Treatment Resistant Depression: A Systematic Approach to Management

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Disclosure

Within the past 3 years, Dr. Thase has been a consultant to Alkermes, Allergan, AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Company, Forest Laboratories (PGx), Janssen Pharmaceutica, Lundbeck, Merck (Organon & Schering-Plough), Mylan (Dey), Neuronetics, Novartis, Otsuka, Pfizer, Rexahn, Shire US, Sunovion, Takeda, Teva, and Transcept. He has received honoraria for talks from AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Company, Lundbeck, Merck, Mylan, Otsuka, and Pfizer. He has received research funding from AstraZeneca, Eli Lilly and Company, Forest, GlaxoSmithKline, NeoSync, Otsuka, and Pfizer, as well as the National Institute of Mental Health and the Agency for Healthcare Research and Quality. His wife is an employee of Peloton Advantage, which does business with Pfizer.

Disclosure: Past Three Years

- Advisory/Consultant—Alkermes, Allergan (Forest, Naurex), AstraZeneca, Bristol-Myers Squibb, Cerecor, Eli Lilly & Co., Gerson Lehrman Group, Fabre-Kramer, Guidepoint Global, Janssen (J&J, Ortho-McNeil), Lundbeck, Moksha8, MedAvante, Merck, Nestlé (PamLab), Neuronetics, Novartis, Otsuka, Pfizer, Sunovion, Takeda
- Grant Support—Agency for Healthcare Research and Quality, Alkermes, Assurex, Avanir, Forest Pharmaceuticals, Jansen, National Institute of Mental Health, Otsuka Pharmaceuticals; Royalties—American Psychiatric Press, Guilford Publications, Herald House, W.W. Norton & Company, Inc.
- Employment (spouse)—Peloton Advantage, which does business with Pfizer, Astra Zeneca, and GSK.

A Simple System for Staging Antidepressant Resistance

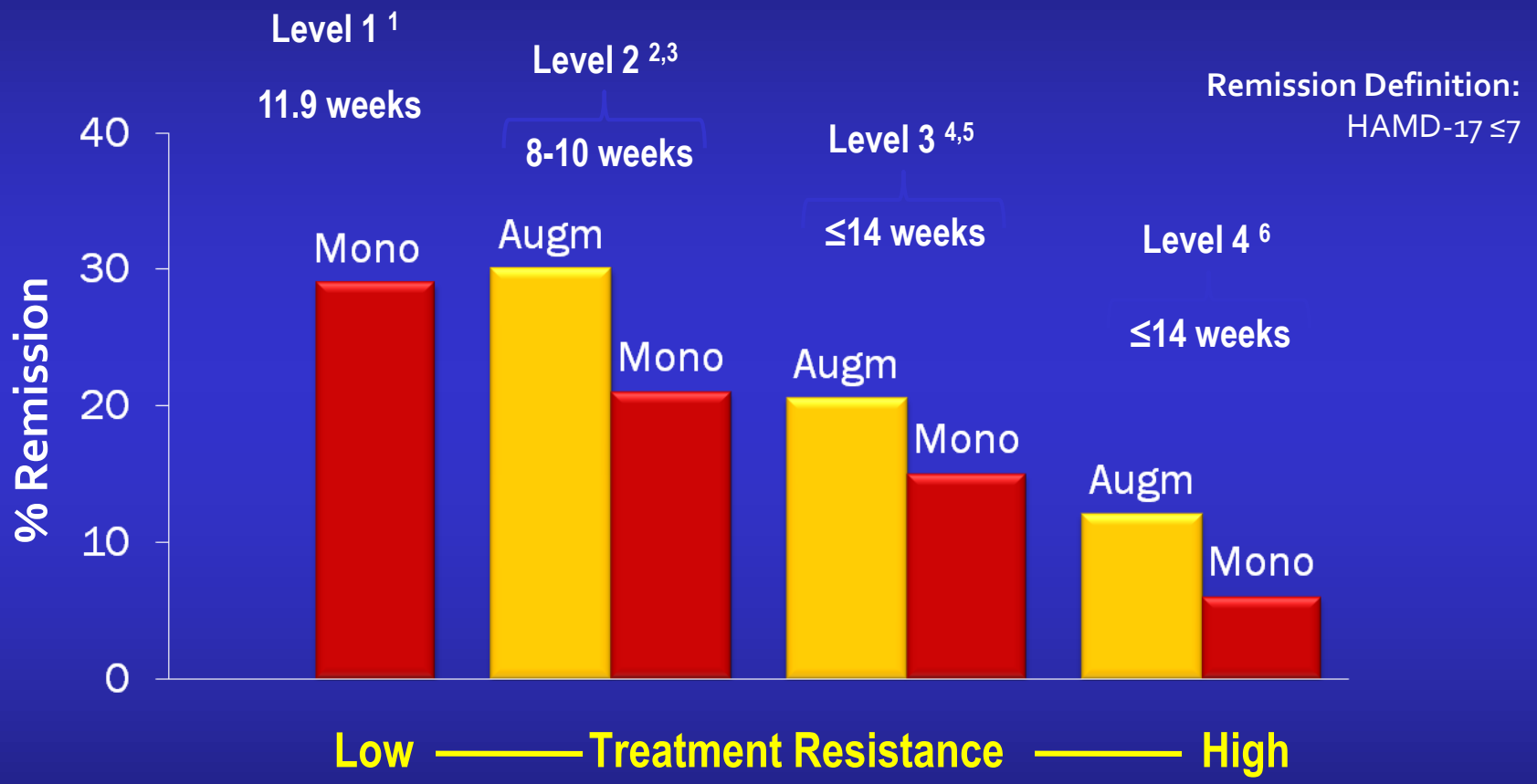
- Stage I: failure of an adequate trial of one class of major antidepressant
- Stage II: failure of adequate trials of two distinctly different classes of antidepressants
- Stage III: stage II plus failure of a third class of antidepressant, including a TCA
- Stage IV: stage III plus failure of an adequate trial of MAOI
- Stage V: stage IV plus failure of an adequate course of ECT

Adapted from Thase ME, Rush AJ. *J Clin Psychiatry*. 1997;58(Suppl 13):23-29.

Should we switch or use adjunctive strategies?

- Parsimony favors switching
- Adjunctive therapies often easier to implement (i.e., avoids washout and cross-titration)
- STAR*D disappointingly did not answer this question aside from demonstrating that adjunctive strategies preferred for partial responders and switching preferred for nonresponders

STAR-D Remission Rates Across All 4 Levels



Mono, single medication regimen; Augm, combination medication treatment.

[1]Trivedi MH et al. *Am J Psychiatry*. 2006;163(1):28-40; [2]Trivedi MH et al. *N Engl J Med*. 2006;354(12):1243-1252; [3]Rush AJ et al. *N Engl J Med*. 2006;354(12):1231-1242; [4]Nierenberg AA et al. *Am J Psychiatry*. 2006;163(9):1519-1530; [5]Fava M et al. *Am J Psychiatry*. 2006;163(7):1161-1172; [6]McGrath PJ et al. *Am J Psychiatry*. 2006;163(9):1531-1541.

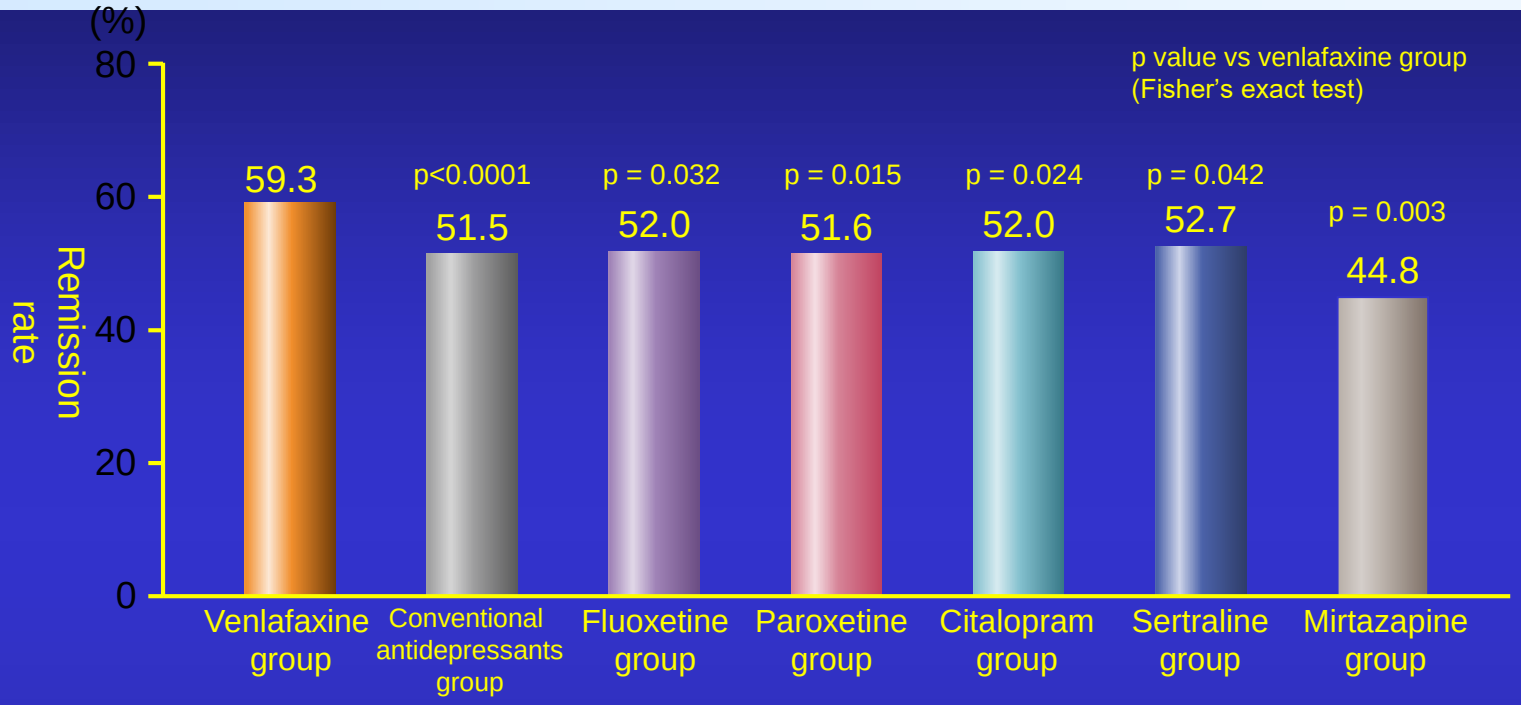
The Case for Switching Antidepressants

- Clinically necessary when first drug is poorly tolerated
- Second drug selection is iterative, guided by outcome with first
- Can pick medications with distinctly different MoAs
- Efficacy of second antidepressant clearly established

Should We Switch Within- or Across Classes?

