Improving Outcomes in Major Depression: A Focus on Cognitive Symptoms

Faculty Disclosure

Dr. Rakesh Jain: Consultant—Addrenex, Allergan, Lilly, Lundbeck, Merck, Otsuka, Pamlab, Pfizer, Shionogi, Shire, Sunovion, Takeda (Spouse: Lilly, Otsuka, Pamlab); Speakers Bureau—Addrenex, Allergan, Lilly, Lundbeck, Merck, Otsuka, Pamlab, Pfizer, Shionogi, Shire, Sunovion, Takeda; Research Support—AstraZeneca, Allergan, Lilly, Lundbeck, Otsuka, Pfizer, Shire, Takeda.

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 buspirone, erythropoietin, lisdexamfetamine, lithium, modafinil, tryptophan, and triiodothyronine 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.
Introduction
&
Taking a Measure of
Major Depression’s Impact

Depression is Associated with Significant Economic Costs

- Unipolar depression is the leading cause of global disease burden among mental, neurological, and substance use disorders
- The total annual cost of depression in Europe was estimated at €118 billion in 2004, which corresponds to a cost of €253 per inhabitant
- $44 billion cost to US employers in 1 year

DALY = disability-adjusted life-year; COPD = chronic obstructive pulmonary disease.


Mental Health Disorders 23%
Cancer 16%
Other Conditions 45%
Cardiovascular Disease 16%

Burden of Disease: Leading Individual Disease/Disorder Contributors

1. Unipolar depression 4.4%
2. Ischemic heart disease 4.0%
3. Alcohol-use disorders 3.4%
4. COPD 3.4%
5. Trachea/bronchus/lung cancer 3.0%
6. Hearing loss, adult onset 3.0%
7. Alzheimer’s disease/dementia 2.9%
8. Cardiovascular disease 2.6%

Total DALYs: USA and Canada (%)

Data courtesy of World Health Organization

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

Sadness
Anxiety
Inability to concentrate
Suicidal ideation
Hopelessness
Guilt

Difficulties with attention and concentration
Short- and long-term memory
Decision-making
Planning and organization
Mental flexibility
Word-finding
Thinking speed

Emotional
Cognitive
Physical

Symptom Dimensions of MDE

- Fatigue or loss of energy
- Indecisiveness or diminished ability to think
- Significant appetite or weight changes
- Worthlessness or guilt
- Suicidal ideation
- Insomnia or hypersomnia
- Psychomotor agitation or retardation

- ALL symptoms are important!
- Symptoms are often under-recognized and underappreciated every day in clinical practice
- Each one of these symptoms, by themselves, or in combinations, can become Residual Symptoms

* Depressed Mood
  * Anhedonia

Point Worthy of Note

Cognitive Dysfunction is under-represented even in DSM-5 criteria (receives only 1 criteria out of 9)

Patient Perception of Burden from Individual Symptoms of Major Depression
Patient Perspective on the Most Common Diagnostic Symptoms of MDD: An Unequal Distribution

From a 13-year study following a general population sample in the Baltimore Epidemiologic Catchment Area (N = 1920)

Proportion of MDD patients with symptoms during MDEs (n = 100)

Depressed mood
Sleep problems
Trouble thinking
Appetite problems
Thoughts of death
Lost of interest
Tiredness
Worthlessness
Trouble thinking


MDD diagnosis was based on DSM-III-R criteria and symptoms were assessed by the National Institute of Mental Health Diagnostic Interview Schedule. MDD = major depressive disorder.

Cognitive Symptoms of Depression Have a Negative Impact on All Aspects of a Patient’s Life

Cognitive dysfunction and general functioning are linked; both have an impact on clinical outcomes


Point Worthy of Note

Cognitive Dysfunction is impairing, and often “lost” in the mix with emotional and physical symptoms of MDD
Neurobiology of MDD: A Brief Examination of Emergent Data
& Clinical Goal Setting in MDD

Cognition Related Brain Networks Underpin Symptoms of Major Depression

How We Humans Create Cognition A Neuropsychiatric Perspective
MDD is Associated with Reductions in Volume in Areas of the Brain Associated with Higher Cognitive Functions

- Working memory
- Executive function
- Strategic planning
- Decision-making
- Emotional processing
- Cognitive flexibility
- Reward processing
- Adaptive learning
- Social cognition
- Facial recognition

27% decrease 19% decrease 8%-11% decrease 11% decrease

MDD is Associated with Reductions in Volume in Areas of the Brain Associated with Higher Cognitive Functions

n = 102, MDD; n = 34, controls. FG = fusiform gyrus.

