

Treatment-Resistant Major Depressive Disorder: Tailoring Strategies for Enhanced Outcomes

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Dr. Spector has served on speakers bureaus for Forest Pharmaceuticals, King Pharmaceuticals, and Jazz Pharmaceuticals.



Learning Objectives

- Describe the factors underlying inadequate response to first-line treatment of major depressive disorder (MDD) and how this can affect management strategies
- Discuss evidence-based approaches for treatment-resistant MDD, including the role of atypical antipsychotics and how to integrate these approaches into your management decisions
- Utilize strategies to enhance patient understanding of therapeutic decisions and the importance of treatment adherence for MDD



Depression – Global Burden of Disease

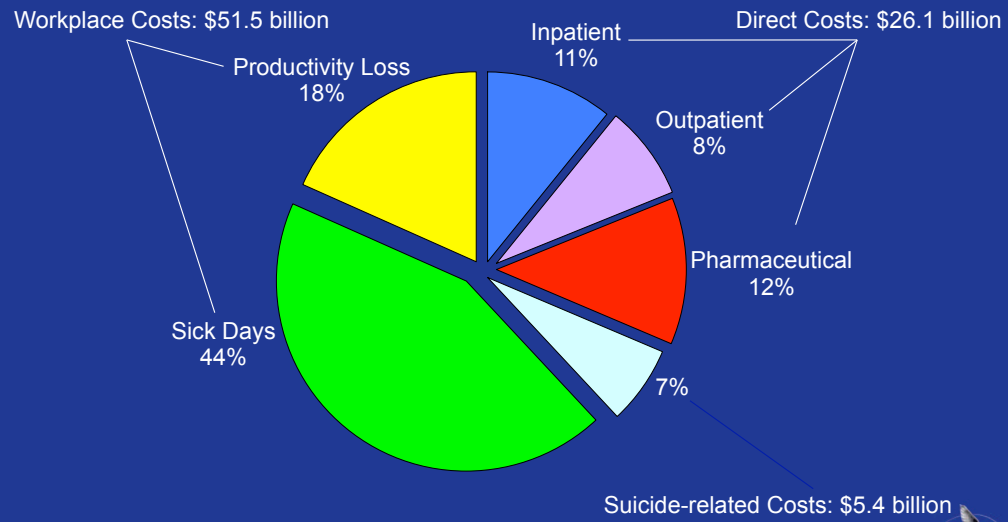
- Depression affects around 120 million people worldwide
- Less than 25% of those affected have access to adequate treatment
- Depression is the 3rd leading cause of burden of disease worldwide (DALYs)

DALY: disability-adjusted life years



Economic Impact of Depression in the US

Total Cost in US Dollars for the Year 2000 = \$83.1 billion



Greenberg P, et al. *J Clin Psychiatry*. 2003;64:1465-1475.



'Signs' of Depression

- S—Suicidal preoccupation
- **I—Interest/pleasure (↓)**
- G—Gain/lose weight
- G—Guilty feelings
- E—Energy (↓)
- C—Concentration
- **A—Affect (↓ mood)**
- P—Psychomotor retardation
- S—Sleep disturbance

DSM-IV-TR Major depression: 5 of 9 x 2 weeks
1 of **BOLDED** must be present

DSM-IV Dysthymia: 2 of 6 x 2 years
no 2-month hiatus

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR). Washington, DC: American Psychiatric Association; 2000.



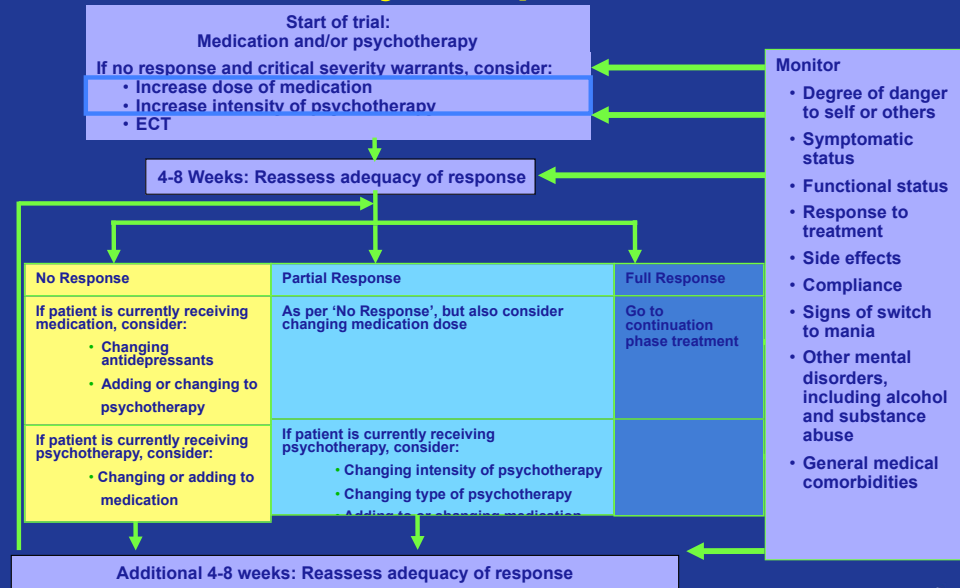
Screening and Diagnosis Measurement-Based Care

- Screening
 - Detect depression (PHQ-9, PHQ-2)
 - Rule out bipolarity (MDQ, WHO CIDI 3.0)
- Diagnosis
 - *DSM-IV* overview
 - Predictors of bipolar depression
- Suicide Assessment
- Symptom Tracking
 - HAMD-7 (physician)
 - QIDS-SR (patient)

Kroenke K, et al. *J Gen Intern Med*. 2001;16:606-613.
Kroenke K, et al. *Med Care*. 2003;41:1284-1292.
Hirschfeld R, et al. *Am J Psychiatry*. 2000;157:1873-1875.
Kessler R, et al. *J Affect Disord*. 2006;96:259-269.
McIntyre R, et al. *Can Med J*. 2005;173:1327-1334.
www.ids-qids.org



Guidelines for Treatment of Major Depression



American Psychiatric Association. *Practice Guideline for Treatment of Patients With Major Depressive Disorder*. 2nd ed. Arlington, VA: American Psychiatric Publishing, Inc; 2000.



MDD Treatment Options

- Antidepressant Medications
 - Selective Serotonin Reuptake Inhibitors (SSRI)
 - Serotonin and Norepinephrine Reuptake Inhibitors (SNRI)
 - Norepinephrine-dopamine Reuptake Inhibitors
 - Mixed Selective Serotonin Reuptake Inhibitors and Receptor Blockers
 - Tricyclic Antidepressants (TCA)
 - Monoamine Oxidase Inhibitors (MAOI)
- Nonpharmacological Therapy
 - Devices
 - Vagal Nerve Stimulation (VNS)
 - Transcranial Magnetic Stimulation (TMS)
 - Electroconvulsive Therapy (ECT)
 - Psychotherapy
 - Cognitive Behavioral Therapy (CBT)
 - Interpersonal Therapy (IPT)



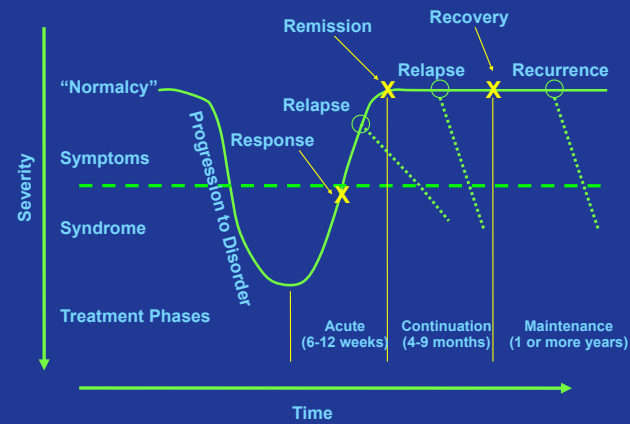
Treating Depression in the 'Real World'

- Remission, not response, is the goal
- Should first treatment fail, either switching or augmenting is reasonable
- For most patients, remission requires repeated trials of **"sustained, vigorously-dosed"** antidepressant medication
- Likelihood of remission substantially decreases after two adequate treatment trials, suggesting need for more complicated regimens and psychiatric consultation



Mission: Remission

- Response
 - $\geq 50\%$ reduction in symptom scores
- Remission
 - Function restored
 - Minimal to no residual symptoms
 - 17-item HAMD ≤ 7
 - MADRS ≤ 10
- Recovery
 - Remission ≥ 6 months



Keller MB. *JAMA*. 2003;289:3152-3160.
Qaseem A, et al. *Ann Intern Med*. 2008;149:725-733.

