Overcoming Cognitive and Residual Symptoms In Major Depression: Enhancing Patient Outcomes in the Primary Care Setting
Faculty

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Disclosures

• **Angela Golden, DNP** serves on the speaker’s bureau for Novo Nordisk and Takeda/Lundbeck. Dr. Golden also serves on the advisory boards of Boehringer Ingelheim, Janssen, Novo Nordisk and Takeda/Lundbeck.

• **J. Sloan Manning, MD** serves on the speaker’s bureau for Otsuka, Takeda Lundbeck, and Sunovion. Dr. Manning is a study investigator for Pearson PLC.

• **Alice R. Mao, MD** is a speaker for Takeda, Sunovion, Otsuka, and Shire.

• **Gregg Mattingly, MD** serves as a speaker for Forest, Lundbeck, Merck, Otsuka, Shire, Sunovion and Takeda. Dr. Mattingly is a consultant for Alcobra, Alkermes, Forest, Forum, Jansen, Lundbeck, Merck, Novartis, Noven, Otsuka, Purdue, Reckitt Benckiser, Rhodes, Shire, Sunovion and Takeda.

• **C. Brendan Montano, MD** serves as an advisor and speaker for Merck, Shire, Takeda, Lundbeck, Otsuka. Dr. Montano is a consultant for Lundbeck, Takeda, Otsuka and Rhodes.
Learning Objectives

After participating in the proposed educational activities, clinicians should be better able to:

1. Recognize the overlap of emotional, physical and cognitive challenges in patients with major depressive disorder (MDD)
2. Explore the impact of residual symptoms and cognitive dysfunction on optimal patient outcomes
3. Develop strategies in the primary care setting to minimize long term side effect burden in an effort to increase adherence to MDD treatment
4. Discuss newly approved treatment options for MDD while exploring their role in residual cognitive symptoms, selective side effect profile and remission of depressive symptoms
Pre-test ARS Question 1

On a scale of 1 to 5, please rate how confident you would be in the diagnosis and management of a patient with Major Depression Disorder:

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident
Pre-test ARS Question 2

Mary – 35 year old mother

- Wakes in the morning struggling with depression
- Makes breakfast for her son and daughter
- Heads to work with her head in a fog
- Makes dinner for her family
- Then tries to force a smile on her face as she puts her kids to sleep
- Lays in bed tossing and turning wondering what she’s done wrong to feel this way
Pre-test ARS Question 2

As you evaluate Mary, you must realize that the 3 most common symptoms in individuals with MDD are?

1. Sleep, mood and energy
2. Sleep, mood and suicidal thoughts
3. Mood, appetite and concentration
4. Mood, sleep and concentration
Pre-test ARS Question 3

*In treating Mary’s depression, the most common residual symptoms will include?*

1. Sleep difficulties
2. Suicidal thoughts
3. Cognitive difficulties
4. Sleep difficulties and suicidal thoughts
5. Sleep and cognitive difficulties
You consider offering Mary an SSRI for which of the following reasons?

1. They have high remission rates
2. They help depression and anxiety
3. They have low sexual side effect rates
4. They improve functional outcomes
Pre-test ARS Question 5

*Which antidepressant has shown improvement in cognitive function?*

1. Escitalopram
2. Vortioxetine
3. Duloxetine
4. Levomilnacipran
Mary would like to be sexually active and is concerned about medications that might impact her libido. To minimize sexual side effects, you want to avoid which serotonin receptor?

1. 5HT-1
2. 5HT-2
3. 5HT-3
4. 5HT-7
Pre-test ARS Question 7

Which antidepressant minimizes 5HT-2 stimulation?

1. Citalopram
2. Vilazodone
3. Desvenlafaxine
4. Vortioxetine
5. Vilazodone and Vortioxetine
Depression

A Neurologic Condition Which Involves Emotional, Physical and Cognitive Centers in the Brain
Bipolar Disorder: Untreated vs Treated Standardized Mortality Ratios

Zurich Cohort, n = 406 1959-1997

- Neoplasm: 1.4* Untreated, 0.6 Treated
- Cardiovascular: 2.2* Untreated, 1.7 Treated
- Cerebrovascular: 1.6† Untreated, 1.3 Treated
- Accidents: 1.6 Untreated, 2.0 Treated
- Suicide: 29.2* Treated
- Other: 2.0* Untreated, 1.3 Treated
- All Causes: 2.2* Untreated, 1.3 Treated

* P < .001. † P < .05.
Suicidal Behavior and Suicide Deaths

500,000 Patients Monitored Over 10 Years
65,000 Treated With Antidepressants
82,000 Treatment Episodes

Suicide Deaths per 100,000

40 per 100,000 Treatment Episodes

Suicide Attempts per 100,000

93 per 100,000 Total
(314 children vs 78 adults)

Simon et al
Am J of Psychiatry, January 2006
Suicide Attempts: Before or After Treatment?

