Treating depression to
remission
Target recovery, and give patients back their lives

Patients with residual depressive symptoms have more recurrences, faster relapse, and shorter intervals when they feel well

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Remission is considered the standard of treatment for major depression, but many patients fall short of this goal:

- 25% to 50% of those who respond to treatment have residual symptoms
- 60% to 70% respond to treatment, but only 20% to 40% achieve remission.

We offer practical, evidence-based suggestions and resources to help you take more of your patients beyond response to remission and then to recovery (Table 1, page 16).

CASE REPORT: MISSING THE TARGET

Ms. M, age 32, develops depressive symptoms after taking on several new projects in her work as an accountant. At first she notices difficulty falling asleep at night and that she seems tired all day. Typically efficient and neat, she finds herself absent-minded while staring at her computer screen while a messy pile of unfinished paperwork accumulates on her desk.

She begins chastising herself for falling behind, yet she feels she will never catch up. When she unexpectedly bursts out sobbing in a board meeting, she knows she needs help.

continued
Ms. M reports that she has been taking fluoxetine, 20 mg/d, for 4 weeks as her primary care physician prescribed, with no improvement. She has no history of depression or other psychiatric illness, is taking no other medication, and has no medical illnesses. Her brother has a history of bipolar disorder.

Initial diagnostic workup includes laboratory tests such as thyroid stimulating hormone, vitamin B12, and folate. All values are within normal limits. Her Hamilton Rating Scale for Depression (HRSD) score is 17, indicating moderate depression.

The psychiatrist increases fluoxetine to 40 mg/d, and after about 3 weeks Ms. M starts feeling better. Her hopelessness lifts, she is more engaged, and her sleep improves, yet she continues to feel sluggish and dazed. Her financial reports contain uncharacteristic errors, and her pace is noticeably slow. Twice her supervisor approaches her about substandard work, then a week later warns that she will lose her job unless she improves.

**Barriers to remission.** Patient, provider, and health care system barriers prevent patients with major depression from achieving remission (Table 2, page 19). Patients may feel better with antidepressant therapy but do not recognize and report residual depressive symptoms, such as Ms. M’s fatigue and substandard job performance.

Clinicians also play a role in depression undertreatment. For example, in a study of 239 patients with ≥ 5 depression symptoms," 28% did not receive treatment consistent with depression management guidelines.

### Table 1

**Outcomes in depression: Defining the 4 ‘R’s**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Definition</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td>Clinically significant reduction of symptoms</td>
<td>50% reduction in symptoms on psychometric scales may leave severely depressed patients with disabling symptoms</td>
</tr>
<tr>
<td>Remission</td>
<td>Depression resolves completely or nearly completely, with return to baseline function</td>
<td>Score of ≤7 on the HRSD used in many studies; ACNP Task Force defines remission by 9 core depression symptoms in DSM-IV-TR</td>
</tr>
<tr>
<td>Recovery</td>
<td>Remission lasts for extended time; signifies end of a major depressive episode</td>
<td>ACNP Task Force defines recovery as 4 months of remission</td>
</tr>
<tr>
<td>Relapse</td>
<td>Return to full symptoms during remission but before recovery; signifies re-emergence of current depressive episode</td>
<td>Residual symptoms during response or remission greatly increase chances of relapse</td>
</tr>
</tbody>
</table>

HRSD: Hamilton Rating Scale for Depression
ACNP: American College of Neuropsychopharmacology
Source: References 7, 8
Barriers to remission during depression treatment

<table>
<thead>
<tr>
<th>Who and what</th>
<th>Behavior and system problems</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>Nonadherence to treatment, underreporting of symptoms, satisfaction with suboptimal outcomes, failure to recognize depressive symptoms, underestimating depression severity, limited access to care, reluctance to see a mental health specialist</td>
</tr>
<tr>
<td><strong>Providers</strong></td>
<td>Medication under-dosing, inadequate treatment duration, inaccurate diagnosis, failure to recognize residual symptoms, limited training in interpersonal skills, inadequate time to evaluate and treat depression, failure to consider psychotherapeutic approaches</td>
</tr>
<tr>
<td><strong>Health care systems</strong></td>
<td>Limited therapeutic choices, limited number of mental health care visits, restricted access to providers</td>
</tr>
</tbody>
</table>

Source: Reference 3

Fava et al. suggested the following reasons for depression undertreatment: “... clinicians have partial therapeutic targets, neglect residual symptoms, and equate therapeutic response with full remission.” Others have found that physicians may underdose medications or fail to plan treatment in clear phases.11

**RELAPSE RISK**

Increased risk of relapse is perhaps the greatest cost of undertreated major depression. Patients with residual subsyndromal depressive symptoms relapse five times faster than patients in full remission.12

