Diagnosis and management of late-life unipolar depression

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INTRODUCTION

The term late-life depression includes both aging patients whose depressive disorder presented in earlier life, and patients whose disorder presents for the first time in later life. Depressive illness in the older population is a common and serious health concern that is associated with comorbidity, impaired functioning, excessive use of health care resources, and increased mortality (including suicide) [1].

Late-life depression remains underdiagnosed and inadequately treated [2-5]. In the United States, older men, especially older African Americans and Hispanic Americans, are at even greater risk of unrecognized depression [6-8]. The public health consequences of inadequately treated depression in late life will increase over time as the population continues to age.

Over 80 percent of mental health treatment for depressed older adults is delivered in the primary care setting. Depression often goes undiagnosed in primary care [9], and is often left untreated, even when diagnosed [10]. Recognition and management of late-life depression is an important responsibility for the primary care clinician. Either pharmacotherapy or psychotherapy can benefit patients [1].

This topic reviews the epidemiology, diagnosis, and treatment of late-life unipolar depression. The clinical features, assessment, diagnosis, and treatment of unipolar major depression in adults age 18 to 65 years, are discussed separately. (See "Unipolar depression in adults: Clinical

features" and "Unipolar depression in adults: Assessment and diagnosis" and "Unipolar major depression in adults: Choosing initial treatment" and "Unipolar depression in adults: Choosing treatment for resistant depression".)

EPIDEMIOLOGY

Depression is not a normal consequence of aging [11,12]. Sadness and grief are normal responses to life events that occur with aging such as bereavement; adjustment to changes in social status with retirement and loss of income; transition from independent living to assisted or residential care; and loss of physical, social, or cognitive function from illness (see "Bereavement and grief in adults: Clinical features"). Despite these losses, healthy independent community-dwelling older adults in the United States have a lower prevalence rate of clinical depression than the general adult population (figure 1) [13].

Rates of depression for community-dwelling older adults range from 2 percent (for patients in community settings who meet strict diagnostic interview criteria) to approximately 10 percent for patients with minor depression [14]. Cultural factors [15] as well as variations in methods of assessment lead to significant variations in reported prevalence. Rates of depression are higher for older adults with comorbid medical illness and in general medical settings. Hospitalized geriatric populations have prevalence rates of depression over 30 percent, and patients with stroke, myocardial infarction (MI), or cancer have rates over 40 percent (figure 1) [16-18].

Although prevalence of depression in the healthy older population is lower than in comparable younger groups, incidence rates may not differ. A cohort study of 5600 community dwelling persons in the Netherlands, age 56 or older (mean age 70 years at baseline) and followed for eight years, found the incidence of depressive syndromes (major depression and dysthymia) to be 7 per 1000 person years [19]. Most depressive episodes occurred in persons with a prior history of depression, with a recurrence rate of 25.5 per 1000 person years. Clinically significant but subthreshold depressive symptoms occurred at twice the rate of depressive syndromes.

The true incidence of depressive disorders in the oldest-old (>85 years old) may be underestimated. This group may have an increased prevalence of depressive symptoms, although few epidemiologic studies have included participants of these ages [20,21].

Risk factors — Patients who experience their first episode of depression later in life are less likely to have a family history of depression or other major mental disorder than patients whose first episode occurred earlier in life. This difference suggests that genetic or familial factors are less likely to have a role in late-onset depression [3,22].

Risk factors for late-life depression include [23]:

- Female sex
- Social isolation
- Widowed, divorced, or separated marital status
- Lower socioeconomic status
- Comorbid general medical conditions
- Uncontrolled pain
- Insomnia
- Functional impairment
- Cognitive impairment

Depression occurring in the course of adverse life events was previously termed "reactive depression" and felt to be an expected consequence of stress or trauma. Clinical major depression should be addressed as a serious medical condition regardless of life precipitants because treatment can be effective.

Insomnia is not only a risk factor for developing dysthymia and depression in older adults, but persistence of insomnia has been associated with persistence of depression [24]. Additionally, a history of sleep disturbance was an independent risk factor for recurrence of depression in older adults in remission from depression [25]. Further studies are indicated to determine whether insomnia, rather than a symptom of depression, is a comorbid disorder in at least some older patients, and whether treatment for insomnia would improve depression response or prevent recurrent depression.

Nursing home residence — As many as 50 percent of nursing home residents are depressed. A study of 634,060 nursing home residents 65 years and older found that during their first year, 54 percent had physician-diagnosed depression [26]. Severe cognitive impairment was associated with lower rates of depression; such impairment may interfere with detecting depression.

Female gender — The prevalence of depression is higher in women across all age groups. Several factors may account for the disproportionate prevalence of depression in older women: greater susceptibility to depression, greater persistence of depression after its onset, and lower mortality [27]. To some extent, this may also be an artifact of how depression is defined and symptoms are elicited [28-30]. Men are more likely to present with anger, irritability, anhedonia, withdrawal or apathy, and alcohol abuse, and less likely to acknowledge sadness or psychological symptoms [31]. With increasing age, the gender gap in depression prevalence

narrows [29]. Men, with a higher prevalence of vascular risk factors, may present with a depression subtype known as vascular depression. (See 'Vascular depression' below.)

