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Treatment-Resistant MDD: Tailoring Treatment Strategies for Enhanced Outcomes

Friday, 3/19/2010

2:00-3:00 pm

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The American College of Osteopathic Family Physicians is accredited by the American Osteopathic Association Council to sponsor continuing medical education for osteopathic physicians.

The American College of Osteopathic Family Physicians has requested that the AOA Council on Continuing Medical Education approve this program for AOA Category 1A CME Credit. Approval is pending.



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



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)

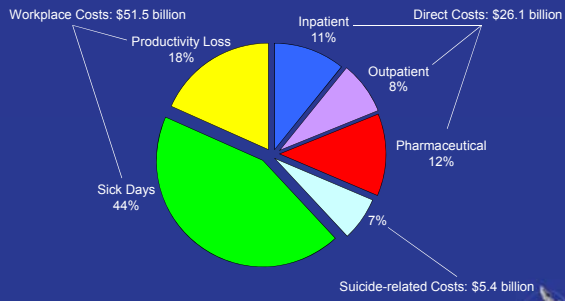
DALY: disability-adjusted life years



World Health Organization. <http://www.who.int/en/>. Accessed February 2010.

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.

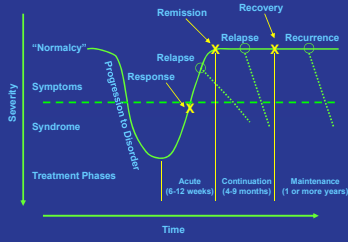
Screening and Diagnosis Measurement-Based Care

- 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

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.

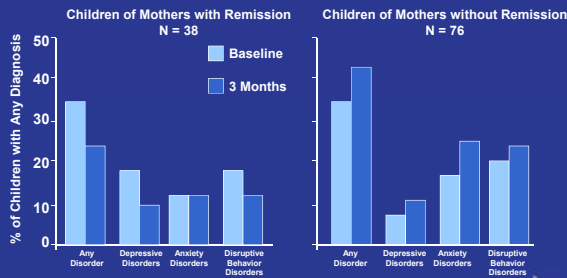
Why Target Remission?

- 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

Papakostas G. *J Clin Psychiatry*. 2009;70(S6):16-25.

Maternal Depression Importance of Remission

Overall **11% decrease** in rates of diagnoses in children of remitted mothers compared with an **8% increase** in children of mothers with continuing depression



Weissman M, et al. *JAMA*. 2006;295(12):1389-1398.

Factors Independently Associated With Greater Chance of Remission (STAR*D)

- Employment
- Greater income
- Greater education
- Caucasian
- Female gender
- No OCD or PTSD
- Greater functioning/quality of life

Trivedi MH, et al. *Am J Psychiatry*. 2006;163:28-40.
Cohen A, et al. *Arch Gen Psychiatry*. 2006;63:50-56.



What Is Treatment-Resistant Depression?

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

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



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
- 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

Papakostas G. *J Clin Psychiatry*, 2009;70(S6):16-25.



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?

Papakostas G. *J Clin Psychiatry*, 2009;70(S6):16-25.



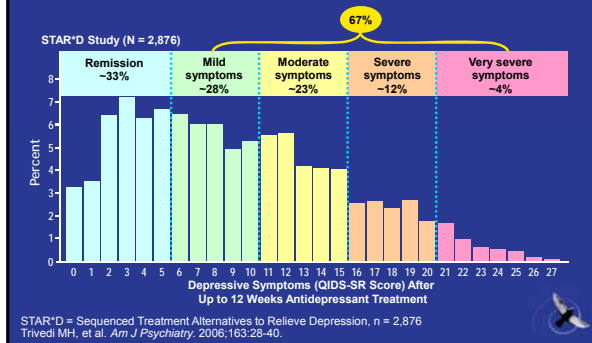
Combination

- 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)

