The Evolving Psychopharmacology of Major Depressive Disorder:

Narrowing the Treatment Gap

Rakesh Jain, MD, MPH
Clinical Professor, Department of Psychiatry
Texas Tech Health Sciences Center Medical School
Midland, Texas

Vladimir Maletic, MD, MS
Clinical Professor, Psychiatry and Behavioral Science
University of South Carolina School of Medicine
Greenville, South Carolina

Consulting Associate
Division of Child and Adolescent Psychiatry
Duke University Medical Center
Durham, North Carolina

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Position: Rakesh Jain, MD, MPH, is Associate Clinical Professor in the Department of Psychiatry at Texas Tech Health Sciences Center Medical School at Permian Basin, Midland, Texas.

Education: Dr Jain received a medical degree from the University of Calcutta in India. He then attended The University of Texas School of Public Health in Houston, and earned a Master of Public Health degree. He completed a residency in Psychiatry and a fellowship in Child and Adolescent Psychiatry at The University of Texas Medical School in Houston. In addition, Dr Jain completed a postdoctoral fellowship in Research Psychiatry at The University of Texas Mental Sciences Institute in Houston.

Practice: Dr Jain’s research focuses on the effects of medications on short- and long-term treatment of depression, anxiety, pain/mood overlap disorders, attention-deficit/ hyperactivity disorder, and psychosis in adult and child/adolescent populations.

Rakesh Jain, MD, MPH, is a paid consultant for Otsuka/Lundbeck.
Presented by: Vladimir Maletic, MD, MS

Position: Vladimir Maletic, MD, MS, is Clinical Professor of Neuropsychiatry and Behavioral Science at the University of South Carolina School of Medicine in Columbia. He is also a consulting associate in the Division of Child and Adolescent Psychiatry at Duke University Medical Center in Durham, North Carolina.

Education: Dr Maletic earned his medical degree from the University of Belgrade in Yugoslavia, where he also completed his postgraduate studies in Neuroscience at the Center for Multidisciplinary Studies. He then completed a residency in Psychiatry at the Medical College of Wisconsin in Milwaukee and a residency in Child Psychiatry at Duke University Medical Center.

Practice: Dr Maletic’s research focuses on the neurobiology of psychiatric illness, including schizophrenia, mood disorders, anxiety disorders, attention-deficit/hyperactivity disorder, and the regulation of sleep and wakefulness.

Vladimir Maletic, MD, MS, is a paid consultant for Otsuka/Lundbeck.
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Objectives

Describe the imbalance of neurotransmitter systems implicated in MDD and the potential need to target multiple systems in treating MDD

Consider the potential impact of MDD and inadequate treatment response on brain structure, function, and patient outcomes

Discuss the psychopharmacology of current treatment options and the role of augmentation in treating MDD
MDD: The Burden of Inadequate Treatment\textsuperscript{1-5}

In 2012, an estimated 16 million US adults had at least one major depressive episode in the past year; representing 6.9\% of all US adults\textsuperscript{1}

In a 2005 analysis of the National Comorbidity Survey Replication (NCS-R), only 38\% of patients treated for MDD received minimally adequate treatment\textsuperscript{*2}

\textbf{US adult patients with MDD in the past 12 months (N=623)}\textsuperscript{2}

51.7\% received treatment in any healthcare setting\textsuperscript{2}

Only 38\% received at least minimally adequate treatment\textsuperscript{2}

\begin{itemize}
  \item ONLY 52\% in a mental health specialty setting\textsuperscript{2}
  \item ONLY 14.9\% in a general medical setting\textsuperscript{12}
\end{itemize}

\textsuperscript{*}Minimally adequate treatment was defined as receiving either pharmacotherapy (≥2 months of an appropriate medication for the focal disorder plus >4 visits to any type of physician) or psychotherapy (≥8 visits with any healthcare or human services professional lasting an average of ≥30 minutes).

\textsuperscript{†}Defined as a primary care physician, other general physician, nurse, or any other health professional in non-mental health setting.