- Across-class switch was the standard until the mid-1990s
- Subsequent study results “muddied the water”
- A second within-class trial with an SSRI or SNRI is now an accepted option
- No consensus on a third within-class trial

Remission rates in patients with treatment-resistant depression after switching drugs



Remission: HAM-D total score ≤7

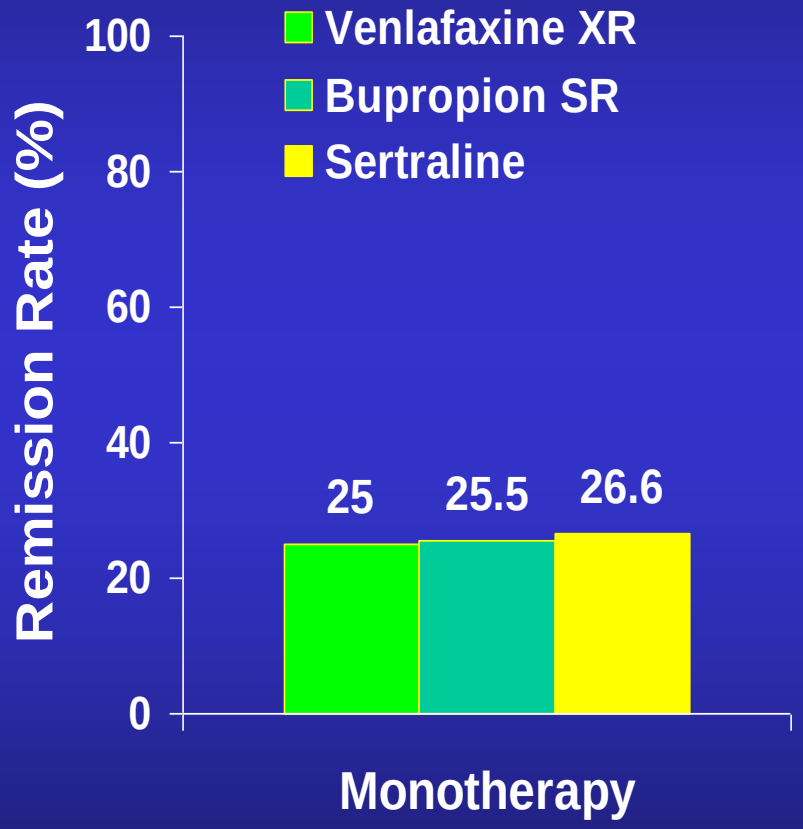
Subjects: 3,097 outpatients at least 18 years old with a diagnosis of major depressive disorder based on DSM-IV classification who had a HAM-D_{17} total score ≥17 and who showed inadequate response or intolerance to treatment with a conventional antidepressant (e.g., **fluoxetine**, paroxetine, sertraline, or **citalopram**) for at least 4 weeks.

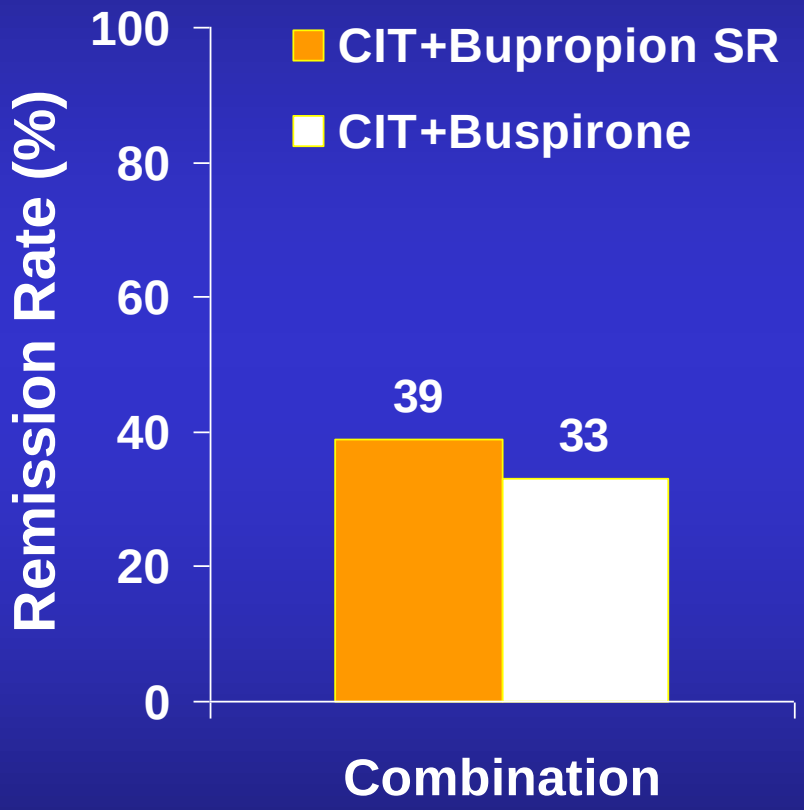
Method: An open-label study. Patients were randomly assigned to orally receive venlafaxine or a conventional antidepressant for 24 weeks. Patients in the venlafaxine group received venlafaxine sustained-release capsules at doses of 75 to 225mg/day, and those in conventional antidepressant group received **fluoxetine**, paroxetine, or **citalopram** at doses of 20 to 60mg, sertraline at doses of 50 to 200mg/day, or mirtazapine at doses of 15 to 45mg/day.

Safety: 483 adverse events occurred in 274 (15.0%) patients in the venlafaxine group. The number of AEs in the conventional antidepressant group was 472 in 266 paents (15.9%).

Baldomero, E. B. et al. : Depress Anxiety 22 (2) : 68, 2005

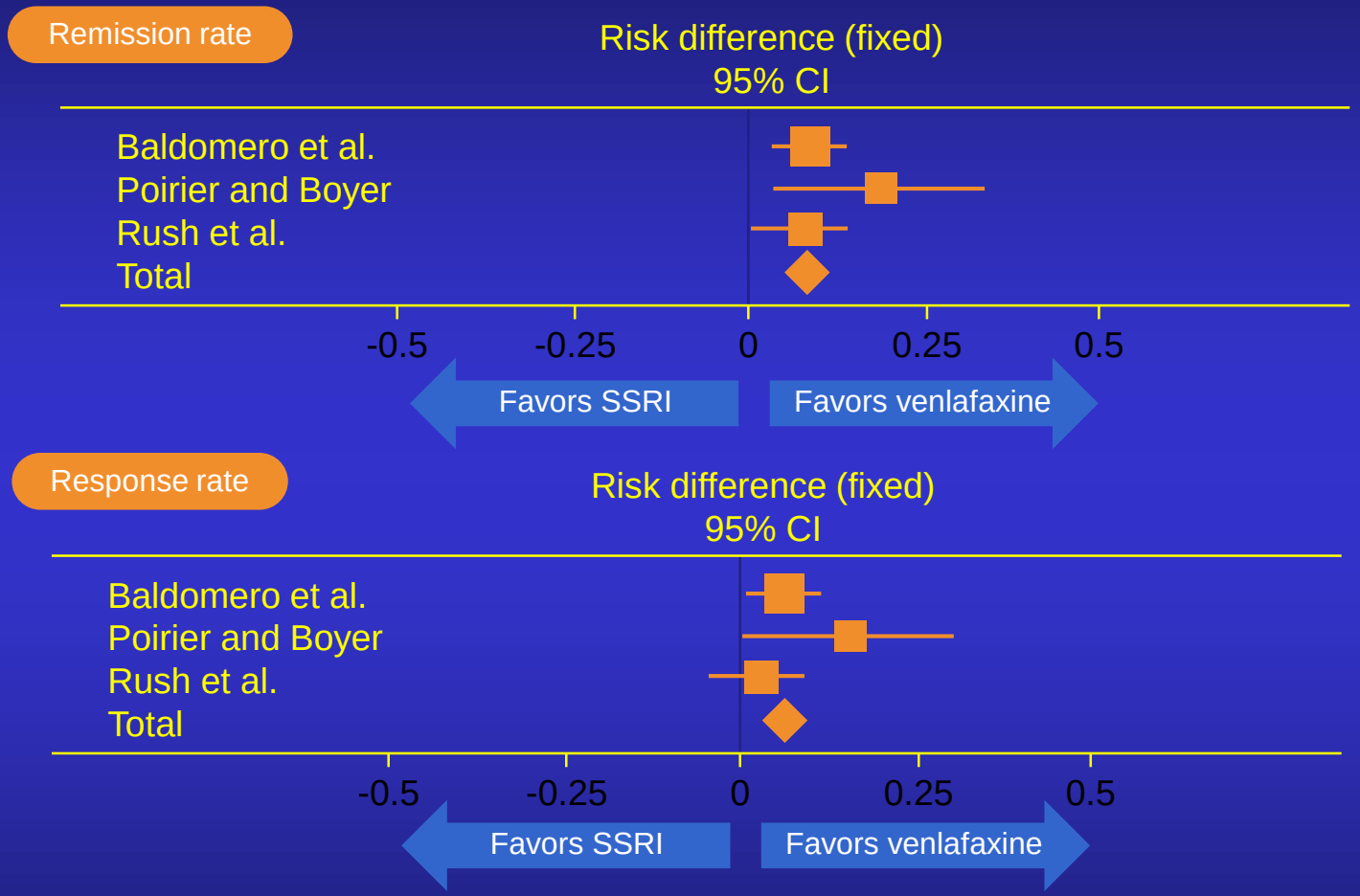
STAR*D Level 2 Results





Rush AJ et al. *N Engl J Med.* 2006;354(12):1231
Trivedi MH et al. *N Engl J Med.* 2006;354(12):1243

Remission and response rates for venlafaxine vs SSRI following nonresponse to SSRI response

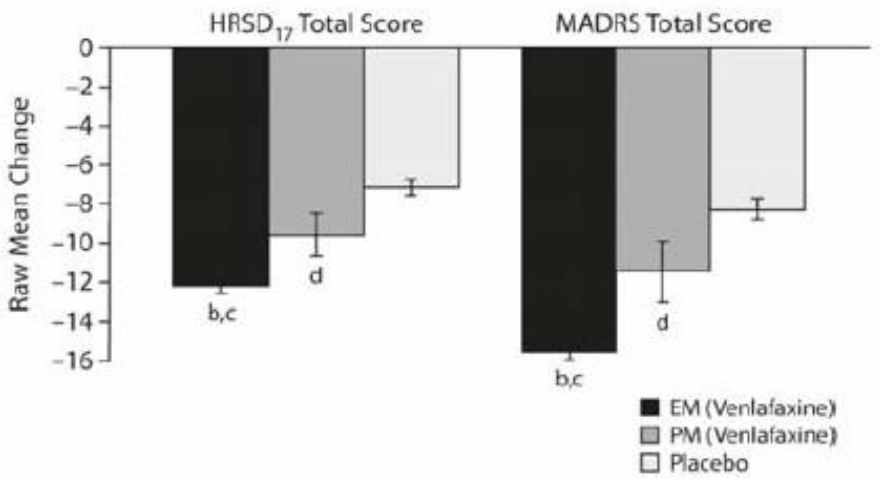


Subjects and methods: Literature searches were performed to obtain randomized comparative studies that investigate antidepressant switching strategies in patients with major depressive disorder and insufficient response to SSRIs. Subsequently, in a meta-analysis, remission and response rates were compared using obtained data. The dosage of venlafaxine was 75 to 375mg/day in 3 studies included in the analysis.

