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

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Dr. Schussler has nothing to disclose.

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


**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

Economic Impact of Depression in the US

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

- **Workplace Costs**: $51.5 billion
- **Productivity Loss**: 18%
- **Inpatient**: 11%
- **Outpatient**: 8%
- **Pharmaceutical**: 12%
- **Sick Days**: 44%
- **Suicide-related Costs**: $5.4 billion
- **Direct Costs**: $26.1 billion


‘Signs’ of Depression

- S—Suicidal preoccupation
- I—Interest/pleasure ↓
- G—Gain/lose weight
- G—Guilty feelings
- E—Energy ↓
- C—Concentration
- A—Affect ↓ m 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


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 22)
- **Few exclusion criteria** → “real world”

STAR*D Treatment Strategies and Options

Citalopram
CT + CIT
VEN-XR
CT
CIT + BUP-SR
SERT
BUP-SR
CIT + BUS


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 (e.g., 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

STAR*D: Unresolved Symptoms Following Antidepressant Treatment

- Remission ~33%
- Mild symptoms ~28%
- Moderate symptoms ~23%
- Severe symptoms ~12%
- Very severe symptoms ~4%

STAR*D Study (N = 2,876)

STRA*D = Sequenced Treatment Alternatives to Relieve Depression, n = 2,876
More than Two-Thirds of Patients Did Not Achieve Remission on Citalopram Monotherapy

- Average duration of time to remission ~ 7 weeks
- 40% required > 8 weeks to reach remission

**STAR*D Level 2**

**Switch or Augment**

Randomize

Switch Options: SER, BUP-SR, VEN-XR, CT
Augmentation Options: CIT + BUP-SR, CIT + BUS, CIT + CT


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

**STAR*D Level 2 Medication Switch**

Remission (%)

- BUP-SR (n = 239):
  - HRSD-17: 21.3
  - QIDS-SR-16: 25.5
- SERT (n = 238):
  - HRSD-17: 17.6
  - QIDS-SR-16: 26.6
- VEN-XR (n = 250):
  - HRSD-17: 24.8
  - QIDS-SR-16: 25.0

Level 2 Augmentation Outcomes: Remission Rates

**BUP-SR:** bupropion sustained release  
**BUS:** buspirone

<table>
<thead>
<tr>
<th>Outcome</th>
<th>BUP-SR (N = 279)</th>
<th>BUS (N = 286)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRSD-17 Remission Rate (%)</td>
<td>29.7</td>
<td>30.1</td>
</tr>
<tr>
<td>QIDS-SR-16 Remission Rate (%)</td>
<td>39.0</td>
<td>32.9</td>
</tr>
</tbody>
</table>

**Remission Rates**

**Level 2 Augmentation Outcomes**

**STAR*D Level 3 Switch or Augment**

- **Randomize**
  - **Switch Options**
    - MRT
    - NTP
  - **Augmentation Options**
    - L-2 Tx + Li
    - L-2 Tx + THY

**STAR*D Treatment Outcomes: Level 3 Switch**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>MRT N = 14</th>
<th>NTP N = 121</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRSD-17 Remission Rate (%)</td>
<td>12.3</td>
<td>19.8</td>
</tr>
<tr>
<td>QIDS-SR-16 Remission Rate (%)</td>
<td>8.0</td>
<td>12.4</td>
</tr>
</tbody>
</table>

**Level 3 Switch Outcomes**
Treatment Outcomes: Level 3 Augmentation


15.9
24.7
13.2
24.7

Lithium
N = 69

Thyroid
N = 72

Remission (%)

HRSD-17  QIDS-SR-16

STAR*D Level 4

Randomize

TCP
VEN-XR + MRT

Switch Options


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

Level 4 Treatment Outcomes: Remission Rates


TCP
(N = 58)

VEN + MIRT
(N = 51)

HRSD-17  QIDS-SR-16

6.9  13.8
13.7  15.7

Percent

Remission Rates
STAR*D Cumulative Remission Rates


Aripiprazole Augmentation: Placebo-Controlled Trials


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

Olanzapine-Fluoxetine Combination for TRD
MADRS Remission Rates

![Chart showing remission rates for different studies.](chart.png)

*P < 0.05 compared with fluoxetine
‡P < 0.05 compared with olanzapine

** Metabolic
- Weight gain
- Glucose intolerance/Type 2 diabetes
- Lipid derangements, especially increased triglycerides

** Neurologic
- EPS (akathisia, parkinsonism, tardive dyskinesia)

** Sedation/somnolence

** Hyperprolactinemia

** Blood dyscrasias


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

Guidelines for Treatment of Major Depression


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

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**Patient Health Questionnaire 9 (PHQ-9)**

<table>
<thead>
<tr>
<th>Name: Rhonda</th>
<th>Date:</th>
<th>Visit 0 (OB/GYN)</th>
</tr>
</thead>
</table>

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

1. Little interest or pleasure in doing things
   - Not difficult at all
   - Somewhat difficult
   - Very difficult
   - Extremely difficult

2. Feeling down, depressed, or hopeless
   - Not difficult at all
   - Somewhat difficult
   - Very difficult
   - Extremely difficult

3. Trouble falling or staying asleep, or sleeping too much
   - Not difficult at all
   - Somewhat difficult
   - Very difficult
   - Extremely difficult

4. Restless, or fidgety
   - Not difficult at all
   - Somewhat difficult
   - Very difficult
   - Extremely difficult

5. Fatigue or loss of energy
   - Not difficult at all
   - Somewhat difficult
   - Very difficult
   - Extremely difficult

6. Poor appetite or overeating
   - Not difficult at all
   - Somewhat difficult
   - Very difficult
   - Extremely difficult