Depressed Patients Display Negative Biases in Attention, Working, and Verbal Memory

Eye-tracking studies show that depressed patients preferentially attend to negatively-valenced stimuli while healthy controls show no such biases

Depressed patients are slower to disengage from sad stimuli during affective working memory tasks and faster to disengage from happy stimuli while healthy controls display the opposite bias


Serotonin, Through Multiple 5-HT Receptor Subtypes, Control a Large Number of Mood Related Functions

SHT = serotonin; DR = dorsal raphe; GABA = gamma-aminobutyric acid; Glu = glutamate; LC = locus coeruleus; mGluR = metabotropic glutamate receptor; MnR = median raphe; mPFC = medial prefrontal cortex; VTA = ventral tegmental area.
The neurobiology of Cognitive Dysfunction in MDD is well characterized, and it involves macrostructures (such as brain networks) to microstructures (individual receptors).

The Ultimate Treatment Goal in Depression is Full Functional Recovery

<table>
<thead>
<tr>
<th>Treatment goals in depression have evolved</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response</strong></td>
</tr>
<tr>
<td>Many symptoms remain</td>
</tr>
<tr>
<td>1970s</td>
</tr>
<tr>
<td>Reduction of symptoms (eg, ≥50% of MADRS or HAM-D score)</td>
</tr>
</tbody>
</table>

HAM-D = Hamilton Rating Scale for Depression; MADRS = Montgomery-Åsberg Depression Rating Scale.

Nearly half of depressed patients who achieve "remission" do not consider themselves to be in remission.

A Focused Examination of the Impact of Cognitive Symptoms and Impairments in MDD

| Definition varies between studies, but commonly ≤20 or ≤11, or HAM-D17 score ≤7 | Expectations not yet formally defined; measures should include clinician ratings, self-reports, and performance testing to assess symptoms and functioning |
### Cognitive Dysfunction across Psychiatric Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Attention</th>
<th>Vigilance</th>
<th>Working Memory</th>
<th>Executive Function</th>
<th>Episodic Memory</th>
<th>Semantic Memory</th>
<th>Visual 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>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Bipolar Disorder</td>
<td>+</td>
<td>+</td>
<td>( + )</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>( + )</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>ASD</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>0 / +</td>
<td>+++</td>
<td>0 / +</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>ADHD</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>0 / +</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>OCD</td>
<td>+++(↑)</td>
<td>+(+)</td>
<td>++</td>
<td>+</td>
<td>0 / +</td>
<td>0 / +</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>PTSD</td>
<td>+++(↑)</td>
<td>+(+)</td>
<td>+(+)</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>0 +</td>
<td>++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Panic disorder</td>
<td>+++</td>
<td>+</td>
<td>0 / +</td>
<td>+</td>
<td>0 / +</td>
<td>0 / +</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>GAD</td>
<td>+</td>
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<td>00+++00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parkinson's Disease</td>
<td>++</td>
<td>++(+)</td>
<td>++</td>
<td>+</td>
<td>0 / +</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Alzheimer's Disease</td>
<td>+(+)</td>
<td>+(+)</td>
<td>+(+)</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

**Note:**
- ++ = consistently present and pronounced;
- +++ = a core, severe, and virtually universal characteristic of the disorder;
- () = an intermediate magnitude of effect;
- ↑ = increased;
- 0 / + = poorly documented;
- ADHD = attention-deficit/hyperactivity disorder;
- ASD = autism spectrum disorder;
- GAD = generalized anxiety disorder;
- OCD = obsessive-compulsive disorder;
- PTSD = posttraumatic stress disorder.