Residual symptoms may be a more powerful relapse predictor than number of past depressive episodes:13

- Chronic mood symptoms for ≥ 2 years double the relapse risk.14
- 50% to 80% of patients in partial remission relapse.15

In a study of patients in recovery from a major depressive episode, 76% (13 of 17) with residual symptoms relapsed within 15 months, compared with 25% (10 of 40) who completely recovered.16

**Illness course**. After a first major depressive episode, 26 patients with residual subsyndromal symptoms showed a more-severe, chronic illness compared with 70 asymptomatic patients:

- those with residual symptoms had more depression recurrences, with faster relapse and shorter intervals when they felt well
- subsequent depressive episodes occurred >3 times sooner
- well intervals between depressive episodes were 7 times shorter.17

The authors noted that “patients recovering from major depressive episodes with residual subsyndromal depression experience very rapid episode relapse and have strikingly more chronic future courses of illness that are characterized by early and more frequent episode relapses and recurrences.”18 Each major depression recurrence increases the risk of a successive episode.13,19,20

**Treatment resistance**. Over time, incomplete remission may contribute to treatment resistance,21 although this theory remains untested.

**SOCIAL HEALTH COSTS**

Residual depressive symptoms and impaired psychosocial, interpersonal, and occupational func-
Depression

Box

4 keys to remission: What patients need to know

- Full remission from depression is the treatment goal, and any lesser outcome requires further attention
- Finding the proper medication may require trial and error, and several weeks may pass before a drug’s therapeutic effect occurs
- Continuing to take the medication as prescribed is important to achieving remission
- Medication may have predictable side effects

Depression is associated with worse outcomes after myocardial infarction and among nursing home patients, stroke patients, and those with cancer or HIV infection.21

HOW TO IMPROVE REMISSION RATES

To improve remission rates, we recommend that you follow a rational treatment progression and observe established guidelines, as described in the follow-up report on Ms. M:

Case continued: Part way there. Back at the psychiatrist’s office for 30-day medication monitoring, Ms. M reports that increasing her antidepressant has worked—no more crying in meetings or feeling down on herself. She even sleeps better. Her HRSD score is now 10, indicating improvement, though with some residual symptoms.

When the psychiatrist asks about her job performance, Ms. M is surprised to learn that her fatigue and disorganized thoughts might be lingering features of depression. She said she thought she just wasn’t trying hard enough.

Following practice guidelines,27 the psychiatrist increases fluoxetine to 60 mg/d. This higher dosage remains less than the maximum recommended 80 mg/d, and Ms. M has shown partial improvement with fluoxetine.

Patients being treated for depression need adequate follow-up to ensure they are improving. As with Ms. M, encourage patients to describe residual symptoms and functional domains that remain suboptimal. Educate them about the importance of taking antidepressants as pre-
An expert panel recommends a stepwise approach for patients who respond inadequately to initial antidepressant therapy. 

**A STEPWISE APPROACH**

An expert panel recommends a stepwise approach for patients who respond inadequately to initial antidepressant therapy (*Algorithm, page 22*).

**Re-evaluate the diagnosis.** Patients with bipolar disorder or comorbid medical or psychiatric disorders may need medications other than antidepressants. Address concomitant substance abuse, which may interfere with depression treatment. Also exclude or appropriately treat depressive symptoms associated with general medical conditions, such as hypothyroidism.

**Optimize dosages.** Consider increasing medication dosages as needed until limited by side effects or the drug’s safety profile. Before exceeding an FDA-recommended dosage (*Table 4, page 27*), obtain the patient’s informed consent and document this discussion in the chart.

**Consider augmenting or switching.** For patients who continue to show partial response, consider combining the initial medication with another antidepressant or augment with another agent,

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**Table 3**

Useful scales to identify and monitor depressive symptoms

<table>
<thead>
<tr>
<th>Scale</th>
<th>Administration</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamilton Rating Scale for Depression (21- or 17-item HRSD versions)</td>
<td>15 to 20 minutes, clinician-rated</td>
<td>Focuses on somatic symptoms, excellent reliability, often used to evaluate response to medications</td>
</tr>
<tr>
<td>Beck Depression Inventory (BDI versions I or II)</td>
<td>5 to 10 minutes, self-administered</td>
<td>Focuses on behavioral and cognitive elements (somatic symptoms added to BDI-II), good for measuring depression severity, not for depression screening</td>
</tr>
<tr>
<td>Zung Self-Rating Depression Scale</td>
<td>5 to 10 minutes, self-administered</td>
<td>Good for screening, not studied as extensively as Hamilton and Beck scales</td>
</tr>
<tr>
<td>Montgomery-Asberg Depression Rating Scale</td>
<td>5 to 10 minutes, clinician-rated</td>
<td>10 items, often used in research</td>
</tr>
</tbody>
</table>

scribed (*Box*). If poor response continues, address possible nonadherence.