Ruhé, H.G. et al. : J Clin Psychiatry 67 (12): 1836, 2006

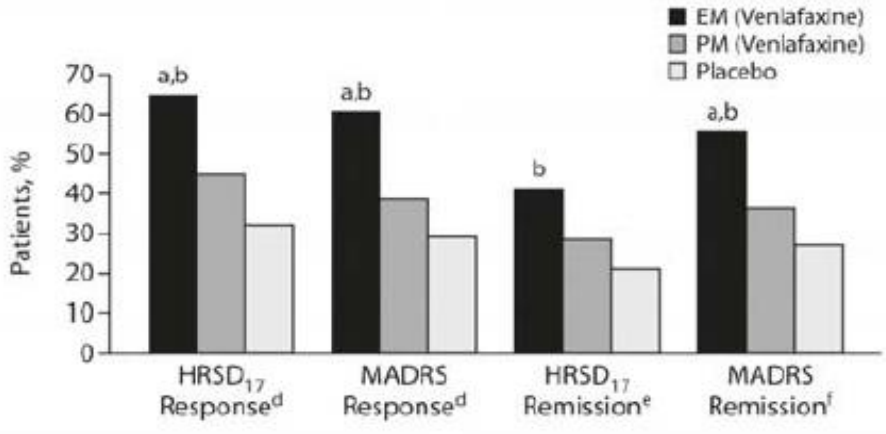
CYP2D6 Status and Response to Venlafaxine: Pooled Analysis of RCTs

Figure 1A. Change in Scores on the $HDRS_{17}$ and MADRS in Patients With Major Depression Treated With Venlafaxine or Placebo, by Metabolizer Status[a]



[a]Error bars represent the SD.
[b]*P* value <.02, EM vs PM.
[c]*P* value <.001, EM vs placebo.
[d]*P* value <.04, PM vs placebo.
Abbreviations: EM = extensive metabolizer, $HDRS_{17}$ = 17-item Hamilton Rating Scale for Depression, MADRS = Montgomery-Åsberg Depression Rating Scale, PM = poor metabolizer.

Figure 1B. Response and Remission Rates Based on the $HDRS_{17}$ and MADRS in Patients With Major Depression Treated With Venlafaxine or Placebo, by Metabolizer Status



[a]*P* value <.02, EM vs PM.
[b]*P* value <.001, EM vs placebo.
[c]*P* value <.04, PM vs placebo.
[d]Response is defined as ≥ 50% decrease from baseline score.
[e]$HDRS_{17}$ remission is defined as total score ≤ 7.
[f]MADRS remission is defined as total score ≤ 12.
Abbreviations: EM = extensive metabolizer, $HDRS_{17}$ = 17-item Hamilton Rating Scale for Depression, MADRS = Montgomery-Åsberg Depression Rating Scale, PM = poor metabolizer.

Lobello K, et al. *J Clin Psychiatry.* 2010;71(11):1482-7.

The Case for Adjunctive Therapy

- Builds on partial success of first therapy
- Avoiding washout is a pragmatic benefit for patients
- When effective, benefits may be rapid
- Can choose rx to target specific sx

Adjunctive Strategies (2016): Ranked from Most to Least Likely to be Used

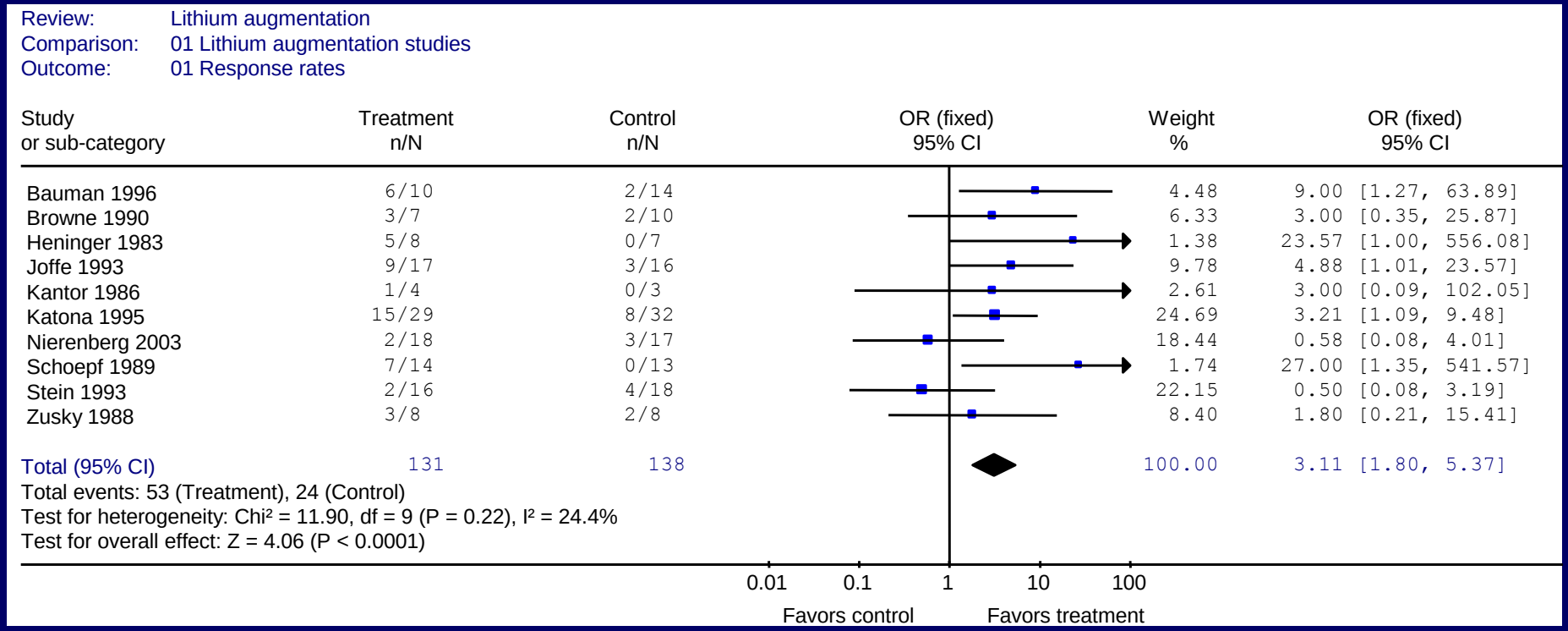
- Lithium & other mood stabilizers
- Thyroid hormones
- Methylfolate (Deplin)
- Modafinil and psychostimulants
- Buspirone and BZs
- 2nd generation antipsychotics (SGAs)

Adjunctive Therapy with Lithium Salts

- More than 60 published studies, but rarely used in the US in 2015
- Definitely effective(meta-analytic $p<10^{-6}$)
- Usual blood level: .4-.8 mEq/L
- Rapid response is rare, so allow 6 weeks for response
- May be both an adjunct and a primary antidepressant

Thase ME, Rush AJ. In: ***Psychopharmacology: The Fourth Generation of Progress*****, FE Bloom, DJ Kupfer (Eds.), New York, NY, Raven Press, 1995, pp 1081-1097.** Crossley and Bauer, J Clin Psychiatry, 2009

Placebo Controlled Lithium Augmentation Studies



Meta-analysis of 10 augmentation studies. Overall pooled rates of response: lithium 53/131 or 40.5% vs 24/138 or 17.4%.

Crossley and Bauer, J Clin Psychiatry, 2009

Augmentation with Other Mood Stabilizers

- Lamotrigine now most widely used; efficacy unproven for all but lithium
- “Quelching” effect for divalproex and carbamazepine for patients with PTSD?
- Coverage of subtle bipolar or mixed syndromes
- Relief of secondary symptoms such as pain

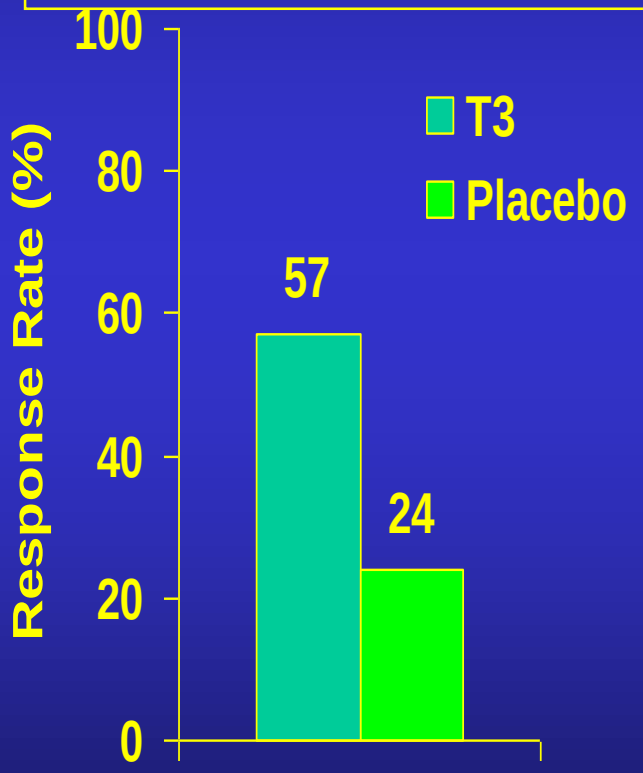
Adjunctive Thyroid Hormone

- 11 published studies
- T_3 preferred over T_4
- 25-50 µg/day of T_3
- Safe and easy, but inconsistent efficacy for patients with normal thyroid functions
- Significantly easier to implement than lithium in STAR*D
- Treatment of choice for patients with elevated TSH levels?

