Suboptimal Response in Psychotic & Mood Disorders: Causes, Consequences, and Management Strategies

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Objectives

• Explore the negative impact and potential causes of suboptimal response in serious mental illness
• Discuss the various definitions of remission and recovery in major depressive disorder, bipolar disorder, and schizophrenia
• Understand pharmacological approaches to suboptimal response
Defining Suboptimal Response in Serious Mental Illness

• Suboptimal response, which refers to any clinical state where a patient is not completely well, symptomatically or functionally,\(^1\) is a common challenge in psychiatric practice\(^2-5\)

• Suboptimal response has been consistently associated with worse clinical outcomes\(^2,6,7\)

First Consider Possible Non-pharmacologic Causes of “Suboptimal” Response

- Incorrect diagnosis\(^1,2\)
- Substance use comorbidities\(^2\)
- Adherence problems\(^1,2\)
- Variability in drug activity due to environmental factors\(^3\)
- Treatment access barriers\(^1\)

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Polling Question

In your experience with psychotic and/or mood disorders, what is the most common cause of suboptimal response in patients?

A. Incorrect diagnosis
B. Substance use comorbidities
C. Adherence problems
D. Treatment access barriers
E. Other
## Working Definitions of Remission and Recovery: Major Depressive Disorder

- Because treatment goals vary in serious mental illness, working definitions of recovery also vary

<table>
<thead>
<tr>
<th></th>
<th>Major Depressive Disorder(^{1,2})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>REMISSION</strong></td>
<td></td>
</tr>
<tr>
<td>Conceptual definition</td>
<td>▪ Symptoms present, but do not meet full criteria, or &lt;2 months without significant symptoms of a major depressive episode (MDE; partial remission)</td>
</tr>
<tr>
<td></td>
<td>▪ No significant signs and symptoms for 2 months (full remission)</td>
</tr>
<tr>
<td>Operational definition</td>
<td>▪ Hamilton Depression Rating Scale-17 items score ≤5 or ≤7 or Montgomery-Åsberg Depression Rating Scale ≤7 or ≤9 (based on the precedent in the literature)</td>
</tr>
<tr>
<td></td>
<td>▪ ≥3 weeks with an absence of both sad mood and reduced interest, and fewer than 3 of the 7 additional core criterion symptoms may be present</td>
</tr>
<tr>
<td>Relationship to full recovery</td>
<td>▪ Distinction between remission and recovery depends on the interval following symptom reduction</td>
</tr>
<tr>
<td><strong>RECOVERY</strong></td>
<td></td>
</tr>
<tr>
<td>Conceptual definition</td>
<td>▪ An extended period of remission such that an MDE is unlikely to occur in the near future</td>
</tr>
<tr>
<td>Operational definition</td>
<td>▪ ≥4 consecutive months of remission</td>
</tr>
</tbody>
</table>

Working Definitions of Remission and Recovery: Bipolar Disorder

- Because treatment goals vary in serious mental illness, working definitions of recovery also vary

<table>
<thead>
<tr>
<th>REMISSION</th>
<th>Bipolar Disorder¹,²</th>
</tr>
</thead>
</table>
| **Conceptual definition** | • Signs and symptoms of a specified episode (eg, manic) present, but do not meet full criteria, or <2 months without significant signs and symptoms of an episode (partial remission)  
• No significant signs and symptoms for 2 months (full remission) |
| **Operational definition** | • Hamilton Depression Rating Scale-17 items score ≤5 or ≤7 or Montgomery-Åsberg Depression Rating Scale ≤7 or ≤9 (based on the precedent in the literature)  
• Young Mania Rating Scale <8 or <5 (based on the precedent in the literature) |
| **Relationship to full recovery** | • Remission may or may not be associated with a return to premorbid day-to-day functioning |

<table>
<thead>
<tr>
<th>RECOVERY</th>
<th>Bipolar Disorder¹,²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conceptual definition</strong></td>
<td>• Recovery refers to recovery relative to the last mood episode, not from the illness</td>
</tr>
<tr>
<td><strong>Operational definition</strong></td>
<td>• 8 consecutive weeks with virtual absence of depressive and manic or hypomanic symptoms</td>
</tr>
</tbody>
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Suboptimal Outcome in Schizophrenia Refers to Persistent Symptoms or Functional Impairment Between Acute Episodes

Symptoms of Schizophrenia

Positive (Psychosis)
- Unusual thought content (delusions)\(^1,3\)
- Hallucinations\(^1,3\)
- Conceptual disorganization\(^1,3\)

