Unipolar depression in adults and initial treatment: General principles and prognosis

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INTRODUCTION

Unipolar major depression is highly prevalent; in high-income countries, the lifetime prevalence of depression is approximately 11 percent, and in low- to middle-income countries is 15 percent [1,2]. The World Health Organization estimates that depression affects 280 million people worldwide each year [1,3].

In addition, disability caused by depression is common. Among 369 diseases and causes of injury in 204 countries and territories, unipolar depressive disorders are the 13th greatest cause of disability and mortality in the world [4]. In the United States, depression was ranked as the 2nd leading cause of years lived with disability [5]. The coronavirus 2019 (COVID-19) pandemic has increased the prevalence and in turn, the disability and mortality of unipolar major depression worldwide [6].

Major depression often follows a recurrent or chronic course. Recovery from an initial episode is followed by a recurrence within two years in more than 40 percent of patients [7]. After recovery from the first recurrence, approximately 75 percent will have a second recurrence within five years.

Nearly 70 percent of individuals with unipolar major depression receive treatment that they regard as beneficial [8]. However, some patients may need to work with 10 or more different clinicians before obtaining helpful treatment.

This topic reviews the general principles and prognosis for the initial treatment of depression. Choosing a specific therapy for the initial treatment of depression is discussed separately, as is the evidence for standard therapies that are used for initially treating depression in primary care patients and in patients with general medical illnesses. Continuation and maintenance treatment of major depression, the treatment of resistant depression, and the clinical manifestations and diagnosis of depression are also discussed elsewhere.

- (See "Unipolar major depression in adults: Choosing initial treatment".)
- (See "Unipolar depression in adult primary care patients and general medical illness: Evidence for the efficacy of initial treatments".)
- (See "Unipolar depression in adults: Continuation and maintenance treatment".)
- (See "Unipolar depression in adults: Choosing treatment for resistant depression".)
- (See "Unipolar depression in adults: Clinical features".)
- (See "Unipolar depression in adults: Assessment and diagnosis".)

GENERAL PRINCIPLES

Recognition/screening — To screen for major depression, we typically use the self-report, two-item Patient Health Questionnaire (PHQ-2) (table 1) or the self-report, nine-item PHQ-9 (table 2). The PHQ-2 uses items one (feeling down, depressed, or hopeless) and two (decreased interest) from the PHQ-9. On the PHQ-2, a score of 3 or more (out of a possible score of 0 to 6) indicates a positive screen, which should be followed by a clinical interview facilitated with the full PHQ-9, to determine if the patient has major depression [9-11]. Scores ≥10 on the PHQ-9 suggest patients are likely suffering from major depression, whereas a score <5 indicates euthymia. Additional information about screening for depression is discussed separately. (See "Screening for depression in adults".)

The PHQ-9 and other standardized instruments can also be used to measure response to therapy and guide treatment. (See 'Optimizing treatment implementation' below.)

Evaluation — The evaluation of depressed patients should include a psychiatric and general medical history as well as a mental status examination. Based upon the findings, a physical examination and focused laboratory testing may be indicated to rule out general medical causes as well as medications that can cause depression. (See "Unipolar depression in adults: Assessment and diagnosis", section on 'Assessment'.)

Diagnosis — We diagnose unipolar major depression according to the criteria in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,

Text Revision (DSM-5-TR) (table 3) [12]. However, a reasonable alternative is to use the criteria in the World Health Organization's International Classification of Diseases-11th Revision (ICD-11) [13]. (See "Unipolar depression in adults: Assessment and diagnosis", section on 'Diagnostic criteria and classification'.)

Comorbidity — Major depressive episodes often co-occur with other psychiatric conditions such as generalized anxiety disorder, panic disorder, posttraumatic stress disorder, obsessive-compulsive disorder (OCD), personality disorders, and substance-related and addictive disorders [14]. Establishing the primary diagnosis when comorbid conditions are present can help focus treatment efforts. As an example, if OCD symptoms are more disabling than concomitant but less severe depressive symptoms, the initial treatment target should be OCD.