Meta-Analysis of RCTs of Adjunctive Thyroid Therapy

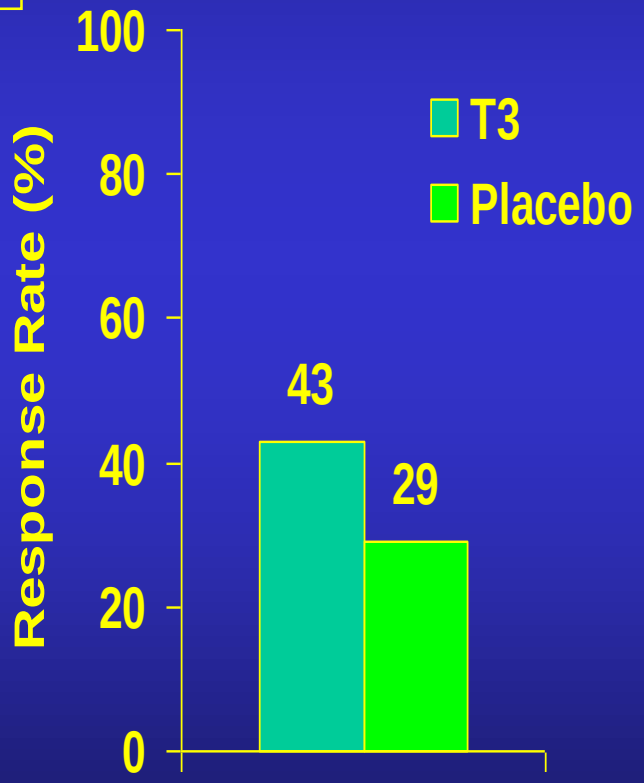
All 8 Trials, N=298

OR=2.09 (95% CI 1.31-3.32), P=0.002



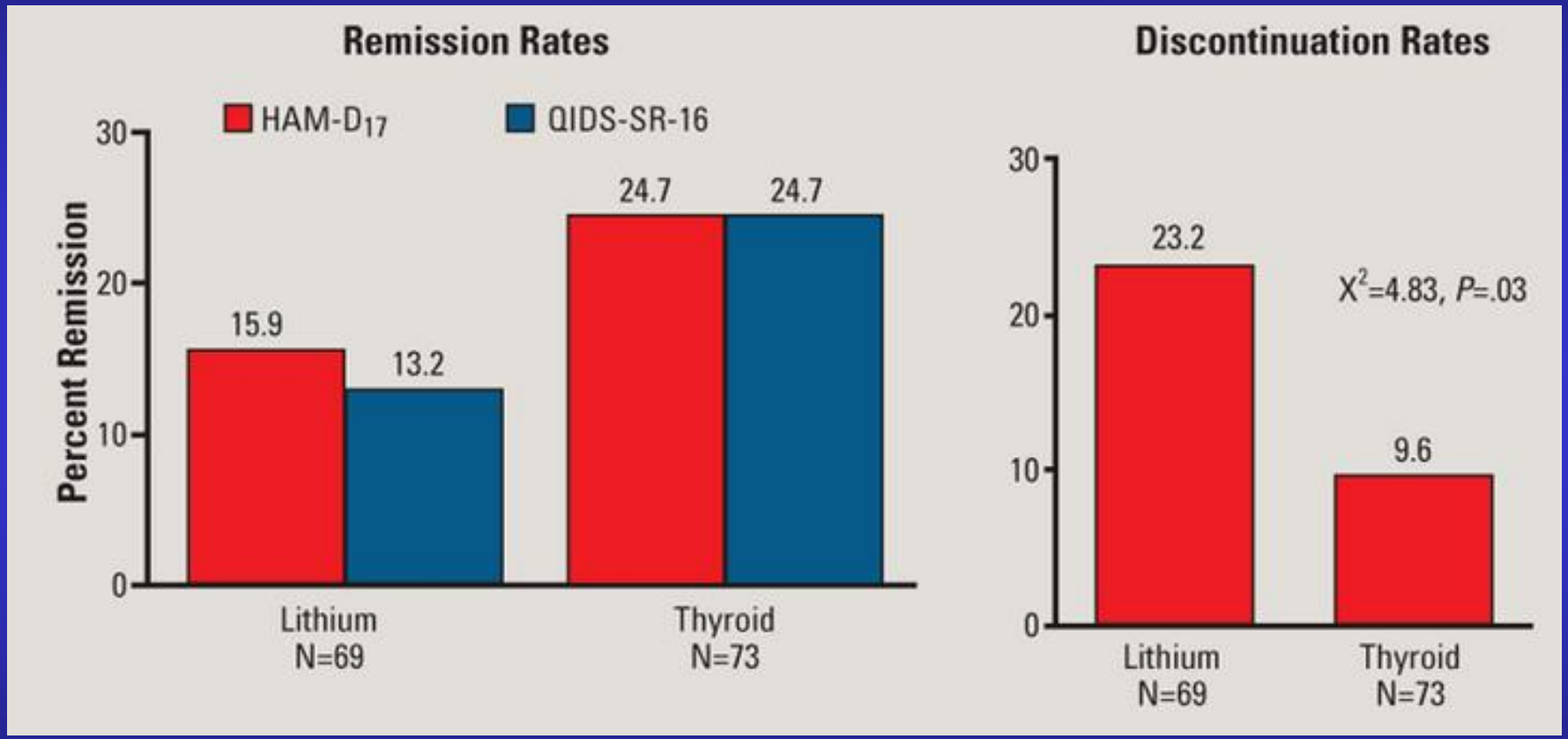
4 Controlled Trials, N=75

OR= 1.53 (95% CI 0.70-3.35), P=.29



Aronson et al. Arch Gen Psychiatry 1996;53:842-848

Adjunctive Therapy With Lithium or Thyroid Hormone: Results of STAR*D Level 3 Comparison



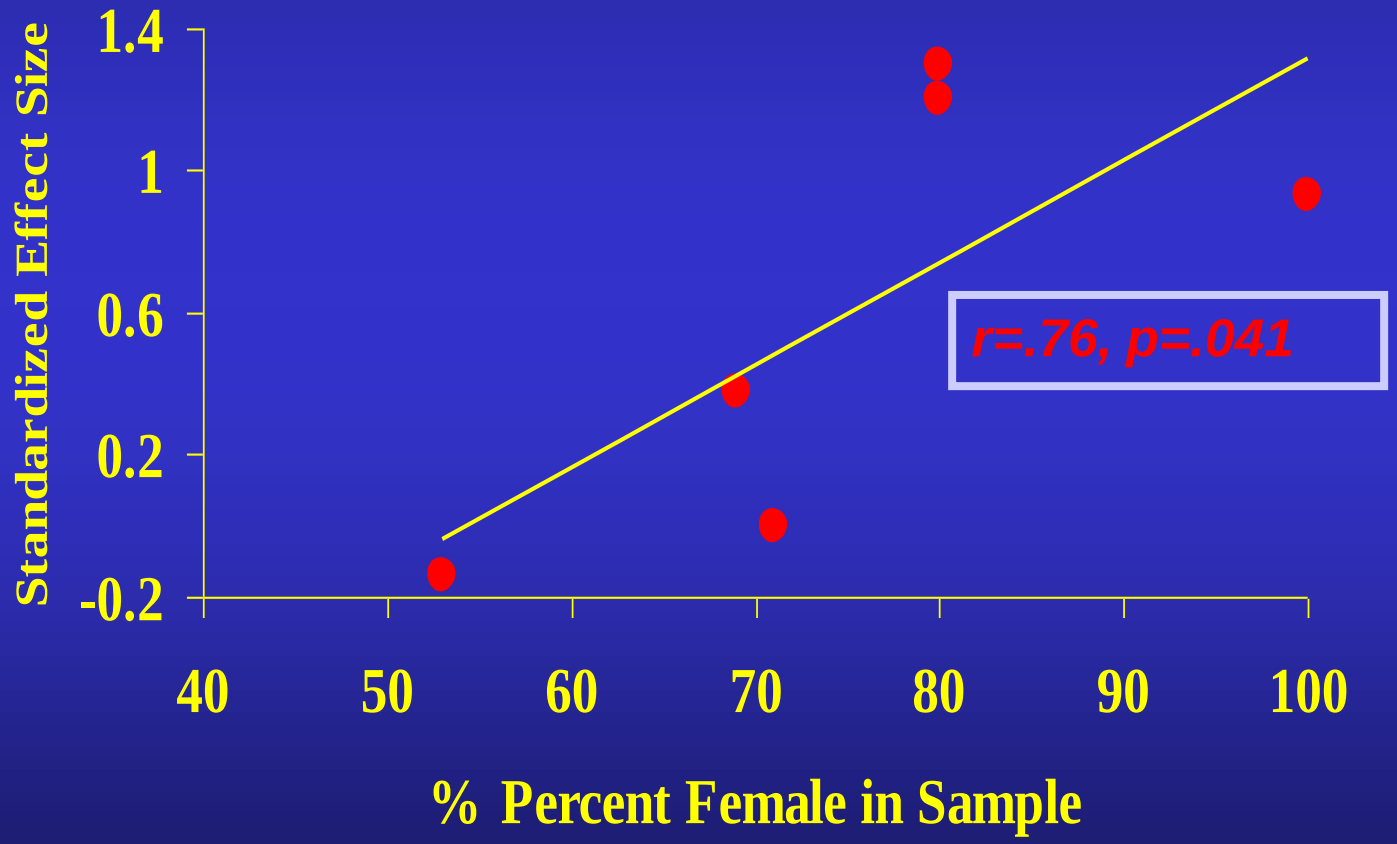
Nierenberg AA, et al. Am J Psychiatry. 2006;163(9):1519-1530.

Potential Pharmacogenetic Relationship with Response to Adjunctive T3?

- There are functional polymorphisms in the genes that code for the enzymes that convert T4 to T3 (deiodinases)
- In a relatively large study of thyroid (T3) acceleration of sertraline response, patients with the DIO1-C785T polymorphism (i.e., lower conversion activity) were more responsive to T3 (Cooper-Kazaz et al., 2009)

Is the benefit of Adjunctive T3 Limited to Women?

Effect Size as a Function of Sample Gender Ratio
(6 Studies, n=125)



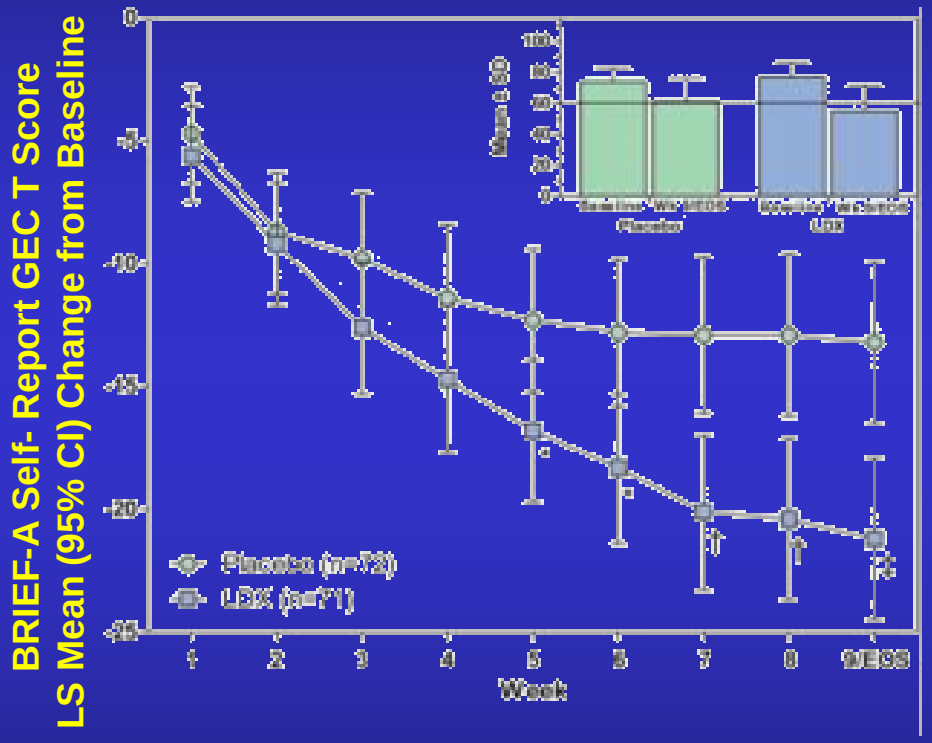
Altshuler et al (2001) Am J Psychiatry

Adjunctive Therapy with Modafinil, Armodafinil, and Other Stimulants

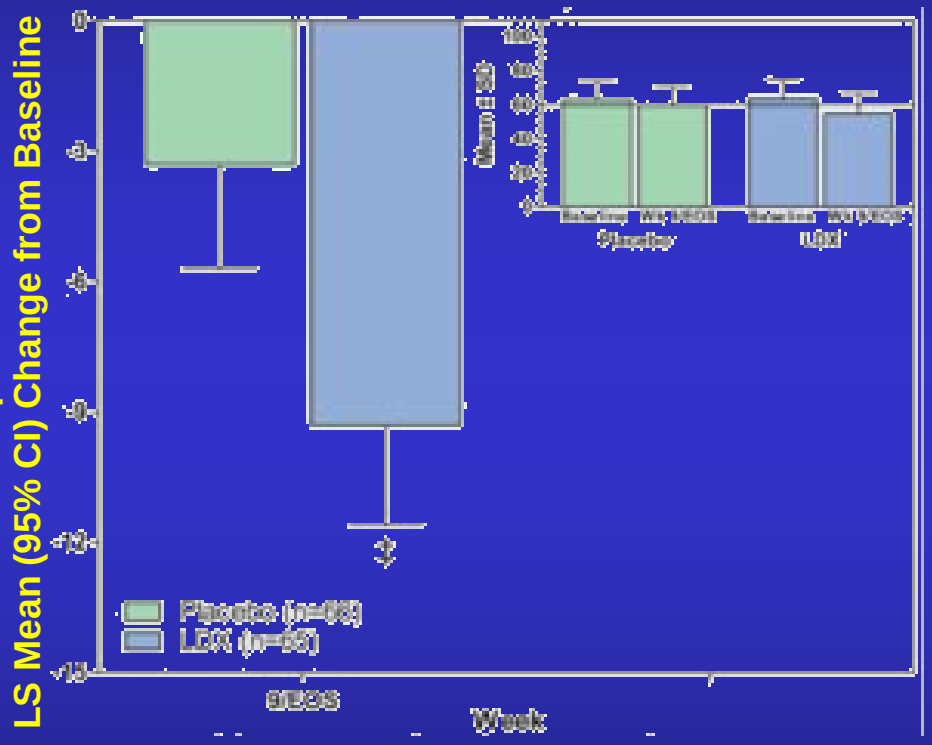
- Modafinil and armodafinil (indirectly) dopaminergic agonists with limited abuse potential
- Though proven to relieve sleepiness and fatigue, effects on other depressive symptoms less certain in MDD
- Inconsistent evidence in RCTs of TRD and bipolar depression

Effect of Adjunctive Lisdexamphetamine on Executive Function in MDD

Self-Report



Informant Report



LDX augmentation is not FDA approved for MDD.
*P <.05. †P < .01. ‡P < .001
BRIEF-A = Behavior Rating Inventory of Executive Function-Adult Version;
GEC = Global Executive Composite; LS = least square; EOS = end of study; LDX = lisdexamfetamine.

