Resistance is Futile: Functional Outcomes for Major Depressive Disorder

Primary Care Updates
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Presenter: Peter J. Knoblich, MD

Educational Partner:
Neuroscience Education Institute
Session 5: Resistance is Futile:
Functional Outcomes for Major Depressive Disorder

Learning Objectives
1. Choose initial evidence-based depression treatment that is specifically suited to the individual patient’s need.
2. Monitor patients with depression over time in order to track treatment adherence, response, and side effects.
3. Make evidence-based treatment adjustments to address residual symptoms and side effects.

Faculty

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Faculty Financial Disclosure Statement
The presenting faculty reports the following:

Dr Knoblich is a consultant/advisor for Lilly USA LLC, and serves on the speakers bureau for Lilly USA LLC and AstraZeneca.

Education Partner Financial Disclosure Statement
The content collaborators at the Neuroscience Education Institute report the following:
Meghan Grady, Director of Content Development, has no financial relationships to disclose.

Acronym List

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHT</td>
<td>serotonin</td>
<td>NRI</td>
<td>norepinephrine reuptake inhibitor</td>
</tr>
<tr>
<td>DA</td>
<td>dopamine</td>
<td>PHQ-9</td>
<td>Patient Health Questionnaire</td>
</tr>
<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual</td>
<td>SERT</td>
<td>serotonin transporter</td>
</tr>
<tr>
<td>EP</td>
<td>Education Partner</td>
<td>SNRI</td>
<td>serotonin norepinephrine reuptake inhibitor</td>
</tr>
<tr>
<td>HA</td>
<td>histamine</td>
<td>SSRI</td>
<td>selective serotonin reuptake inhibitor</td>
</tr>
<tr>
<td>MAOI</td>
<td>monoamine oxidase inhibitor</td>
<td>TCA</td>
<td>tricyclic antidepressant</td>
</tr>
<tr>
<td>NDRI</td>
<td>norepinephrine dopamine reuptake inhibitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NE</td>
<td>norepinephrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNT</td>
<td>number needed to treat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NOS</td>
<td>nitric oxide synthase</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Suggested Reading List


Resistance is Futile: Functional Outcomes for Major Depressive Disorder

SPEAKER
Peter J. Knoblich, MD

Presenter Disclosure Information
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Off-Label/Investigational Discussion
• In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Demographic ARS
How many patients do you see each week who may require treatment for major depression?

1. None
2. 1 to 10
3. 11 to 20
4. 21 to 30
5. 31 to 40
6. 41 to 50
7. 51 to 60
8. > 60

Outcomes Question 1
A 31-year-old man presents complaining of insomnia, constant fatigue, lack of appetite, psychomotor retardation, depressed mood, and feelings of helplessness. He completes the Patient Health Questionnaire with a score of 16, indicating moderate depression. Which of his symptoms might be a particular warning sign for suicidality, warranting further assessment?

1. Insomnia
2. Fatigue
3. Helplessness
4. 1 and 2
5. 1 and 3
Outcomes Question 2

A 44-year-old woman has been taking an SSRI for 3 months. At her follow-up visit, she informs you that although her mood has improved with treatment, she is having problems engaging in sexual activity with her husband. What treatment option might be appropriate to address her sexual dysfunction?

1. Serotonin 2 partial agonist or serotonin 1A partial agonist
2. Serotonin 1A partial agonist or serotonin 2 antagonist
3. Serotonin 2 antagonist or serotonin 1A antagonist
4. Serotonin 1A antagonist or serotonin 2 partial agonist

Outcomes Question 3

A 29-year-old woman has just been diagnosed with major depressive disorder and is being prescribed a selective serotonin reuptake inhibitor (SSRI). In addition to depressed mood, lack of interest in her work or friends, and difficulty sleeping, she has been experiencing aches and pains in her arms, shoulders, and torso. She asks if the SSRI is likely to alleviate her painful physical symptoms as well as her emotional ones. Which of the following statements is true?