Why Target Remission?

- Compared with patients who achieve full remission, those with **residual symptoms** have:
 - Greater risk of relapse and recurrence
 - More chronic depressive episodes
 - Shorter duration between episodes
 - Continued professional and social impairment
 - Increased overall mortality
 - Increased morbidity and mortality from comorbid medical disorders, including
 - Stroke, diabetes, myocardial infarction, cardiovascular disease, congestive heart failure, HIV
 - Ongoing increased risk of suicide



What Is Treatment-Resistant Depression?

- Failure of a patient to respond to at least 2 antidepressant trials of adequate dose, duration, and treatment adherence



Factors Associated with Treatment Resistance

- Misdiagnosis
- Specific depressive subtypes
 - Psychotic depression, atypical depression, melancholic features
- Psychiatric comorbidities
 - Anxiety disorders, panic disorder, personality disorder
- Age at onset before 18 years
- Substance abuse
- Depression severity
- Chronicity
- Medical comorbidities
- Patient noncompliance with treatment
- Pharmacokinetics, pharmacogenetics

Gaynes B. *J Clin Psychiatry*. 2009;70(S6):10-15.



Strategies for Refractory Depression

- Switch to a different antidepressant (within class or across class)
- Augment the treatment regimen with a non-antidepressant agent
- Combine the initial antidepressant with a second antidepressant



Switching

- Different mechanism of action
 - Such as from an SSRI to a dual mechanism agent or to a predominantly noradrenergic/dopaminergic agent
- Reduce side effects
- Reduced risk of drug interactions
- Possibly cheaper
- Switch within class or across classes?



Combination

- Maximize benefit by affecting multiple neurotransmitters
- Could increase adherence and lower drop-out rates
- Could target side effects of first agent (eg, insomnia, fatigue, sexual dysfunction)



Augmentation

- Broadens the neurochemical targets
- Maximize therapeutic benefit associated with the first-line agent
- Allows more time for the current agent
- Avoid potential withdrawal symptoms

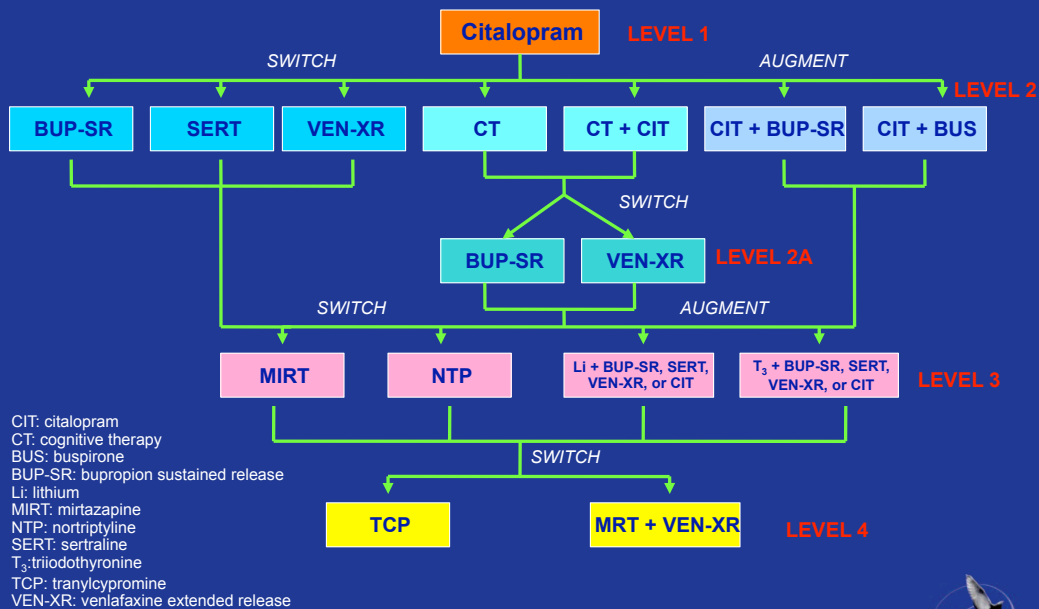


The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Trial (www.star-d.org)

- Primary outcome measured: **Remission**
- Largest clinical trial of depression to date
 - 7 years (1999–2006)
 - Enrolled 4,041 adult subjects
- Conducted in primary care as well as psychiatric settings (18 vs 23)
- Few exclusion criteria → “real world”



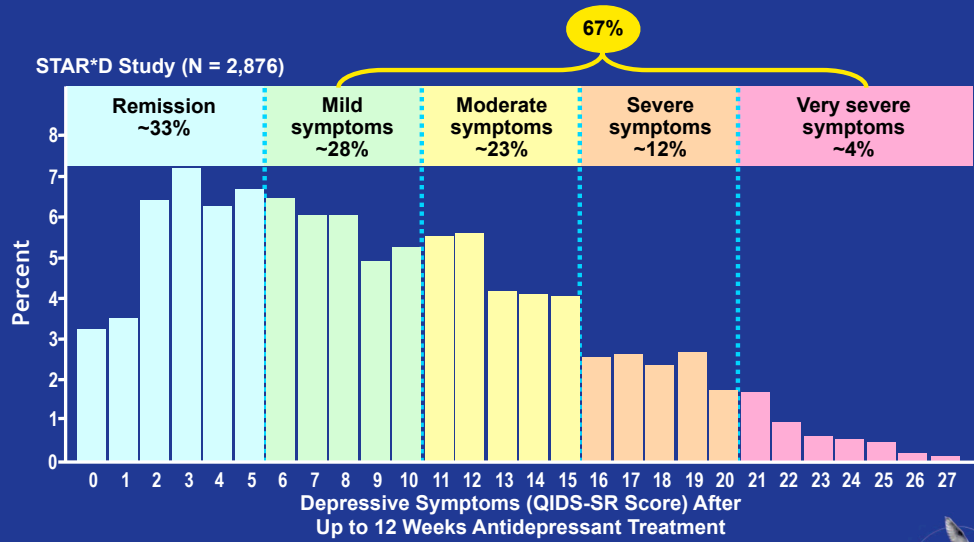
STAR*D Treatment Strategies and Options



Adapted from Warden D, et al. *Curr Psychiatry Rep.* 2007;9:449-459.