MDD: Treatment Practices

*Up to two-thirds of adult patients will not achieve remission with a selective serotonin reuptake inhibitor (SSRI); APA Guidelines recommend the first strategy when a treatment change is necessary may be to try to optimize SSRI dose

- VNS may be an additional option for individuals who have not responded to at least 4 adequate trials of antidepressant treatment, including ECT

SNRI=serotonin-norepinephrine reuptake inhibitor; NDRI=norepinephrine-dopamine reuptake inhibitor; MAOI=monoamine oxidase inhibitor; TCA=tricyclic antidepressant; ECT=electroconvulsive therapy; VNS=vagus nerve stimulations.

Suicide Rates and Antidepressants: Increased Availability Has Had Limited Effect

- Use of antidepressants among adults 18–64 years of age has increased in the United States from 2.2% (1988–1994) to 10.6% (2007–2010)\(^1\)
- Depression is present in at least 50% of all suicides; 15% of patients with treated depression eventually die by suicide\(^2\)

**US Rates of Suicide and Estimated Clinical Introduction of Monoaminergic Antidepressants\(^2,3\)**

- TCAs
- MAOIs
- TeCAs
- NaSSAs
- SSRIs, SDRIs, SNRIs, and RIMAs
- Next Generation SSRI

NaSSAs=noradrenergic and specific serotonergic antidepressants; RIMAs=reversible and selective inhibitors of MAO; SDRIs=selective dopamine reuptake inhibitors; TeCAs=tetracyclic antidepressants.

DISCUSSION
MDD: MANY THEORIES OF PATHOLOGY

Vladimir Maletic, MD, MS
MDD Pathophysiology: Several Evolving Theories

Monoamine depletion studies have demonstrated the importance of competent monoaminergic pathways in combating depression.1,2

GABA=gamma-aminobutyric acid.

One theory of depression is that it may arise from a deficit or underactivity in the brain of monoamine signaling (dopamine [DA], serotonin [5HT], and norepinephrine [NE])[1]

Deficiency in monoaminergic neurotransmission may be in the monoamine levels themselves, or through disrupted receptor signaling[2,3]

Evidence that supports the monoamine imbalance hypothesis is that antidepressants can, selectively or in concert, raise monoamine neurotransmission tone (5HT, NE, and/or DA) and reduce depressive symptoms[2,4]

MAO-A=monoamine oxidase A; PLC=phospholipase-C; PI=phosphoinositide; cAMP=cyclic adenosine monophosphate; AC=adenylate cyclase; IP,DAG=ionsitol triphosphate diacylglycerol.

Monoamine Pathways Overlap in Several Areas of the Brain

- Norepinephrine fibers: originate from locus coeruleus of the brain stem
- Dopamine fibers: originate from ventral tegmental area and substantia nigra
- Serotonin fibers: originate from the brain stem
The Neural Circuitry of Monoamines Also Overlap

Cortical pyramidal neurons


Hypothetical model of brain neural circuitry, primarily supported through animal models*1

*Although the exact cellular taxonomy and neural circuitry of the human brain is still being determined, animal models have been, and continue to be, an important contributing factor to this effort, as discussed by members of the human BRAIN Initiative2

DISCUSSION
WHAT ARE SOME OF THE BRAIN STRUCTURES ALTERED IN PATIENTS WITH MDD?

Vladimir Maletic, MD, MS
Gray Matter Volume: Changes Found in Patients With MDD

Volume smaller in patients with MDD

- Hippocampus, total
- Frontal gray and white matter, total
- Orbitofrontal gray matter, total
- Caudate, total
- Putamen, total
- Globus pallidus, total
- Thalamus, total
- Gyrus rectus gray matter, total

Volume larger in patients with MDD

- Lateral ventricles, total

CI = confidence interval.
Decreased Hippocampal Volume Correlates With Number of Untreated Days Depressed

- There is a negative correlation between duration of untreated depressive symptoms and gray matter (GM) volume in both the left (L) and right (R) hippocampal regions in untreated MDD.

![Graph showing correlation between duration of untreated depressive symptoms and average modulated GM per voxel for left and right hippocampal regions.](Image)


Decreased PFC Volume and Increased Symptom Severity Observed in Patients With MDD

Comparison of 15 Subjects With MDD and 14 Healthy Controls

MADRS=Montgomery-Asberg Depression Rating Scale; VBM=voxel-based morphometry.