1. SSRIs may have inconsistent effects on pain because serotonin can both inhibit and facilitate ascending nociceptive signals
2. SSRIs may worsen pain because serotonin can facilitate but not inhibit ascending nociceptive signals
3. SSRIs generally alleviate pain because serotonin can inhibit but not facilitate ascending nociceptive signals
4. SSRIs generally have no effect on pain because serotonin neither facilitates nor inhibits nociceptive signals

Treating Depression in Adults

Guidelines and Monitoring Patients

Apps for Mood Monitoring and/or Adherence

- Use Apps that track mood to save time, engage the patient, and monitor mood between visits
  - MoodTracker.com https://www.moodtracker.com/
  - MyMoodTracker.com http://www.mymoodtracker.com/

Depression Treatment Guidelines

<table>
<thead>
<tr>
<th>Severity / Impairment</th>
<th>PHQ-9 Score</th>
<th>Initial Strategy</th>
<th>Follow-up (2 weeks):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>10–14</td>
<td>Monotherapy – psychotherapy or antidepressant</td>
<td>Symptoms improving (PHQ-9) Treatment well-tolerated Adherent</td>
</tr>
<tr>
<td>Moderate</td>
<td>15–19</td>
<td>Antidepressant, psychotherapy, or combination</td>
<td>Continue current treatment Reassess by 4-6 weeks</td>
</tr>
<tr>
<td>Severe</td>
<td>≥ 20</td>
<td>May start with antidepressant or psychotherapy but prefer combination</td>
<td>Full remission? Continue to prevent relapse Possible long-term maintenance</td>
</tr>
</tbody>
</table>

Subtotal: TOTAL

Adjust treatment

Antidepressants and Risk of Suicidality

• Efficacy, tolerability, and safety of antidepressants have been studied mostly in individuals between the ages of 19 to 64
• Limited data in children and adolescents suggest increased risk of suicidality
  – Efficacy not well studied, particularly in younger children
• Data show reduced risk of suicidality with antidepressant treatment (vs. without) for adults ages 65 years and older


Suicide Risk Assessment

• Identify risk factors and/or warning signs
• Identify possible protective factors
• Assess level of risk
• Document


Risk Factors for Suicide

<table>
<thead>
<tr>
<th>Immutable</th>
<th>Circumstantial</th>
<th>Modifiable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient's history (experience of trauma/loss, previous attempt, psychiatric illness)</td>
<td>Unemployment</td>
<td>Drinking/drug use</td>
</tr>
<tr>
<td>Family history</td>
<td>Financial difficulties</td>
<td>Nicotine use</td>
</tr>
<tr>
<td>Demographics (male, unmarried, early 20s)</td>
<td>Relationship difficulties</td>
<td>Unstructured time</td>
</tr>
<tr>
<td>Cultural/religious belief about suicide</td>
<td>Physical injury/illness, chronic physical pain</td>
<td>Perceived stress</td>
</tr>
<tr>
<td>Personality traits (impulsive, aggressive)</td>
<td>Life transitions</td>
<td>Current psychiatric illness (depression, alcohol abuse)</td>
</tr>
<tr>
<td>Access to lethal means</td>
<td>Hopelessness, helplessness</td>
<td>Hopelessness, helplessness</td>
</tr>
<tr>
<td>Anxiety, panic attacks, agitation, insomnia*</td>
<td>Anxiety, panic attacks, agitation, insomnia*</td>
<td>Anxiety, panic attacks, agitation, insomnia*</td>
</tr>
<tr>
<td>Delusions</td>
<td>Delusions</td>
<td>Delusions</td>
</tr>
</tbody>
</table>

*Often precede suicide within hours/days/weeks.

Warning Signs: Are Some Symptoms Precursors to Suicidality?

• Anxiety
• Agitation
• Panic attacks
• Insomnia
• Irritability
• Hostility
• Aggressiveness
• Impulsivity
• Restlessness
• Hypomania and mania


Suicide Risk is Highest When:

• The person sees no way out and fears things may get worse
• The predominant emotions are hopelessness and helplessness
• The person is anxious, agitated, has insomnia
• Thinking is constricted with a tendency to perceive his or her situation as all bad
• Judgment is impaired by use of alcohol or other substances


Asking About Suicidality

• Be direct but non-confrontational
• Start with general and move on to more specific
  – Thoughts of death → Suicidal ideation → Suicide plan → Means available → Suicidal intent
• Also ask about family history of suicide and previous suicide attempts