Madhoo M, et al. *Neuropsychopharmacology*. 2013

Other Dopaminergic Options

- Pramipexole
  - dopamine agonist approved for PD
  - some evidence of efficacy in small studies
- Classic psychostimulants
  - subjective benefits for drive, energy, and concentration
  - four contemporary placebo-controlled trials with SSRI nonresponders have yielded mixed results

Buspirone Augmentation

- Popularity has waned despite good overall showing in STAR*D
- Reasonably safe (10 mg - 40 mg/day), but unproven efficacy
- Secondary effects
  - anxiety relief? (failed in STAR*D)
  - reversal of sexual side effects

Other Reasonable Options for Anxious Depression?

- Adjunctive benzodiazepines – effective but concerns about dependence and tolerance
- Adjunctive second generation antipsychotics – effective, but concerns about longer term safety
- MAOIs?

Rationale for Adjunctive L-Methylfolate

- L-methylfolate, not folate, is the necessary cofactor for synthesis of monoamines
- About 2/3rds of the population have a polymorphism of the C677T MTHFR gene that slows synthesis of L-methylfolate
- As a “medical food”, Deplin 15 mg/day is safe, generally well-tolerated and much less expensive than branded SGAs
- Efficacy data starting to emerge

THE AMERICAN JOURNAL OF PSYCHIATRY

From: l-Methylfolate as Adjunctive Therapy for SSRI-Resistant Major Depression: Results of Two Randomized, Double-Blind, Parallel-Sequential Trials

American Journal of Psychiatry

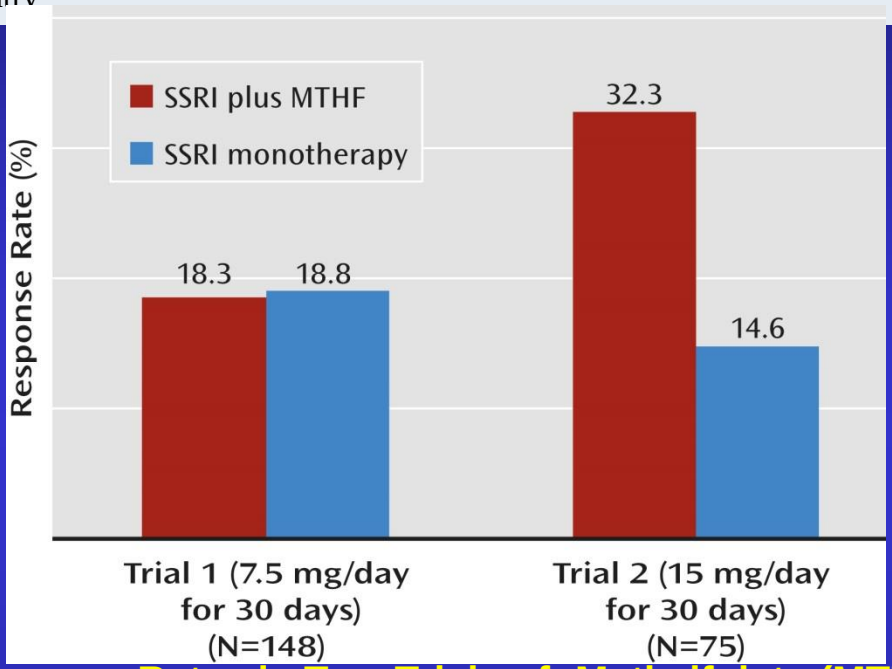


FIGURE 1. Pooled Response Rates in Two Trials of -Methylfolate (MTHF) Compared With Placebo as an Adjunct to SSRIs in Patients With SSRI-Resistant Depression[a]

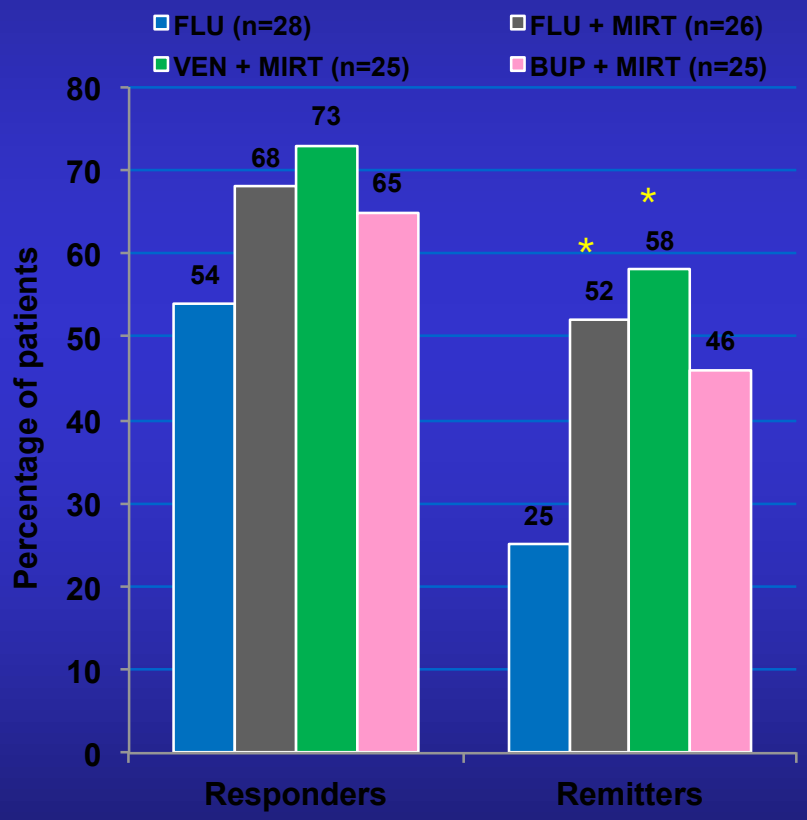
a Response was defined as a reduction of ≥50% in Hamilton Depression Rating Scale score during treatment or a final score of ≤7. Significant difference between groups in trial 2 (p=0.04). The pooled analysis was conducted as described in Fava et al..

Combining Antidepressants: Advanced Practice or Fad?

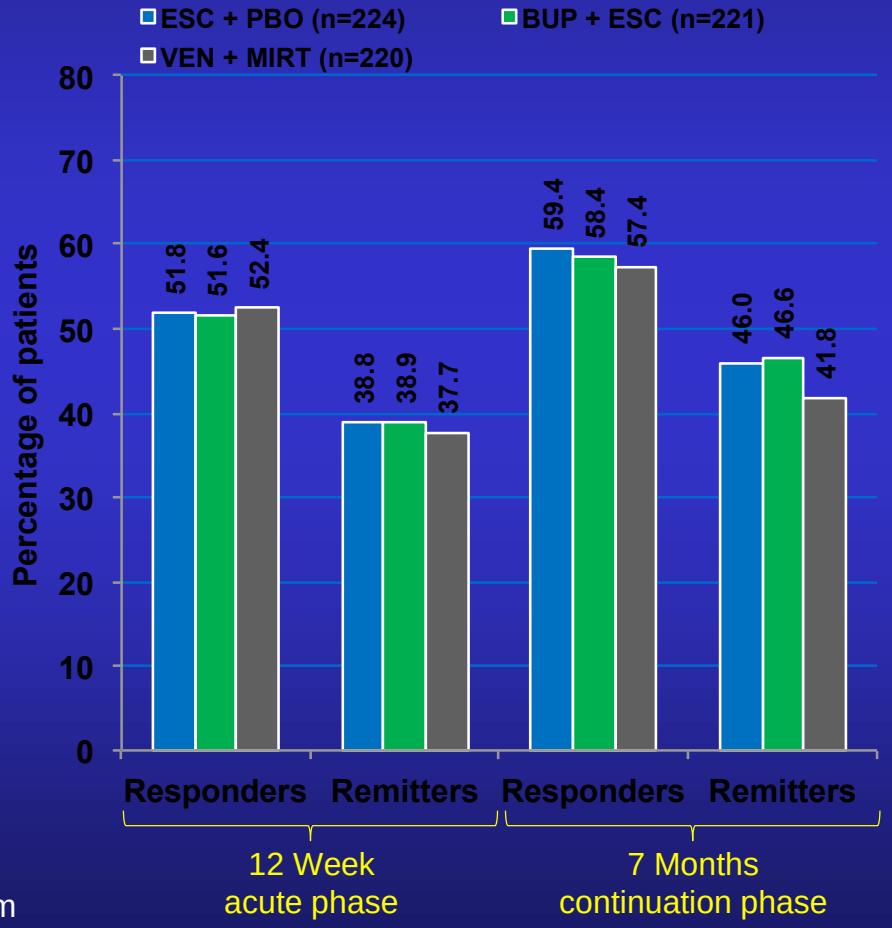
- Once considered indicative of bad practice, combining antidepressants is now commonly done for TRD
- Bupropion & mirtazapine now preferred
- No antidepressant has FDA approval for this use and only one (mirtazapine) has the support of two positive studies
- Most newer combos safe; caveats

Concurrent Combined Antidepressants: Contrasting Results of Two RCTs

Blier et al. 2010[1]



Rush et al. 2011[2]



*p<0.05; FLU=fluoxetine; MIRT=mirtazapine; VEN=venlafaxine; BUP=bupropion; ESC=escitalopram