General medical illness — The risk of depression in physically ill older adults increases with:

- Recent onset of physical illness
- Greater severity of physical illness
- Functional disability and limited mobility
- Poorly treated pain
- Multiple illnesses

Depressed mood may be the first symptom of a number of medical conditions affecting older adults including stroke, diabetes, cancer, hypothyroidism, and coronary disease [32].

Impact — Depression amplifies disability and lessens quality of life. Late-life depression is associated with increased office and emergency department visits, increased drug use and cost for both prescription and over-the-counter medications, higher risk for use of alcohol or illicit drugs, increased length of inpatient stay, and overall higher costs of care [33,34]. Depression in late life also tends to be a recurrent or persistent condition and adversely impacts both medical and psychiatric morbidity and mortality [28,35].

Medical comorbidity — Treatment of depression can have beneficial effects on health outcomes in patients with chronic medical conditions such as chronic pain, diabetes, and osteoarthritis [36,37]. The impact of depression on medical mortality is being recognized and quantified:

- Depression onset in post-MI patients was associated with a fourfold increase in death [38].
- Patients who developed depression after a stroke were 3.4 times more likely to have died over a 10-year follow-up period [39,40].
- Depression at the time of admission to a nursing home increased one year mortality [41].
- A modified diagnosis of major depressive disorder and a past history of depression independently predicted in-hospital death with an odds ratio of 7.8 after controlling for severity of illness [42].

Treatment of depression may also impact medical mortality. A decrease in overall risk of death at five years, attributed to fewer cancer deaths, was seen in patients age 60 and older with major depression who were randomly assigned to an intervention to improve depression

treatment (involving a care manager), compared to patients assigned to a control group receiving usual care [43].

Psychiatric comorbidity — Comorbidity of depressive illness with other psychiatric syndromes such as anxiety, somatization, and substance abuse may affect overall treatment response and increase the risk of relapse and recurrence [3,23,44]. Comorbid substance abuse with alcohol, prescription pain, or hypnotic medications is underrecognized, and increases the risk of falls, accidents, and cognitive impairment [4,23,44].

Comorbidity with anxiety may be a particular problem in the older population. The presence of anxiety with depression, especially if somatic complaints are over emphasized or primarily addressed, can lead to a missed diagnosis or inappropriate treatment with anxiolytic, hypnotic, or pain medications [4,44,45].

Suicide risk — Depression is a major risk factor for suicide in older adults, who account for approximately 13 percent of the United States population, but for nearly 24 percent of all completed suicides [46]. Older patients attempt suicide less often than younger patients, but are more successful at completion [47]. Older adult men have the highest suicide rate: 28.9 per 100,000 in 2004 [48]. White men age 85 or older have the highest rate of completed suicide, 55 per 100,000 [46]. Most older adult suicide victims were in their first episode of depression and had seen a physician within the last month of life.

Particular care should be paid to the older patient who might be at acute risk for suicide and presents with the following: hopelessness, insomnia, agitation or restlessness, impaired concentration, active psychosis, active alcohol use or intoxication, and untreated unremitting pain. (See "Suicidal ideation and behavior in adults".)

Other risk factors for suicide include [47,49,50]:

- Comorbid physical illness
- Chronic and inadequately treated pain
- Terminal illness or worsening of physical illness
- Widowhood and social isolation
- Personality disorders
- Prior suicide attempt
- Family history of suicide

Compared with usual care, collaborative care interventions for depressed older primary care patients can lower rates of suicidal ideation [51,52]. (See 'Collaborative care' below.)

Subsequent dementia — Late life depression is associated with an increased risk of subsequently developing dementia:

- A meta-analysis of 23 prospective, community-based, observational studies included more than 49,000 subjects who did not have dementia at baseline and were followed for a median of five years [53]. The risk of all-cause dementia was greater in subjects with late life depression than the nondepressed controls (risk ratio 1.9, 95% CI 1.7-2.0). Specifically, late life depression was associated with an increased risk of Alzheimer disease and vascular dementia, and the risk of vascular dementia was greater than the risk of Alzheimer disease. The elevated risk for all-cause dementia persisted in analyses that included only those studies (n = 17) that adjusted for potential confounders (risk ratio 1.6, 95% CI 1.4-1.8).

- A retrospective study of medical records (n >13,500 individuals who did not have dementia at baseline) over a six-year follow-up period found that after adjusting for potential confounds, the risk of all-cause dementia was increased 70 percent in subjects who had late life depressive symptoms (hazard ratio 1.7, 95% CI 1.5-1.9) [54]. Specifically, depression was associated with an increased risk of Alzheimer disease and vascular dementia.

Late life depression may reflect a prodromal stage of dementia or may act as an independent risk factor for dementia.

In addition, dementia may give rise to episodes of depression. (See 'Alzheimer disease and other dementias' below.)

PATHOGENESIS

The pathogenesis of late-life depression is multifactorial and likely involves a complex interplay of biochemical abnormalities, alteration of neural networks, neuroinflammation, neuroimmune dysregulation, deposition of beta-amyloid (and tau), and genetic factors [55-57]. Subclinical cerebrovascular disease may also influence the susceptibility to, and expression of, late-life depression. Cerebral atrophy, subcortical deep white matter and periventricular ischemic lesions, and decreased volumes in specific brain regions may be implicated [58-61].