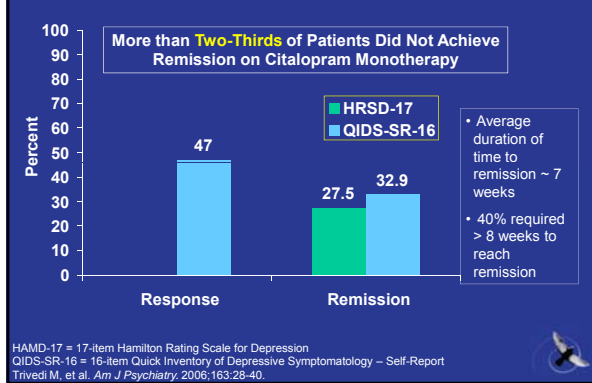
Papakostas G. *J Clin Psychiatry*, 2009;70(S6):16-25.



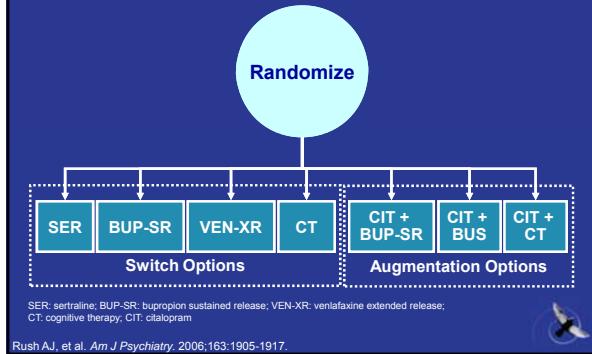
STAR*D: Unresolved Symptoms Following Antidepressant Treatment



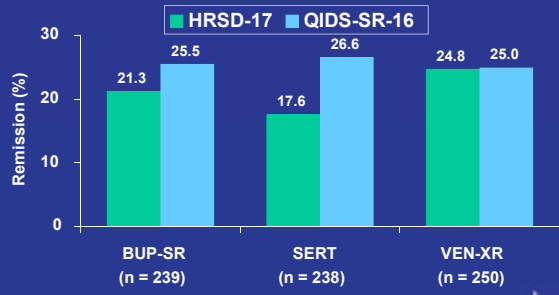
Treatment Outcome: Level 1



STAR*D Level 2 Switch or Augment

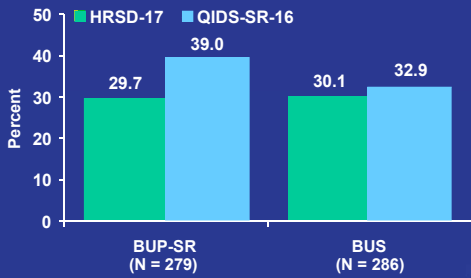


STAR*D Level 2 Medication Switch



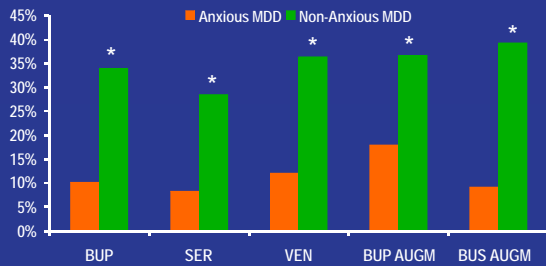
Rush A, et al. *N Engl J Med* 2006;354(12):1231-1242.
 BUP-SR: bupropion sustained release
 SERT: sertraline
 VEN-XR: venlafaxine extended release