1. Blier, et al. *Am J Psychiatry.* 2010;167(3):281–288;
2. Rush, et al. *Am J Psychiatry*. 2011;168(7):689–701

Antipsychotic Augmentation

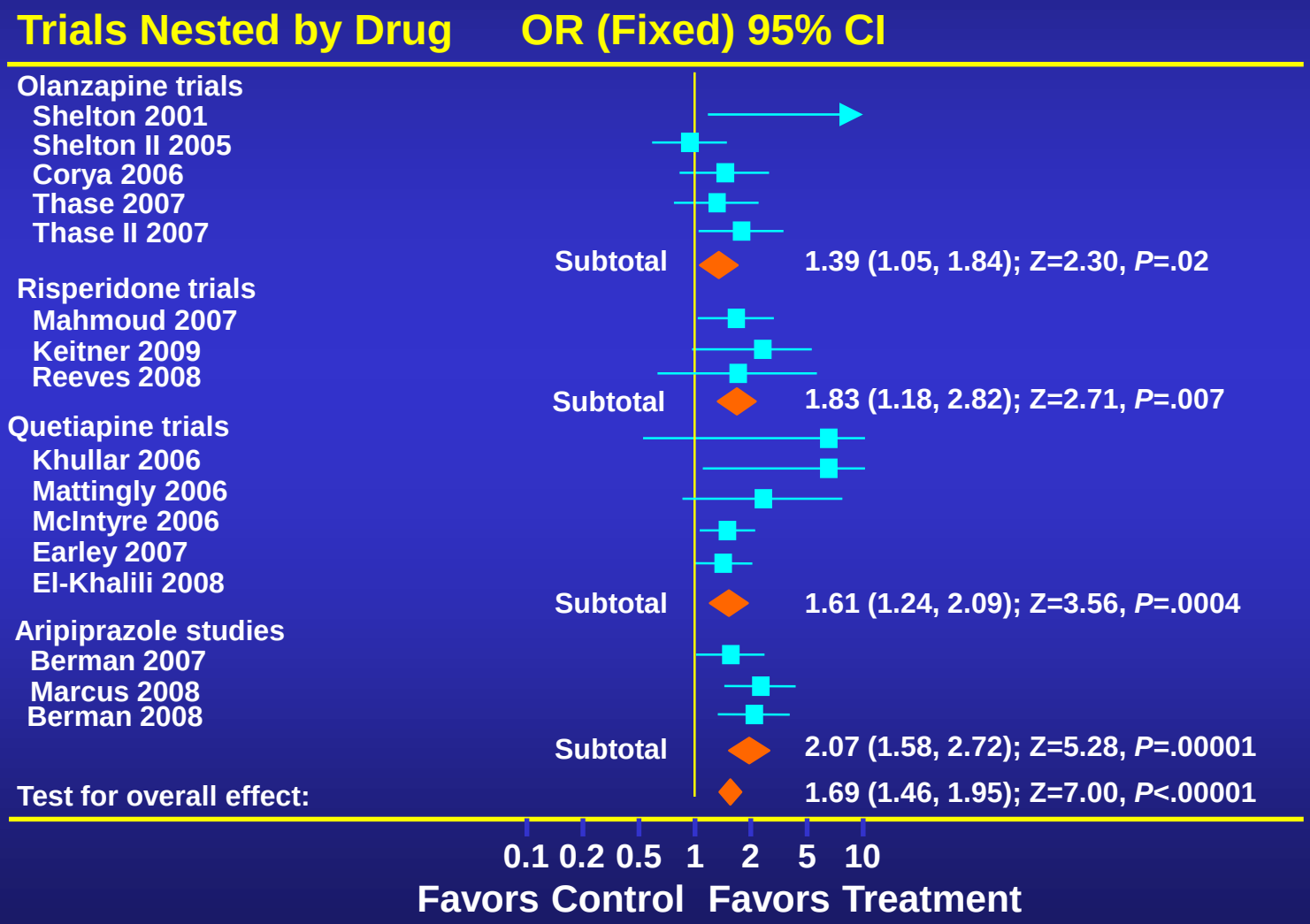
- SGAs now widely used
- Efficacy likely across the class
- Not delimited to psychotic depression or bipolar depression
- Important differences in side effects among drugs

Atypical antipsychotics as adjunctive therapy for MDD

- Adjunctive efficacy has been demonstrated for four SGAs:
  - risperidone (not FDA approved)
  - olanzapine (in combination with fluoxetine)
  - aripiprazole
  - quetiapine XR
  - brexpiprazole

Meta-Analysis of Response Rates in Double-Blind, Placebo-Controlled, Atypical Augmentation Trials

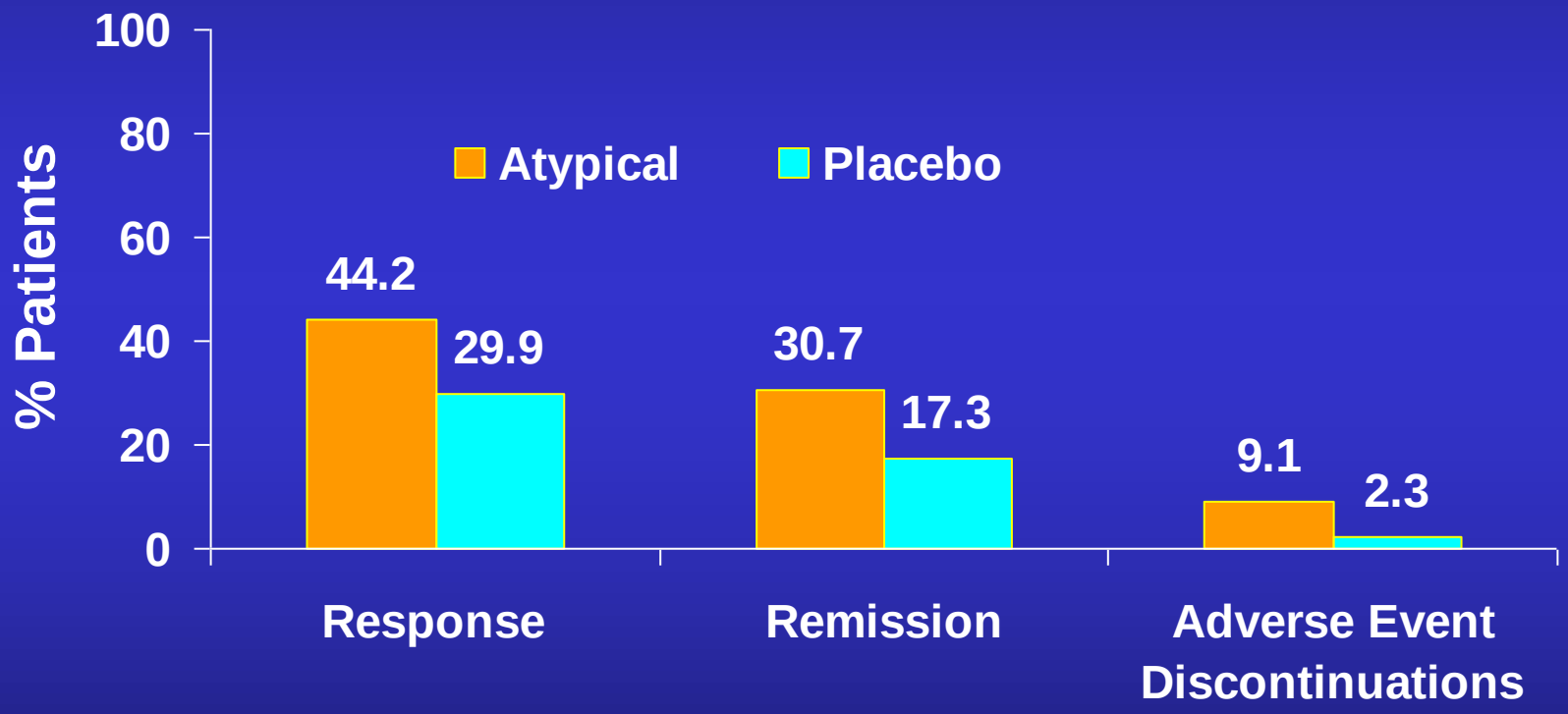
Odds Ratios of Response Rates With Atypicals and Placebo



Nelson JC, Papakostas GI; AJP, 2009

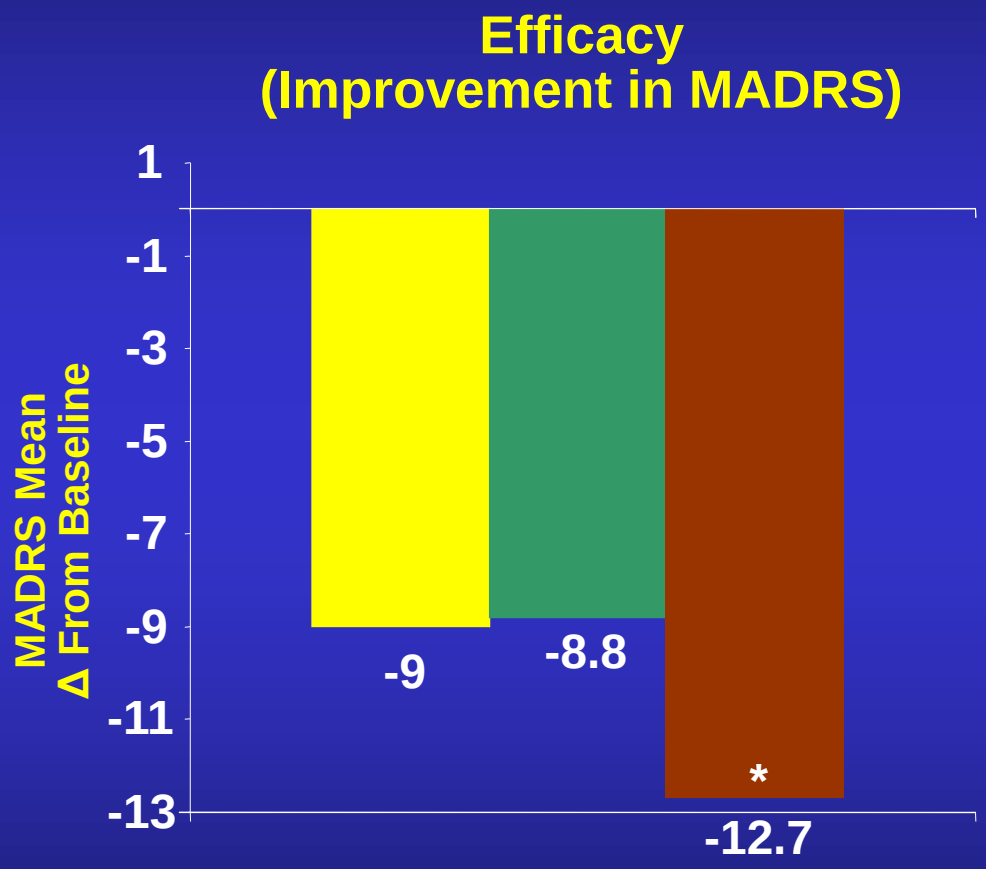
Updated Systematic Review and Meta-Analysis of Adjunctive SGAs

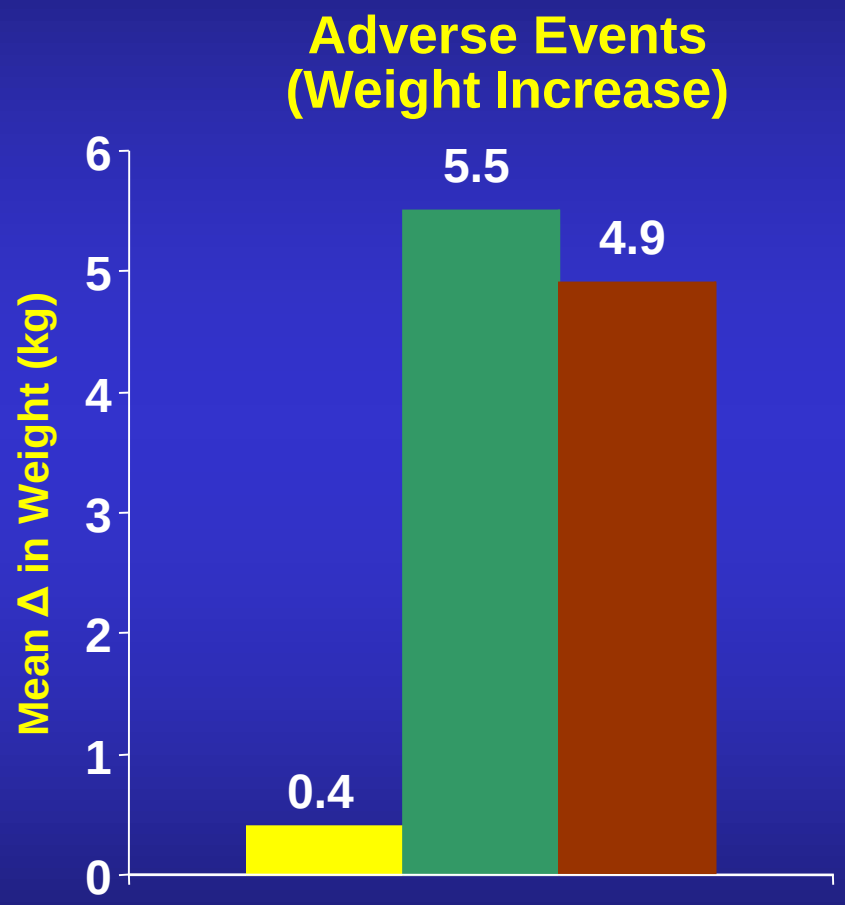
Pooled Response, Remission, and Adverse-Event Rates



Nelson JC, Papakostas GI; AJP, 2009

Olanzapine Augmentation to Fluoxetine in Treatment-Resistant Depression





FLX OLZ OFC

*P<.001 vs FLX and OLZ.