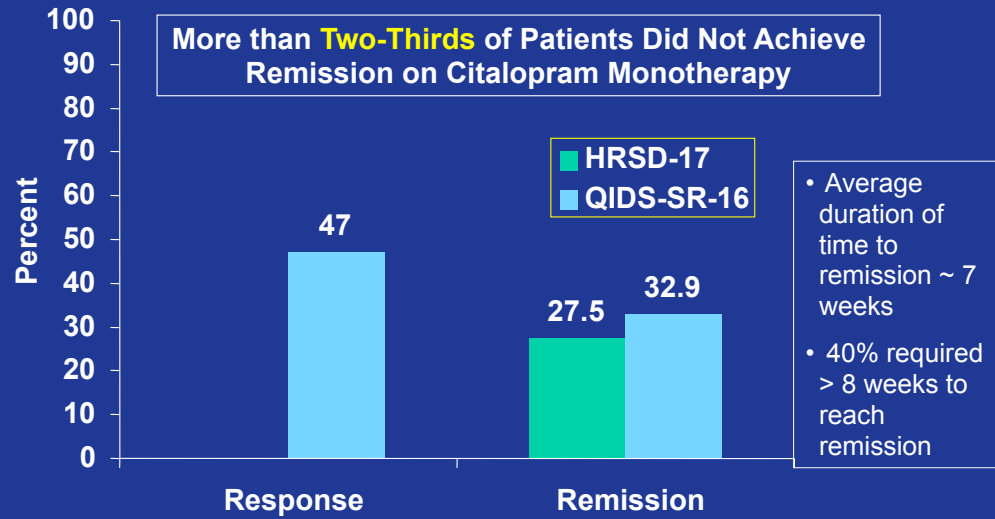
STAR*D: Unresolved Symptoms Following Antidepressant Treatment



STAR*D = Sequenced Treatment Alternatives to Relieve Depression, n = 2,876
 Trivedi MH, et al. *Am J Psychiatry*. 2006;163:28-40.



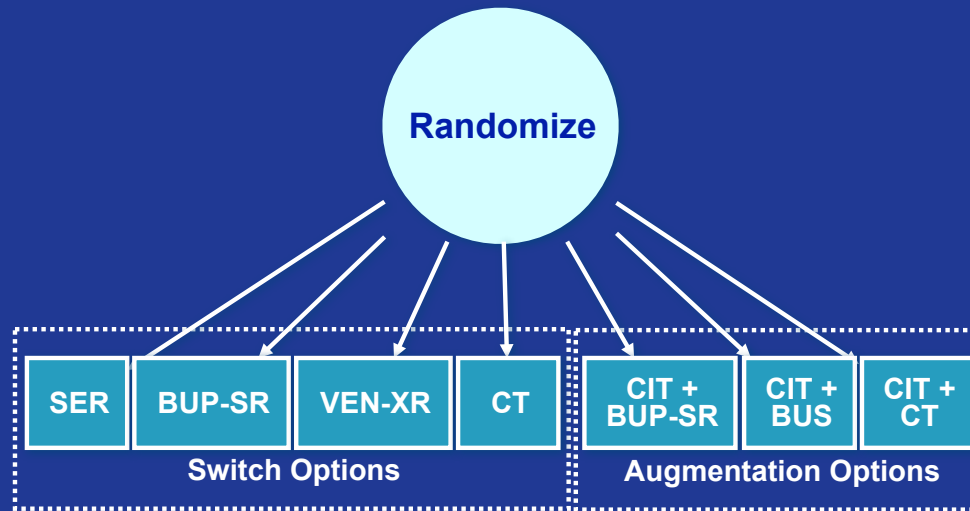
Treatment Outcome: Level 1



HAMD-17 = 17-item Hamilton Rating Scale for Depression
QIDS-SR-16 = 16-item Quick Inventory of Depressive Symptomatology – Self-Report
Trivedi M, et al. *Am J Psychiatry*. 2006;163:28-40.



STAR*D Level 2 Switch or Augment

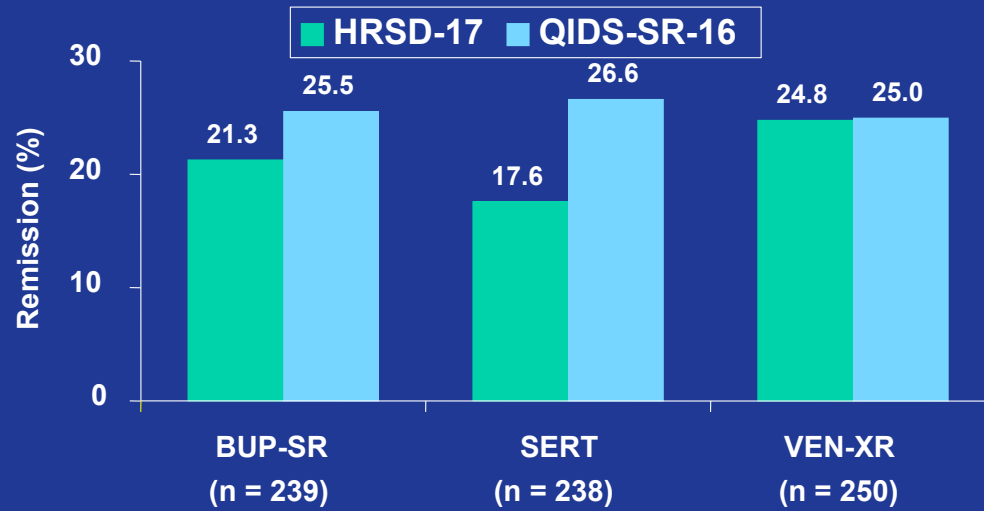


SER: sertraline; BUP-SR: bupropion sustained release; VEN-XR: venlafaxine extended release;
CT: cognitive therapy; CIT: citalopram

Rush AJ, et al. *Am J Psychiatry*. 2006;163:1905-1917.



STAR*D Level 2 Medication Switch

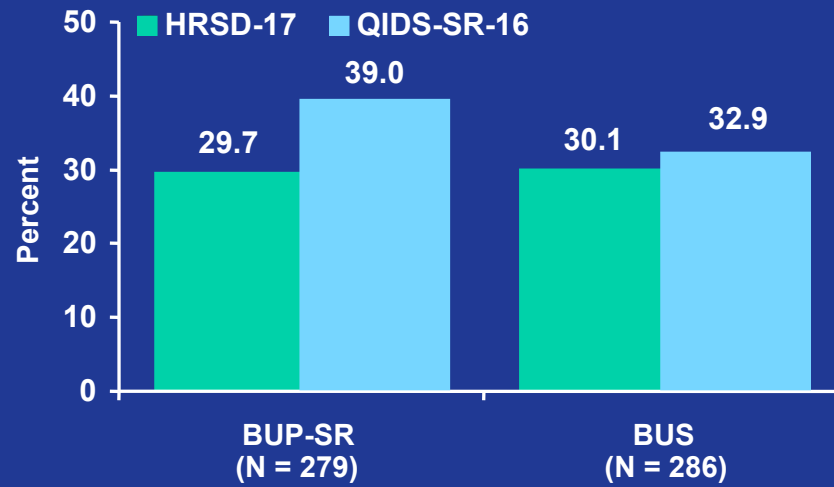


Rush A, et al. *N Engl J Med* 2006;354(12):1231-1242.

BUP-SR: bupropion sustained release
SERT: sertraline
VEN-XR: venlafaxine extended release



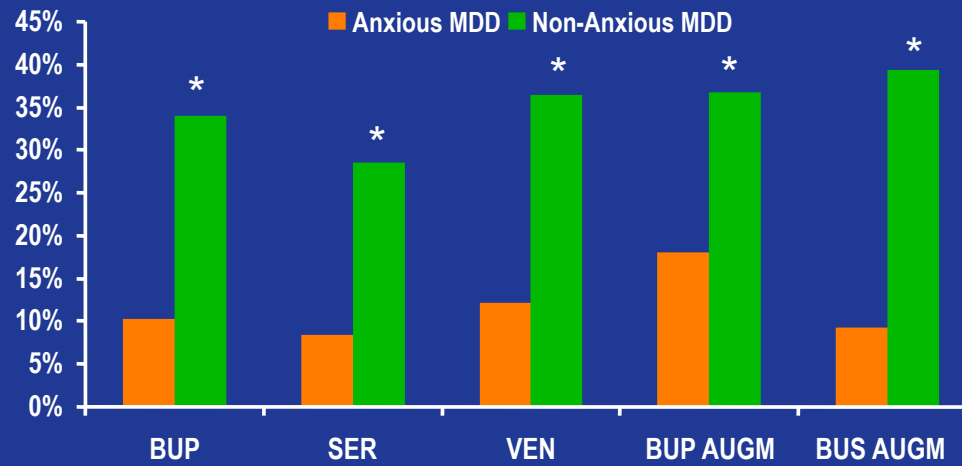
Level 2 Augmentation Outcomes: Remission Rates



BUP-SR: bupropion sustained release; BUS: buspirone
Trivedi MH, et al. *N Engl J Med.* 2006;354:1243-1252.