### All 3 Domains of Depression

(Emotional, Cognitive, and Physical)

are Highly Prevalent Residual Symptoms of Depression

**Percentage of time that patients met DSM-IV criteria per symptom cluster**

![Percentage of time that patients met DSM-IV criteria per symptom cluster](image)


### Incidence of Residual Symptoms Self-Reported Remission Rates

Depressive symptoms in remitted depressed outpatients according to HAM-D_17, who do and do not consider themselves to be in remission

<table>
<thead>
<tr>
<th>CISDR Symptom</th>
<th>Self-Reported Remission (n=77)</th>
<th>Self-Reported Not in Remission (n=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed onset</td>
<td>17.1%</td>
<td>5.6%</td>
</tr>
<tr>
<td>Poor appetite</td>
<td>14.1%</td>
<td>29.4%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>19.7%</td>
<td>29.2%</td>
</tr>
<tr>
<td>Arterial</td>
<td>14.1%</td>
<td>29.2%</td>
</tr>
<tr>
<td>Hypochondria</td>
<td>5.3%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Hypochondria</td>
<td>5.3%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Psychomotor agitation</td>
<td>7.9%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Psychomotor retardation</td>
<td>11.8%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>19.7%</td>
<td>57.1%</td>
</tr>
<tr>
<td>Hypersomnia</td>
<td>5.3%</td>
<td>41.9%</td>
</tr>
<tr>
<td>Psychomotor agitation</td>
<td>7.9%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Psychomotor agitation</td>
<td>7.9%</td>
<td>7.6%</td>
</tr>
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<td>7.6%</td>
</tr>
<tr>
<td>Psychomotor agitation</td>
<td>7.9%</td>
<td>7.6%</td>
</tr>
</tbody>
</table>

**Note:**
- *P < .05, **P < .01, ***P < .001;
- Due to missing data, sample size varied from 75 to 71.
- Due to missing data, sample size varied from 60 to 63.

Depressive Symptoms Persist during Periods of Remission and Subsequent Depressive Episodes


Mean proportion of time symptoms are present during 3-year follow-up period (N = 267)

Importance of all 3 sets of residual symptoms is highlighted:
- Emotional Symptoms
- Cognitive Symptoms
- Physical Symptoms

Lack of energy
Sleeping problems
Worthlessness/guilt
Eating problems
Psychomotor problems
Death ideations
Cognitive problems
Core symptoms: depressed mood/↓interest

Disease State
Acute Episode
Severity of affective symptoms
>1/3 suffer in remission

Disease Course Variables
- Number of depressive episodes
- Number of hospitalizations
- Course of illness
- Age of onset
- Years with illness

Function
- Poor reintegration at work
- Employment
- Social function
- Readiness for cognitive therapies

CLINICAL CHARACTERISTICS
- severity of affective symptoms
- >1/3 suffer in remission

Patients with Depression Often Report Experiencing Cognitive Symptoms

Key Domains of Cognitive Function
- Brain is cloudy
- Slow motion
- Inadequate
- Loss of short- and long-term memory
- Forgetful
- Lacked confidence
- Lack of focus
- Concentration difficulties
- Not listening
- Less brain of thought
- Attention deficit


2 Points Worthy of Note

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

Now That We Appreciate That Cognitive Dysfunction is Common and Impactful, How Do We Screen for It in Everyday Clinical Practice?

Some Practical Tips

There are Multiple Ways to Measure Clinical Outcomes in Depression

In clinical practice, physicians and patients take a less empirical approach, often with differing priorities

<table>
<thead>
<tr>
<th>Key Treatment Priorities</th>
<th>Physician</th>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Remission</td>
<td>1. Response</td>
<td></td>
</tr>
<tr>
<td>2. Avoidance of relapse</td>
<td>2. Reduction in cognitive symptoms</td>
<td></td>
</tr>
<tr>
<td>3. Improvements in social function</td>
<td>3. Reduction in anxiety symptoms</td>
<td></td>
</tr>
<tr>
<td><strong>Criteria for Remission</strong></td>
<td><strong>Decrease in negative affect symptoms</strong></td>
<td><strong>Increase in positive affect symptoms</strong></td>
</tr>
<tr>
<td><strong>Return to normal function</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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>
</tr>
</thead>
<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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>• I have greater difficulty in making decisions than I used to</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PHQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Trouble concentrating on things, such as reading the newspaper or watching TV</td>
</tr>
</tbody>
</table>

Standard depression scales do not assess all cognitive or physical symptom domains

HAM-D = Hamilton Rating Scale for Depression; MADRS = Montgomery-Åsberg Depression Rating Scale; BDI = Beck Depression Inventory; PHQ = Patient Health Questionnaire.