CLASSIFICATION

The effects of age of onset, changes in the aging brain, and the presence of medical comorbidity influence the type and expression of depression as well as treatment responsiveness. Some patients may have clinically significant depressive symptoms but do not totally fulfill the criteria for syndromal major depression as defined by the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (table 1) [62]. (See "Unipolar depression in adults: Assessment and diagnosis".)

Major depression — The DSM-5 criteria for major depression (table 1) are identical for both older and younger patients [62]. Of note, major depression in later life is more likely to become chronic and recovery may be more transient, leading to frequent relapses. The risk of relapse and chronicity appears heightened by extensive comorbidity.

Older patients with major depression may have cognitive impairment that develops coincident with or after the onset of mood symptoms, a condition previously termed pseudodementia and now referred to as dementia syndrome of depression, because the cognitive deficits are demonstrable. Antidepressant treatment can resolve the cognitive and mood symptoms of these patients. By contrast, mild to moderate depression in patients with Alzheimer disease may not respond to antidepressant therapy (eg, sertraline or mirtazapine) [63], or if depressive symptoms do improve [64-66], the primary cognitive deficits of Alzheimer disease persist or become worse. It is worth noting that patients with cognitive impairment secondary to major depression may be at higher risk of converting to an irreversible dementia syndrome such as Alzheimer disease [64-68].

Persistent depressive disorder (dysthymia) — Older patients should fulfill the same DSM-5 criteria for persistent depressive disorder (table 2) as younger patients [62]. Dysthymia manifests with depressive symptoms that occur on the majority of days for at least two years. Older patients with late onset dysthymia have a higher prevalence of cardiovascular disease, but are otherwise similar to older patients with late onset major depression [69]. Patients with persistent depressive disorder are at greater risk of developing major depression, so-called "double-depression," and may be particularly treatment resistant.

Minor depression — Minor depression (subsyndromal depression) is diagnosed in patients with depressive syndromes that do not meet DSM-5 criteria for major depression (table 1) or persistent depressive disorder (dysthymia) (table 2) because of too few symptoms or the duration of symptoms is too short. In DSM-5, minor depression is classified as "other specified depressive disorder," followed by the reason that the depressive syndrome does not meet criteria for a specific disorder such as major depression or persistent depressive disorder [62]. Reasons include "depressive episode with insufficient number of symptoms" or "short duration depressive episode."

Minor depression in late life is more prevalent than major depression, and minor depression is important in the older population because these patients suffer disease burdens comparable to patients with major depression, including poorer health and social outcomes, functional impairment, and higher health care utilization and treatment costs [70-73].

In addition, patients with minor depression are at high risk for subsequently developing major depression, and may develop suicidal ideation. In one study, patients with minor depression, age 60 years and older, had a sixfold risk of developing major depression at one year compared to patients without depression [73].

The clinical features, diagnosis, and treatment of minor depression in mixed age populations are discussed separately. (See "Unipolar minor depression in adults: Epidemiology, clinical presentation, and diagnosis" and "Unipolar minor depression in adults: Management".)

Psychotic depression — Unipolar major depression with psychotic features (delusions or hallucination) is a severe subtype of unipolar major depression (major depressive disorder), which occurs at least as often in older patients as younger patients [74-77]. The epidemiology, clinical features, assessment, diagnosis, treatment, and prognosis of unipolar psychotic depression are discussed separately. (See "Unipolar major depression with psychotic features: Epidemiology, clinical features, assessment, and diagnosis" and "Unipolar major depression with psychotic features: Acute treatment" and "Unipolar major depression with psychotic features: Maintenance treatment and course of illness".)

Vascular depression — Cerebrovascular disease may increase an older person's risk for depression through a variety of neurobiological mechanisms [78,79]. Depression may develop after an acute cerebrovascular event (termed "post-stroke depression" [PSD]) [80] or may develop in association with chronic ischemic changes in the brain (termed "vascular depression") [79,81]. Post-stroke depression is discussed elsewhere. (See "Complications of stroke: An overview".)

The importance of chronic ischemic cerebral changes is only recently recognized. A study of depressed patients with and without MRI abnormalities demonstrated that positive MRI findings correlated with older age at onset of depression, vascular comorbidity, greater psychomotor slowing or Parkinsonism, anhedonia, increased functional impairment, and lower incidence of psychosis [81,82]. Another study found that patients with late onset depression and cerebrovascular risk factors, compared with other late onset patients, had more cognitive impairment and disability, more psychomotor retardation, less agitation, less guilt, and less insight into their illness [79]. Depressed patients with vascular risk factors have been found to

be at higher risk of developing vascular dementia [83]. (See "Etiology, clinical manifestations, and diagnosis of vascular dementia".)

Preliminary data suggest that these patients may preferentially respond to nonstandard antidepressant therapy, including older antidepressants, combination therapies, or electroconvulsive therapy [78,80,84].

The syndrome of depression with executive dysfunction may also be related to cerebrovascular disease or age-related neurodegeneration [85,86]. Patients present with frontal executive impairment manifested by difficulties with motivation, organization, planning, sequencing, and abstracting. They typically exhibit anhedonia and apathy rather than sadness, and have cognitive impairment with psychomotor retardation [86,87].