Remission Rates in Level 2 of STAR*D: Anxious vs Non-Anxious MDD



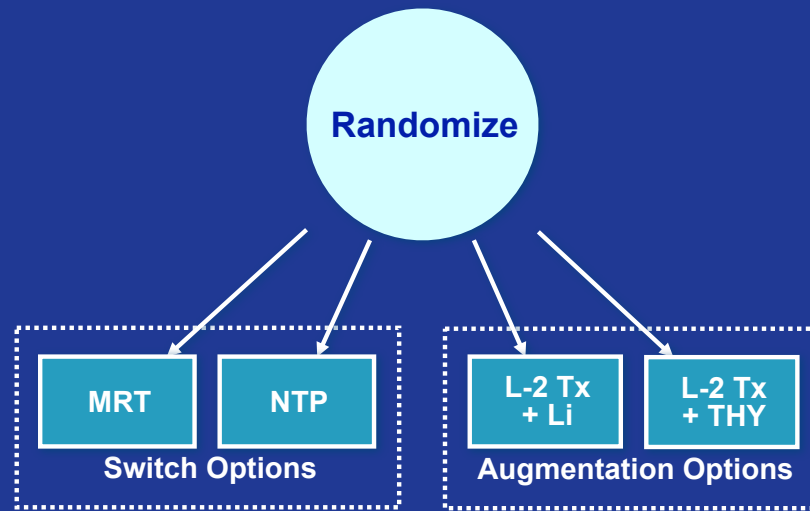
* $P < 0.05$

Fava M, et al. *Am J Psychiatry*. 2008;165:342-351.

BUP: bupropion; SER: sertraline; VEN: venlafaxine;
BUS: buspirone



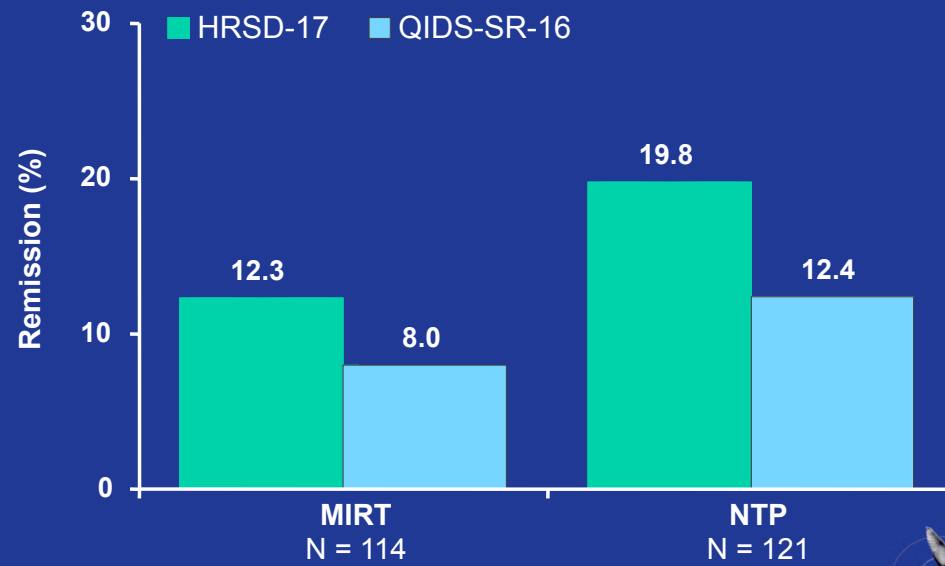
STAR*D Level 3 Switch or Augment



MRT: mirtazapine; NTP: nortriptyline;
Li: lithium; THY: triiodothyronine (T₃)



Treatment Outcomes: Level 3 Switch

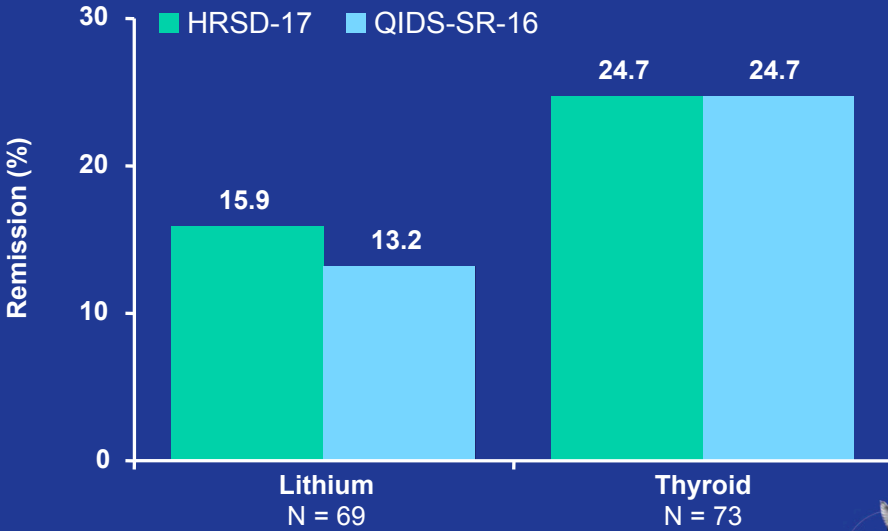


Fava M, et al. *Am J Psychiatry*. 2006;163(7):1161-1172.

MIRT: mirtazapine; NTP: nortriptyline



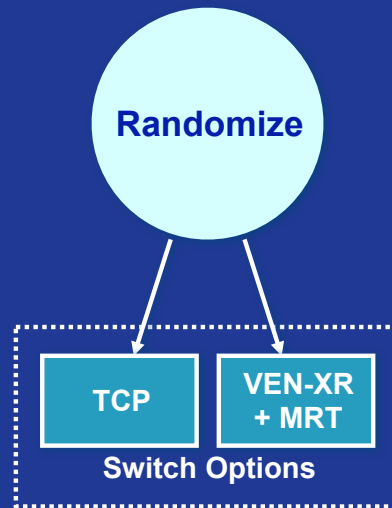
Treatment Outcomes: Level 3 Augmentation



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



STAR*D Level 4

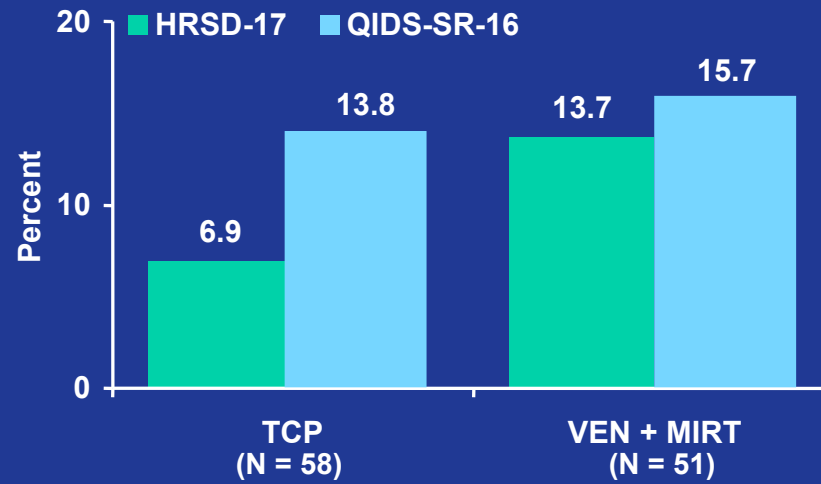


Rush AJ, et al. *Am J Psychiatry*. 2006;163:1905-1917.

