MAJOR DEPRESSIVE DISORDER: CHALLENGES AND OPPORTUNITIES
Objectives

• **Review the impact** of MDD

• **Discuss the challenges** of achieving remission in patients with MDD

• **Outline potential causes** of MDD beyond the monoaminergic pathway

MDD, major depressive disorder.
Meet Anne: Initial Presentation

Medical history
- Type 2 diabetes; recent A1C level of 8.4

Current presentation
- “Lost interest in life” starting 6 months earlier
- Disinterested in work, but fears losing her job
- Feels depressed for most of every day
- Increased appetite and weight gain
- Insomnia
- Loss of energy
- Trouble concentrating

Family and social history
- Brother suffers from depression
- Married for 10 years
- Has 3 young children
The Impact of MDD
MDD Is One of the Most Common Mental Disorders in the United States\textsuperscript{1}

59.3% of people with 12-month MDD reported either severe or very severe role impairment\textsuperscript{2}

Lifetime prevalence of MDD in adults in the United States\textsuperscript{3}

16.6%

DSM-5 Diagnostic Criteria for MDD: Allows for Significant Diagnostic Heterogeneity\textsuperscript{1,2}

For a diagnosis of MDD, \textbf{5 or more symptoms} must be present during the same \textbf{2-week period} and represent a change from previous functioning.\textsuperscript{1}

\begin{itemize}
  \item \textbf{At least 1} of the symptoms is either\textsuperscript{1}
    \begin{itemize}
    \item depressed mood or
    \item loss of interest or pleasure
    \end{itemize}
\end{itemize}

\begin{itemize}
  \item Other symptoms can include\textsuperscript{1}
    \begin{itemize}
    \item Significant weight loss or weight gain
    \item Insomnia or hypersomnia
    \item Psychomotor agitation or retardation
    \item Fatigue or loss of energy\textsuperscript{1}
    \item Feelings of worthlessness or excessive or inappropriate guilt
    \item Diminished ability to think or concentrate, or indecisiveness
    \item Suicidal thoughts or suicide attempts
    \end{itemize}
\end{itemize}

\textit{DSM-5, Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)}.
\textsuperscript{2} Zimmerman M et al. Compr Psychiatry. 2015;56:29-34.
Patient Burden Increases With Severity of MDD\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>PHQ-9 score\textsuperscript{1}</th>
<th>Severity\textsuperscript{1}</th>
<th>Symptom level\textsuperscript{2}</th>
<th>Mean disability days (in past 3 months)\textsuperscript{1}</th>
<th>Symptom-related difficulty\textsuperscript{1,*}</th>
<th>Mean physician visits (in past 3 months)\textsuperscript{1}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to 4</td>
<td>Minimal</td>
<td>1 to 4 symptoms, functional impairment</td>
<td>2.4</td>
<td>1.5%</td>
<td>1.0</td>
</tr>
<tr>
<td>5 to 9</td>
<td>Mild</td>
<td>1 to 4 symptoms, functional impairment</td>
<td>6.7</td>
<td>10.2%</td>
<td>1.8</td>
</tr>
<tr>
<td>10 to 14</td>
<td>Moderate</td>
<td>2 to 4 symptoms, functional impairment</td>
<td>11.4</td>
<td>24.4%</td>
<td>2.0</td>
</tr>
<tr>
<td>15 to 19</td>
<td>Moderately severe</td>
<td>≥5 symptoms, functional impairment</td>
<td>16.6</td>
<td>45.1%</td>
<td>2.4</td>
</tr>
<tr>
<td>20 to 27</td>
<td>Severe</td>
<td>≥5 symptoms, functional impairment</td>
<td>28.1</td>
<td>57.1%</td>
<td>3.7</td>
</tr>
</tbody>
</table>

PHQ-9, 9-item Patient Health Questionnaire.
*Patients reporting “very” or “extremely” difficult.

Burden of MDD Includes Increases in the Relative Risk of Various Diseases

- Heart disease: RR=1.8
- Diabetes mellitus: RR=1.6
- Cancer: RR=1.3
- Disability: RR=1.7
- Obesity: RR=1.6
- Cognitive impairment: RR=1.8

MDD

Reproduced with permission from Otte et al.

RR, relative risk.
Challenges of Achieving Remission in Patients With MDD
A Closer Look at Initial Presentation

Measurement assessment

- PHQ-9=19
- A1C=8.4; increased from 7.1 taken 6 months ago
- Has gained 10 pounds over the past 6 months

Additional comments

- Does not prefer psychotherapy
- Concerned about missing work or losing job
- Has difficulty juggling her family and work demands

This is a hypothetical patient.
What percentage of your patients with MDD receive pharmacotherapy as part of their initial treatment plan?