Alzheimer disease and other dementias — The development of depression as a complication of Alzheimer disease is increasingly recognized. Presentation and treatment responsiveness may significantly differ from early onset and other types of depression [88,89]. A proposal from the American Association for Geriatric Psychiatry suggests revised diagnostic criteria for depression in Alzheimer disease (table 3) [90]. Additionally, depression is a common complication in many other dementia syndromes including Parkinson Dementia, Lewy Body dementia, frontotemporal dementia, and Huntington dementia. (See "Management of neuropsychiatric symptoms of dementia".)

DIAGNOSIS

Assessing patients to make the diagnosis of depression in late life is challenging, especially in physically frail older adults. Multiple factors complicate the diagnosis of depression in older adults:

- Concurrent medical illness with overlapping symptoms of depression (fatigue, psychomotor slowing, loss of appetite, sleep disturbance, lack of sexual interest, memory complaints)
- Medication side effects overlapping depression symptoms
- Impaired communication skills in older adults
- Patient presentation with multiple somatic complaints
- Lack of time in the clinical exam to evaluate psychological problems in patients with complex medical issues

- Therapeutic nihilism regarding depression on the part of the patient, family, or provider
- Patient's reluctance to acknowledge psychological distress due to perceived stigma of mental illness [91]

Depression diagnosis with medical comorbidity — A few clues are helpful in diagnosing late-life depression in the setting of medical comorbidity. Depression should be considered when the following are present:

- Mood or somatic symptoms out of proportion to what is expected
- Poor response to standard medical treatment
- Poor motivation to participate in treatment
- Lack of engagement with care providers

Depression diagnosis in frail older adults — Dysphoric mood may be less reliable as an indicator of depression in the oldest old (>85 years of age) [31]. Depression criteria in frail older adults should emphasize a change in mood or interest with at least two weeks duration, nonphysical symptoms, and social regression or incapacity. Physical symptoms used to support the diagnosis of depression should occur with or worsen after mood symptoms, and should be out of proportion to what is expected of the illness or usual treatments. Depression is less likely to be present if the patient responds to affection from family and caregivers, retains humor, looks forward to visits, and accepts assistance and care.

Screening instruments — Several screening instruments have been developed and validated for use in primary care and other settings [92]. As screening tools, these should not be the sole basis for diagnosing depression. When patients screen positive with an instrument, a clinical diagnostic interview is necessary to determine if criteria for major depression are met and if treatment is indicated.

Several screening tools are available (table 4). The instruments vary by whether they are self- or interviewer-reported, applicable to patients with cognitive or language barriers, or validated for monitoring treatment response. These tools are:

- Two-question screener – A two-question screener is easily administered and likely to identify patients at risk if both questions are answered affirmatively [93,94]. The questions are:
  - "During the past month, have you been bothered by feeling down, depressed or hopeless?"

- "During the past month, have you been bothered by little interest or pleasure in doing things?"

A similar instrument, the Patient Health Questionnaire 2 (PHQ-2), was evaluated in a United States sample of over 8000 noninstitutionalized adults age 65 years and older [95]. Compared with DSM-5 criteria for major depression, the PHQ-2 had a sensitivity of 100 percent and specificity of 77 percent in this population; specificity increased with age, male gender, and varied with racial and ethnic groups.

- The Geriatric Depression Scale – This self-report instrument has been studied in multiple settings [96,97]. A five-item version demonstrated good receiver operating characteristics across the full spectrum of older populations [97]. The five items are:

  - Are you basically satisfied with your life?
  - Do you often get bored?
  - Do you often feel helpless?
  - Do you prefer to stay at home rather than going out and doing new things?
  - Do you feel pretty worthless the way you are now?

Two out of five depressive responses ("no" to question 1 or "yes" to questions 2 through 5) suggests the diagnosis of depression [98].

- The PHQ-9 – This was developed specifically for use in primary care settings and has demonstrated ease, validity, and reliability (table 5) [99]. It covers all nine DSM-5 criteria for major depression and can be used to help establish a diagnosis of major depression. The PHQ-9 was shown to be a reliable measure of depression treatment outcomes in a large study of older adults [100]. The tool can be used to assess response to treatment in individual patient care.

- Cornell Scale for Depression in Dementia – This incorporates both observer and informant-based information and is helpful in evaluating cognitively impaired patients for depression [101].

- The Center for Epidemiologic Studies Depression Scale – This is one of the most common instruments applied in community studies and commonly used in primary care settings [102,103].

The general screening of depression is discussed separately. (See "Screening for depression in adults".)

TREATMENT

Successful treatment of depression in late life is dependent upon several factors: addressing comorbid conditions, tailoring pharmacologic or other interventions to the individual patient, monitoring therapy for side effects and effectiveness, and assuring close follow-up. Consultation with a mental health specialist should be considered for patients who have failed multiple trials of antidepressants or who have a preference for nonpharmacologic treatment.