TCP: tranylcypromine; MRT: mirtazapine;
VEN-XR: venlafaxine extended release



Level 4 Treatment Outcomes: Remission Rates

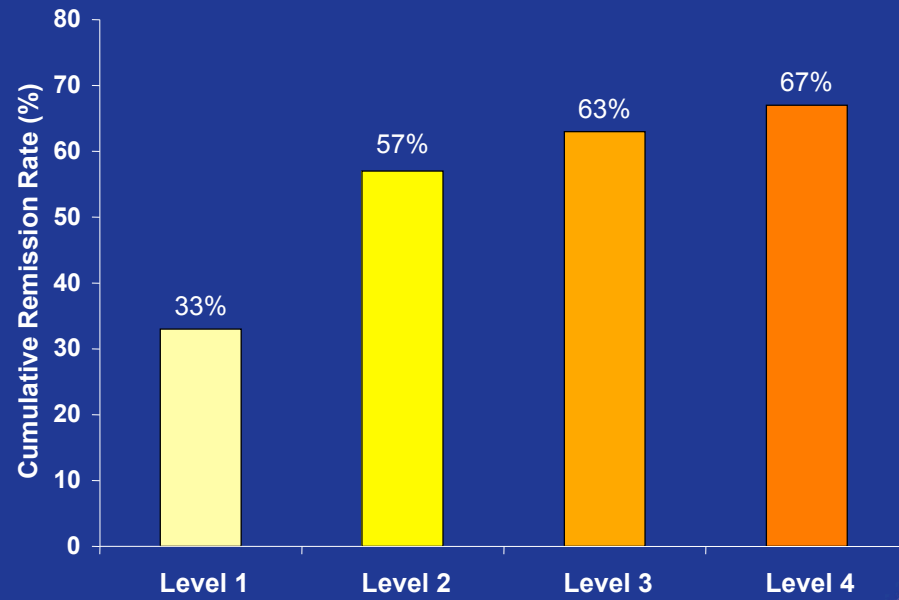


McGrath PJ, et al. *Am J Psychiatry*. 2006;163:1531-1541.

TCP: tranylcypromine; MRT: mirtazapine;
VEN: venlafaxine extended release



STAR*D Cumulative Remission Rates

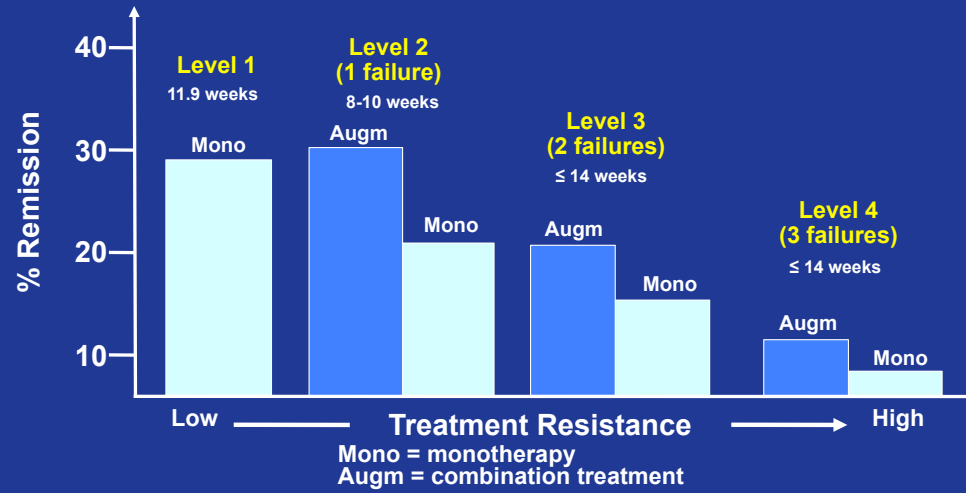


Gaynes B, et al. *Clev Clin J Med*. 2008;75(1):57-65.



STAR*D Clinical Study Results

Remission Rates (HAM-D-17 < 8)



McGrath PJ, et al. *Am J Psych*. 2006;163:1531-1541.

Rush AJ, et al. *Am J Psych*. 2006;163:1905-1917.

Nierenberg AA, et al. *Am J Psych*. 2006;163:1519-1530.

Trivedi MH, et al. *J Clin Psychiatry*. 2006;67:1458-1465.

Trivedi MH, et al. *N Engl J Med*. 2006;354:1243-1252.



Patient Interview



Rhonda – Present Illness

- Concern regarding depression
 - Loss of motivation
 - No interest in family or activities
 - Interfering with job productivity
 - Medication not helping much
 - Counseling not as affective as in previous episode



History

- Social history
 - MBA, RN, BS in Health Education
 - Married 8 years
 - Two children ages 2 and 4, husband stays at home
 - Active in church and community



History (cont)

- Medical history
 - G₂P₂A₀
 - Non-toxic goiter on thyroid suppression
 - Tubal ligation after second birth, birth control pills prior
 - No hospitalization other than childbirth



History (cont)

- Psychiatric history
 - Previous episode of depression 5 years ago
 - Prior treatment with citalopram which was stopped prior to first pregnancy
 - Prior treatment included psychotherapy, which was beneficial and continued with less frequent visits
 - Denies history of suicidality



History (cont)

- Family history
 - Father is smoker, has emphysema and coronary artery disease
 - Mother on antidepressant, thyroidectomy on replacement, non-insulin dependent diabetes mellitus
 - Younger brother killed in Iraq 8 years ago
 - Negative for suicide or psychiatric hospitalizations



Patient Health Questionnaire 9 (PHQ-9)

Name: Rhonda

Date: Visit 0 (OB/GYN)

Over the last 2 weeks, how often have you been bothered by any of the following problems?
(use "✓" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself in some way	0	1	2	3
Total	19			
10. If you checked off any problems, how <i>difficult</i> have these problems made it for you to do your work, take care of things at home or get along with other people	Not difficult at all _____ Somewhat difficult _____ Very difficult _____ Extremely difficult _____			



Patient Health Questionnaire 9 (PHQ-9)

Name: Rhonda

Date: Visit 1

Over the last 2 weeks, how often have you been bothered by any of the following problems?
(use "✓" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself in some way	0	1	2	3
Total	15			
10. If you checked off any problems, how <i>difficult</i> have these problems made it for you to do your work, take care of things at home or get along with other people	Not difficult at all _____ Somewhat difficult _____ Very difficult _____ Extremely difficult _____			



Generalized Anxiety Disorder 7 (GAD-7)

Name: Rhonda

Date: Visit

1

Over the last 2 weeks, how often have you been bothered by any of the following problems?
(use "✓" to indicate your answer)

	Not at all 0	Several days 1	More than half the days 2	Nearly every day 3
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3
Total	4			



Mood Disorder Questionnaire - Rhonda

INSTRUCTIONS: Please answer each question as best you can.