- a) <20%
- b) 20% to 25%
- c) 25% to 40%
- d) 40% to 50%
- e) >50%
MDD Treatment Options

Antidepressant medications: monoamine-based foundation
- SSRIs
- SNRIs
- NDRI
- Mixed SSRIs and receptor blockers
- TCAs
- MAOIs
- Second-generation antipsychotics

Evidence-based psychotherapies
- Cognitive behavioral therapy
- Interpersonal therapy
- Mindfulness-based psychotherapy
- Psychodynamic psychotherapy
- Problem-solving therapy

Other modalities
- Electroconvulsive therapy
- Transcranial magnetic stimulation
- Deep brain stimulation

MAOI, monoamine oxidase inhibitor; NDRI, norepinephrine-dopamine reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Many Factors to Consider When Individualizing Antidepressant Selection

Multiple patient-specific factors to consider

- Patient preference
- Patient and family history
- Nature of prior response to medication
- Relative efficacy and effectiveness
- Safety, tolerability, and anticipated side effects

- Co-occurring psychiatric or general medical conditions
- Potential drug interactions
- Half-life
- Cost
- Pharmacogenetics

Initiation of Therapy

Antidepressant selection

• SSRI

Concomitant medications

• Metformin
• Insulin

This is a hypothetical patient.
Algorithm-Based Care Has Been Shown to Lead to Better Outcomes Than Usual Care

Prospective trial evaluating clinical outcomes for patients with MDD (N=350) receiving algorithm-guided treatment or treatment as usual

Adapted from Trivedi et al.

IDS-C30: 30-item Inventory of Depressive Symptomatology—Clinician-Rated scale.
Clinical Measurement Can Guide Management of MDD

<table>
<thead>
<tr>
<th>Degree of improvement</th>
<th>PHQ-9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission¹</td>
<td>Score: &lt;5</td>
</tr>
</tbody>
</table>

**Treatment response**

<table>
<thead>
<tr>
<th>Adequate¹,²</th>
<th>Score: &lt;10 (50% decrease or drop of ≥5 points from baseline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possibly inadequate²</td>
<td>Drop of 2 to 4 points from baseline</td>
</tr>
<tr>
<td>Inadequate²</td>
<td>1-point drop or no change or increase from baseline</td>
</tr>
</tbody>
</table>

Failure to Achieve Response or Remission Is Not Uncommon, Despite Receiving Treatment

Of those patients who achieved remission, 90.2% had ≥1 residual symptoms, and 33.5% would relapse at a mean of 4.4 months.1,2

Phone Assessment at 1 Week

**Phone assessment**
- Filled prescription 3 days ago
- Did not and does not plan to make psychotherapy appointment
- Took first dose of SSRI 2 days ago

**Treatment response**
- Still feels “down” and continues to worry about work
- PHQ-9=18 (baseline PHQ-9=19)

**Tolerability**
- Nausea
- Decreased appetite

This is a hypothetical patient.
Variability in Treatment Response Often Necessitates Reassessment and Changes to Therapy

<table>
<thead>
<tr>
<th>Initial weeks</th>
<th>4 to 8 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Full response</strong></td>
<td><strong>Full response</strong></td>
</tr>
<tr>
<td>Maintain current approach</td>
<td>Go to continuation phase</td>
</tr>
<tr>
<td><strong>No or partial response</strong></td>
<td><strong>No or partial response</strong></td>
</tr>
<tr>
<td>Consider increasing medication dose or intensity of psychotherapy</td>
<td>Consider</td>
</tr>
<tr>
<td></td>
<td>1) optimizing initial treatment,</td>
</tr>
<tr>
<td></td>
<td>2) changing to a different treatment, or</td>
</tr>
<tr>
<td></td>
<td>3) combining treatments</td>
</tr>
</tbody>
</table>

Assess response, adherence, and tolerability

In your experience, what percentage of patients require augmentation (vs switching) after trial with a first-line therapy?

- a) <10%
- b) 10% to 25%
- c) 25% to 40%
- d) 40% to 55%
- e) >55%
Decision to Switch or Augment Therapy Should Be Individualized Based on Clinical Factors

Consider monotherapy switch

- First antidepressant trial
- Poorly tolerated side effects
- No response (<25% improvement)
- More time to wait for response
  - Less severe, less functional impairment

Consider adjunctive therapy

- Already tried ≥2 antidepressants
- Initial antidepressant is well tolerated
- Partial response (>25% improvement)
- Specific residual symptoms or side effects that can be targeted
- Less time to wait for response
  - More severe, more functional impairment
- Patient preference

Rates of Response and Remission Decreased With Each Additional Change in Therapy

Response and remission rates at each step exit in the STAR*D trial

<table>
<thead>
<tr>
<th>Step</th>
<th>Response Rate (%)</th>
<th>Remission Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48.6</td>
<td>36.8</td>
</tr>
<tr>
<td>2</td>
<td>28.5</td>
<td>30.6</td>
</tr>
<tr>
<td>3</td>
<td>16.8</td>
<td>13.7</td>
</tr>
<tr>
<td>4</td>
<td>16.3</td>
<td>13.0</td>
</tr>
</tbody>
</table>

Each step included options to switch or augment therapy.
Options included various SSRIs, SNRIs, lithium, T₃, and cognitive therapy.