**Use objective assessments.** Global, haphazard, or subjective assessments of patient progress can miss important ongoing depressive symptoms. We recommend using patient- or clinician-rated symptom scales to rapidly identify and monitor residual symptoms (*Table 3*).

You may wish to design your own questionnaires to elicit easily missed data or symptoms particular to a certain treatment—such as common side effects of the medication a patient is taking. Nurses or other providers in a busy practice can help assess patients between or before doctor visits.

Keep in mind that the common practice of defining treatment response as a 50% reduction in HRSD scores leaves many patients with residual depressive symptoms. For example, an HRSD score reduction from 32 to 16 would signify treatment response, but this patient would remain quite depressed.
Depression

such as lithium, stimulants, thyroid hormone, or even atypical antipsychotics. For patients with no response to optimal dosages of the initial medication after 3 to 4 weeks, try switching to another antidepressant—not necessarily in a different class. One switch within the same class is reasonable.

Some authors emphasize the choice of antidepressant in attaining remission. Although no antidepressant is clearly more efficacious than another, those with fewer side effects (such as selective serotonin reuptake inhibitors vs. tricyclics) may improve adherence.

Numerous trials have shown higher remission rates with serotonin/norepinephrine reuptake inhibitors such as venlafaxine or duloxetine than with other antidepressants. This evidence is not universally accepted, however. Depressive illness probably has a heterogeneous biology, and with greater understanding we may eventually tailor treatment to individual patients’ needs.

**Consider psychotherapy or ECT.** Patients who do not achieve remission with medication may be candidates for combined treatment with psychotherapy or electroconvulsive therapy (ECT). Life issues—such as family or work stressors—may need to be addressed along with depressive symptoms.

**CASE: MONITORING AFTER REMISSION**

Ms. M feels back to normal 2 weeks after starting fluoxetine at 60 mg/d. She experienced some transient nausea and headache at this dosage but did not stop the medication because her psychiatrist had told her these side effects might occur.

Ms. M also agrees to short-term psychotherapy to address self-esteem issues that may have contributed to her depressive episode. She soon files the mountain of papers on her desk and corrects erroneous financial statements she has made. Her supervisor is relieved—and so is she.
Using common antidepressants for adults with major depression

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>FDA-approved maximum dosage*</th>
<th>Common side effects at maximum dosage*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SSRIs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>80 (1.0)</td>
<td>Nausea, dry mouth, somnolence</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>20</td>
<td>Nausea, delayed ejaculation, insomnia</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>80 (1.33)</td>
<td>Nausea, headache, insomnia</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>50 (0.83)</td>
<td>Nausea, somnolence, headache</td>
</tr>
<tr>
<td>Sertraline</td>
<td>200 (3.33)</td>
<td>Nausea, headache, insomnia</td>
</tr>
<tr>
<td><strong>SNRIs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duloxetine</td>
<td>120</td>
<td>Nausea, dry mouth, fatigue</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>375 (6.25)</td>
<td>Nausea, somnolence, dry mouth</td>
</tr>
<tr>
<td><strong>Tricyclics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>300 (5.0)</td>
<td>Drowsiness, dry mouth, dizziness</td>
</tr>
<tr>
<td>Desipramine</td>
<td>300 (5.0)</td>
<td>Same as above</td>
</tr>
<tr>
<td>Imipramine</td>
<td>300</td>
<td>Same as above</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>200 (1.67)</td>
<td>Same as above</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion</td>
<td>450 (7.5)</td>
<td>Insomnia, dry mouth, headache</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>45 (0.75)</td>
<td>Somnolence, dry mouth, increased appetite</td>
</tr>
</tbody>
</table>

SSRIs: selective serotonin reuptake inhibitors
SNRIs: serotonin-norepinephrine reuptake inhibitors
* Informed consent discussion and documentation is recommended for dosages that exceed FDA-approved maximums.

The psychiatrist schedules monthly medication monitoring and plans to gradually reduce the fluoxetine dosage if depressive symptoms remain in remission for 6 months. Because Ms. M had no past depressive episodes, the medication trial may not need to be extended past 6 months.

References
Many patients with major depression fail to reach remission. To improve remission rates, optimize antidepressant dosages and consider augmenting or switching to another antidepressant when initial response is inadequate. Educate patients about the importance of taking antidepressants as prescribed, and address possible noncompliance if poor response continues.