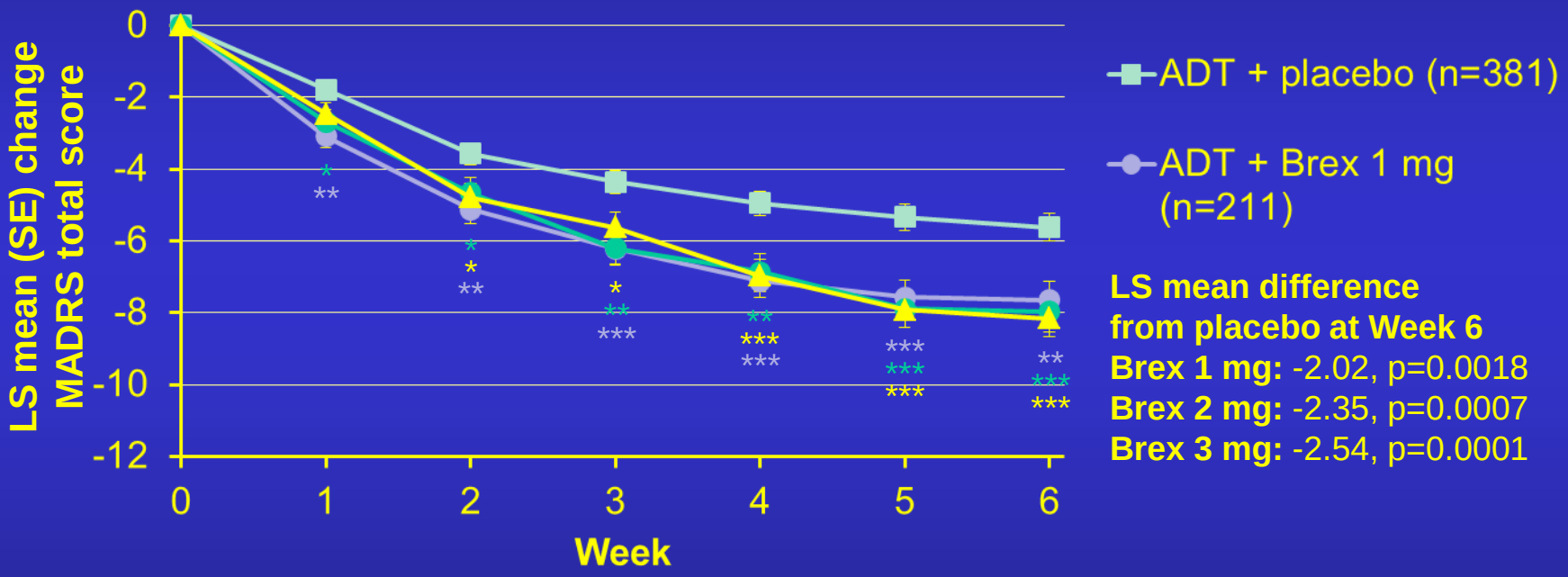
Thase ME et al. *J Clin Psychiatry*. 2007;68:224-236.

Studies of Newer SGAs

- Brexpiprazole recently approved
- Lurasidone efficacy shown in bipolar depression and MDD with mixed features
- Studies of cariprazine ongoing

Adjunctive Brexpiprazole: Efficacy on Depressive Symptoms (MADRS)

Studies 227 and 228: Primary endpoint – mean change in MADRS total score



*p<0.05, **p<0.01, ***p<0.001 versus placebo; MMRM analysis; efficacy per final protocol population; pooled placebo group

MADRS baseline: ADT + placebo 26.9, ADT + Brex 1 mg 26.9, ADT + Brex 2 mg 26.9, ADT + Brex 3 mg 26.5

Source: Thase et al. JCP 2015a&b

Adjunctive SGA Therapy: Key Issues & Questions

- Is efficacy sustained?
- Cost effectiveness vs other options?
- Ultimate risks of TD and metabolic complications
- Syndromal indications & possible differences for symptomatic efficacy and metabolic side effects

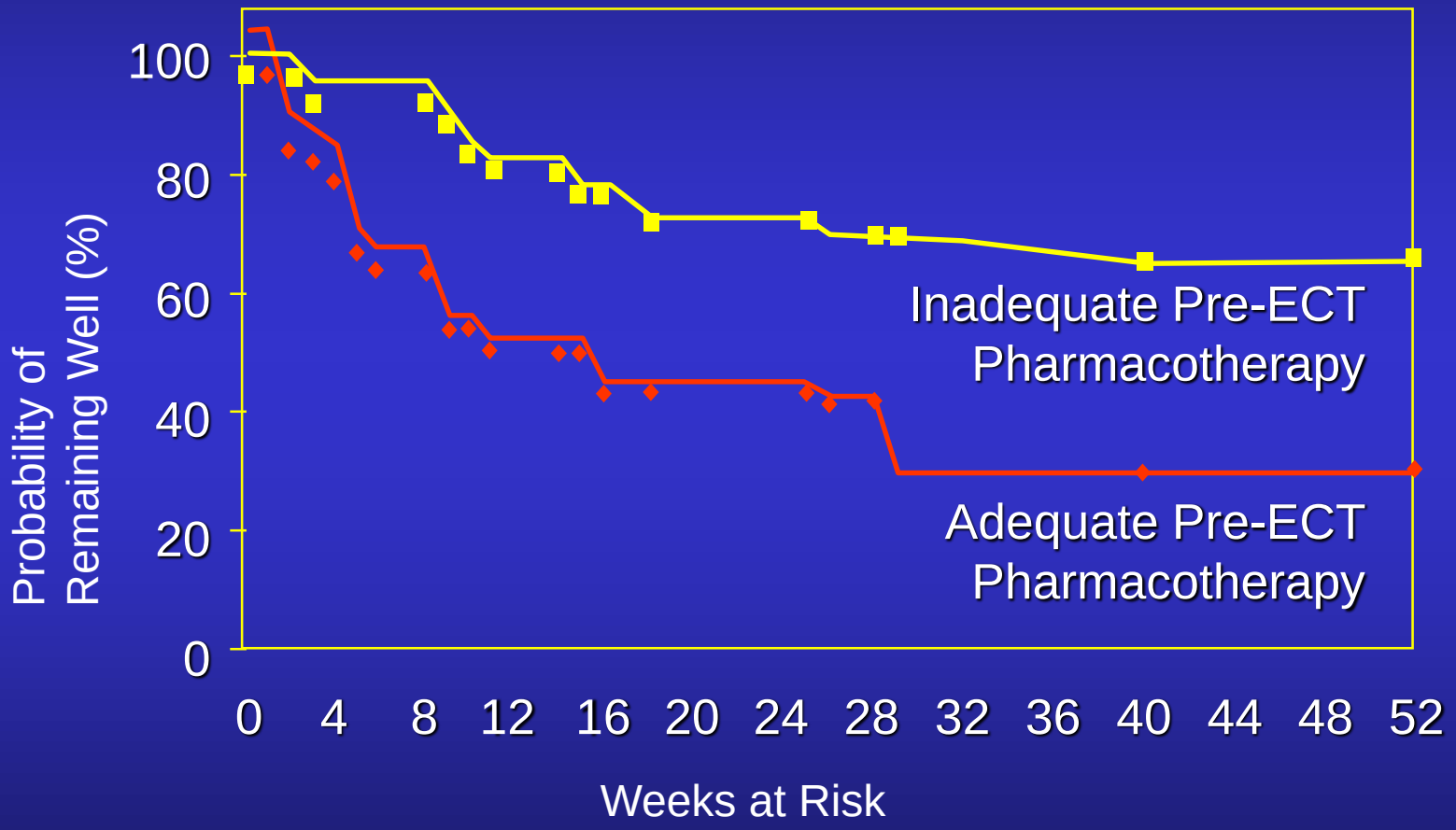
Treatment Strategy of Choice for Stage III TRD: *Monoamine Oxidase Inhibitors*

- 30%-60% response rates in TCA era
- More effective in:
  - atypical depression (Columbia)
  - anergic depression (Pittsburgh)
  - bipolar depression
- Poor showing for tranylcypromine in STAR*D
- ? role of seligiline patch