Things to Tell Your Patients About Antidepressants

- Antidepressants only work if taken every day
- Antidepressants are not addictive
- Benefits from medication appear slowly; some symptoms may take longer to resolve than others
- Mild side effects are common, happen early (before therapeutic effects), and usually improve with time
- Notify you of any late-developing or persistent side effects—may require treatment adjustment
- Antidepressants should still be taken even after symptoms abate
- Stopping antidepressant treatment abruptly is dangerous
- Sometimes it takes a few tries to attain remission

Collaboration With a Psychiatrist

- For patients who do not initially respond
- For patients who have intolerable side effects
- When to refer
  - Severe depression with significant impairment in functioning
  - Psychotic or manic features, or history of psychotic/manic symptoms
  - Comorbid psychiatric disorders
  - Suicidal ideation, plan, or intent; family history of suicide
  - Other complicating factors or concerns

Side Effects

Options to Avoid or Address the Most Troublesome Side Effects

Most Troubling Antidepressant Side Effects

Mechanisms Associated With Troubling Short-Term Side Effects
Management of Short-Term Side Effects

- Headaches
  - Slower dose titration
  - Use non-SSRI/SNRI
  - Use OTC analgesics
  - Avoid migraine serotonergic meds and tramadol
- Nausea
  - Slower titration
  - Use OTC symptomatic treatments
  - Add serotonin 3 blockers


Management of Activation

- Propensity for SSRIs to induce activation
  - fluoxetine > sertraline > citalopram/escitalopram/paroxetine
- SNRIs activate too...
  - Activation usually subsides in the first few weeks of treatment
  - First consider a temporary dose reduction or a more gradual up titration
  - Can consider adding a benzodiazepine short term
  - Can consider adding trazodone or mirtazapine


Mechanisms Associated With Troubling Long-Term Side Effects

<table>
<thead>
<tr>
<th>Sedation</th>
<th>Sexual Dysfunction</th>
<th>Weight Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin reuptake inhibition</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Serotonin 2 antagonism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha 1 antagonism</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Histamine 1 antagonism</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Anti-cholinergic</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Nitric oxide synthase inhibition</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Management of Sedation

- Dose at night or take larger dose at night
- Increase daytime exercise
  - If patient is responding and otherwise tolerating current treatment
    - Augment (modafinil/armodafinil, bupropion, atomoxetine, stimulant)*
  - If patient is not responding or if sedation is truly intolerable
    - Switch to a non-sedating antidepressant

* Not FDA approved for this indication


Management of Sexual Dysfunction

- Assess sexual function before starting medication
- Switch to mirtazapine
- Switch to vilaazodone (serotonin 1A effects ≥ serotonin reuptake inhibition)
- Add cyproheptadine, trazodone, or high-dose (60 mg/day) buspirone*
- Add amantadine, bupropion, or stimulant
- Add phosphodiesterase 5 (PDE-5) inhibitor
  - Does not increase desire
- For women, consider estrogen creams

* Not FDA approved for this indication


Short-Term Weight Gain: Meta-analysis

*Filled squares indicate a significant effect

Long-Term Weight Gain: Meta-analysis

*Filled squares indicate a significant effect


Management of Weight Gain

- In meta-analysis, average weight gain is small
  - A few patients may experience large weight gain due to their own genetic predispositions and other factors
  - Large weight gain typically occurs gradually over many months
  - Monitor patients for change in weight, appetite, metabolic factors
  - Diet and exercise
  - If significant weight gain occurs, consider switching to an agent with less risk of weight change
  - Can also consider augmentation (bupropion*, topiramate*, zonisamide*, metformin*, orlistat)*
  - New obesity drugs: topiramate/phentermine, lorcaserin*

* Not FDA approved for this indication

Partial Response

Common Augmentation Strategies

STAR*D: Percent Response and Remission by Levels

The further along treatment goes, the less change actually occurs


Lithium Augmentation: What is the Evidence?

- Augmenting response (meta-analysis)¹
  - 10 studies, various antidepressants
  - Significant benefit vs. placebo; NNT = 4
- Augmenting remission (STAR*D)²
  - Benefit not confirmed
- Accelerating response (meta-analysis)¹
  - 5 studies, tricyclic antidepressants (TCAs)
  - No benefit (trend)
- Overall: evidence strongest for augmenting TCAs

¹ Not FDA approved for this indication

NNT: number needed to treat.