In addition, unipolar depression and general medical illnesses often co-occur. Further information about depression and comorbid psychiatric and/or general medical illnesses is discussed separately. (See "Unipolar depression in adults: Clinical features", section on 'Comorbidity'.)

Depression subtypes — Major depressive episodes may occur in either unipolar depressive disorders or bipolar disorders [12]. Depressed patients should be assessed for bipolar disorder because treatment of bipolar depression differs from treatment of unipolar depression. (See "Bipolar disorder in adults: Assessment and diagnosis", section on 'Assessment' and "Bipolar major depression in adults: Choosing treatment".)

Bipolar disorders include bipolar I disorder and bipolar II disorder [12]. Bipolar I disorder is characterized by a history of mania (table 4), and nearly always includes episodes of hypomania (less than mania) (table 5) as well as depressive episodes. Bipolar II disorder is diagnosed in patients with a history of hypomanic and depressive episodes and no history of mania.

Major depressive episodes that are part of a bipolar disorder are frequently misdiagnosed as unipolar depression. As an example, a study of 576 primary care patients with a working diagnosis of unipolar depression found that between 10 and 22 percent met criteria for bipolar disorder (depending upon how missing data were handled) [15]. Misdiagnosing bipolar major depression as unipolar depression is particularly likely in bipolar II patients, because hypomania can be difficult to distinguish from anxiety or extroverted personality traits. The differential diagnosis of bipolar disorder and unipolar depression is discussed separately. (See "Bipolar disorder in adults: Assessment and diagnosis", section on 'Unipolar major depression'.)

Another subtype of depression involves psychotic symptoms, which can occur during unipolar or bipolar major depressive episodes [12]. Psychotic features typically manifest with false, fixed

beliefs (delusions) or less frequently, with auditory or visual hallucinations. Psychotic depression is associated with a higher risk of completed suicide and generally requires antipsychotic medications [16]. (See "Unipolar major depression with psychotic features: Epidemiology, clinical features, assessment, and diagnosis" and "Unipolar major depression with psychotic features: Acute treatment".)

Additional depression subtypes include depression with melancholic features or seasonal pattern, as well as persistent depressive disorder and minor depression. (See "Unipolar depression in adults: Assessment and diagnosis".)

Suicidal ideation and behavior — All patients with depression should be assessed for suicidal ideation and behavior. However, the ability of clinicians to identify individuals at substantial short-term risk of suicide is poor. More than half of depressed outpatients experience suicidal ideation, yet the vast majority do not act on these thoughts [17,18].

Brief self-report questionnaires such as the PHQ-9 (table 2) are not sufficient to discriminate imminent risk [19], but they can identify patients who need further assessment. Clinical characteristics that may help identify patients at increased risk for suicidal behavior include [19-24]:

- Suicidal ideation, plan, and intent
- Greater intensity of suicidal thinking (eg, multiple times per day for longer durations)
- Access to means for suicide (eg, firearms), and the lethality of those means
- Psychotic symptoms (eg, delusions or command auditory hallucinations)
- Severe anxiety
- Substance-related and addictive disorders
- History and seriousness of previous suicide attempts
- Family history of or recent exposure to suicide

Patients at immediate risk of suicide should be evaluated in an emergency department and/or hospitalized until the patient's safety is stabilized. Additional information about suicidal ideation and behavior, including evaluation and management, is discussed separately. (See "Suicidal ideation and behavior in adults".)

Patient engagement and retention in treatment — Patients with unipolar depression are often reluctant to engage in treatment. In a prospective study of patients who presented for initial treatment of depression (n >4000), more than 10 percent did not return for treatment after the initial evaluation [25,26]. Another 30 percent did not complete the first eight weeks of treatment, indicating a failure to retain patients who were initially engaged.

If it is feasible, one technique that we use to enhance engagement is to schedule the initial visit face-to-face, rather than doing so digitally. Subsequent in-person visits may also help.