Level 2 Augmentation Outcomes: Remission Rates

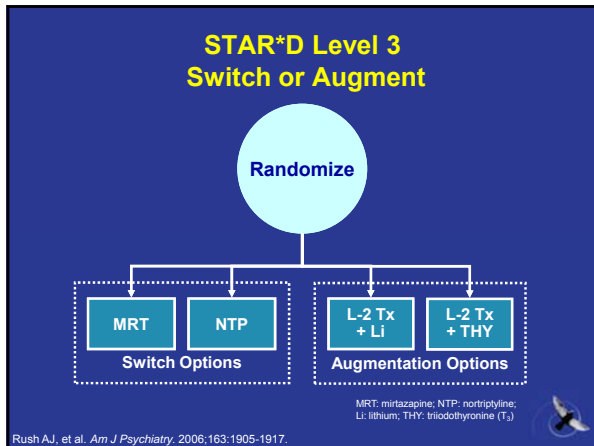


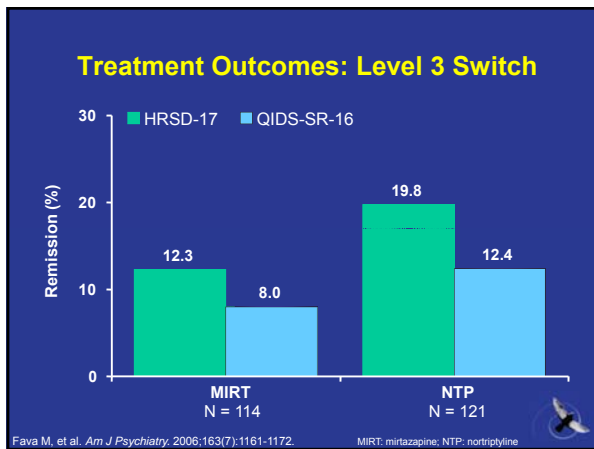
BUP-SR: bupropion sustained release; BUS: buspirone
 Trivedi MH, et al. *N Engl J Med*. 2006;354:1243-1252.

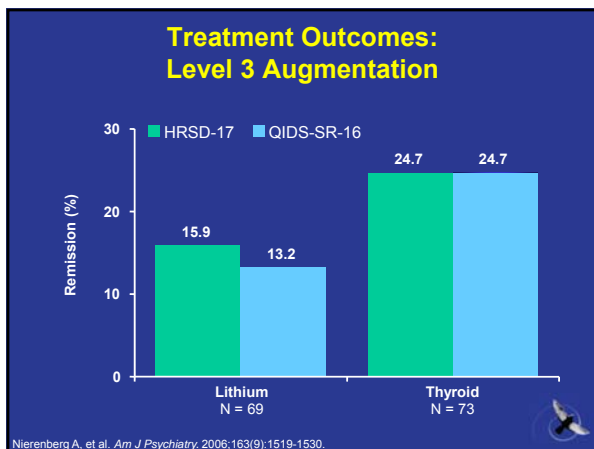
Remission Rates in Level 2 of STAR*D: Anxious vs Non-Anxious MDD