Triiodothyronine (T3) Augmentation: What is the Evidence?

- Augmenting remission (STAR*D)²
  - Trend favoring T3 over lithium (methodological factors?)
- Augmenting response (meta-analysis)¹
  - 8 studies, TCAs
  - Significantly increased response rate; NNT = 4.3
- Augmenting response to SSRI's (various studies)³
  - Mixed results; placebo-controlled study showed no benefit
- Overall: evidence strongest for augmenting TCAs

¹ Not FDA approved for this indication

Atypical Antipsychotic Augmentation: What is the Evidence?

- Studied as adjuncts to SSRIs/SNRIs
- Aripiprazole and quetiapine XR are approved as adjuncts; olanzapine-fluoxetine combo is approved, risperidone has data, lurasidone is being studied...
- Most studies show a beneficial effect of combination treatment over monotherapy, but...
  - Effect sizes have been modest
  - There is little head-to-head data with other strategies
  - The adverse event profiles of atypical antipsychotics should put them late in a treatment algorithm
  - None have been studied systematically for "advanced resistant depression" (>2 failure)

Common but Unsupported and/or Understudied Strategies

- Buspirone¹-⁴
  - Mechanistically makes sense
  - The limited data are mixed/weak
- Stimulants⁵
  - Limited controlled data show trend of benefit


Common but Unsupported and/or Understudied Strategies (cont.)

- DA agonists
  - Pramipexole: evidence of efficacy in unipolar and bipolar depression and for depressive symptoms in Parkinson’s disease¹
  - Ropinirole: effective and well tolerated in a small pilot study of unipolar and bipolar depression²
  - Modafinil/armodafinil: evidence of efficacy in unipolar and bipolar depression³⁴


Common but Unsupported and/or Understudied Strategies (cont.)

- Antidepressant combinations
  - Limited data in poorly responding population
  - Theoretical advantages over switching
    - Preserves the response to the first antidepressant
    - Adds mechanisms of action to "broaden" the neurochemical and thus clinical actions
  - Is any response attributable to Drug B, Drug A+B, or to continued time on Drug A?

¹. Connolly KR, Thase ME. Drugs 2011;71(7):43-64.

Symptom-Specific Strategies for Common Residual Symptoms

### Residual Sleep Disturbances

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Neurotransmitter system involved</th>
<th>Treatment strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia</td>
<td></td>
<td>Optimize sleep hygiene</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cognitive behavioral therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Add melatonin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Add sedative hypnotic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Switch to a sedating antidepressant</td>
</tr>
<tr>
<td>Hypersomnia</td>
<td></td>
<td>Close at night</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ Add modafinil, armodafinil,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>bupropion, atomoxetine, or stimulant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Switch to a less sedating antidepressant</td>
</tr>
</tbody>
</table>

*Not FDA approved for this indication
HA: Histamine. GABA: Gamma Aminobutyric Acid.


### Residual Fatigue and Concentration Problems

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Neurotransmitter system involved</th>
<th>Treatment strategy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>NE</td>
<td>Add switch to bupropion</td>
</tr>
<tr>
<td>Concentration</td>
<td></td>
<td>Add modafinil, armodafinil,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>atomoxetine, or stimulant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Switch to SNRI or MAOI</td>
</tr>
</tbody>
</table>

*Not FDA approved for this indication
MAOI: Monoamine oxidase inhibitor.

### Symptom-Specific Strategies for Common Residual Symptoms

- Fatigue: Add/switch to bupropion, modafinil, armodafinil, atomoxetine, or stimulant.
- Concentration: Use SNRI, TCA, add alpha 2 delta ligand (calcium channel blocker) or sodium channel blocker.

### Residual Pain

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Neurotransmitter system involved</th>
<th>Treatment strategy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>NE</td>
<td>Use SNRI, TCA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Add alpha 2 delta ligand (calcium channel</td>
</tr>
<tr>
<td></td>
<td></td>
<td>blocker) or sodium channel blocker</td>
</tr>
</tbody>
</table>

*Not FDA approved for treating pain in depression

### Depressed Mood Disrupts Brain Deactivation and Enhances Pain Unpleasantness

- 20 healthy volunteers
- Red/green: activation vs. rest
- Blue: deactivation vs. rest
- Significant lack of deactivation during pain in the depressed mood state
- Patients reporting greatest increase in pain unpleasantness after sad mood induction showed greater inferior frontal gyrus and amygdala activation

Plotted on the average MNI 152 brain. Z coordinates are on the MNI system.