DISCUSSION
IS THERE EVIDENCE TO SUGGEST THAT ACHIEVING REMISSION IN MDD CAN IMPROVE BRAIN STRUCTURE?

Vladimir Maletic, MD, MS
Gray Matter Volume (GMV): Comparing Patients With Unremitted and Remitted MDD

- Objective: examine brain-volume changes in patients with treatment-resistant depression, comparing those who achieved sustained remission with those who did not remit
- Prospective observational cohort study
- Compared to nonremitters (n=15), remitters (n=12) demonstrated:
  - significant mean increase in whole-brain volume during follow-up (p=0.005)
  - increased gray-matter volume in right orbitofrontal cortex (p=0.006) and the right inferior temporal gyrus (p=0.004).

Changes in White Matter Volume Observed With Remission

The neural circuits involved in emotional and cognitive function may be disrupted by white matter alterations.

Remission resulted in white matter volumes not significantly different to healthy controls.

*P*<0.05, †*P*<10^-6.

DLPFC=Dorsolateral prefrontal cortex; IPL=inferior parietal lobe.

DISCUSSION
CURRENT MDD TREATMENT OPTIONS: PSYCHOPHARMACOLOGY AND LIMITATIONS

Rakesh Jain, MD, MPH
Proposed Mechanisms for Antidepressant Activity\textsuperscript{1-7}

Antidepressants

- Reuptake inhibitors
  - SSRIs, SNRIs, NDRIs
  - TCAs
- MAOIs

Mood Stabilizers

- Evidence suggests some may enhance serotonergic neurotransmission

Antipsychotics

- All alter D\textsubscript{2} neurotransmission
- Some atypical antipsychotics also target 5HT receptors, NE receptors, and a variety of other receptor types


Long-term SSRI Antidepressant Treatment May Alter NE and DA Neurotransmission

SSRI treatment can result in a sustained increase of 5HT activity and thus an increased inhibitory tone, which may lead to a decrease in both NE and DA neurotransmission and a negative outcome in task performance measures.

What Does Inadequate Response to an Antidepressant Look Like?

Proportion of Responders Who Had Symptoms at Baseline That Persisted at Exit*

- Midnocturnal Insomnia: 81.6%
- Sad Mood: 70.8%
- Concentration/Decision Making: 70.6%
- Energy: 64.6%
- Restlessness: 63.0%
- Hypersomnia: 60.4%
- Sleep Onset Insomnia: 57.5%
- General Interest: 55.0%
- Early Morning Insomnia: 49.0%
- Negative Self-View: 38.9%
- Slowed Down: 35.6%
- Increased Weight: 35.5%
- Decreased Appetite: 31.0%
- Increased Appetite: 27.1%
- Decreased Weight: 25.1%
- Suicidal Ideation: 17.1%

*Percentages are reported as the remaining percent of those with each symptom at baseline that continued to have the symptom at exit. Response was defined as ≥50% reduction in QIDS-SR16. Presence of symptoms was indicated by a QIDS-SR16 domain score ≥1.
Residual Symptoms and Repeated Episodes Predict Worse Outcomes for Patients With MDD

In a 10-Year Naturalistic Study, Patients With No Symptoms and Fewer Episodes Remained Well Longer

<table>
<thead>
<tr>
<th>Recovery With</th>
<th>Previous Episodes</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>no symptoms</td>
<td>1-3</td>
<td>121</td>
</tr>
<tr>
<td>no symptoms</td>
<td>3+</td>
<td>34</td>
</tr>
<tr>
<td>1+ mild symptoms</td>
<td>1-3</td>
<td>57</td>
</tr>
<tr>
<td>1+ mild symptoms</td>
<td>3+</td>
<td>25</td>
</tr>
</tbody>
</table>

- Patients with asymptomatic recovery remained well for a median of 231 weeks compared to 68 weeks for those with residual symptoms
  - Patients with more residual symptoms relapsed faster

Survival Distribution Function = cumulative proportion of cases surviving to given time interval.


