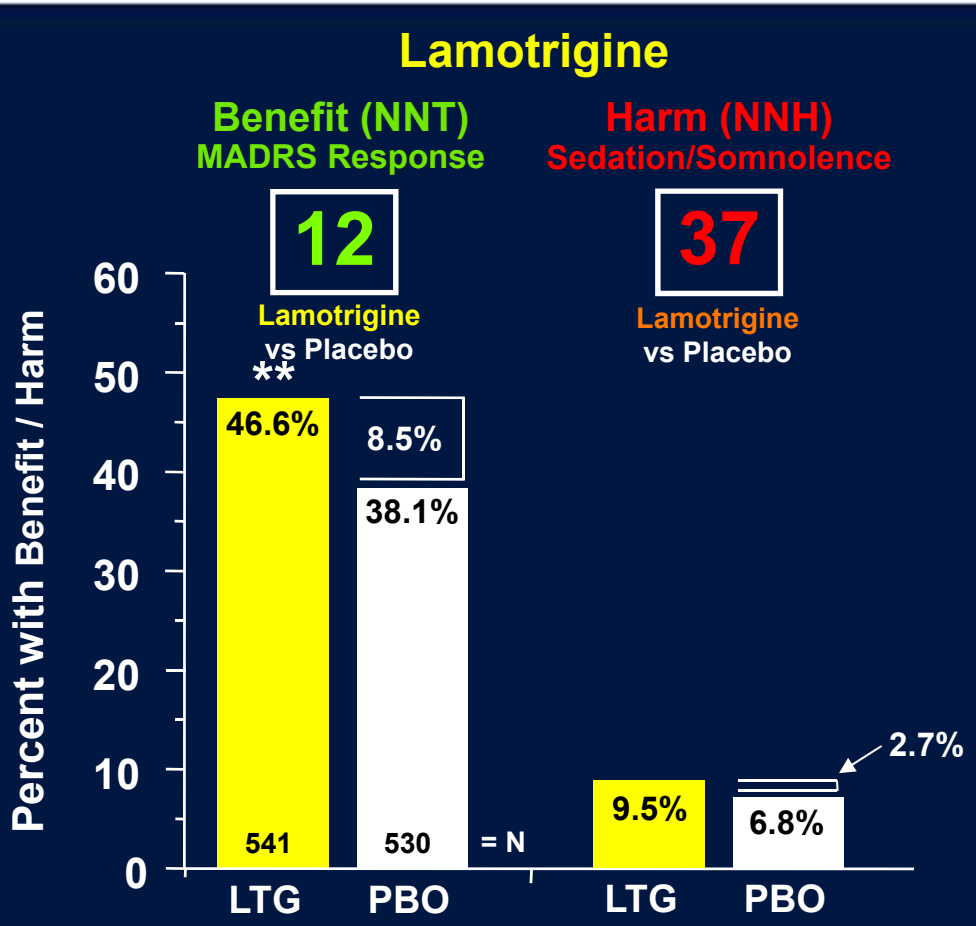


Sidor MM, Macqueen GM. *J Clin Psychiatry*. 2011;72(2):156-67.

Antidepressants more than twice as likely to yield benefit as harm compared with placebo.

Unapproved Bipolar Depression Rx Benefits & Harms

Numbers Needed to Treat & Harm, Response & Adverse Effect Rates



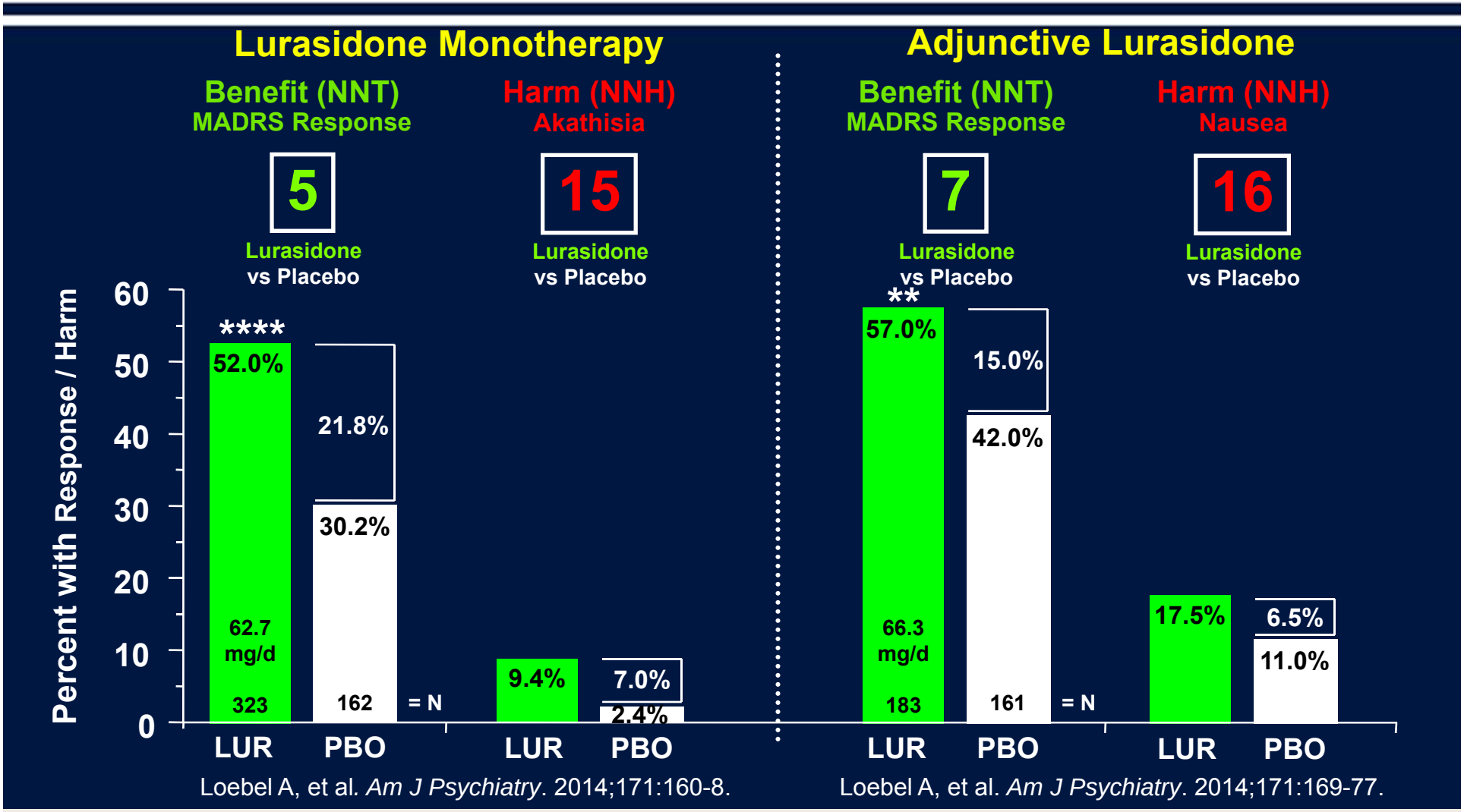
Geddes JR, et al. *Br J Psychiatry*. 2009;194(1):4-9.
Calabrese JR, et al. *Bipolar Disord*. 2008;10(2):323-33.