### Pain in Depression: The Role of Norepinephrine

SNRIs for Painful Symptoms

- Duloxetine (approved for multiple neuropathic pain disorders)
  - 60 mg once daily; higher doses increase side effects without increasing efficacy in pain disorders
- Milnacipran (approved for fibromyalgia)
  - 30–200 mg/day in 2 doses
- Venlafaxine XR
  - 75–225 mg once daily
- Desvenlafaxine
  - 50 mg once daily
- Tricyclic antidepressants
- Cyclobenzaprine (muscle relaxant)
  - 15 mg/day in 3 doses; 15–30 mg/day in 1 dose (ER)
  - Not recommended for long-term use


Alpha 2 Delta Ligands (Calcium Channel Blockade) for Painful Symptoms

- Pregabalin (approved for multiple neuropathic pain disorders)
  - 150–600 mg/day in 2–3 doses
- Gabapentin (approved for postherpetic neuralgia)
  - 900–1800 mg/day in 3 doses


Relief of Painful Excessive Nociceptive Activity With Alpha 2 Delta Ligands

- Antiepileptic and neuropathic pain medications may be helpful
  - Carbamazepine
  - Lamotrigine
  - Topiramate


Sodium Channel Blockers

- Carbamazepine
- Oxcarbazepine
- Zonisamide


Non-Pharmacologic Treatments to Address Partial Response

- Electroconvulsive therapy (ECT)
- Vagus nerve stimulation (VNS)
- Repetitive transcranial magnetic stimulation (rTMS)
- Deep brain stimulation (DBS)
- Psychotherapy
  - Augmentation may decrease depressive symptoms as much as pharmacologic augmentation
- Family therapy
- Coping skills including assertiveness training and problem solving strategies

## Nutraceutical Treatments for Depression

- **I-methylfolate**<sup>1</sup>
  - 15 mg/day
- **S-adenosyl methionine**<sup>2</sup>
  - 800 mg twice per day
- **N-acetyl cysteine**<sup>3</sup>
  - 1000 mg twice per day

<sup>1</sup> Medical food for suboptimal folate levels in depressed patients (adjunct to antidepressant)

<sup>2</sup> Not FDA approved for this indication


## Summary

- Patient education and slower titration can often be sufficient to address early, short-term side effects
- Long-term side effects do not often spontaneously disappear and may require switching or augmentation to avoid patient discontinuation of medication
- Establishing markers and using rating scales can aid in the detection of troubling residual symptoms
- Common residual symptoms can be targeted by using augmentation strategies that apply mechanistic rationale

## Outcomes Question 1

A 31-year-old man presents complaining of insomnia, constant fatigue, lack of appetite, psychomotor retardation, depressed mood, and feelings of helplessness. He completes the Patient Health Questionnaire with a score of 16, indicating moderate depression. Which of his symptoms might be a particular warning sign for suicidality, warranting further assessment?

1. Insomnia
2. Fatigue
3. Helplessness
4. 1 and 2
5. 1 and 3

## Outcomes Question 2

A 44-year-old woman has been taking an SSRI for 3 months. At her follow-up visit, she informs you that although her mood has improved with treatment, she is having problems engaging in sexual activity with her husband. What treatment option might be appropriate to address her sexual dysfunction?

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2. Serotonin 1A partial agonist or serotonin 2 antagonist
3. Serotonin 2 antagonist or serotonin 1A antagonist
4. Serotonin 1A antagonist or serotonin 2 partial agonist

## Outcomes Question 3

A 29-year-old woman has just been diagnosed with major depressive disorder and is being prescribed a selective serotonin reuptake inhibitor (SSRI). In addition to depressed mood, lack of interest in her work or friends, and difficulty sleeping, she has been experiencing aches and pains in her arms, shoulders, and torso. She asks if the SSRI is likely to alleviate her painful physical symptoms as well as her emotional ones. Which of the following statements is true?

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## Question & Answer