Management of Major Depressive Disorder: Breaking Through the Barriers

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Objectives

To understand that Major Depressive Disorder (MDD) is a serious illness leading to decreased overall patient health and quality of life

To investigate the effect of inadequate treatment response in MDD on patients and their families

To recognize predictors of and important considerations for inadequate treatment response in MDD, including the new DSM-5 specifier for anxious distress

To consider the importance of proactive treatment decisions
MDD IS A SERIOUS ILLNESS OF THE BRAIN THAT MAY LEAD TO DECREASED PATIENT HEALTH AND QUALITY OF LIFE\(^1-3\)

Greg Mattingly, MD

Patients Comment About Their Long Journey With Depression*

“So I would say, maybe, in 10th grade, in high school, is when I realized I needed to get help for it [depression] because it runs [very] heavily in my mother’s side of the family…I didn’t want to have this…I got pretty bummed out and it was hard making choices and just going through every day…”

– Anna F, Diagnosed with first MDD episode 10 years ago, but reports longstanding, chronic dysphoria

“…having been a product of depression my whole life and seeing what it did for my mother. She didn’t even want a stent put in her arteries. She just said let me die… It’s a debilitating disease. And that’s why I’m not ashamed of it. If I broke my leg I’d go get it set.”

– Sheila M, Multiple documented episodes of MDD

*Pictures and names are fictitious and used for illustrative purposes only.
Increased Availability of Antidepressants Has Had Limited Effects on the Rate of Suicide

- Use of antidepressants among adults 18 to 64 years of age has increased in the US 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\(^2\)

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

MAOIs=monoamine oxidase inhibitors; NaSSAs=noradrenergic and specific serotonergic antidepressants; RIMAs=reversible and selective inhibitors of MAO; SDRIs=selective dopamine reuptake inhibitors; SNRIs=serotonin and norepinephrine reuptake inhibitors; SSRIs=selective serotonin reuptake inhibitors; TCAs=tricyclic antidepressants; TeCAs=tetracyclic antidepressants.

Prevalence of Depression Across the United States


- 12-Month prevalence of MDD is 7.1%²
- Lifetime prevalence of MDD is 14.4%²

*Age standardized to the 2000 US standard population. †Based on responses to Patient Health Questionnaire 8.
Major Depressive Disorder Is as Common as Diabetes and Coronary Heart Disease

- MDD* 7.1%
- High Cholesterol† 13.8%
- Hypertension 33%
- Diabetes Mellitus 8.3%
- Coronary Heart Disease 6.4%
- Stroke 2.8%
- Hepatitis C 1.6%

*12-month prevalence in patients aged 13 years and older.
†Total serum cholesterol levels ≥240 mg/dL.
The Health-related Quality of Life (QoL) Reported by Patients With Major Depression Is Similar to Congestive Heart Failure, Severe Hepatitis, and Dialysis

The SF-36® is a multipurpose, short-form health survey (36 questions). It yields an 8-scale profile of functional health and well-being scores, as well as psychometrically-based physical- and mental-health-summary measures and a preference-based health-utility index. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group.\(^2\)

BP=bodily pain; CHF=congestive heart failure; Dialysis=chronic hemodialysis; GH=general health perceptions; MH=mental health; PF=physical functioning; RE=role limitations caused by emotional problems; RP=role limitations due to physical limitations; SF=social functioning; SF-36=36-item Short-form Health Survey; VT=vitality


SF-36® is a registered trademark of the Medical Outcomes Trust.
MDD Significantly Changes the Brain’s Responses to Negative Stimuli (Measured by fMRI)

- Compared with healthy subjects, patients with MDD showed higher baseline activity in the pulvinar nucleus.
- In response to negative stimuli:
  - MDD patients showed greater response in the amygdala, insula, and dorsal anterior cingulate cortex, compared with control.
  - MDD patients showed lower response in the dorsal stratum and dorsolateral prefrontal cortex, compared with control.

Various Brain Regions Have Been Theorized to Be Associated With Different MDD Symptoms

A=amygdala; BF=basal forebrain; Cb=cerebellum; H=hippocampus; Hy=hypothalamus; NA=nucleus accumbens; PFC=prefrontal cortex; S=striatum; SC=spinal cord; T=thalamus


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Deficits in Monoamine Neurotransmitter Systems Are Hypothesized to Mediate Behavioral Effects of MDD$^{1,2}$

Antidepressant effects of available medications are thought to be mediated through modulating serotonin and dopamine activity along with noradrenergic activity.$^2$

5-HT=serotonin; A=amygdala; BF=basal forebrain; Cb=cerebellum; DA=dopamine; H=hippocampus; Hy=hypothalamus; NA=nucleus accumbens; NE=norepinephrine; PFC=prefrontal cortex; S=striatum; T=thalamus