It may also help to ask about fears or misconceptions that interfere with engagement in treatment; as an example, patients often equate depression as a character defect or a sign of personal weakness. Engagement can thus be enhanced if patients understand and accept the diagnosis, by emphasizing that depression is [22,23]:

- Common
- Associated with:
  - Emotional symptoms, such as anger, anxiety, and sadness
  - Physical symptoms (eg, fatigue, headache, abdominal pain, and muscle tension), as well as increased perception and impact of physical symptoms
- A potentially serious brain disease that affects the chemistry and functioning of the brain
- Analogous to other diseases such as asthma that affects the lungs, or diabetes that affects the pancreas
- Often time limited
- Usually treatable with a variety of medications and/or psychotherapies

The clinical features and diagnosis of depression are discussed separately. (See "Unipolar depression in adults: Clinical features" and "Unipolar depression in adults: Assessment and diagnosis".)

Another means of facilitating engagement and retention in treatment is to initially manage the depressive syndrome solely with active surveillance (watchful waiting); this is a reasonable choice for patients with mild or moderate unipolar depression (eg, PHQ-9 score 5 to 14 (table 2) without suicidal plans or behavior). Active surveillance includes regular, brief follow-up visits (eg, every two to three weeks), during which clinicians assess symptoms and provide support. The goal is to help patients recognize problems with mood, sleep, appetite, energy, and cognition, as well as impaired social and occupational functioning, which may help them accept treatment. Framing medication or psychotherapy as a trial (rather than a long-term commitment) may also be useful.

Active surveillance is not appropriate for depressed patients who are severely symptomatic (eg, PHQ-9 score ≥15), chronically depressed (eg, ≥2 years), or substantially impaired (eg,

unemployed). Clinicians should inform severely ill patients that delaying treatment may delay recovery [27]. As an example, a meta-analysis of three studies (two observational studies and one randomized trial, total n = 486 patients with unipolar depression) found that remission was more likely in patients with a shorter duration of untreated illness, compared to patients with a longer duration (relative risk 1.7, 95% CI 1.3-2.1) [28]. Additional information about the clinical features that distinguish severe from mild to moderate depression are discussed separately. (See "Unipolar major depression in adults: Choosing initial treatment", section on 'Severe major depression'.)

Optimizing treatment implementation — Depressed outpatients who start a new antidepressant should generally be seen relatively soon (eg, one to two weeks) afterwards and subsequently monitored (by phone, video, or in-person visit) at least every two to four weeks for six to eight weeks, depending upon the clinical urgency [29,30]. Clinicians should assess therapeutic response, adverse effects, and adherence, with particular attention given to suicidal ideation and behavior, psychosis, agitation, and anxiety [31]. Following remission, the frequency of assessments can be tapered. (See "Unipolar depression in adults: Continuation and maintenance treatment", section on 'Monitoring patients'.)

At each visit, we suggest that clinicians provide measurement based care, which is the systematic, quantitative assessment of symptoms and side effects [32,33]. Tolerability of treatment, adherence, psychosocial functioning, and quality of life can also be measured. Among the standardized instruments that are available to ascertain response to pharmacotherapy or psychotherapy, the PHQ-9 (table 2) is the most widely used and studied. A decrease ≥50 percent during treatment is typically regarded as a meaningful response to treatment, and a score <5 indicates euthymia or remission. Measurement based care is consistent with multiple practice guidelines [22,23,31,34-36].

The PHQ-9 and additional information about measurement based care are discussed separately. (See "Using scales to monitor symptoms and treat depression (measurement based care)".)

Adherence to treatment

Overview — Optimal outcomes in the medication management of depressed patients require adherence to prescribed treatments [25]. However, nonadherence to medications is common. A nationally representative survey of depressed patients in the United States who initiated antidepressants (n = 829) found that the medications were discontinued within one month by 42 percent of patients, and within three months by 72 percent [37]. Clinical risk factors that are associated with poor adherence to antidepressants include concerns over side effects;

comorbid substance abuse and personality disorders; various fears, misconceptions, and misguided beliefs about treatment; and a poor therapeutic alliance [25,38,39]. Sociodemographic risk factors include younger age (eg, less than 30 or 40 years) [38,40], fewer years of education [26,37,38], and race/ethnicity other than non-Hispanic White [38,40].