YES NO

1. Has there ever been a period of time when you were not your usual self and...

- | | | |
|--|----------------------------------|----------------------------------|
| ... you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble? | <input type="radio"/> | <input checked="" type="radio"/> |
| ... you were so irritable that you shouted at people or started fights or arguments? | <input type="radio"/> | <input checked="" type="radio"/> |
| ... you felt much more self-confident than usual? | <input type="radio"/> | <input checked="" type="radio"/> |
| ... you got much less sleep than usual and found that you didn't really miss it? | <input checked="" type="radio"/> | <input type="radio"/> |
| ... you were more talkative or spoke much faster than usual? | <input type="radio"/> | <input checked="" type="radio"/> |
| ... thoughts raced through your head or you couldn't slow your mind down? | <input type="radio"/> | <input checked="" type="radio"/> |
| ... you were so easily distracted by things around you that you had trouble concentrating or staying on track? | <input checked="" type="radio"/> | <input type="radio"/> |
| ... you had much more energy than usual? | <input type="radio"/> | <input checked="" type="radio"/> |
| ... you were much more active or did many more things than usual? | <input checked="" type="radio"/> | <input type="radio"/> |
| ... you were much more social or outgoing than usual, for example, you telephoned friends in the middle of the night? | <input type="radio"/> | <input checked="" type="radio"/> |
| ... you were much more interested in sex than usual? | <input type="radio"/> | <input checked="" type="radio"/> |
| ... you did things that were unusual for you or that other people might have thought were excessive, foolish or risky? | <input type="radio"/> | <input checked="" type="radio"/> |
| ... spending money got you or your family in trouble? | <input type="radio"/> | <input checked="" type="radio"/> |

2. If you checked YES to more than one of the above, have several of these ever happened during the same period of time?

3. How much of a problem did any of these cause you - like being able to work; having family, money or legal troubles; getting into arguments or fights?

- No problem
 Minor problem
 Moderate problem
 Serious problem

Handout Information

Depression and Bipolar Support Alliance: www.dbsalliance.org

National Alliance on Mental Illness: www.nami.org

Mental Health America: www.nmha.org

MedlinePlus: Drugs, Supplements and Herbal Information: [http://
www.nlm.nih.gov/medlineplus/druginformation.html](http://www.nlm.nih.gov/medlineplus/druginformation.html)



Patient Health Questionnaire 9 (PHQ-9)

Name: Rhonda

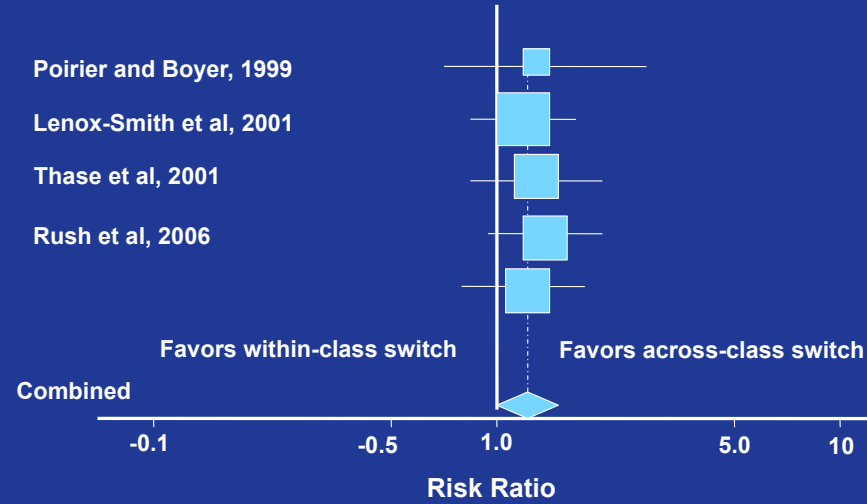
Date: Visit 2

Over the last 2 weeks, how often have you been bothered by any of the following problems?
(use "✓" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself in some way	0	1	2	3
Total	7			
10. If you checked off any problems, how <i>difficult</i> have these problems made it for you to do your work, take care of things at home or get along with other people	Not difficult at all <input checked="" type="checkbox"/> _____ Somewhat difficult _____ Very difficult _____ Extremely difficult _____			



Meta-Analysis: Switch Within vs Across Classes – Remission



Data from 4 clinical trials; n = 1496

Nonsignificant trend suggested that switch within class was better tolerated

Papakostas G, et al. *Biol Psychiatry*. 2008;63:699-704.



Atypical Antipsychotic Neuropharmacology

Neuroreceptor Binding Affinities

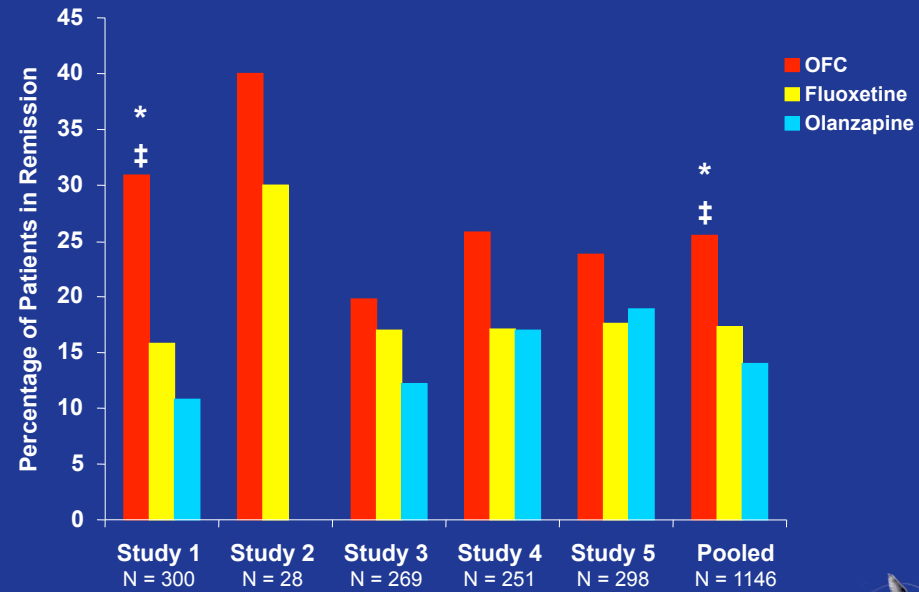
Receptor	ARI	OLZ	QUE	RIS	ZIP
D ₁	265*	31	455	430	525
D ₂	0.34*	11	160	4	5
D ₃	0.80*	49	340	10	7
D ₄	44*	27	1,600	9	32
5-HT _{1A}	1.7*	> 10,000	2,800	210	3
5-HT _{2A}	3.4*	4	295	0.5	0.4
5-HT _{2c}	15	23	1,500	25	1
α ₁	57	19	7	0.7	11
H ₁	61	7	11	20	50
M ₁	> 10,000	1.9	120	> 10,000	> 1,000

ARI = aripiprazole; OLZ = olanzapine; RIS = risperidone; QUE = quetiapine; ZIP = ziprasidone
 Data represented as K_i (nM); *data with cloned receptors



Weiden P, et al. *J Clin Psychiatry*. 2007;68(S7):1-48.

Olanzapine-Fluoxetine Combination for TRD MADRS Remission Rates



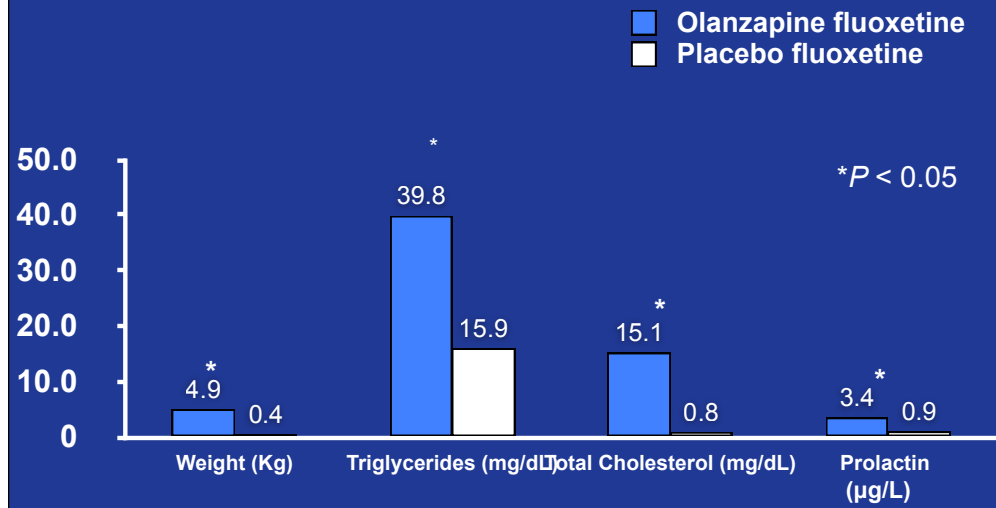
Trivedi M, et al. *J Clin Psychiatry*. 2009;70(3):387-396.