Overlap Between Monoamine Neurotransmitter Systems Plays a Role in Emotional Behavior

Changes in Brain Structure and Function Are Observed in Some Patients with MDD

- A recent meta-analysis of fMRI studies suggests that changes in the way negative and positive emotions are processed in MDD are associated with functional changes in the dorsal lateral prefrontal cortex, anterior and dorsal cingulate cortex, amygdala, striatum and cerebellum
  - It is unclear whether changes in brain volume are the result of the disease or treatments

- In a study comparing healthy controls (n=107) to patients with current depression (n=58) using voxel-based morphometry and high-resolution MRI, depressed patients showed reduced gray matter volume in the left inferior (VLPFC) frontal gyrus and the right middle (DALPFC) and superior (DMPFC) frontal gyri

DALPFC=dorsal anterolateral prefrontal cortex; DMPFC=dorsomedial prefrontal cortex; fMRI=functional magnetic resonance imaging; HC=healthy control; VLPFC=ventrolateral prefrontal cortex
DISCUSSION
INADEQUATE TREATMENT RESPONSE IN MDD

Robert Nelson, MD

Patients With MDD May Face a Long Journey

• The phases of treatment for depression are typically defined as acute (~6-12 weeks), continuation (~4-9 months), and maintenance (≥ 1 year)¹
• Even patients who respond to treatment and who are diagnosed as being in remission may still relapse periodically, and recurrences of depressive symptoms may still occur during long-term maintenance therapy¹
• These relapses may vary markedly in severity and may occur during any phase of treatment¹
• Following an initial depressive episode, ~50% of patients recover with no further episodes, ~35% of patients suffer from recurrent MDD, and ~15% of patients experience unremitting MDD²

Patients Comment About Their Long Journeys With Depression*

“I did go on medication then and was on it for about 6 months and then went off of it… I think that was why I stopped because it wasn’t helping… But I was going to a different doctor then—one of those who rush you in and rush you out and this pill is going to cure everything. And it didn’t.”

– Anna F, a depressed patient with inadequate treatment response

*Pictures and names are fictitious and used for illustrative purposes only.
Less Than Half of Patients With MDD May Respond to Initial Therapy

Response Rate at Each Step in STAR*D

• Coping skills may need to be assessed in patients who fail to respond to adequate doses of multiple classes of antidepressant therapy

STAR*D=Sequenced Treatment Alternatives to Relieve Depression
Persistent Symptoms\(^a\) in MDD Remitters Are Common and Negatively Affect Outcomes

- Residual symptoms increase the risk for suicide and relapse\(^1\)
- Residual symptoms have an adverse impact on psychosocial and occupational functioning\(^2, 3\)

\(^a\)Persistent symptoms defined as QIDS-SR\(_{16}\) item score ≥1.
Potentially Significant Unresolved Symptoms May Persist in Patients Who Meet Treatment Response Criteria*

**Case 1: Anna F**

- Feelings of guilt over past errors (2 points)
- Moderate somatic anxiety (2 points)
- Hypochondriasis: self-absorbed with body (1 point)
- Slight psychomotor retardation (1 point)

**Case 2: Sheila M**

- Psychological anxiety: apprehensive attitude apparent in face or speech (3 points)
- Agitation: hand wringing, nail biting, biting of lips (2 points)
- Nightly difficulty falling asleep (2 points)

- Based on results of a large, naturalistic study, a reduction of approximately 50% on HAM-D, MADRS, or BDI is considered the gold standard for defining treatment response criteria

*Pictures and names are fictitious and used for illustrative purposes only.
*aCorresponding to a Clinical Global Impression Severity rating of 1 (normal).
BDI=Beck Depression Inventory; HAM-D=Hamilton Depression Rating Scale; MADRS=Montgomery-Åsberg Depression Rating Scale
Persistent Symptoms Increase the Risk of Relapse in MDD Remitters

- An increasing number of residual symptom domains leads to an increased risk of relapse ($x^2 [5]=17.7155, P=0.0033$)

### Symptom domains:
- Sleep disturbance
- Sad mood
- Appetite/weight
- Concentration
- Outlook
- Suicidal ideation
- Involvement
- Energy/fatigue
- Psychomotor

QIDS-IVR=Quick Inventory of Depressive Symptomatology, Self Report—Interactive Voice Response
QoL and Functioning Are Reduced for MDD Patients Even With Multiple Steps of MDD Therapy

Remitters and Nonremitters Within Normal QoL During Step Therapy for Depression (Q-LES-Qa)¹

- Nonremitters show more pronounced impairment in functioning than do remitters following treatment²

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²As measured by Q-LES-Q short version; "normal" defined as Q-LES-Q within 10% of community norms (≥70.47).

²P<0.001 vs remitters.