Poor adherence to antidepressants is associated with greater mortality. As an example, a four year study of an administrative claims database identified patients who were prescribed antidepressants and were either nonadherent (n >80,000) or demonstrated good adherence (n >80,000) [41]. After adjusting for potential confounding factors (eg, age, smoking status, and general medical comorbidities), the analyses showed that all-cause mortality was modestly greater in patients with poorer adherence (hazard ratio 1.14, 95% CI 1.10-1.18).

Enhancing adherence — The cornerstone of optimizing adherence is patient education about depression, and the purpose and administration of pharmacotherapy, including how to take medications and the necessity of dose adjustments based upon efficacy and adverse effects. Helping patients understand and recognize the symptoms, clinical course, treatment options, and the timing of and likelihood of various treatment outcomes serves to establish rapport and reduce ambiguity and ambivalence. Thus, if therapeutic effects are not achieved or adverse effects occur, the patient understands that there are many treatment options and that more than one treatment trial is often needed to resolve the problem. These management principles are consistent with multiple practice guidelines and reviews. [22,23,34,35,42-45].

Patients starting pharmacotherapy should be told the following [33,46]:

- Take the medication as prescribed rather than on an as-needed basis.
- There may be a lag of several weeks (eg, three weeks) before a discernible response is apparent.
- Side effects (eg, anxiety or agitation, headache, and stomach upset) (table 6) frequently occur during the first few days, but typically resolve within a week of starting the medication.
- If a dose is missed, the next scheduled dose should not be doubled.
- If medication is acutely effective, it is important to continue treatment for several (eg, six) months to prevent relapse. (See "Unipolar depression in adults: Continuation and maintenance treatment", section on 'Continuation treatment'.)
- Call to discuss distressing side effects or other concerns or questions.

- Talk with the prescribing clinician before stopping medications.

In addition, the following techniques can enhance medication adherence [22,23,39,45,47,48]:

- Help patients accept the diagnosis.
- Ask about prior use of pharmacotherapy.
- Take a flexible approach to customize pharmacotherapy and accommodate patient preferences when feasible. As an example, ask patients to choose from several medications with different in side effects. This shared decision-making increases patients' willingness to take the chosen medication.
- Simplify dosing regimens. Multiple reviews of different illnesses indicate that adherence is superior with medications administered once per day compared with more frequent doses.
- Help patients set realistic expectations of benefits and adverse effects.
- Discuss plans for dose titrations and how the clinician will monitor the use and benefit of medications.
- Provide simple and clear written instructions for taking prescribed medications.
- If patients are taking the antidepressant multiple times per day, or multiple medications each day, suggest pill boxes to organize daily doses.
- Suggest the use of cues (eg, smart phone alarms, a written record, or pairing pill taking with another regular activity such as eating breakfast) as reminders to take medications.
- Explicitly discuss barriers to adherence and plans to overcome them. As an example, employ a pill box when traveling to avoid leaving pills at home.
- Praise desirable behavior and results.

Motivational interviewing is used to enhance adherence in many illnesses [39,49]. The basic aim of motivational interviewing is to help patients acknowledge that adherence with pharmacotherapy is problematic, make a commitment to change their behavior, and take action to change. The general approach is to initially ask questions and to give advice later. Other elements include expressing empathy (eg, "I know this is hard"), focusing upon collaboration (Let's work together on this"), and avoiding arguments.

Other means to enhance adherence include focusing upon the therapeutic alliance (relationship) with patients and encouraging them to actively participate in treatment as partners [22,23,34,38,39,45].

Adherence can also be improved with the use of allied health professionals to proactively monitor patients, and to schedule return visits for patients with persistent symptoms [50]. Adherence may be further enhanced by facilitating telephone access or secure messaging to the clinician for patient questions about side effects.

Monitoring adherence — Regularly scheduled follow-up contacts, especially following onset of pharmacotherapy, may improve medication adherence and allows clinicians to monitor patients and adjust doses for efficacy and side effects [22,23,45].