A complete history will guide treatment decisions. Aspects of the history of special importance in managing depression in older adults are:

- Assessment for suicidality, including ideation and plan (lethality, intent, and means). Acute suicidal ideation requires urgent psychiatric referral [51].
- Assessment for psychotic symptoms, hopelessness, insomnia, and malnutrition.
- Determination of whether the patient is using medication(s) with depressant side effects (benzodiazepines, central nervous system depressants, opiates, other pain medications) or is abusing alcohol.
- Consideration of other medical conditions commonly associated with depressive symptoms, particularly unrecognized thyroid disease, or diabetes. Additionally, pain syndromes can be a barrier to treatment response in depression and should be treated along with the depression [104].
- Determination of history of prior depressive episodes, age of depression onset, prior drug therapy and outcome, and length of prior remission if achieved.
- Determination of a family history of depression and family response to medication. Older patients with mild depressive symptoms and first degree relatives with confirmed depression diagnosis have a 1.5 to 3 times greater risk for depression than the general population [105].

First-line treatment of depression consists of psychotherapy and somatic therapy (medication or electroconvulsive therapy [ECT]). A meta-analysis of 89 controlled studies involving older adults with depression of varied severity (major depression, minor depression and dysthymia) found that well-designed randomized studies were limited, but that the overall effect size of either

psychotherapy or medication was moderate to large, and roughly equivalent [106]. The choice of treatment will depend upon the severity, type, and chronicity of the depressive episode, contraindications to medication, treatment access, and patient preference. Psychotherapy and pharmacotherapy may be used singly or in combination [107]. For moderate to severe forms of depression, we recommend pharmacotherapy. For chronic forms of depression, the combination of pharmacotherapy and psychotherapy may be most effective [108].

Several studies suggest that treatment programs that offer a choice of medication and/or psychotherapy in primary care, often combined with patient outreach by a care manager in a collaborative care model, have significantly better outcomes than usual care [51,109-111]. (See 'Collaborative care' below.)

Antidepressants are efficacious for late-life depression, based upon meta-analyses of randomized trials [112,113]. As an example, a patient-level data meta-analysis of seven randomized trials (n = 2283 patients) compared antidepressants (bupropion, citalopram, duloxetine, escitalopram, fluoxetine, or paroxetine) with placebo, and found that response (reduction of baseline symptoms ≥50 percent) occurred in more patients who received active treatment than placebo (49 versus 40 percent) [114]. Duration of illness (current age minus age at onset of depression) was associated with response, such that response was greater in patients with a duration of illness >10 years, compared with patients with a duration of illness <2 years.

Although antidepressants are efficacious for late-life major depression, efficacy may be less robust in older patients than younger patients:

- A meta-analysis of 15 randomized trials compared antidepressants with placebo in 4756 patients age 55 years and older (mean age 70 years). Response was greater with antidepressants (relative risk 1.3, 95% CI 1.2-1.5) [112]. However, in the subgroup of patients with a minimum age of 65 or 75 years (mean age 74 years; six trials, 1840 patients), response was comparable for antidepressants and placebo. Both analyses were limited by heterogeneity across pooled trials, the lack of trials that focused upon patients older than 80 years, and the exclusion of more severely depressed patients.

- A meta-analysis of patient level data from four randomized trials compared fluoxetine (10 to 30 mg per day) with placebo in 960 geriatric patients (older than 60 years) who were treated for six weeks [115]. Although rating scale scores improved more with fluoxetine than placebo, both response and remission were comparable for the two groups. In addition, a separate analysis of adults (12 trials, 2635 patients) found that the improvement of rating scale scores for adults was nearly double that for geriatric patients.

- A subsequent randomized trial compared duloxetine with placebo in 299 patients age 65 years or more [116]. For both groups, remission was comparable (approximately 50 percent).

Exercise may be effective in the treatment of minor or major depression in older adults [117]. Patients with major depression, however, may be difficult to engage in an exercise program and would likely benefit from concomitant pharmacotherapy or psychotherapy. Exercise is discussed elsewhere in this topic. (See 'Exercise' below.)

Psychotherapy — Psychotherapy is a useful but frequently underutilized treatment for older adult depressed patients [107,118]. The availability of adequately trained therapists is a limiting factor, and health insurance coverage for psychotherapy is often incomplete. Available formats include individual, couples, family, or group therapy. Settings include private offices, community senior centers, partial hospital day programs or intensive outpatient group programs. The discussion below focuses upon the efficacy of psychotherapy in older adults; a general discussion of psychotherapy is presented separately. (See "Overview of psychotherapies".)

Multiple randomized trials have found that psychotherapy is beneficial for late-life depression. As an example, a meta-analysis of 27 trials (n >2000 patients) compared various psychotherapies with different controls and found a significant, clinically moderate to large effect favoring psychotherapy [119]. However, heterogeneity across studies was substantial and publication bias was significant.

Short-term treatments include cognitive-behavioral therapy (CBT), interpersonal psychotherapy, and problem-solving therapy, which are delivered over a period of two to four months and are effective for older patients [120-124]. CBT is the most widely studied psychotherapy. A meta-analysis of 10 randomized trials (380 older adult depressed patients) found a significant, clinically large effect favoring CBT over treatment as usual or waiting list controls; heterogeneity across studies was small to moderate [125]. A prior meta-analysis of three trials found that improvement of depression was comparable for CBT and interpersonal psychotherapy [124]. Additional information about the efficacy of interpersonal psychotherapy for older adult depressed patients is discussed separately. (See "Interpersonal Psychotherapy (IPT) for depressed adults: Indications, theoretical foundation, general concepts, and efficacy", section on 'Older patients'.)