Selection of Neuropsychological Tests Involves Cognitive Domains Known to Be Affected in MDD

DSST = Digit Symbol Substitution Test; RAVLT = Rey Auditory Verbal Learning Test.


Primary endpoint (composite score)

- DSST: A measure of executive function, working memory, processing speed, and insspatial attention
- RAVLT: A measure of verbal learning and memory
- STROOP: A measure of mental [attentional] vitality and cognitive flexibility/response inhibition
- Trail Making B: A measure of executive control and cognitive flexibility/set-shifting
- Trail Making A: A measure of attention, visual searching, and mental processing speed
- Simple Reaction time task: A measure of psychomotor function/speed of processing
- Choice Reaction time task: A measure of psychomotor function/speed of processing
2 Excellent Supplemental Scales to Measure Cognitive Dysfunction:
Perceived Deficits Questionnaire (PDQ-5)
Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ)

### PDQ-5

The following questions describe problems people may have with their memory, attention, or concentration. Please select the best response based on your experiences during the past 7 days.

<table>
<thead>
<tr>
<th>Question</th>
<th>Never</th>
<th>Rarely</th>
<th>Slightly</th>
<th>Often</th>
<th>Almost Always</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Have you trouble getting things organized?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>2. Have you trouble communicating or speaking well?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>3. Forget the details involved in writing a report?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>4. Forget what you learned after a short lesson?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>5. Feel like you need more mental focus?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

- **Patient-reported**
- **Total score 0–20**
  - The higher the score, the more frequent the symptoms

### 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

Fehnel SE, et al. CNS Spectr. 2013; [Epub ahead of print]
We Can Elevate Our Clinical Practices by Inquiring about the Following Symptoms in Symptomatic, Partial Responder, and Remitted Patients

Dear Patient, Are You Having Trouble with...

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

Routine, Routine, Routine Assessment for Residual Symptoms is Appropriate

Real World, Clinical Examples of Questions We Clinicians Can Ask Our Patients...

<table>
<thead>
<tr>
<th>Cognition Domain</th>
<th>What is it?</th>
<th>Real-World Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention/vigilance</td>
<td>Responding correctly to targets while not responding to distractions during a series of rapidly presented stimuli</td>
<td>Being able to read a book or pay attention in a meeting</td>
</tr>
<tr>
<td>Working memory</td>
<td>Maintaining and retrieving information in mind for brief (approximately 5-20 seconds) periods of time</td>
<td>Remembering a phone number just given to you</td>
</tr>
<tr>
<td>Verbal learning and memory</td>
<td>Remembering verbal information over longer periods of time (minutes to years)</td>
<td>Remembering the items someone told you to purchase at the supermarket</td>
</tr>
<tr>
<td>Visual learning and memory</td>
<td>Remembering visual information over longer periods of time (minutes to years)</td>
<td>Remembering where you put something in a closet</td>
</tr>
<tr>
<td>Reasoning and problem solving</td>
<td>The ability to apply strategies effectively</td>
<td>Arriving on time for work even though your bus schedule has changed</td>
</tr>
<tr>
<td>Speed of processing</td>
<td>Responding quickly and accurately when executing relatively simple tasks</td>
<td>Using a touch-screen computer to serve customers at a fast-food restaurant</td>
</tr>
<tr>
<td>Social cognition</td>
<td>Effectively processing social information, such as facial expressions and emotions, and the meaning of social interactions</td>
<td>Avoiding by looking at someone-whether they are angry at you or not-being able to take someone’s point of view in a conversation</td>
</tr>
</tbody>
</table>
Examining Treatment Options: Focus on Both Nonpharmacologic and Pharmacologic Treatment Options

First, Let’s Examine the Nonpharmacologic Treatment Options

Nonpharmacologic Treatments to Improve Cognitive Dysfunction in MDD

The following treatments have demonstrated positive studies in improving cognitive dysfunction in MDD
- Neuropsychological Educational Approach to Remediation (NEAR), a computerized cognitive retraining package (PSSCogReHab)
- Psychodynamic psychotherapy
- Sahaj Yoga Meditation
- Electroconvulsive Therapy
- Physical Exercise

At a cellular level, preliminary research suggests that cognitive training may influence spine density, synaptogenesis, and vascular supply to the brain. Additionally, it may promote glial and metabolic activity, brain-derived neurotrophic factor and hippocampal neurogenesis.