Simon et al, Am J of Psychiatry, January 2006
Sadness, Depression and Recovery: Reciprocal Limbic-Cortical Function and Mood

Recurrent Depression Causes Cell Death

Recurrent Depression Had a 48% Decrease in Cell Volume

Drevets et al, Nature 2002
Mary

- At the urging of her family comes to see her PCP for a routine visit
- Not sure she’s depressed but states “I just don’t feel right”
Symptoms of Depression

- Depressed mood
- Loss of interest or pleasure
- Diminished ability to think/concentrate or indecisiveness
- Significant change in weight or appetite
- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Fatigue or loss of energy
- Feelings of worthlessness or excessive guilt
- Suicidal ideation
Top 3: Sleep, mood and concentration
Prevalence of Symptoms During MDD Episodes

- 13-year NIMH Study of 1,920 Individuals in the Baltimore Epidemiologic Catchment Area

Mary

- PCP orders routine health panel with TSH
- Has Mary fill out a PHQ 9 while waiting for her blood to be drawn
Depression rating scales measure symptom reduction in clinical trials, but are rarely used in clinical practice\(^1\)

**MADRS\(^2\)**
Depressive symptoms

**HAM-D\(^3\)**
Depressive, anxious, and somatic symptoms

**CGI-S\(^1\)**
Global illness

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CGI-S, Clinical Global Impression-Severity scale; HAM-D, Hamilton Depression Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale.

PHQ-9: Nine-Item Patient Health Questionnaire Designed to Help Primary Care Clinicians Diagnose Depression and Grade Symptom Severity

Over the last 2 weeks, how often have you been bothered by any of the following problems?

<table>
<thead>
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<th>Problem</th>
<th>Not at all</th>
<th>Several days</th>
<th>More than half the days</th>
<th>Nearly every day</th>
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</thead>
<tbody>
<tr>
<td>1. Little interest or pleasure in doing things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<td>2. Feeling down, depressed, or hopeless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td>3. Trouble falling or staying asleep, or sleeping too much</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<td>4. Feeling tired or having little energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<td>5. Poor appetite or overeating</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<td>7. Trouble concentrating on things, such as reading the newspaper or watching television</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<td>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</td>
<td>0</td>
<td>1</td>
<td>2</td>
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<td>9. Thoughts that you would be better off dead or of hurting yourself in some way</td>
<td>0</td>
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<td>2</td>
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If you circled any problems on this questionnaire so far, mark how difficult these problems have 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

**ADD COLUMNS** + + +

**TOTAL**

For healthcare professionals: Because this questionnaire relies on patient self-report, all responses should be verified by the clinician. A definitive diagnosis should be made on clinical grounds, taking into account how well the patient understands the questionnaire, as well as other relevant information from the patient. Be sure to exclude responses to a significant loss, substance abuse, or other medical condition.

Mary

- PHQ is positive for 8 of 9 symptoms
- With a total score of 21 out of 27
- Sx on PHQ include fragmented sleep, decreased energy, increased appetite, poor concentration and feeling hopeless
- PCP starts Mary on an antidepressant and reassures that he will “get her feeling better”
Which antidepressant would you start?

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Mary

- Returns to her PCP 1 month later
- Feels “better”
- Sx on PHQ 50% improved
- PCP says lets leave things alone and “give it another month”
Patient Response In Early MDD Could be Predictive of Overall Response

Early improvers: patients having a reduction in HAM-D-17 score of ~ 20% compared with baseline within the first 2 weeks of treatment.

Stable responders: patients having a reduction in HAM-D-17 score of ~ 50% from baseline at 4 weeks of treatment and at all subsequent assessments.

Stable remitters: patients having a reduction in HAM-D-17 score to ~ 7 points at week 4 of treatment and at all subsequent assessments.