Multiple randomized trials have found problem-solving therapy can be beneficial [109]:

- A 12-week trial compared problem-solving therapy with supportive therapy in 221 nondemented patients with major depression and executive dysfunction (difficulty with goal setting and planning, and with initiating and sequencing behavior) [126,127].

Executive dysfunction is associated with poor response to antidepressants. Remission of depression occurred in more patients who received problem-solving therapy compared with controls (46 versus 28 percent). In addition, improvement of disability (self-care, communicating, and psychosocial functioning) was greater with problem-solving therapy, and the advantage was retained at the 24-week follow-up after the end of treatment.

- Another 12-week trial compared problem-solving therapy with supportive therapy in 74 patients with major depression and cognitive impairment ranging from mild deficits to moderate dementia [128]. Both interventions were administered weekly in the home. Remission of depression was greater with problem-solving therapy than supportive therapy (38 versus 14 percent). In addition, reduction of disability was greater with problem-solving therapy.

Life review therapy can help older patients with depression. A three-month randomized trial compared life review therapy (eight group therapy sessions, two hours each) with usual care in 202 patients with mild to moderate depressive syndromes. Improvement of depression as well as anxiety was greater with active treatment [129].

Psychotherapy and community-based programs for older adults may be particularly helpful for patients with minor depression, for whom pharmacologic intervention has not demonstrated consistent effectiveness [73,125].

Treatment for anxiety — One randomized trial of older patients with generalized anxiety disorder found that cognitive behavioral therapy (CBT) delivered in the primary care setting by clinicians with expertise in CBT, compared with enhanced usual care (biweekly telephone contact), decreased worry symptoms and moderately improved depressive symptoms in these patients [130]. Whether CBT is effective for anxiety in association with major depression has not been studied in randomized trials.

Medication acceptance by patients — Many older patients are reluctant to take medication for their depression. Interviews with patients 60 years and older with depression (N = 68) found the following concerns expressed: fear of medication dependence, rejection of concept of depression as a medical illness, belief that medications would inhibit normal emotional reactions, and prior negative experience with medications for depression [131]. Understanding why a patient may be reluctant to initiate medication can promote clinician-patient dialogue to address their specific concerns and initiate effective treatment.

Medication selection and management — A systematic review of 26 randomized trials that compared antidepressants from different classes in head-to-head trials in patients age 55 and older found little difference in efficacy between medication classes [132]. However, there was a

higher withdrawal rate due to side effects for patients treated with tricyclic antidepressants, compared with selective serotonin reuptake inhibitors (SSRIs). These findings suggest that side effect profiles should be a major determinant in medication selection [133,134].

Medications typically take up to four to six weeks to show efficacy. In older patients, a full antidepressant response may not occur until 8 to 12 or even 16 weeks of therapy [133,135,136]. However, one study of 472 older patients with major depression found that patients who had no improvement at all by four weeks of treatment were unlikely to respond even after eight additional weeks, and would be candidates for an early change in their treatment plan [137].

Monotherapy is preferred in older adults in order to minimize drug side effects and drug-drug interactions. Although one nonrandomized open label study demonstrated good response to augmentation for treatment-resistant older patients with no medical contraindication to augmentation medications (lithium, bupropion, or nortriptyline) [138], combination strategies for augmented or accelerated responses in older adults are preferably avoided in the primary care setting.

Initial medication dosage should be adjusted for the older adult, typically cutting the usual starting dose for younger patients in half. Lower starting doses will compensate for decreased drug clearance in older adults, minimize initial side effects, and promote medication compliance and maintenance. However, under-treatment of older adult depressed patients is well documented; it is important to reach the same therapeutic dosage range as in younger adults in order to maximize the chances of achieving complete remission.

Patients should be contacted or seen within two weeks of initiating medication to discuss tolerance, address concerns, and adjust dose as indicated. Patients should have an office visit within two to four weeks of initiation of medication treatment to assess for response, complications, or deterioration. Depression-specific case management, (involving specially trained nurses or social workers collaborating with primary care physicians to assist with depression identification, guideline-based treatment and follow-up) was effective, compared with usual care, in reducing mortality and depressive symptoms in older patients with major depression in a randomized trial involving 20 primary care practices in three United States cities [139]. (See 'Collaborative care' below.)

Duration of treatment — The usual course of treatment for the first lifetime episode of unipolar major depression in adults is 6 to 12 months beyond the time of achieving full remission. The goal of continuation and maintenance treatment is to prevent relapse. Relapse rates in older adults are higher than in younger populations, which may indicate a need for longer periods of maintenance therapy [140]. Prior to discontinuing maintenance treatment,

clinicians should educate patients about monitoring themselves for symptoms of recurrent episodes, and restarting treatment if symptoms recur.

Evidence for the efficacy of maintenance treatment includes a meta-analysis of six randomized trials that compared antidepressants (citalopram, dothiepin, escitalopram, nortriptyline, or sertraline) with placebo for up to three years in 708 older patients who remitted from unipolar major depressive episodes [141]. Recurrent episodes occurred in fewer patients who received antidepressants than placebo (37 versus 59 percent). In addition, discontinuation of treatment due to side effects was comparable.