"Running Away from Your Problems"
Physical Exercise and Cognition


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 (\(P < .04\)).

Diet and Exercise Change Gut Microbiota – and Both Positively and Independently Impact Cognition


Impact of Diet and Exercise are “orthogonal” – ie, independent of each other.

2 Points Worthy of Note

1. Nonpharmacologic 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 Pre-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


Pharmacologic Approaches for the Treatment of Symptoms following Inadequate Response to SSRIs

Treatment-Resistant Depression

Early Pharmacologic Approaches
- Increase dose
- Switch

Switch

Then, discontinue use of a different pharmacologic class if new symptoms are less well tolerated

Pharmacologic Approaches for the Treatment of Symptoms following Inadequate Response to SSRIs

(continued)

Further Management

1. Add CBT
2. Augmentation
3. Antidepressant combination (mirtazapine with SSRI or SNRI)
4. Atypical antipsychotic augmentation
5. Lithium augmentation

Further Management

Switch to another class
Augmentation
Residual Symptoms of Depression


Within or Out of Class Treatment Switch in SSRI-Resistant Patients: Which is Superior?

A meta-analysis of 4 clinical trials (N = 1496) found a modest yet statistically significant advantage in remission rates when switched to a different class rather than another SSRI

*The top box represents the sertraline-venlafaxine pairwise comparison and the bottom box the sertraline-bupropion pairwise comparison. NNT = number needed to treat; SSRI = selective serotonin reuptake inhibitor. Papakostas GI, et al. Biol Psychiatry. 2008;63(7):699-704.

A meta-analysis of 4 clinical trials (N = 1496) found a modest yet statistically significant advantage in remission rates when switched to a different class rather than another SSRI

Risk Ratio

Combined

NNT = 22

"Real-World" Efficacy of Antidepressants: Evidence from Second-Line Treatment in STAR*D

Response and remission rates in patients following switch from first-line treatment with citalopram

Switch

Response Remission

n = 2876 n = 239 n = 238 n = 250

Citalopram
Bupropion
Sertraline
Venlafaxine

At entry, 80% of patients had recurrent or chronic depression; mean number of episodes: 6; mean duration: 25 months

**Real-World** Efficacy of Antidepressants Evidence from Third-Line Treatment in STAR*D

- Treatment augmentation with an atypical agent resulted in
  - Response rate 44.2% vs 29.9% for placebo
  - Remission rate 30.7% vs 17.2% for placebo
- Efficacy risk difference between augmentation with an atypical agent vs placebo translated into
  - NNT of 9 for response
  - NNT of 9 for remission
- Risk difference for discontinuation due to adverse events with atypical agent vs placebo resulted in an NNH of 17

Atypical Antipsychotic Augmentation of SSRI Treatment: A Meta-Analysis of Placebo-Controlled Trials

- In a multicenter, randomized, double-blind, placebo-controlled study of 362 patients with MDD, remission rates were 26.0% with adjunctive aripiprazole and 15.7% with adjunctive placebo (P = .011)
  - At 6 weeks, the mean change in MADRS total score was significantly greater in patients receiving adjunctive aripiprazole than in those receiving placebo
Common Adverse Effects Responsible for Treatment Discontinuation

In an observational study, adverse events were the most common reason cited for SSRI discontinuation after 3 months.

Most Bothersome Side Effects (N = 406)

- Defined as decreased sexual drive and functioning.


Patients (%)

Sexual Dysfunction in Patients with Untreated MDD

- A meta-analysis of 12 studies revealed a bidirectional association between untreated depression and sexual dysfunction:
  - 6 studies (N = 3285) showed that depression increased the risk of sexual dysfunction by 50% to 70%.
  - 6 studies (N = 11,171) showed that sexual dysfunction increased the risk of depression by 130% to 210%.