Sleep and Concentration Are Frequent Residual Symptoms

MDD, major depressive disorder; STAR*D, Sequenced Treatment Alternatives to Relieve Depression.

Vortioxetine improves cognitive function in depression in three clinical trials

DSST – Replication: Number of correct symbols, change from baseline at Week 8 (FAS, ANCOVA, LOCF, path analysis; *p<0.05, ***p<0.001)

Duloxetine was included as active reference in the CONNECT and Elderly studies for study validation, not for comparison of effect sizes. DSST scores were assessed as predefined primary outcome of CONNECT, secondary outcome of FOCUS, and exploratory outcome of the Elderly study, with path analyses performed post hoc.

Early Remission Yields Better Functional Outcome

Nonremitters show more pronounced impairment in functioning than remitters following treatment.

-Q = Quality of Life, Enjoyment, and Satisfaction Questionnaire.
*Within normal defined as Q-LES-Q within 10% of community norms (≥70.47); †P<0.001 vs remitters.
# Side effects leading to long term noncompliance:
**Weight gain, Sedation, Sexual Dysfunction**

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Limitations of SSRI treatment

One half unresponsive to first antidepressant in the STAR*D trial\(^1\)

Remission rates were:
• 27% after first trial

Few adults experience full symptomatic and functional remission between depressive episodes\(^2,3\)
• Residual symptoms and loss of function are common\(^2,3\)

Long term compliance of SSRIs often limited by weight gain, blunting and sexual side effects\(^3\)

Inadequate SSRI response increases risk of relapse

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\textsuperscript{2}Kennedy SH, et al. \textit{Prim Care Companion CNS Disord.} 2013;15(2);3;

STAR*D, Sequenced Treatment Alternatives to Relieve Depression.
Mary

• Returns several months later
• And states “I’m better but still not great”
• Sx on PHQ continue to show poor sleep, anxiety, poor concentration and decreased energy
• Now also complains about low libido and gaining weight

What would you do next?
What would be your next step for Mary?

1. Change to another SSRI
2. Change to an SNRI
3. Switch to bupropion
4. Augment with an atypical
5. Other…….
Current antidepressants are associated with a range of side-effects

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<td>Amitriptyline, nortriptyline, imipramine, desipramine, doxepin</td>
<td>Cardiovascular effects, arrhythmias, orthostatic hypotension, dry mouth, sexual dysfunction, tachycardia, impaired vision, memory and concentration impairments, sedation, weight gain, myoclonus&lt;sup&gt;1,2&lt;/sup&gt;</td>
</tr>
<tr>
<td>MAOIs</td>
<td>Phenelzine, tranylcypromine, isocarboxazid, selegiline</td>
<td>Hypertensive crisis, potential for serotonin syndrome, orthostatic hypotension, weight gain, sexual dysfunction, headaches, insomnia&lt;sup&gt;1,2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Others</td>
<td>Bupropion, nefazodone, trazodone, mirtazapine, agomelatine</td>
<td>Nausea, headaches, dizziness, insomnia, somnolence, tremors, seizures, dry mouth, sedation, weight gain&lt;sup&gt;1,3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Multimodal Antidepressants</td>
<td>Vilazodone, Vortioxetine</td>
<td>Nausea, diarrhoea&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

AD, antidepressant; GI, gastrointestinal; MAOI, monoamine oxidase inhibitor; SNRI, serotonin and noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

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<sup>1</sup> American Psychiatric Association A. Practice guideline for the treatment of patients with major depressive disorder. 3<sup>rd</sup> ed. Arlington, VA: American Psychiatric Association; 2010;
<sup>2</sup> Taylor et al. Maudsley Prescribing Guidelines, 10<sup>th</sup> Edition, 2009;
The 3 New Kids

Levomilnacipran (Fetzima) - a NSRI
Vilazodone (Viibryd) - Mild SRI plus 5HT1a
Vortioxetine (Brintellix) - Mild SRI plus 5HT1
Levomilnacipran (Fetzima) - a NSRI

- 2:1 Norepinephrine/Serotonin ratio
- No weight gain
- Renally excreted
- No p450 interactions
- Has shown improvement in function*
- Side effects due to NE-heart rate…and 5HT stimulation-sexual…..
- Dosing 40-120 mg qd (20mg starting dose)