Maintenance treatment with monthly psychotherapy, either alone or as add-on treatment with pharmacotherapy, does not appear to be effective for preventing recurrent late life depressive episodes. As an example, a two year randomized maintenance trial found that interpersonal psychotherapy did not prevent recurrence [142]. Among patients 70 years of age and older who had responded to treatment for unipolar major depression (N = 116) and were then assigned to one of four maintenance treatments, the rate of recurrence was as follows:

- Paroxetine (10 to 40 mg per day) plus monthly interpersonal psychotherapy – 35 percent
- Paroxetine plus monthly "sham" psychotherapy (clinical management sessions) – 37 percent
- Pill placebo plus psychotherapy – 68 percent
- Placebo plus clinical management – 58 percent

For older patients who experience frequent relapses or recurrences, or who have dysthymic disorder, long-term treatment may be needed; for patients requiring continuous treatment beyond two to three years, consultation with a psychiatrist may be helpful. Studies in adult populations younger than age 65 suggest that chronic antidepressant therapy should be considered for patients with three or more serious episodes of depression before age 50. However, similar data are lacking for treatment of recurrent depression in older populations and consultation with a psychiatrist may be helpful in such cases, too.

Discontinuing antidepressants may be prompted by tachyphylaxis or side effects, or by the need to initiate another medication that may cause a drug-drug interaction with the existing antidepressant. Development of an intercurrent illness, especially of major organ, cerebral, or systemic disease, may also make continuation of antidepressants problematic. Long-term safety data on chronic antidepressant use in older adults with chronic comorbid medical conditions are lacking.

Additional information about continuation and maintenance treatment is discussed separately. (See "Unipolar depression in adults: Continuation and maintenance treatment".)

Antidepressant medications

Selective serotonin reuptake inhibitors — SSRIs are considered first line for treatment of depressive disorders in older adults due to better tolerability, ease of use, and general safety, especially in overdose (table 6) [135].

Resolution of depressive symptoms, usually between four to six weeks, may take longer in older adults. Potential side effects of SSRIs of special concern in older adults include Parkinsonism, akathisia, anorexia, sinus bradycardia, and hyponatremia [143]. A dose-related increased risk for fragility fractures (fractures resulting from minimal trauma) was reported in one observational study [144]. Risk factors may include extensive medical or neurologic comorbidity or concurrent use of multiple medications. Careful monitoring is advised in more frail populations.

One study did suggest an increased rate of suicide in men 66 years and older in the first month of treatment with an SSRI, compared to other antidepressant drugs; this effect was not seen during subsequent treatment [145]. Monitoring for suicide risk is recommended in early therapy with an SSRI. Nonetheless, and as previously noted, treating depression can reduce suicidal ideation [51,146]. (See 'Suicide risk' above.)

Despite greater acceptance and clinical recommendations, SSRIs are probably not more efficacious than older antidepressants. Comparison studies in older adults show that the difference in clinical efficacy is small, the range of placebo response is broad, and that a significant number of older adults retain significant residual depressive symptomatology [134-136]. For severe forms of melancholic and psychotic depression, SSRI agents may be less efficacious than other drugs or ECT [134,147].

The US Food and Drug Administration issued warnings that citalopram causes dose-dependent QT interval prolongation that can lead to arrhythmias, and thus recommends that the maximum dose in patients >60 years of age should not exceed 20 mg per day [148,149]. Additional information about the citalopram warnings and cardiac effects of SSRIs is discussed separately, as are the pharmacology, administration, and other side effects of SSRIs. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects".)

Serotonin-norepinephrine reuptake inhibitors — Serotonin-norepinephrine reuptake inhibitors (SNRIs), which include venlafaxine and duloxetine, are currently used as second-line agents for treatment failure with SSRIs (table 6).

These agents may also be useful in patients with comorbid pain. In a nine-week randomized study comparing duloxetine and placebo for treatment of major depression in patients over age

55, the duloxetine group had a greater treatment response for depression as well as reduction in overall pain, back pain, and pain while awake [150]. However, discontinuation due to adverse events was significantly greater in the duloxetine group (21 percent compared to 7 percent).

Few comparison studies exist between SSRIs and SNRIs in older adults. Frail nursing home patients showed a poorer tolerance to venlafaxine when compared to sertraline in one study [151].

The SNRIs are considered safe for use in most older populations, although both carry a dose-dependent risk for diastolic hypertension. In a study of older adults, venlafaxine extended-release (XR) was found to cause less gastrointestinal distress and agitation than the immediate release preparation [152].

The SNRIs, as well as SSRIs, have resulted in the serotonin syndrome, but more data are needed to identify risk factors for older patients [153]. Serotonin syndrome manifests as altered mental status, myoclonus, tremors, hyperreflexia, fever, and autonomic changes among other findings [154,155]. (See "Serotonin syndrome (serotonin toxicity)".)

The pharmacology, side effects, and general administration of SNRIs are discussed separately. (See "Serotonin-norepinephrine reuptake inhibitors: Pharmacology, administration, and side effects".)

Atypical antidepressants — Atypical antidepressants include agomelatine, bupropion, and mirtazapine (table 6). Few studies exist in populations of older adults [156].

