Cognitive Dysfunction in Major Depression: Impactful Education for Impactful Outcomes

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Faculty Disclosure

- Dr. Rakesh Jain: Paid Speaker—Addrenex, Alkermes, Allergan (Actavis/Forest), Lilly, Lundbeck, Merck, Neos Therapeutics, Otsuka, Pamlab, Pfizer, Rhodes Pharmaceuticals, Shionogi, Shire, Sunovion, Takeda, Tris Pharmaceuticals; Advisory Board—Addrenex, Alkermes, Forum, Lilly, Lundbeck, Merck, Neos Therapeutics, Otsuka, Pamlab, Pfizer, Shionogi, Shire, Sunovion, Takeda; Research—AstraZeneca, Allergan (Actavis/Forest), Lilly, Lundbeck, Otsuka, Pfizer, Shire, Takeda; Spouse: Consultant—Lilly, Otsuka, Pamlab.
Disclosure

• The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).
  – The off-label use of erythropoietin, galantamine, lisdexamfetamine, minocycline, modafinil, N-acetylcysteine, omega-3 polyunsaturated fatty acids, S-adenosyl methionine, scopolamine, statins, and thiazolidinediones for the treatment of major depressive disorder will be discussed.

• Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.

• This activity has been independently reviewed for balance.

Learning Objectives

• Apply validated assessment tools, such as CPFQ, to routine practice in order to adequately identify and monitor cognitive dysfunction and other symptoms of major depressive disorder (MDD)

• Describe the latest data on available therapies for MDD, including mechanisms of action, receptor affinity, and the relevance to targeted symptom control

• Utilize the latest evidence to make informed MDD treatment decisions that accommodate specific patient needs and optimize outcomes in patients experiencing cognitive dysfunction

Introduction
The Course of Major Depression – and Why Early and Sustained Control is Critical

MDD is major depressive disorder.

Depression is a Clinically Heterogeneous Disorder with Emotional, Physical, and Cognitive Symptoms

MDD is like a 3-legged stool (all 3 legs are important).

Cognitive Symptom Complex is Number 2 among All Symptoms of MDD in Causing Impairment

Data from 3703 depressed outpatients in the first treatment stage of the STAR*D study.

STAR*D = Sequenced Treatment Alternatives to Relieve Depression.
The Impact of Individual Depressive Symptoms on Impairment of Psychosocial Functioning – Importance of Cognitive Dysfunction

Cognitive Dysfunction is:
- Common
- Commonly missed
- Commonly underestimated in importance
  - Under-represented even in DSM-5 criteria

(receives only 1 criteria out of 9)
Cognitive Dysfunction is impairing, and often “lost” in the mix with emotional and physical symptoms of MDD

Can SSRIs Induce Cognitive Dysfunction? Results from a Survey

Even response to an antidepressant is not a guarantee of cognitive symptom improvement. In fact, they may worsen cognitive symptoms in a fair number of patients.

“...it is likely that these symptoms are both side effects of the antidepressants as well as residual symptoms of MDD.”

Many Antidepressants Can Actually Harm Cognition – Clinicians Beware

Prospective cohort study of 104 with assessments at 6 and 12 months post-injury. On and off antidepressants, and with and without MDD
Neurobiology of MDD: A Brief Examination of Emergent Data and Clinical Goal Setting in MDD

In MDD, Network Efficiency is Impaired

Increased in Affective Processing and Decreased in Cognitive Processing

Nodal efficiency was found to increase in affective processing regions (e.g., amygdala, thalamus, hippocampus).

Decrease in cognitive control-related regions, which included dorsolateral prefrontal cortex and anterior cingulate cortex.

MDD and Cognition: A Downward Spiral with Strong Neurobiological Underpinnings

Cognitive-vulnerability factors for MDD and corresponding neural mechanisms in intrinsic networks using a dual-process framework. The study authors propose that the dynamic alteration and imbalance among the intrinsic networks, both in the resting state and the rest-task transition stages, contribute to the development of cognitive vulnerability and MDD.
Serotonin, Through Multiple 5-HT Receptor Subtypes, Control a Large Number of Mood Related Functions

5-HT = serotonin; DR = dorsal raphe; GABA = gamma-aminobutyric acid; Glu = glutamate; LC = locus coeruleus; mGluR = metabotropic glutamate receptor; mPFC = medial prefrontal cortex; VTA = ventral tegmental area.