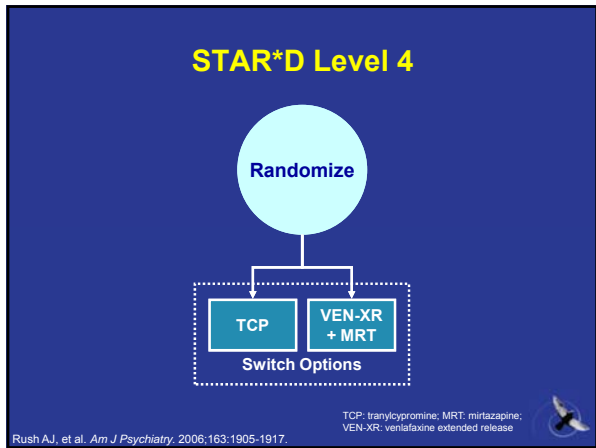


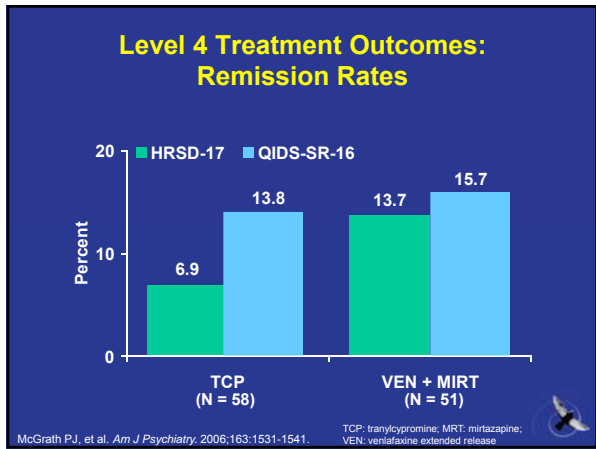
*P < 0.05
 Fava M, et al. *Am J Psychiatry*. 2008;165:342-351.
 BUP: bupropion; SER: sertraline; VEN: venlafaxine; BUS: buspirone

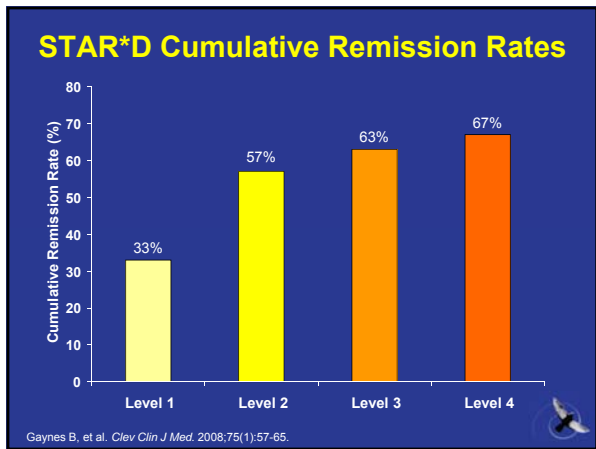


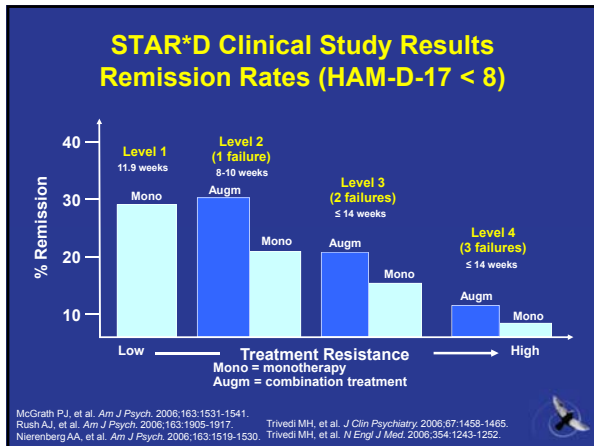


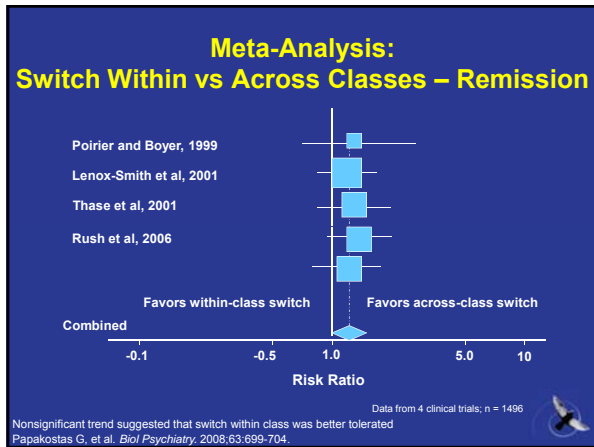










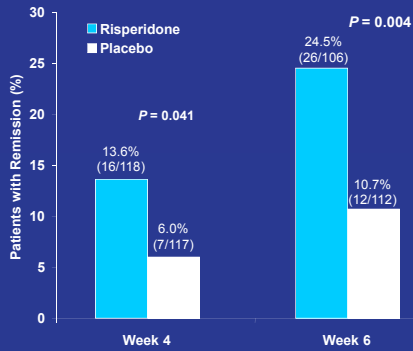


Atypical Antipsychotic Neuropharmacology Neuroreceptor Binding Affinities

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.