Asking patients about adherence in a nonjudgmental manner at each follow-up visit highlights its importance and provides an opportunity to trouble shoot adherence obstacles. Patients may be more likely to discuss concerns or problems with the medication if clinicians initially ask open-ended questions (eg, "How are you taking your medications?"), normalize poor adherence (eg, "Nearly everybody has trouble taking their medications"), and explain that information about adherence is important in treatment decisions (eg, determining the right dose or changing treatment) [51]. The last step is to explicitly ask about missed doses. For patients who acknowledge poor adherence, follow-up questions should explore the reasons (eg, "What gets in the way of taking your medications?" or "Did you feel better when you stopped the medicines?"). Clinicians may ascribe noncompliance to incorrect reasons.

The frequency of monitoring adherence depends upon the patient's clinical status and presumed level of adherence. Noticeable worsening in symptoms or missed appointments should prompt an assessment. Patients whose adherence is problematic or who are not responding to treatment are monitored weekly. Relatively new patients who regularly adhere to treatment are monitored monthly. Well-known patients who are thought to be fully compliant are generally assessed every two to three months.

Referral to specialty care — Most patients with unipolar depression can be successfully treated in primary care settings. A prospective observational study of depressed patients administered full doses of citalopram for up to 14 weeks in primary care settings (n = 1091 patients) or psychiatric clinics (n = 1785 patients); both settings implemented measurement based care and scheduled medication visits every two to three weeks [52]. Remission in the two groups were nearly identical (approximately 27 percent).

Nevertheless, some patients presenting to primary care clinicians for initial treatment of major depression are typically referred to a psychiatrist or other mental health clinician. Indications

for referral include the following:

- Suspicion of bipolar disorder (eg, history of mania or hypomania). (See "Bipolar disorder in adults: Assessment and diagnosis", section on 'Assessment'.)
- Severe depression (eg, PHQ score ≥20 (table 2). (See "Unipolar major depression in adults: Choosing initial treatment", section on 'Severe major depression'.)
- Depression with complicating features that require more frequent and longer visits, such as:
  - Suicidal thoughts and behavior. (See "Suicidal ideation and behavior in adults".)
  - Psychotic depression, which can include delusions or hallucinations. (See "Unipolar major depression with psychotic features: Epidemiology, clinical features, assessment, and diagnosis".)
  - Unipolar major depression with mixed features (ie, depression accompanied by subthreshold [not meeting full criteria] symptoms of hypomania/mania). (See "Unipolar depression in adults: Assessment and diagnosis", section on 'Depressive episode subtypes (specifiers)'.)
  - Comorbid psychiatric disorders, such as anxiety, personality, and/or substance use disorders (comorbidities in depressed patients who are treated with antidepressants are associated with poorer outcomes [53]). (See "Unipolar depression in adults: Clinical features", section on 'Comorbidity'.)
- Patient preference for psychotherapy, either as the primary treatment or in combination with antidepressant medication. (See "Overview of psychotherapies" and "Unipolar major depression in adults: Choosing initial treatment", section on 'Psychotherapy'.)

Collaboration between primary care and mental health clinicians is critical in facilitating a successful referral and subsequently, returning the patient to primary care when appropriate.

PROGNOSIS

In patients with mild to moderate unipolar major depression (eg, Patient Health Questionnaire [PHQ] score 5 to 14 (table 2), and no psychotic features or suicidal behavior), initial treatment with antidepressants leads to response or remission in approximately 50 to 60 percent:

- A pooled analysis of 182 randomized trials (n >23,000 patients treated with antidepressants for an average of seven weeks) found that response (reduction of baseline symptoms ≥50 percent) occurred in 54 percent of patients [54].

- In a pooled analysis of 93 randomized trials that included more than 20,000 patients who were treated with second-generation antidepressants (bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, or venlafaxine) for 6 to 12 weeks [55]:

  - Remission in 47 percent
  - Response (including those who remitted) occurred in 63 percent of patients

- In the prospective, observational Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, 2876 outpatients (nearly 80 percent had chronic or recurrent unipolar major depression) were initially treated with full doses of citalopram for up to 14 weeks [56]. Response or remission occurred in 48 percent, with a mean time to remission of seven weeks [57].