A Point Worthy of Note

The neurobiology of Cognitive Dysfunction in MDD is well characterized, and it involves macrostructures (such as brain networks) to microstructures (individual receptors)

A Focused Examination of the Impact of Cognitive Symptoms and Impairments in MDD
Cognitive Dysfunction across Psychiatric Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Attention</th>
<th>Memory</th>
<th>Working Memory</th>
<th>Executive Function</th>
<th>Semantic Memory</th>
<th>Visuospatial Memory</th>
<th>Verbal Memory</th>
<th>Procedural Memory</th>
<th>Processing Speed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Depression</td>
<td>++ (+)</td>
<td>++ (+)</td>
<td>++ (+)</td>
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<td>++ (+)</td>
<td>++ (+)</td>
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<tr>
<td>Bipolar Disorder</td>
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<tr>
<td>Schizophrenia</td>
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<tr>
<td>ASD</td>
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<td>+ (+)</td>
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<tr>
<td>ADHD</td>
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<td>++</td>
<td>++</td>
<td>++ (+)</td>
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<tr>
<td>PTSD</td>
<td>+++</td>
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<td>++</td>
<td>++</td>
<td>++</td>
<td>++ (+)</td>
<td>+ (+)</td>
</tr>
<tr>
<td>Panic Disorder</td>
<td>+ (+)</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+ (+)</td>
<td>+ (+)</td>
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<tr>
<td>SAD</td>
<td>+ (+)</td>
<td>+</td>
<td>+ (+)</td>
<td>+ (+)</td>
<td>+ (+)</td>
<td>+ (+)</td>
<td>+ (+)</td>
<td>+ (+)</td>
<td>+ (+)</td>
</tr>
<tr>
<td>Parkinson’s Disease</td>
<td>+ (+)</td>
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<td>+ (+)</td>
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</tbody>
</table>

1. Cognitive Dysfunction can be present during “active” disease, as well as a residual symptom
2. Also, the 4 areas of Cognitive Dysfunction to note in MDD are
   1) Attention
   2) Memory
   3) Executive Function
   4) Psychomotor Speed
We Could Just Rely on Standard Depression Rating Scales, BUT…

They Underestimate Cognitive Difficulties

Assessing Residual Cognitive and Physical Symptoms are Poorly Done by Most Depression Rating Scales

<table>
<thead>
<tr>
<th>HAM-D</th>
<th>MADRS</th>
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<tbody>
<tr>
<td>Retardation (slowness of thought and speech; impaired ability to concentrate, decreased motor activity)</td>
<td>Difficulties in concentrating and sustaining thought, which reduces ability to read or hold a conversation</td>
</tr>
<tr>
<td>BDI</td>
<td>PHQ</td>
</tr>
<tr>
<td>I have greater difficulty in making decisions than I used to</td>
<td>Trouble concentrating on things, such as reading the newspaper or watching TV</td>
</tr>
</tbody>
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Standard depression scales do not assess all cognitive or physical symptom domains

Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ)

An excellent instrument to detect and monitor Cognitive Dysfunction
Massachusetts General Hospital CPFQ

- Self-rated scale, sensitive to treatment, short, easy to use clinically
- 7 items, 4 specifically assess cognition
  - Motivation/interest/enthusiasm
  - Wakefulness/alertness
  - Energy
  - Focus/sustain attention
  - Remember/recall information
  - Find words
  - Sharpness/mental acuity
- Each item rated 1 (greater than normal) to 6 (totally absent)
  - Higher scores indicate greater impairment

We Can Elevate Our Clinical Practices by Inquiring about the Following Symptoms in Symptomatic, Partial Responder, and Remitted Patients

1. Memory problems
2. Poor concentration
3. Expressing thoughts
4. Word finding
5. Slow thinking
6. Problem solving

Key is: Routine, Routine, Routine Assessment!
Examining Treatment Options: Focus on Both Non-pharmacologic and Pharmacologic Treatment Options

First, Let’s Examine the Non-pharmacologic Treatment Options

Why Physical Exercise Matters in Reversing Cognitive Challenges

“Many psychiatric and neurological disorders have been associated with hippocampal dysfunction, which may underlie the expression of certain symptoms common to these disorders, including aspects of cognitive dysfunction.”

Major Depression causes the following damage / NEGATIVE changes in the hippocampus:

1. Macro Changes
   1. Gray matter changes
   2. White matter changes
2. Micro Changes
   1. Neurogenesis
   2. Synaptic plasticity
   3. Vasculature
   4. Neurotrophic factors

Aerobic Exercise causes the following damage / POSITIVE changes in the hippocampus:

1. Macro Changes
   1. Gray matter changes
   2. White matter changes
2. Micro Changes
   1. Neurogenesis
   2. Synaptic plasticity
   3. Vasculature
   4. Neurotrophic factors

Changes in spatial working memory outcomes over 12 weeks of exercise. Participants randomized to receive high dose exercise (16 KKW) performed significantly better on the spatial working memory task with respect to generation of fewer errors on the most complex problems (8 boxes) \((P < .04)\) and showed trends \((P < .06)\) on the 4 box problems as well as the strategy score, which is indicative of effective completion of the task. In contrast, participants in the low dose exercise group generated more errors \((P < .04)\) and showed less efficient use of strategy over time \((P < .04)\).