7. Thoughts that you would be better off dead, or of hurting yourself in some way
   - Not difficult at all
   - Somewhat difficult
   - Very difficult
   - Extremely difficult

8. Trouble concentrating on things such as reading the newspaper or watching television
   - Not difficult at all
   - Somewhat difficult
   - Very difficult
   - Extremely difficult

9. Feeling bad about yourself— or that you are a failure or have let yourself or your family down
   - Not difficult at all
   - Somewhat difficult
   - Very difficult
   - Extremely difficult

10. Moving or speaking so slowly that other people would have noticed, or the opposite—being so fidgety or restless that you have been moving around a lot more than usual
    - Not difficult at all
    - Somewhat difficult
    - Very difficult
    - Extremely difficult

11. Rating how difficult various problems have been for you
    - Not difficult at all
    - Somewhat difficult
    - Very difficult
    - Extremely difficult

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**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
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
**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)

1. Little interest or pleasure in doing things  ○  (2)
2. Feeling down, depressed, or hopeless  ○  (2)
3. Trouble falling or staying asleep, or waking too much  ○  (2)
4. Feeling tired or having little energy  ○  (2)
5. Poor appetite or overeating  ○  (2)
6. Feeling that you would be better off dead, or of wanting to hurt yourself  ○  (2)
7. Trouble concentrating on things such as reading the newspaper or watching television  ○  (2)
8. Moving or speaking so slowly that other people could have noticed  ○  (2)
9. Thoughts that you have been moving around a lot more than usual  ○  (2)
10. If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home or get along with other people  ○  (5)

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**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)

1. Feeling nervous, anxious, or on edge  ○  (2)
2. Not being able to stop or control worrying  ○  (2)
3. Worrying too much about different things  ○  (2)
4. Trouble relaxing  ○  (2)
5. Being so restless that it is hard to sit still  ○  (2)
6. Feeling nervous, anxious or on edge  ○  (2)
7. Feeling afraid as if something awful might happen  ○  (2)

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**Mood Disorder Questionnaire - Rhonda**

**INSTRUCTIONS:** Please answer each question as best you can.

1. Have you ever been a period of time when you were not your usual self and...  ○  (Yes)  ○  (No)
   - ...you felt so good or so happy that other people thought you were not your normal self or so happy that you got into trouble?  ○  (Yes)  ○  (No)
   - ...you were soritable that you shouted at people or started fights or arguments?  ○  (Yes)  ○  (No)
   - ...you felt much more self-confident than usual?  ○  (Yes)  ○  (No)
   - ...you were more talkative or spoke much more than usual?  ○  (Yes)  ○  (No)
   - ...thoughts rushed through your head or you couldn't slow your mind down?  ○  (Yes)  ○  (No)
   - ...you were so anxious that you felt things around you that you had trouble concentrating or sleeping or track?  ○  (Yes)  ○  (No)
   - ...your mood more up than usual?  ○  (Yes)  ○  (No)
   - ...your mood more down than usual?  ○  (Yes)  ○  (No)
   - ...you were much more efficient or did much more things than usual?  ○  (Yes)  ○  (No)
   - ...you were much more excited or sleeping than usual?  ○  (Yes)  ○  (No)
   - ...you were much more relaxed or sleeping than usual?  ○  (Yes)  ○  (No)
   - ...the things that were unusual for you or that other people might have thought were unusual for you?  ○  (Yes)  ○  (No)
   - ...spending money got you or your family in trouble?  ○  (Yes)  ○  (No)

2. If you checked YES  (Yes)  to more than one of the above, have several of these ever happened during the same period of time?  ○  (Yes)  ○  (No)

3. How much of a problem did any of these cause you - like being able to work; getting along; 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.mhfa.org

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)

1. Little interest or pleasure in doing things
2. Feeling down, depressed, or hopeless
3. Trouble falling or staying asleep, or sleeping too much
4. Feeling tired or having little energy
5. Trouble concentrating on things such as reading the newspaper or watching television
6. 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
7. Thoughts that you would be better off dead, or of injuring yourself in some way

1. Not at all
2. Several days
3. More than half the days
4. Nearly every day
5. Not at all

Total Score: 32

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 (PT)
**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

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**Choosing an Add-on Strategy**

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<tr>
<th>1st Line</th>
<th>Level 1 Evidence</th>
<th>Level 2 Evidence</th>
</tr>
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<tbody>
<tr>
<td>1st Line</td>
<td>Lithium</td>
<td>Liassine</td>
</tr>
<tr>
<td>1st Line</td>
<td>Aripiprazole</td>
<td>Olanzapine</td>
</tr>
<tr>
<td>1st Line</td>
<td>Quetiapine XR 75</td>
<td>Quetiapine XR</td>
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</table>

<table>
<thead>
<tr>
<th>2nd Line</th>
<th>Level 2 Evidence</th>
<th>Level 3 Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd Line</td>
<td>Bupropion</td>
<td>Other antidepressant</td>
</tr>
<tr>
<td>2nd Line</td>
<td>Mirtazapine/mianserin</td>
<td></td>
</tr>
<tr>
<td>2nd Line</td>
<td>Quetiapine IR</td>
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<tr>
<td>2nd Line</td>
<td>Triiodothyronine</td>
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<table>
<thead>
<tr>
<th>3rd Line</th>
<th>Level 2 Evidence</th>
<th>Level 3 Evidence</th>
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</thead>
<tbody>
<tr>
<td>3rd Line</td>
<td>Buspirone</td>
<td>Stimulants</td>
</tr>
<tr>
<td>3rd Line</td>
<td>Modafinil</td>
<td></td>
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**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


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