DISCUSSION
TREATING MDD: THE ROLE OF ATYPICAL ANTIPSYCHOTIC AUGMENTATION

Rakesh Jain, MD, MPH
Adjunctive Atypical Antipsychotics in MDD: Clinical Evidence Supports Their Use

Efficacy of Adjunctive Treatment With Atypical Antipsychotics (N=3549)²,*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Treatment n/N</th>
<th>Placebo n/N</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical Antipsychotic 1</td>
<td>142/540</td>
<td>79/525</td>
<td>2.01 (1.48–2.73)</td>
</tr>
<tr>
<td>Atypical Antipsychotic 2/SSRI</td>
<td>135/584</td>
<td>88/537</td>
<td>1.42 (1.01–2.00)</td>
</tr>
<tr>
<td>Atypical Antipsychotic 3</td>
<td>231/645</td>
<td>78/332</td>
<td>1.79 (1.33–2.42)</td>
</tr>
<tr>
<td>Atypical Antipsychotic 4</td>
<td>48/199</td>
<td>18/164</td>
<td>2.37 (1.31–4.30)</td>
</tr>
<tr>
<td>Overall</td>
<td>556/1968</td>
<td>263/1558</td>
<td>1.77 (1.49–2.09)</td>
</tr>
</tbody>
</table>

• Patients with MDD receiving adjunctive antipsychotics were more likely to show efficacy and remission† compared to placebo however, the effect sizes were small or small-to-moderate in magnitude²
• However, use of atypical antipsychotics adjunctive therapy in MDD has been associated with akathisia, weight gain, abnormal metabolic lab results, and sedation²

*Data are from a systematic review of the efficacy and safety profiles of atypical antipsychotic medications used for the adjunctive treatment of depression. †Definition of remission varied across 14 studies.
Binding Affinities of Select Atypical Antipsychotics Demonstrate Receptor Targeting Differences

Size of circle indicates affinity, with higher affinity represented by larger circle.

- Largest circle = $K_i < 1 \text{ nM}$
- Medium circle = $K_i \geq 1 \text{ nM} \text{ thru } < 10 \text{ nM}$
- Small circle = $K_i \geq 10 \text{ nM} \text{ thru } < 100 \text{ nM}$
- Smallest circle= $K_i \geq 100 \text{ nM} \text{ thru } < 1000 \text{ nM}$

Augmentation Therapy May Double the Chance of Remission

Pooled Response and Remission Rates (10 RCTs, N = 1500)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Response Rate, % of patients</th>
<th>Remission Rate, % of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical antipsychotic + antidepressant</td>
<td>57.2</td>
<td>47.4</td>
</tr>
<tr>
<td>Placebo + antidepressant</td>
<td>35.4</td>
<td>22.3</td>
</tr>
</tbody>
</table>

Meta-analysis of randomized, double-blind, placebo-controlled clinical trials assessed adjunctive treatment of standard antidepressants with an atypical antipsychotic for MDD; studies had to meet all of the following inclusion criteria:
1) used the HAM-D or the MADRS as their primary outcome measure
2) studies that exclusively focused on treatment-resistant depression.
Remission was defined by either a HAM-D-17 < 8 or MADRS < 11.

Helping to Narrow the MDD Treatment Gap


Unmet Needs Still Exist

Earlier Use of Augmentation Needed

More Proactive Focus on Neurotransmitters

5% to 26%

Of adults are affected by MDD lifetime prevalence

33% to 66%

Of patients with MDD do not respond to initial treatment

Augmentation with an atypical antipsychotic has been found to double the rate of remission in patients with inadequate response to antidepressant therapies

Atypical antipsychotics target multiple receptor systems that may help to address the theorized neurotransmitter system imbalance thought to be implicated in MDD
Key Takeaways

1. Imbalance in the monoamine neurotransmitter systems is strongly implicated in the etiology of MDD.

2. Untreated MDD has been found to be associated with numerous structural changes in the brain.

3. An inadequate response to antidepressant therapy has been associated with residual symptoms, functional impairment, and increased risk of relapse.

4. Atypical antipsychotics target multiple receptor systems which may help to address the theorized neurotransmitter system imbalance thought to be implicated in MDD.

5. Augmentation with an atypical antipsychotic has been found to double the chance of remission in patients with inadequate response to antidepressant therapies.
DISCUSSION
QUESTIONS
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