Q-LES-Q=Quality of Life, Enjoyment, and Satisfaction Questionnaire


Remission Status of MDD Patients Has Significant Effects on Family Members

Decrease in Problem Behaviors and Symptoms for Children of Depressed Mothers, by Maternal Remission Status (N=80)

- Children of early- and late-remitting mothers significantly improved compared with those of nonremitting mothers (early vs nonremitting: $P=0.005$; late vs nonremitting: $P=0.002$)

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Only data for the 9 months following remission is shown, due to high dropout rate among non-remitters prior to month 12.

Child Behavior Checklist was used; higher scores = greater number or severity of symptoms.

DISCUSSION
PREDICTORS OF INADEQUATE RESPONSE IN MDD, INCLUDING THE DSM-5 SPECIFIER FOR ANXIOUS DISTRESS\textsuperscript{1-2}

Greg Mattingly, MD

Variables Associated With Inadequate Treatment Response in MDD

Factors Associated With Treatment Resistance (Initial Univariable Logistic Regression Using Nonresistance/Resistance as the Dependant Variable) N=702

- Comorbid anxiety disorder
- Comorbid panic disorder
- Current suicide risk
- Severe intensity vs moderate intensity
- No. of hospitalizations >1
- Social phobia
- Recurrent episodes vs single episode
- Age at onset before 18 yr
- Melancholic features
- Non-response to first antidepressant treatment lifetime
- Personality disorder (DSM-IV criteria)

Odds Ratio (95% CI)

- a P<0.001
- b P<0.01
- c P<0.05

At Least Half of Patients With Depression Can Have Symptoms of Anxious Depression, Which May Worsen Their Prognosis$^{1,2}$

Anxious depression predicts greater morbidity and has been associated with$^{2,3}$:

- Increased Suicidality
- Greater Functional Impairment
- Worse Health-Related QoL
- Depressed Episodes of Longer Duration
- Poorer Response to Treatment

Remission Rates Are Significantly Lower in Patients With Anxious Depression Following the First Antidepressant Treatment

REMISION RATES

- Anxious Depression: 22.2%
- Non-Anxious Depression: 33.4%

P < 0.0001

N = 2876

Remission was defined as a score ≤7 on the HAM-D17.

Time to First Remission Found to Be Longer in Patients With Co-occurring Depression and Anxiety

- Median time to remission in the depression group was 6 months for depression versus 12 months for comorbid depression and anxiety.
- Median time to remission in the anxiety group was 16 months for anxiety and 24 months for comorbid depression and anxiety.

*Survival curve illustrating time until first remission across baseline psychiatric status (n=1209). The dotted lines (-----) are projected lines since by definition no remission could have occurred within the first 3-month period.

Anxiety in Depressive Patients Results in Worse Outcomes

2-Year Course Indicators According to Baseline Psychiatric Status (N=1209)

- After 2 years, only 25.1% of patients with comorbid depression/anxiety were disease free, compared with 47.6% and 46%, respectively, of patients with depression only and anxiety only (P<0.001)
- 56.8% of depressed and anxious patients never achieved remission, whereas 24.5% of depressed patients and 41.9% of anxious patients never achieved remission

P value based on chi-square statistics for categorical variables and Mann Whitney nonparametric statistics for continuous variables.

Irritability Negatively Impacts the Course of MDD in About Half of Patients\textsuperscript{1-3}

Irritable MDD may be associated with\textsuperscript{1-3}:

- Increased Depressive Severity
- More Chronic and Severe Course of MDD
- Poor Impulse Control
- Higher Rates of Drug Dependence and Anxiety Disorders
- Greater Psychosocial Impairment
- Reduced Life Satisfaction

MDD Patients With Irritability Are at Increased Risk for Earlier and Longer Disease Course

Onset and Course of Irritable and Non-Irritable DSM-IV/CIDI MDD

<table>
<thead>
<tr>
<th></th>
<th>Irritable</th>
<th>Non-irritable MDE</th>
<th>F/χ²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age of onset</td>
<td>26.7a</td>
<td>31.3</td>
<td>13.7a,b</td>
</tr>
<tr>
<td>Mean years in episode</td>
<td>5.7</td>
<td>5.1</td>
<td>0.1b</td>
</tr>
<tr>
<td>12-month: lifetime</td>
<td>40.3a</td>
<td>28.8</td>
<td>9.0a,c</td>
</tr>
<tr>
<td>Prevalence (n)d</td>
<td>(497)</td>
<td>(480)</td>
<td></td>
</tr>
</tbody>
</table>

- In this study, irritable patients tended to have an earlier onset of disease, a longer course of disease, and a higher 12-month lifetime prevalence of MDD

aSignificant difference between irritable and non-irritable cases at the 0.05 level, 2-sided test.
bF-test with 1 and 953 degrees of freedom.
cχ²-test with 1 degree of freedom.
dThe reported sample sizes are unweighted and assessed in the part 1 sample.
CIDI=Composite International Diagnostic Interview; Est=estimated; SE=standard error