* $P < 0.05$ compared with fluoxetine

† $P < 0.05$ compared with olanzapine



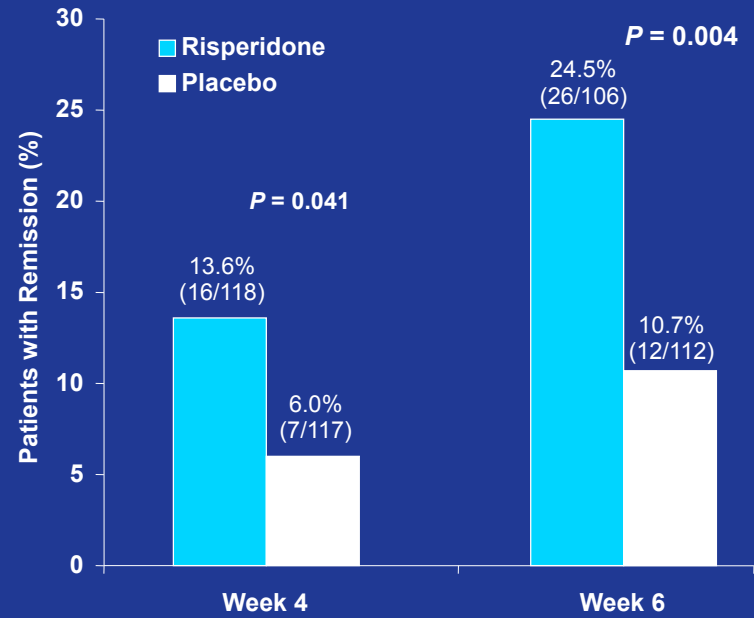
Olanzapine Augmentation: Metabolic and Endocrine Parameters



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



Risperidone Augmentation for TRD



Mahmoud R, et al. *Ann Intern Med.* 2007;147(9):593-602.



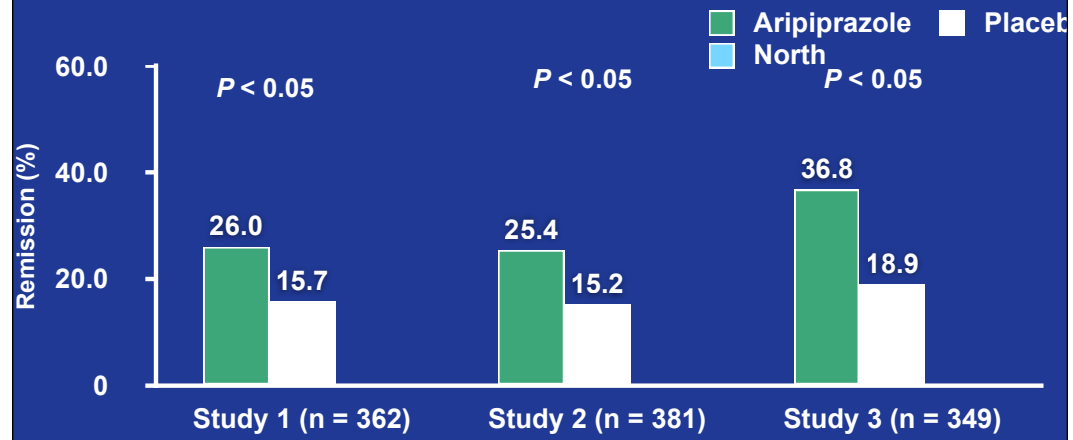
Risperidone Augmentation Side Effects

- Somnolence
- Dry mouth
- Increased appetite
- Weight gain

Mahmoud R, et al. *Ann Intern Med.* 2007;147(9):593-602.
Keitner G, et al. *J Psychiatric Res.* 2009;43:205-214.



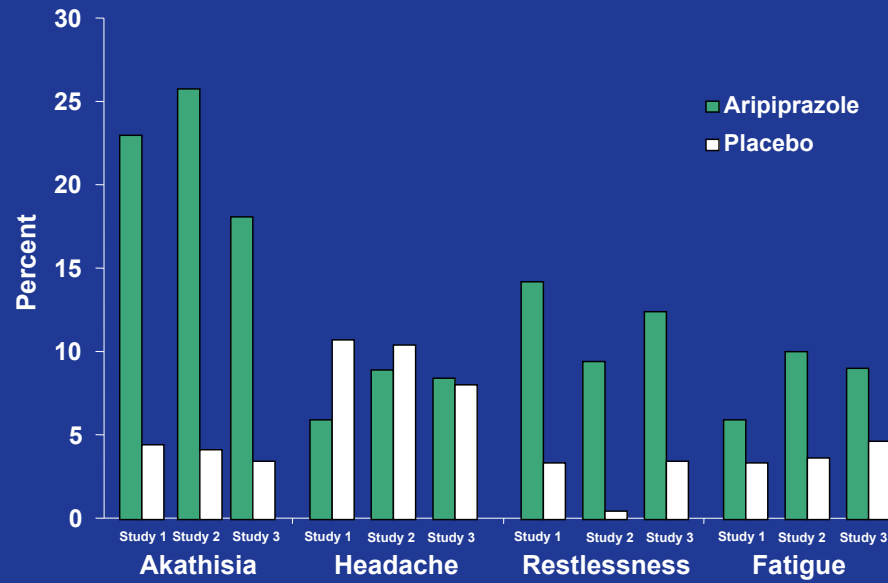
Aripiprazole Augmentation: Placebo-Controlled Trials



Study 1: Berman R, et al. *J Clin Psychiatry*. 2007;68:843-853.
Study 2: Marcus R, et al. *J Clin Psychopharmacol*. 2008;28:156-165.
Study 3: Berman R, et al. *CNS Spectrums*. 2009;14:197-206.



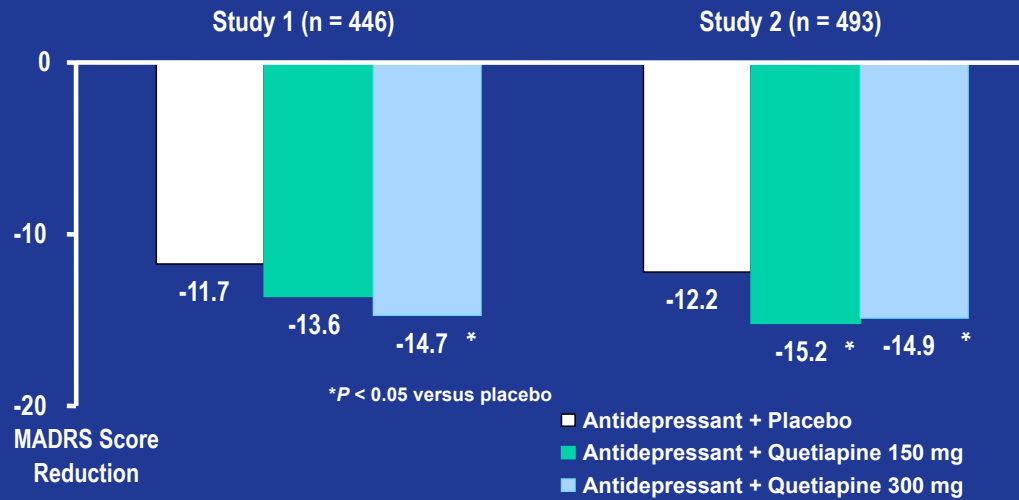
Aripiprazole Augmentation



Study 1: Berman R, et al. *J Clin Psychiatry*. 2007;68:843-853.
Study 2: Marcus R, et al. *J Clin Psychopharmacol*. 2008;28:156-165.
Study 3: Berman R, et al. *CNS Spectrums*. 2009;14:197-206.