“Hot” and “Cold” Cognition: An Emerging Concept in Mental Health

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

- "Cold" cognition: Emotion-independent; logical thinking and executive control (executive, attention, perception, and psychomotor functions).

What Do We Mean When We Say “Cognitive Problems in Depression”?
Examining the Different Cognitive Domains


**Cognition Examples**

<table>
<thead>
<tr>
<th>Hot cognition</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rumination</td>
<td></td>
</tr>
<tr>
<td>Catastrophic reactions</td>
<td></td>
</tr>
<tr>
<td>Bias towards negative stimuli (internal/external)</td>
<td></td>
</tr>
<tr>
<td>Anhedonia (eg, anticipatory anhedonia)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cold cognition</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive function</td>
<td></td>
</tr>
<tr>
<td>Information processing speed</td>
<td></td>
</tr>
<tr>
<td>Learning and memory</td>
<td></td>
</tr>
<tr>
<td>Attention/concentration</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Social cognition</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theory of mind</td>
<td></td>
</tr>
<tr>
<td>Mentalization</td>
<td></td>
</tr>
</tbody>
</table>

"Hot" and "Cold" Cognition Have Different Brain Pathways and Connectivity

Image provided by Roger S. McIntyre, MD, FRCPC

VMPFC = ventromedial prefrontal cortex.


**Effects of Antidepressants on Cognitive Function in MDD**

Drug | Duloxetine | Escitalopram | Fluoxetine | Paroxetine | Vortioxetine
-----|------------|--------------|------------|------------|------------

<table>
<thead>
<tr>
<th>Study Design/ Cognitive Domain</th>
<th>Elderly N = 194 8 wks</th>
<th>Adults N = 37 24 wks</th>
<th>Elderly N = 18 4 wks</th>
<th>Adults N = 36 24 wks</th>
<th>Elderly N = 119 1 year</th>
<th>Elderly N = 123 1 year</th>
<th>Elderly N = 304 8 wks</th>
</tr>
</thead>
</table>

(v) = function still remained lower than that of controls.

Mechanism of Action of Various Antidepressants


2 pharmacologic targets (receptor activity + reuptake inhibition)
SERT 5-HT1A
6 pharmacologic targets (receptor activity + reuptake inhibition)
5-HT7 SERT
Vortioxetine

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
Week 8: FAS, ANCOVA, Cohen’s d
- Vortioxetine 5 mg/day (n = 156)
- Duloxetine 60 mg/day (n = 151)

* * *
†

* P < .05, † P < .01 vs placebo; nominal P-values; n numbers are APTS.

ANCOVA = analysis of covariance; APTS = all-patients-treated set; DSST = Digit Symbol Substitution Test; FAS = full analysis set; RAVLT = Rey Auditory Verbal Learning Test.


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).

On RAVLT acquisition, vortioxetine had a 71% direct effect & duloxetine 65%
On RAVLT delayed recall, vortioxetine had a 72% direct effect & duloxetine 96%

DSST
Vortioxetine
Direct effect
HAM-D
On RAVLT acquisition, vortioxetine had a 71% direct effect & duloxetine 65%
On RAVLT delayed recall, vortioxetine had a 72% direct effect & duloxetine 96%

Data for duloxetine was included as active reference for study validation, not for comparison of effect sizes.

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

<table>
<thead>
<tr>
<th>Learning/ Memory</th>
<th>Attention/ Concentration</th>
<th>Executive Function</th>
<th>Processing Speed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venlafaxine</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>1</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Lisdexamfetamine</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Other (eg, SSRI, SNRI, andripiprazole)</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Modafinil</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Oxytroxetine</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Independent effects indicated by a priori specification, cognition as primary, pathoanalysis, subgroup analysis in nonresponders and nonremitters.
Level 1 replicated placebo-controlled trial evidence with demonstration of independent effect.
Level 2 single placebo-controlled trial evidence with demonstration of independent effect.
Level 3 uncontrolled evidence (eg, testing placebo and case-series) with lack of demonstration of independent effect.


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 2016