How Antidepressants and Exercise May Work on Depression and Cognition

AD = antidepressant.

Normal epigenetic regulation of hippocampal neurogenesis promotes the stable generation of new neurons in the dentate gyrus, maintaining the homeostatic brain function.

ADs administration may restore the regulatory function of epigenetic regulation thus allowing the recovery from depressive symptomatology.

Impaired epigenetic regulation of hippocampal neurogenesis due to environmental stressors results in reduced formation of new neurons possibly accounting for the behavioral and cognitive deficits associated to depression.

2 Points Worthy of Note

1. Non-pharmacologic treatments for cognitive dysfunction are a growing body of literature

2. How much we exercise and what we eat, does matter – even from a cognitive perspective
Pharmacologic Treatment Options

Question to Ponder: How Can an Antidepressant Have Pro-Cognitive Effects?

- By positively impacting "hot" cognition
- By positively impacting "cold" cognition
- Through neurogenesis, particularly in the dentate region of the hippocampus
- Through reducing cognitive bias that is inherent in major depression
- Through altering glucose metabolism in various pro-cognitive regions of the brain
- Through impacting glutamate / GABA balance


Effects of Antidepressants on Cognitive Function in MDD

<table>
<thead>
<tr>
<th>Drug</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>Duloxetine</td>
<td></td>
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<tr>
<td>Escitalopram</td>
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<tr>
<td>Fluoxetine</td>
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<tr>
<td>Paroxetine</td>
<td></td>
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<tr>
<td>Vortioxetine</td>
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</tbody>
</table>

Study Design/Endpoint Duration: Elderly 8 vs 8 weeks, Adults 21 vs 28 weeks, Elderly 4 vs 8 weeks, Elderly 8 vs 156 weeks, Elderly 8 vs 30 weeks, Elderly 6 vs 1 year, Elderly 4 vs 1 year, Elderly 8 vs 4 weeks

- Cognitive Isaac: 
  - Attention
  - Working memory
  - Executive function
  - Processing speed
  - Memory
  - Inital memory

(1) = function still remained lower than that of controls.
"Hot" and "Cold" Cognition: An Emerging Concept in Mental Health

Emotional processing; response to negative feedback. Changes in the "hot" system are more likely to be associated with antidepressant response.

Emotion-independent; logical thinking and executive control (executive, attention, perception, and psychomotor functions)

Mechanism of Action of Various Antidepressants

SSRI and Bupropion Treatment Can Improve Cognition
Comparing 2 Different Mechanisms of Action: Antidepressants in Patients with Depression

Improvement from baseline compared with placebo at week 8 in patients ≥ 65 years

DSST and RAVLT Exploratory Endpoints

**Effects on Cognitive Function Cannot Be Solely Explained by Improvements in Mood**

Path analysis showed that in addition to improving cognitive function indirectly through the alleviation of depressive symptoms, vortioxetine exerts direct effects on depression-related cognitive impairments as measured by patient performance in relevant tests (DSST) and RAVLT acquisition.

**Examining the Evidence for Direct Impact on Cognitive Symptoms in MDD**

Antidepressants and psychotropic agents that improve measures of cognition in individuals with MDD independent of improvements in measures of depressive symptom severity.
Cognitive Remission

Cognitive Remission
Emerging Concept, Emerging Agents


Ascending level of evidence for Cognitive Symptom Improvement

We Clinicians Should Re-examine Our Own Understanding of Cognitive Symptoms in MDD


Those cognitive signs can persist even after remission or recovery of MDD symptoms.

Stakeholders Need to Come to a Consensus

2 Points Worthy of Note

1. Pharmacologic treatments can impact cognitive dysfunction, and a growing body of literature is emerging on this topic

2. Receptor pharmacology of various agents appears to have some importance in addressing cognitive dysfunction

Take-Home Messages

1. Residual symptoms, including Cognitive Dysfunction, are the rule, and not the exception in MDD

2. All 3 sets of residual symptoms are frequent – and they matter
   • Emotional
   • Cognitive
   • Physical

3. Mechanism of action of various antidepressants is important in both its efficacy and side-effect profile

4. Fitting the appropriate intervention with the specific patient needs is state of the art practice in 2017