Risperidone Augmentation for TRD



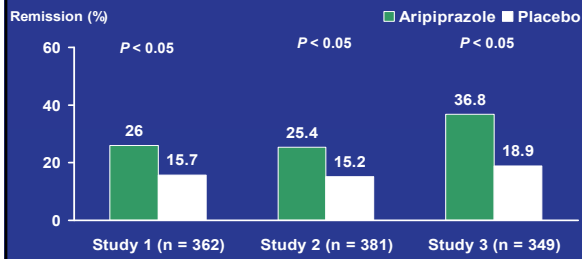
Mahmoud R, et al. *Ann Intern Med*. 2007;147(9):593-602.

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.

Atypical Antipsychotic Augmentation Meta-Analysis

16 Trials, 3,480 patients
Atypical antipsychotic (AA) vs placebo

Response

- OR: 1.69 (95% CI 1.46-1.95); $P < 0.00001$
- Number needed to treat = 9
- Overall pooled response rate for AA 44.2% vs 29.9% for placebo

Remission

- OR: 2.00 (95% CI 1.69-2.37); $P < 0.00001$
- Number needed to treat = 9
- Overall pooled remission rate for AA 30.7% vs 17.2% for placebo

Discontinuation for Adverse Events

- OR: 3.91 (95% CI 2.68-5.72); $P < 0.00001$
- Number needed to harm = 17
- Pooled adverse event discontinuation rate for AA 9.1% vs 2.3% for placebo

AAs included olanzapine, risperidone, quetiapine, aripiprazole

Nelson JC, Papakostas G. *Am J Psychiatry*. 2009;166:980-991.



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

Meyer J. *J Clin Psychiatry*. 2007;68(S14):20-26.



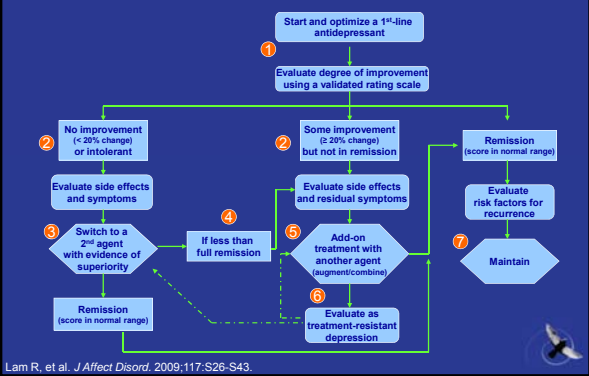
Long-Term Antidepressant Use and Diabetes Mellitus

- 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

Andersohn F, et al. *Am J Psychiatry*. 2009;166:591-598.



Algorithm for Managing Limited Improvement with First-line Antidepressant



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

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

Choosing an Add-on Strategy

1st Line	Level 1 Evidence <ul style="list-style-type: none"> • Lithium • Aripiprazole • Olanzapine • Quetiapine XR* 	Level 2 Evidence <ul style="list-style-type: none"> • Risperidone
2nd Line	Level 2 Evidence <ul style="list-style-type: none"> • Bupropion • Mirtazapine/mianserin • Quetiapine IR • Triiodothyronine 	Level 3 Evidence <ul style="list-style-type: none"> • Other antidepressant
3rd Line	Level 2 Evidence <ul style="list-style-type: none"> • Buspirone • Modafinil 	Level 3 Evidence <ul style="list-style-type: none"> • Stimulants

* Recently published data not included in the 2009 CANMAT MDD guidelines

Adapted from Lam R, et al. *J Affect Disord.* 2009;117:S26-S43.
 *Bauer M, et al. *J Clin Psychiatry.* 2009;70:540-549.
 Nelson JC, Papakostas G. *Am J Psychiatry.* 2009;166:980-991.

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



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

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

*HDRS₇ (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