STAR*D, Sequenced Treatment Alternatives to Relieve Depression; T₃, triiodothyronine.
Treatment Discontinuation Due to Side Effects Also Increased With Each Additional Change in Therapy

Discontinuation due to intolerable side effects at each step exit in the STAR*D trial

Each step included options to switch or augment therapy.
Options included various SSRIs, SNRIs, lithium, T₃, and cognitive therapy.

Office Visit at 6 Weeks

Treatment response

- After switch to new SSRI, feels “better,” but still not feeling quite like her “usual self”
- Still having difficulty coping with job and family
- PHQ-9=12 (baseline PHQ-9=19)

Tolerability

- Mild insomnia
- Anxious

This is a hypothetical patient.
Audience Polling Question

What percentage of your patients with MDD continue to suffer from residual symptoms despite treatment?

- a) <10%
- b) 10% to 25%
- c) 25% to 40%
- d) 40% to 55%
- e) >55%
Common Residual Symptoms in Patients With MDD Despite Receiving Treatment

- Anxiety\textsuperscript{1,2}
- Anhedonia\textsuperscript{2,3}
- Sad mood\textsuperscript{4}
- Irritability\textsuperscript{1,2}
- Dysfunctional attitude\textsuperscript{1,2}
- Interpersonal friction\textsuperscript{1,2}
- Inhibited communication\textsuperscript{1}
- Social maladjustment\textsuperscript{1}
- Insomnia\textsuperscript{2,4}
- Fatigue\textsuperscript{2-4}
- Change in weight/appetite\textsuperscript{3,4}
- Guilt and lowered self-esteem\textsuperscript{2,4}
- Impaired concentration/decision-making\textsuperscript{4}
- Impaired work function and interests\textsuperscript{2}
- Excessive reactivity to social stress\textsuperscript{2}

Residual Symptoms Can Increase Risk of Relapse After Remission Among Other Serious Consequences\textsuperscript{1-3}

Proportion of patients with and without residual symptoms who relapsed after remission ($P<.001$)\textsuperscript{1}

Consequences of not reaching remission may include

- Recurrent episodes of MDD\textsuperscript{2}
- Significant psychosocial disability\textsuperscript{2}
- Faster relapse rate\textsuperscript{2}
- More chronic future course\textsuperscript{2}
- Work impairment\textsuperscript{3}

Adapted from Paykel et al.\textsuperscript{1}

Achieving Response Alone Did Not Return Patients to Baseline Levels of Functioning

*P ≤ .05 vs nonresponse
†P ≤ .05 vs response

Social Adjustment Scale—Self-Report total score, mean

- Normal: n=482
- Remission: n=202*,†
- Response: n=122*
- Nonresponse: n=299

What Outcomes Are Patients Trying to Achieve? Remission From the Patient Perspective

Factors identified as “very important” by >70% of patients included

1. Presence of positive mental health (e.g., optimism, vigor, self-confidence)
2. Feeling like your usual, normal self
3. Returning to usual level of function at work, home, and school
4. Feeling in emotional control
5. Participating in and enjoying relationships with family and friends
6. Absence of symptoms of depression

Pathways and Processes of MDD
Numerous Pathways and Biological Processes Have Been Associated With MDD

Possible pathways involved
- Neuronal plasticity
- Neuro-inflammation
- Glutamate
- Stress/HPA axis
- GABA
- Monoamines
- Cholinergic/adrenergic balance
- Endogenous opioid

Possible biological processes involved
- Synaptogenesis
- Epigenetic gene regulation
- Neuronal plasticity
- Neurogenesis

Disease
DEPRESSION

Adapted from Dale et al.