The DSM-5 Delineated 2 New Specifiers in MDD: Anxious Distress and Mixed Features

Inclusion of the Anxious Distress Specifier Highlights Its Clinical Implications

Anxious distress specifier:
- Feeling keyed up or tense
- Feeling unusually restless
- Difficulty concentrating because of worry
- Fear that something awful may happen
- Feeling that the individual might lose control of himself or herself


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Anxious Distress Decreases Functioning in Patients With MDD

Patient-reported Psychosocial Function Impairment Based on DSM-5 Anxious Distress Specifier

- Patients who met the anxious distress specifier had greater impairment of QoL and greater functional impairment compared with those who did not

*P<0.001.
CUDOS-A=Clinically Useful Depression Outcome Scale−Anxious Distress Specifier Subscale; DID=Diagnostic Inventory for Depression
DISCUSSION
PROACTIVE TREATMENT

Robert Nelson, MD

Brain Structure and Function of Patients with Full Remission vs Controls

- Structural changes: In a voxel-based morphometry and MRI study, patients who met DSM-IV criteria for recurrent MDD in full remission (n=27) had gray matter volume similar to healthy controls (n=107)\(^1\)
  - Compared to currently depressed patients (n=58), remittent MDD patients showed increased gray matter in the superior, middle, and inferior frontal gyri on the left side, the left insula, the precuneus bilaterally, the right inferior and superior parietal lobule, the right superior temporal gyrus, and the pregenual and left subgenual anterior cingulate cortex\(^1\)

Functional changes: In a separate meta-analysis of 3 PET studies involving 119 MDD patients and 42 healthy controls, differences in circuit connectivity between antidepressant responders and nonresponders were seen in pathways involving the dorsal lateral prefrontal cortex, orbital frontal cortex, hippocampus, anterior thalamus, and the anterior and subgenual cingulate cortexes\(^2\)

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PET=positron emission tomography
Many Nonresponders Remain on Ineffective Therapy for Longer Than Recommended

- Study of US patients treated for a depressive disorder (N=56,521), in which 8.6% (n=4844) switched their antidepressant during the first 90 days of therapy\(^1\)
  - 2.4% (n=1333) added an adjunctive antipsychotic
- Prolonging the time to effective antidepressant therapy may have a negative effect on the doctor-patient relationship\(^2\)

SNRIs=Serotonin and Norepinephrine Reuptake Inhibitors; SSRIs=Selective Serotonin Reuptake Inhibitors.

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Early Patient Response in MDD Could Be Predictive of Overall Response

- Early response: patients having a reduction in HAM-D_{17} score of ≥20% compared with baseline within the first 2 weeks of treatment
- Stable responders: patients having a reduction in HAM-D_{17} score of ≥50% from baseline at 4 weeks of treatment and at all subsequent assessments
- Stable remitters: patients having a reduction in HAM-D_{17} score to ≤7 points at week 4 of treatment and at all subsequent assessments

HAM-D=Hamilton Depression Rating Scale
Switching Antidepressant Therapy May Not Lead to Remission for All MDD Patients

Patients Not Achieving Remission Following Switch From a Primary SSRI

- Nearly 75% of patients with MDD who were switched to a 2nd-line antidepressant did not achieve remission in the STAR*D trial

*Remission defined as QIDS-SR16 score ≤5 at exit from the indicated treatment step

NDRI=Norepinephrine-Dopamine Reuptake Inhibitors; SNRIs=Serotonin and Norepinephrine Reuptake Inhibitors; SSRIs=Selective Serotonin Reuptake Inhibitors.

The Use of Adjunctive Atypical Antipsychotics in MDD Is Supported by Clinical Evidence

Efficacy of adjunctive treatment with atypical antipsychotics (N=3549)\(^2,a\)

<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>

- MDD patients receiving adjunctive antipsychotics were more likely to show efficacy and remission\(^b\) compared to placebo\(^2\)
- However use of atypical antipsychotics adjunctive therapy in MDD has been associated with akathisia, weight gain, abnormal metabolic lab results, and sedation\(^2\)

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\(a\)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.
DISCUSSION
Conclusions

• MDD is a serious disease that leaves the brain in an abnormal state, causing decreased functional QoL deficits comparable with congestive heart failure, dialysis, and hepatitis\(^1,2\)

• More than half of patients do not achieve MDD symptom remission following the first round of treatment: inadequate treatment response may be a source of QoL deficits in some patients\(^3-5\)

• Individuals with MDD and comorbid irritability or anxiety may have a worse prognosis, which led to the creation of an “anxious distress” specifier in the DSM-5\(^6-8\)

• Proactive, targeted treatment decisions may be important\(^9,10\)

QUESTIONS
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