Quetiapine Augmentation: Randomized, Double-Blind, Placebo-Controlled Trials



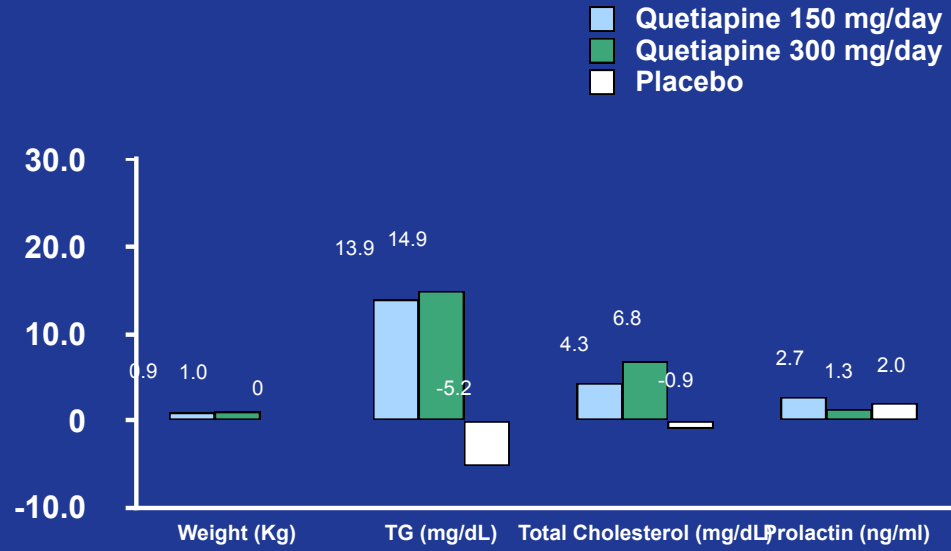
MADRS: Montgomery-Asberg Depression Rating Scale

Study 1: El-Khalili N, et al. 161st Annual APA Meeting. May 3-8, 2008. Washington, DC.

Study 2: Bauer M, et al. *J Clin Psychiatry*. 2009;70:540-549.



Quetiapine Augmentation: Metabolic and Endocrine Parameters



Bauer M, et al. *J Clin Psychiatry*. 2009;70:540-549.



Atypical Antipsychotics: Side Effect Burden

- Metabolic
 - Weight gain
 - Glucose intolerance/Type 2 diabetes
 - Lipid derangements, especially increased triglycerides
- Neurologic
 - EPS (akathisia, parkinsonism, tardive dyskinesia)
- Sedation/somnolence
- Hyperprolactinemia
- Blood dyscrasias

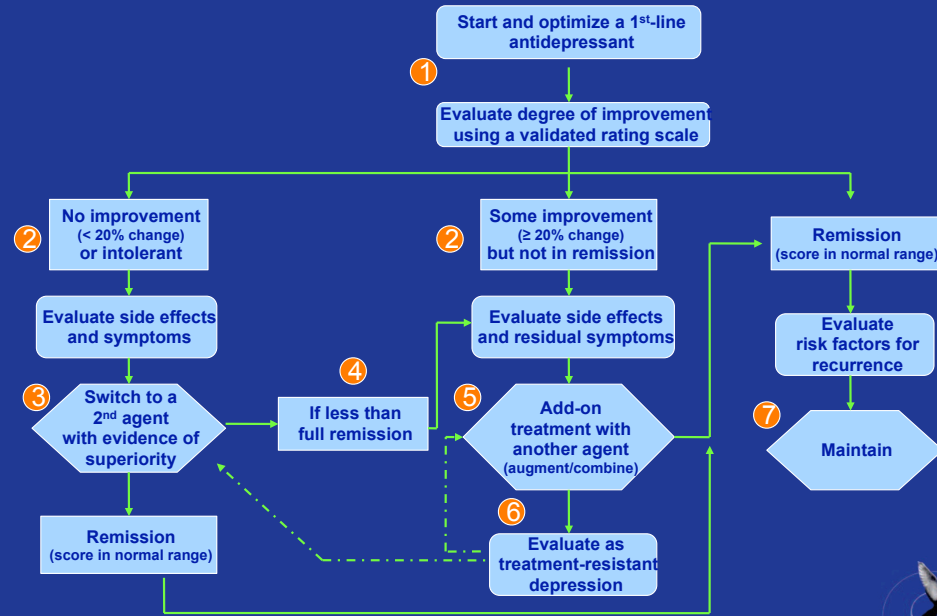


Long-Term Antidepressant Use and Diabetes Mellitus

- Nested case-control study; cohort of 165,958 patients with depression
- 2,243 cases of diabetes mellitus; 8,963 matched controls
- Recent long-term (> 24 months) use of antidepressants (moderate to high daily doses) associated with increased risk of diabetes – incidence rate ratio = 1.84 (95% CI = 1.35-2.52)
 - Tricyclic antidepressants: RR = 1.77 (95% CI = 1.21-2.59)
 - SSRIs: RR = 2.06 (95% CI = 1.20-3.52)
- Short-term treatment or lower daily doses of antidepressants were not associated with increased risk for diabetes



Algorithm for Managing Limited Improvement with First-line Antidepressant



Lam R, et al. *J Affect Disord.* 2009;117:S26-S43.



Switch Therapy or Add-on?

Monotherapy switch:

- No drug interactions
- No additive side effects
- Dosing simplicity

Add-on therapy:

- Faster onset of response
- Address specific residual symptoms or side effects
- Psychological advantage
- Late responders

Primarily a clinical decision (lack of evidence) based on whether there is at least a partial response to initial treatment



Additional Treatment Options for TRD

- Neuromodulation
 - Electroconvulsive Therapy (ECT)
 - Vagal Nerve Stimulation (VNS)
 - Transcranial Magnetic Stimulation (TMS)
 - Deep Brain Stimulation (DBS)
- Sleep Deprivation with Phase Advancement



Measurement-Based Care for MDD

- Systematically using measurement tools to monitor progress and guide treatment choices
 - Set visit schedule
 - Regularly monitoring symptom improvement, side effects, medication adherence
 - Use a set dose titration and treatment algorithm
 - Critical decision points



Measurement-Based Care for MDD Assessment Tools

Measurement	Assessment Tool
Medication adherence and reasons for nonadherence	BMQ (Brief Medication Questionnaire)
Side effects	FIBSER (Frequency, Intensity, and Burden of Side Effects-Rating)
Symptomatic improvement*	QIDS-C/QIDS-SR (Quick Inventory of Depressive Symptomatology, Clinician Rated/Self-Report) PHQ-9 (Patient Health Questionnaire) BDI: Beck Depression Inventory

*HDRS₁₇ (Hamilton Depression Rating Scale) and MADRS (Montgomery-Asberg Depression Rating Scale) are used in research settings, but not typically in clinical practice

Trivedi M. *J Clin Psychiatry*. 2009;70(S6):26-31.



Summary

- Over half of patients treated for major depressive disorder fail to achieve remission with initial therapy ~‘Better is not well’
- Factors associated with treatment resistance
 - Misdiagnosis, psychiatric comorbidities, depression severity and chronicity, medical comorbidities, patient noncompliance with treatment, pharmacogenetics
- STAR*D provides a framework for an evidence-based, individualized treatment plan
- Use measurement-based care
 - Establish critical decision points
 - Monitor symptomatic status of patients, side effects, medication adherence
 - Individualize pharmacotherapy to balance clinical benefit and side effects
 - Treating to remission requires sustained and sufficient dosing and monitoring
- Good efficacy data for augmentation, combination and switching strategies
- Adjunctive treatment with atypical antipsychotics
 - Effective during acute phase of treatment; side effect burden is a concern
 - Long-term safety and efficacy not known