GABA, gamma-aminobutyric acid; HPA, hypothalamic-pituitary-adrenal.
Reduced Neurogenesis and Synaptogenesis Are Associated With MDD Symptoms

Regions showing reduced gray matter in medication-free patients with MDD vs healthy controls\textsuperscript{1}

Number of spine synapses were decreased in the dlPFC of patients with MDD\textsuperscript{2}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure}
\caption{Regions showing reduced gray matter in medication-free patients with MDD vs healthy controls. Reproduced with permission from Zhao et al.\textsuperscript{1} dIPFC, dorsolateral prefrontal cortex.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{bar_chart}
\caption{Number of spine synapses per $\mu m^3$. Reproduced with permission from Kang et al.\textsuperscript{2}}
\end{figure}


*\textit{P}<0.05 compared with controls (unpaired t test).
All FDA-Approved Antidepressants Modulate the Monoamine Pathway

Antidepressant medications: monoamine-based foundation

- SSRIs
- SNRIs
- NDRI
- Mixed SSRIs and receptor blockers
- TCAs
- MAOIs
- Second-generation antipsychotics

Neuronal Atrophy Seen in MDD May Be Induced by Reduced Brain-Derived Neurotrophic Factor (BDNF) Levels\textsuperscript{1,2}

In depression, low monoamine levels correspond with low BDNF levels\textsuperscript{2}

- BDNF is necessary for sustaining the viability of brain neurons
- Low monoamine and BDNF levels can result in neuronal atrophy and/or loss
- Antidepressant restoration of monoamine-related signaling can increase BDNF and potentially restore lost synapses

CaMK, calcium/calmodulin-dependent protein kinase; CREB, cAMP response element-binding protein; PKA, protein kinase A.

Dysfunctional Glutamate Signaling Results in Impaired Neuroplasticity in MDD\textsuperscript{1}

Adapted from Duman et al.\textsuperscript{2}

Increased Cholinergic Activity Is Associated With Depression

- Cholinergic hyperactivity and decreased noradrenergic activity are implicated in the development of depressive symptoms
  - Cholinergic effects on mood may be mediated through either the nicotinic or muscarinic acetylcholine receptors
- Imaging of actively depressed patients have shown elevated acetylcholine levels, as measured by occupancy of nicotinic acetylcholine receptors
- Anticholinergic agents have been associated with antidepressant effects
  - These antidepressant effects are thought to be mediated through downstream neuroplasticity

The Endogenous Opioid System Includes 3 Key Neurotransmitters and Associated Receptors

Endogenous Opioid Neurotransmitters

POMC, pro-opiomelanocortin.

Role of μ-Opioid Receptor: Agonism Well Established for Analgesia and Hedonia; Implicated in Mood Disorders

• μ-opioid receptors are widely recognized for their role in analgesia¹
  – Act as the binding site for many common pain killers

• Plays key role in reward processing for natural stimuli²
  – Overstimulation of this system can lead to drug abuse and addiction¹

• μ-opioid receptors have also been shown to regulate emotional states³
  – Receptors distributed in key limbic brain areas associated with mood regulation⁴,⁵
  – In patients with MDD, the μ-opioid system is dysregulated⁶

During Social Rejection, Reduced $\mu$-Opioid Receptor Activation Has Been Observed in Patients With MDD


NAcc, nucleus accumbens.
Role of δ-Opioid Receptor: Agonism Demonstrated Analgesic and Antidepressant Effects in Animal Studies

• Limited research to date; however, multiple physiological effects of the δ-opioid receptor have been suggested
  – Agonism results in analgesic effect\(^1\)
  – Agonism also reduced potential for respiratory depression vs μ-opioid receptors\(^2,3\)
  – Less abuse potential than μ-opioid receptor agonists in animal studies\(^4\)

• Similar to μ-opioid receptors, agonism of the δ-opioid receptor has also been shown to produce antidepressant-like activity in animal studies\(^5\)

Research Has Suggested That Agonism of the δ-Opioid Receptor May Have Antidepressant and Anxiolytic Effects¹

δ-opioid receptor-deficient mice showed increases in immobility time in the forced swim test²

Adapted from Filliol et al.²

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Role of κ-Opioid Receptor: Antagonism Demonstrated Antidepressant Effects in Animal Studies

• Agonism is associated with dysphoria, anti-reward, and pro-depressive effects$^{1-3}$

• Antagonism produces antidepressant-like effects in animal studies$^3$

• Other physiological effects include anxiolytic effects upon antagonism of the receptor$^4$

κ-Opioid Receptor in MDD: Antagonism Associated With Antidepressant-Like Effects

Administration of κ-opioid receptor antagonist in rats showed decreased occurrences of immobility in the forced swim test

Adapted from Mague et al.

*P<.05.
Achieving Antidepressant Effect May Involve Appropriate Balance and Impact on the Key Endogenous Opioid Receptors

Activation of the 3 different opioid receptor types can have varying levels of impact on emotion regulation and reward processing

Summary
It May Be Time to Look Harder at Multiple Pathways Associated With MDD

• All FDA-approved antidepressants modulate the monoamine pathway\(^1\)
• Residual symptoms are associated with serious consequences in current MDD episodes, as well as future course of the disease\(^1\)
• Multiple pathways and biological processes have been associated with MDD, and further research is warranted to better understand the role of these pathways in the cause of MDD\(^2\)