Negative
- Affective flattening\(^1,2\)
- Apathy\(^3\)
- Anhedonia\(^3\)
- Avolition\(^1,2\)
- Asociality\(^5\)
- Alogia\(^5\)

Cognitive
- Impaired attention\(^3,4\)
- Impaired working memory\(^3,4\)
- Impaired executive functioning\(^3,4\)


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## Working Definitions of Remission and Recovery: Schizophrenia

- Because treatment goals vary in serious mental illness, working definitions of recovery also vary

### Remission

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<tr>
<th>Conceptual definition</th>
<th>Operational definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement in core signs and symptoms and only partial fulfilment of the defining criteria of the disorder (partial remission)</td>
<td>Ratings of mild or less (PANSS, BPRS [using the 1-7 range] scores ≤3; SAPS and SANS scores ≤2) on all items, maintained for 6 months</td>
</tr>
<tr>
<td>Absence of disorder-specific symptoms (full remission)</td>
<td>Severity score ≤3 on CGI-Schizophrenia rating scale</td>
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</table>

### Recovery

<table>
<thead>
<tr>
<th>Conceptual definition</th>
<th>Operational definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ability to function socially and vocationally</td>
<td>Consensus lacking; normative levels of social and occupational functioning; independent living; and remission or non-intrusive levels of psychiatric symptoms</td>
</tr>
<tr>
<td>Being relatively free of disease-related psychopathology</td>
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### Relationship to Full Recovery

- Remission necessary but not sufficient step toward recovery

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**Schizophrenia**

1-5

BPRS, Brief Psychiatric Rating Scale; PANSS, Positive and Negative Syndrome Scale; SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms.


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Despite Guideline-based Treatment, Suboptimal Outcomes Remain a Challenge in Serious Mental Illness

<table>
<thead>
<tr>
<th>Major Depressive Disorder</th>
<th>STAR*D study</th>
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<tbody>
<tr>
<td></td>
<td>Of &gt;3500 patients, 63% to 70% patients did not achieve remission(^1,2)</td>
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</table>

<table>
<thead>
<tr>
<th>Schizophrenia</th>
<th>CATIE study</th>
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<tbody>
<tr>
<td></td>
<td>Of &gt;1400 patients,</td>
</tr>
<tr>
<td></td>
<td>• 12% attained and maintained remission for 6 months(^3)</td>
</tr>
<tr>
<td></td>
<td>• 21% attained and maintained remission for at least 3 months(^3)</td>
</tr>
<tr>
<td></td>
<td>• 56% had no symptom remission at any visit(^3)</td>
</tr>
<tr>
<td></td>
<td>• 74% discontinued treatment before 18 months(^4)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Bipolar Disorder</th>
<th>STEP-BD study</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Of &gt;1400 patients, less than one-third of symptomatic bipolar patients achieved recovery without recurrence over 2 years of follow-up(^5)</td>
</tr>
</tbody>
</table>

Note: All of these studies are NIMH-funded.

Suboptimal response is quite common and is a challenge across major psychiatric syndromes

CATIE, Clinical Antipsychotic Trials of Intervention Effectiveness; STAR*D, Sequenced Treatment Alternatives to Relieve Depression; STEP-BD, the Systematic Treatment Enhancement Program for Bipolar Disorder.

Several Factors Contribute to Suboptimal Outcomes in Serious Mental Illness


PD, pharmacodynamics; PK, pharmacokinetic.
Polling Question

Assuming that you did not identify any secondary reason for suboptimal response in a patient with Major Depressive Disorder, who has been on an adequate therapeutic dose of an approved first-line monotherapy, your preferred next step for a partial but suboptimal responder after 6 weeks of treatment is:

A. Continue with “watchful waiting” without any changes
B. Raise the dose higher than your usual target dose
C. Suggest adding a psychotherapy targeting remaining symptoms
D. Change to your next antidepressant choice
E. Add an adjunctive therapy
Pharmacologic Approaches to Suboptimal Response

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Make no changes</td>
<td>Decide that the best option is to continue with the current medication regimen</td>
</tr>
<tr>
<td>Optimize current dose</td>
<td>Change the dose of the current medication</td>
</tr>
<tr>
<td>Change primary medication</td>
<td>Change the primary medication for the given diagnosis (usually change within the same class of medication)</td>
</tr>
<tr>
<td>Add an adjunctive medication</td>
<td>Add a new medication to the regimen either within class or in a new class</td>
</tr>
<tr>
<td>Discontinue a medication</td>
<td>Discontinue one or more medications from the current regimen</td>
</tr>
</tbody>
</table>

Consideration of Multiple Outcome Categories in Serious Mental Illness

QUESTIONS
CLOSING
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