Treatment Strategy of Choice for Stage IV TRD: *Electroconvulsive Therapy*

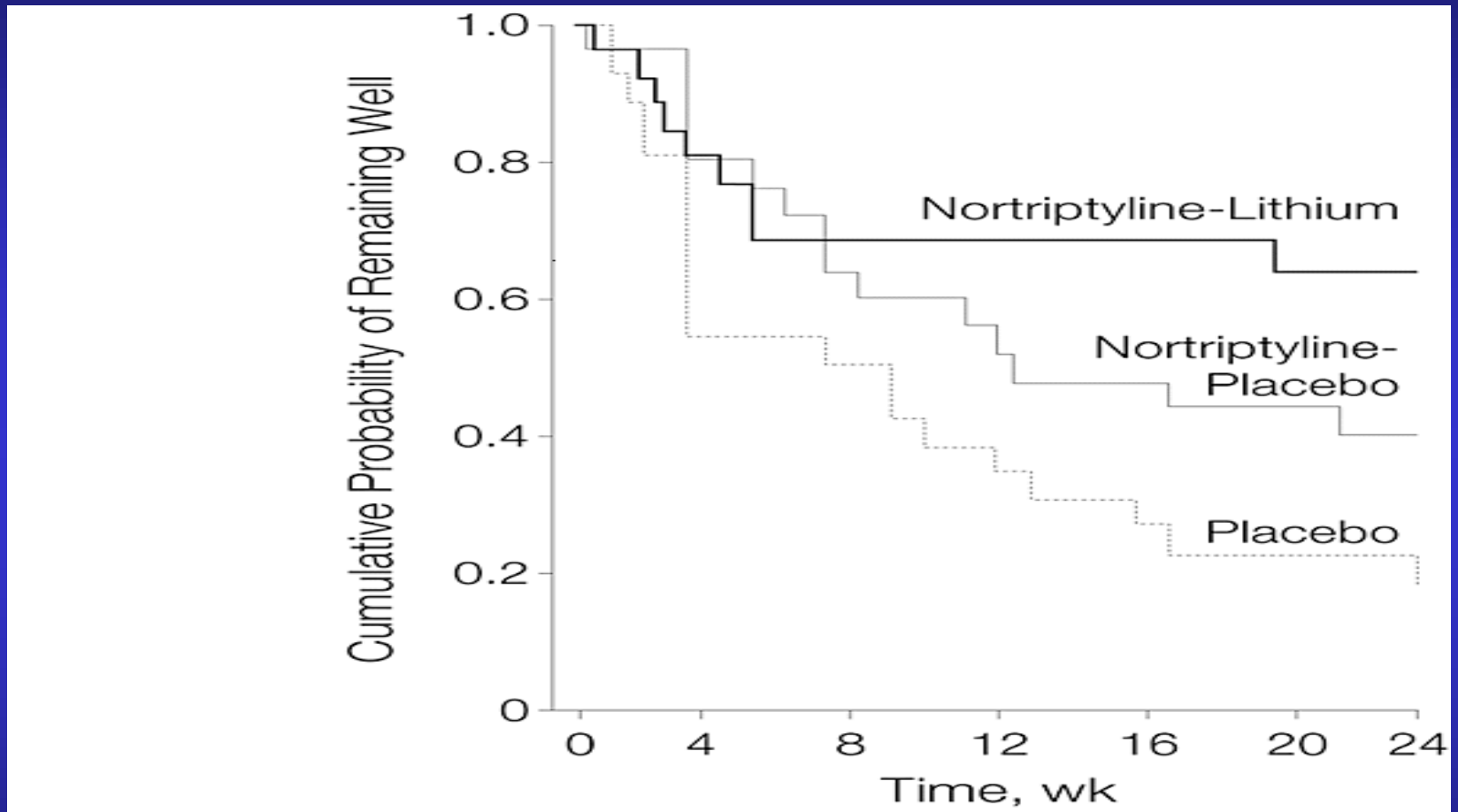
- Most effective treatment available
- Two options: bilateral or ultrahigh energy RUL
- Treatment of choice for delusional and melancholic cases of TRD
- Less effective in TRD than in uncomplicated depression (i.e., 50%-60% vs 90%)
- Majority of TRD cases will relapse within 1 year of successful ECT

High Risk of Relapse Following Successful ECT of TRD



Sackeim HA, et al. *J Clin Psychopharmacol.* 1990;10:96-104.

Prevention of Relapse Following ECT: Efficacy of Lithium + Nortriptyline



No. at Risk

Placebo	29	14	13	9	6	5	4
Nortriptyline-Placebo	27	20	15	13	12	11	10
Nortriptyline-Lithium	28	18	15	15	15	14	14

Sackeim HA, et al. *JAMA.* 2001;285(10):1299-1307.

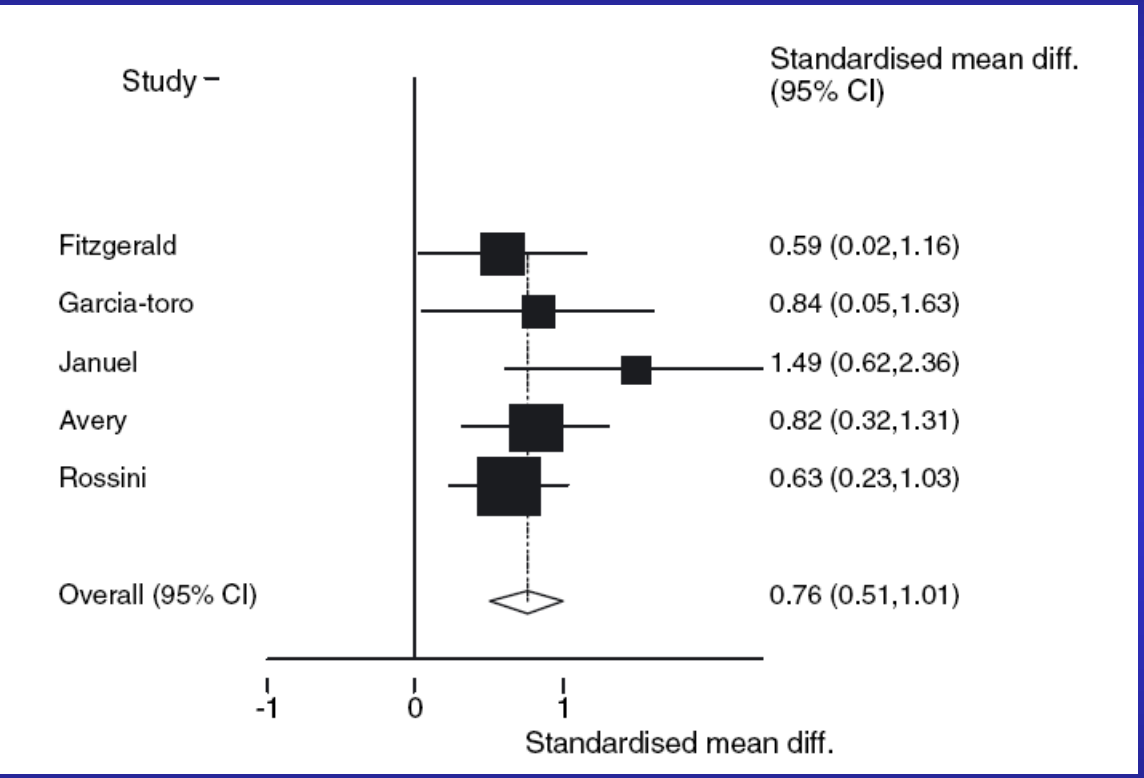
Other Neuromodulation Strategies

- Transcranial Magnetic Stimulation (rTMS)
- Vagus Nerve Stimulation
- Deep Brain Stimulation

Repetitive Transcranial Magnetic Stimulation (rTMS): Summary

- Better tolerated and safer than ECT
- Definite therapeutic effects (nonpsychotic MDD and less advanced cases of TRD); efficacy confirmed by recent NIMH-funded multi-center trial
- Dose/response/duration characteristics still not well developed
- Labor-intensive and – until coverage issues addressed - expensive
- Perhaps delimited to patients who are too mild for or who refuse or can't tolerate ECT

Recent Clinical Studies Replicate Antidepressant Effects of TMS



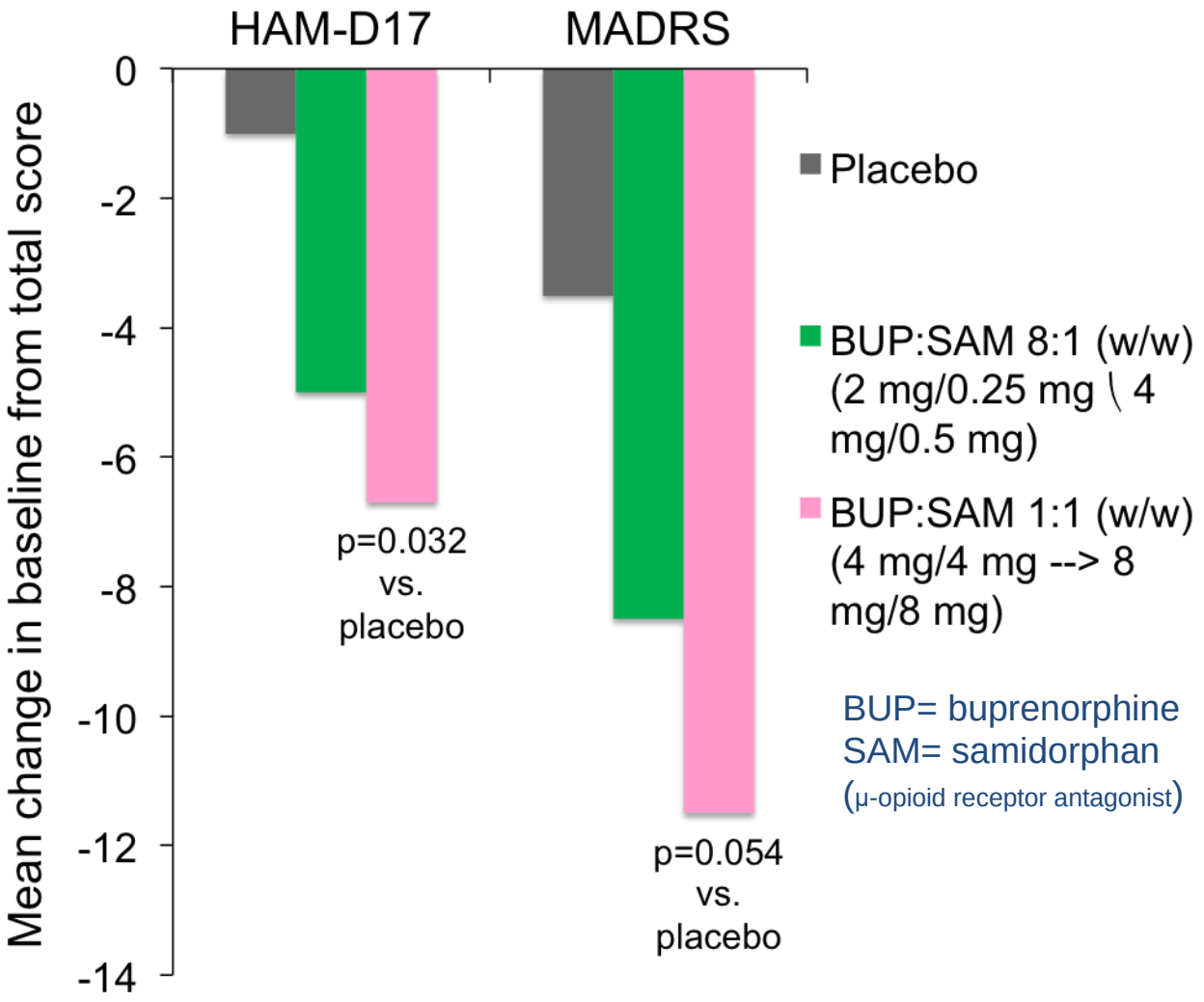
- Improved study designs
  - Larger samples
  - More treatment sessions
  - Optimized stimulation parameters
- Recent meta-analysis from 2006-7
  - Five sham-controlled studies
  - N=274 patients
  - Effect size = 0.76
- Pivotal trial effect size = 0.83 for ATHF 1 group

Gross et al (Acta Psych Scand, 2007)

Uncommon Treatment Strategies

- Chronotherapies (sleep deprivation, phototherapy)
- Other nutriceuticals (e.g., SAM-e)
- Opiates
- Experimental pharmacotherapies (e.g., ketamine infusion)

Efficacy of a Combination Opiate Medication (ALKS 5461) in Major Depressive Disorder



Ehrich, et al. *Neuropsychopharmacology*. AOP 14 January 2015.
Efficacy of BUP/SAM therapy in MDD. Displayed are mean decreases from baselne in HAM-D17 (left) and MADRS (right) total scores after 7 days of therapy. P-values are from Exact Wilcoxon tests and are based on observed data.

Psychotherapeutic Issues in Refractory Depression

- Reestablishing morale
- Increased activity
- Coping behaviors
- Noncompliance
- Focused, specific goals
- Mobilization of resources
- Rehabilitation issues

- Avoid “blaming the victim”

Conclusions

- Focus first on assessment and staging
- Logical choices are available for careful, sequential trials
- When in doubt, try again
- New developments every year
- Ample room for improvement
- Requires an ongoing systematic nationwide approach