Based upon a pooled analysis of 15 randomized trials (n >5600 patients treated with antidepressants or placebo), the number of prior major depressive episodes is not related to outcome of antidepressant treatment for an acute episode [58]. However, remission of a depressive episode may be more likely if treatment commences soon after onset of symptoms [28]. (See 'Patient engagement and retention in treatment' above.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Depressive disorders".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, “The Basics” and “Beyond the Basics.” The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading

level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on “patient info” and the keyword(s) of interest.)

- Basics topics (see "Patient education: Depression in adults (The Basics)" and "Patient education: Coping with high drug prices (The Basics)" and "Patient education: When you have depression and another health problem (The Basics)")

- Beyond the Basics topics (see "Patient education: Depression in adults (Beyond the Basics)" and "Patient education: Depression treatment options for adults (Beyond the Basics)" and "Patient education: Electroconvulsive therapy (ECT) (Beyond the Basics)" and "Patient education: Coping with high prescription drug prices in the United States (Beyond the Basics)")

SUMMARY

- **Adverse consequences of depression** – Unipolar depression is highly prevalent, disabling, and recurrent or chronic. (See 'Introduction' above.)

- **General treatment principles** – The general principles and issues involved in treating unipolar major depression include:

  - **Recognition/screening** – We typically use the two- or nine-item, self-report Patient Health Questionnaire (PHQ) (table 1 and table 2) to screen for major depression. (See 'Recognition/screening' above and "Screening for depression in adults".)

  - **Evaluation** – The evaluation of depressed patients should include a psychiatric and general medical history as well as a mental status examination. Based upon the findings, a physical examination and focused laboratory testing may be indicated to rule out general medical causes as well as medications that can cause depression. (See "Unipolar depression in adults: Assessment and diagnosis", section on 'Assessment'.)

  - **Diagnosis** – To diagnose unipolar major depression, we typically use the criteria from the American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR) (table 3). (See 'Diagnosis' above and "Unipolar depression in adults: Assessment and diagnosis", section on 'Diagnostic criteria and classification'.)

- **Comorbidity** – Major depressive episodes often co-occur with other psychiatric conditions such as generalized anxiety disorder, panic disorder, and/or personality disorders, as well as general medical illnesses. (See 'Comorbidity' above and "Unipolar depression in adults: Clinical features", section on 'Comorbidity'.)

- **Depression subtypes** – Depression can occur in patients with bipolar disorder as well as those with unipolar depression. Rule out bipolar disorder by ruling out a history of mania (table 4) and hypomania (table 5). (See 'Depression subtypes' above.)

- **Suicidality** – Assess all depressed patients for suicidal ideation and behavior. (See 'Suicidal ideation and behavior' above.)

- **Engagement and retention in treatment** – Engage and retain patients in treatment by educating them about the diagnosis of and treatment options for depression. (See 'Patient engagement and retention in treatment' above.)

- **Monitoring** – Monitor patient outcomes during treatment with a standardized instrument such as the PHQ-9 (table 2). (See 'Optimizing treatment implementation' above.)

- **Adherence to treatment** – At the onset of therapy, encourage adherence to treatment by educating patients and setting realistic expectations about the potential benefits and adverse effects.

  Patients starting pharmacotherapy should be told the following: take the medication as prescribed; there may be a lag of several weeks before a discernible response is apparent; side effects (table 6) frequently occur during the first few days, but typically resolve within a week of starting the medication; continue treatment despite feeling better; and call to discuss side effects, other concerns, or questions.

  Other techniques for promoting adherence include taking a flexible approach and customizing pharmacotherapy to accommodate patient preferences to the extent that they are feasible, providing simple and clear written instructions for taking prescribed medications, and motivational interviewing.

(See 'Adherence to treatment' above.)

- **Making referrals** – Refer patients who need specialty care, including those with suicidal behavior or psychotic features. (See 'Referral to specialty care' above.)

- **Prognosis** – Initial treatment of mild to moderate unipolar major depression with antidepressants leads to response or remission in approximately 50 to 60 percent of patients. (See 'Prognosis' above.)

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