Lamotrigine more than twice as likely to yield benefit as harm compared with placebo.

** p < 0.01 vs. PBO.

Lurasidone in Bipolar Depression Benefits & Harms

Numbers Needed to Treat & Harm, Response & Adverse Effect Rates



Loebel A, et al. *Am J Psychiatry*. 2014;171:160-8.

Loebel A, et al. *Am J Psychiatry*. 2014;171:169-77.

Lurasidone more than twice as likely to yield benefit as harm compared with placebo.

** p < 0.01, **** p < 0.0001 vs. PBO.

Lurasidone Tolerability

- NNH vs placebo for discontinuation due to AE for monotherapy: 642 (20-60 mg/d), 181 (80-120 mg/d)
- NNH vs placebo for discontinuation due to AE for adjunctive therapy: 54
- NNH vs placebo for somnolence: 130
- Lurasidone not associated with any meaningful weight gain

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

Polypharmacy

- Patients with bipolar depression and bipolar disorder tend to be on multiple medications
- STEP-BD:
  - 40% taking 3 or more meds
  - 18% taking 4 or more
  - Patients receiving an atypical antipsychotic had 64% risk for receiving ≥ 4 or more meds
- Drugs that are not contributing benefit may be exacerbating side effect profile
- Once patient stable, clinicians should consider if some medications might be pared

Goldberg JF, et al. *J Clin Psychiatry*. 2009;70(2):155-62.

Ratio of NNH to NNT = Likelihood to be Helped or Harmed (LHH)

- LHH can quantify trade-offs between benefits and harms
  - For example, for a hypothetical medication, if NNT vs placebo is 4 for a clinically relevant therapeutic response, and the NNH vs placebo for persistent tremor is 6, LHH is 6/4 or 1.5
  - This LHH of 1.5 for response vs persistent tremor can be interpreted that “treatment was 1.5 times more likely to help (therapeutic response) than to harm (tremor) the patient”

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

Ratio of NNH to NNT = Likelihood to be Helped or Harmed (LHH)

What is an acceptable LHH?

LHH >> 1	LHH > 1	LHH ≤ 1
NNH >> NNT	NNH > NNT	NNH ≤ NNT
When comparing a desired outcome, eg, remission, with a very severe adverse event	When comparing a desired outcome, eg, remission, with an adverse event that is usually mild or moderate but that may still lead to discontinuation	When comparing a desired outcome, eg, remission, with an adverse event that is usually mild or moderate but that is usually temporary and does not lead to discontinuation

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

What to Make of All These Numbers?

- **The concept of NNT allows the clinician to estimate a medication's potential relevant effect**
- **Examining the magnitudes of NNT (and NNH), the clinician can start to make risk-benefit decisions tailored to the individual patient's needs or preferences**

Citrome L. *Acta Psychiatr Scand.* 2008;117(6):412-419.

Citrome L, Ketter TA. *Int J Clin Pract.* 2013;67(5):407-411.

Role of Psychotherapy

- Adjunctive to medication
- Best evidence is around prevention of episodes
- Some techniques have NNT comparable to medication

Bowden CL. *J Clin Psychiatry*. 2005;66 Suppl 1:3-6.

Conclusions

Take-home Points

- **Good patient history is invaluable**
  - Response to prior medications, if any
  - Recognize the unique characteristics for each patient
- **Given likelihood of complex pharmacologic regimens, confirm that each medication is providing more benefit than harm**
  - Especially if patient is not improving, or are seeing a new patient for consultation

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