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>Anxiety, depression, aggression, impulsivity, temperature, REM sleep, neuronal firing</td>
</tr>
<tr>
<td>1C</td>
<td>Anxiety, depression, learning, aversion</td>
</tr>
<tr>
<td>1D</td>
<td>Cerebral vasoconstriction</td>
</tr>
<tr>
<td>2A</td>
<td>Anxiety, psychosis, cognition</td>
</tr>
<tr>
<td>2C</td>
<td>Food intake, locomotion, sexual function</td>
</tr>
<tr>
<td>3</td>
<td>Nausea, gastric motility, mood</td>
</tr>
<tr>
<td>4</td>
<td>Muscle contraction</td>
</tr>
<tr>
<td>5</td>
<td>Anxiety, vasoconstriction, sleep</td>
</tr>
<tr>
<td>7</td>
<td>Circadian rhythm, mood, cognition</td>
</tr>
</tbody>
</table>
Vilazodone (Viibryd)-
Mild SRI plus $5HT1a$

- Works well for depression and anxiety
- Very low sexual side effects-2 to 5%
- Weight neutral
- Absorbed better with food
- 3A4 metabolism
- Primarily GI side effects
- Dosing 20-40 mg qd (10mg starting dose)
Vortioxetine (Brintellix)-
Mild SRI plus *5HT1, 5HT3* and *5HT7*

- Works well for depression and anxiety
- Sexual side effect data-libido, arousal….
- Weight neutral
- 61% remission after 3 months of treatment
- 2D6 Metabolism
- Primarily GI side effects
- Dosing 10-20 mg qd (5 mg starting dose)
Major Depression is associated with significant neurologic and physiologic dysfunction
Residual symptoms and cognitive dysfunction lead to poor long term outcomes
SSRIs are the mainstay of clinical practice but quite often yield partial response and bothersome long term side effects
Among newer options Levomilnacipran-Fetzima raises NE>5HT, has been shown to improve function and is renally excreted
By minimizing 5HT2-Vilazadone-Viibryd and Vortioxetine-Brintellix, have minimal sexual side effects, no weight gain and minimal cognitive blunting
Treat till the brain returns to normal and patients return to normal function
On a scale of 1 to 5, please rate how confident you would be in the diagnosis and management of a patient with Major Depression Disorder:

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident
Post-test ARS Question 2

Mary – 35 year old mother

• Wakes in the morning struggling with depression
• Makes breakfast for her son and daughter
• Heads to work with her head in a fog
• Makes dinner for her family
• Then tries to force a smile on her face as she puts her kids to sleep
• Lays in bed tossing and turning wondering what she’s done wrong to feel this way
Post-test ARS Question 2

As you evaluate Mary, you must realize that the 3 most common symptoms in individuals with MDD are?

1. Sleep, mood and energy
2. Sleep, mood and suicidal thoughts
3. Mood, appetite and concentration
4. Mood, sleep and concentration
Post-test ARS Question 3

In treating Mary’s depression, the most common residual symptoms will include?

1. Sleep difficulties
2. Suicidal thoughts
3. Cognitive difficulties
4. Sleep difficulties and suicidal thoughts
5. Sleep and cognitive difficulties
Post-test ARS Question 4

You consider offering Mary an SSRI for which of the following reasons?

1. They have high remission rates
2. They help depression and anxiety
3. They have low sexual side effect rates
4. They improve functional outcomes
Which antidepressant has shown improvement in cognitive function?

1. Escitalopram
2. Vortioxetine
3. Duloxetine
4. Levomilnacipran
Post-test ARS Question 6

Mary would like to be sexually active and is concerned about medications that might impact her libido. To minimize sexual side effects, you want to avoid which serotonin receptor?

1. 5HT-1
2. 5HT-2
3. 5HT-3
4. 5HT-7
Post-test ARS Question 7

Which antidepressant minimizes 5HT-2 stimulation?

1. Citalopram
2. Vilazodone
3. Desvenlafaxine
4. Vortioxetine
5. Vilazodone and Vortioxetine
Which of the statements below describes your approach to participating in diagnosing and treating Major Depression Disorder (MDD)?

1. I do not participate in the diagnosis and treatment of MDD, nor do I plan to this year.
2. I did not participate in the diagnosis and treatment of MDD before this course, but as a result of attending this course I’m thinking of doing this now.
3. I do participate in the diagnosis and treatment of MDD and I now plan to change my treatment methods based on completing this course.
4. I do participate in the diagnosis and treatment of MDD and this course confirmed that I don’t need to change my methods.