Bupropion is generally considered an activating agent, so it may be useful in patients who complain of lethargy, daytime sedation, or fatigue. Bupropion is contraindicated in patients with seizure disorders, concurrent use of benzodiazepines or other central nervous system depressants, alcohol detoxification, or prior or current diagnosis of bulimia nervosa. Dose-dependent diastolic hypertension is a concern in the older patient.

Mirtazapine is also used as a second-line agent. Mirtazapine appears to be useful for older patients with insomnia, agitation or restlessness, and anorexia or weight loss. It may also be useful in patients with Parkinsonism, essential tremor, or nausea from chemotherapy, and is available as a rapidly dissolving sol-tab preparation [157].

Common side effects of mirtazapine include sedation, especially at initiation and at lower dosages, appetite increase and weight gain, dry mouth, and constipation. The sedating effects of mirtazapine tend to diminish with acclimation and also tend to be less pronounced at higher dosages where the noradrenergic effects predominate over the antihistaminergic effects.

Agomelatine was approved for use in Europe in 2009 but is not approved in the United States. A review identified only one controlled trial (unpublished) in older adults, in which 218 patients 60 years and older with major depression, were randomly assigned to agomelatine 25 mg per day or placebo for six weeks [158]. There was no significant difference in Montgomery Asberg Depression Rating Scale scores. In addition, the rate of response, defined by at least a 50 percent decrease in scores, did not differ significantly between agomelatine and placebo (46 versus 52 percent).

The pharmacology, side effects, and general administration of atypical antidepressants are discussed separately. (See "Atypical antidepressants: Pharmacology, administration, and side effects".)

Serotonin modulators — Serotonin modulators include nefazodone, trazodone, and vilazodone.

Nefazodone is available in the United States in a generic preparation only, as the brand (Serzone) was voluntarily removed from the market due to hepatotoxicity concerns. Nefazodone has been withdrawn from several countries outside the United States, including European countries and Canada. Common side effects include sedation and restlessness. It appears to have relatively good gastrointestinal tolerance. Nefazodone may be useful in depressed patients who complain of insomnia, anxiety, or agitation. Nefazodone is a potent inhibitor of the CYP450-3A4 isoenzyme, so significant drug-drug interactions may occur with commonly used macrolide antibiotics, cardiac antiarrhythmics, and other psychotropic agents.

Trazodone is rarely used solely as an antidepressant but is still commonly used as a soporific and mild sedative, especially at lower doses. Antidepressant effects tend to be seen only at higher dosages, where concerns about orthostatic hypotension and excessive daytime sedation limit its use. Both nefazodone and trazodone have been associated with hyponatremia and trazodone has been associated with the rare but potentially serious side effect of priapism [154].

The pharmacology, side effects, and general administration of serotonin modulators are discussed separately. (See "Serotonin modulators: Pharmacology, administration, and side effects".)

Tricyclic and tetracyclic antidepressants — While no longer considered first- or second-line agents for the treatment of depression in any age group, these agents may be useful for treatment failure with other antidepressants (table 6). A few studies suggest that cyclic antidepressants may have superior efficacy in older adults with melancholic or delusional

depression, and these antidepressants are the only class shown to reduce the risk of relapse after a course of ECT [136,147,159].

Cyclic antidepressants must be used cautiously in patients with cardiac conduction abnormalities, arrhythmias, narrow angle glaucoma, urinary retention, or benign prostatic hyperplasia, and patients should be followed for development or worsening of orthostatic hypotension and constipation. Additionally, patients with Alzheimer-type dementia may experience worsening confusion. Tricyclic and tetracyclic antidepressants are discussed separately. (See "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects".)

Monoamine oxidase inhibitors — This class of antidepressants is rarely used except when previously initiated and tolerated, or in the patient who is treatment resistant to all other antidepressants (table 7). Monoamine oxidase inhibitors (MAOIs) do have proven benefit, with some studies suggesting superior efficacy in atypical (reverse neurovegetative) depression, mixed anxiety-depressive states, and panic disorder, although limited research studies are found in older populations [160].

Patients treated with MAOIs require special dietary and medication restrictions to prevent the serotonin syndrome and hyperadrenergic crisis. Because of potential severe side effects, these medications are best prescribed by a psychiatrist or physician with extensive experience in use of these medications. Aside from these concerns, these medications are surprisingly well tolerated in older adults. Common side effects include orthostatic hypotension, activation, and insomnia. In contrast to tricyclic antidepressants, these medications are relatively devoid of cardiac conduction effects.

The pharmacology, side effects, and general administration of monoamine oxidase inhibitors are discussed separately. (See "Monoamine oxidase inhibitors (MAOIs): Pharmacology, administration, safety, and side effects".)

Adjunctive medications

Methylphenidate — For patients with late-life major depression, simultaneously prescribing an antidepressant with methylphenidate at the onset of treatment may improve outcomes. A 16-week randomized trial enrolled patients (n = 143; mean age 70 years) with unipolar major depression who were free of psychotropic medications for at least two weeks, and assigned them to receive citalopram plus methylphenidate, citalopram plus placebo, or methylphenidate plus placebo [161]. Electrocardiograms were performed at baseline, and patients with atrial or ventricular arrhythmias or acute ischemic features were excluded. Citalopram doses ranged from 20 to 60 mg/day and methylphenidate from 5 to 40 mg/day. Improvement was greater

and occurred more quickly with combination treatment than either citalopram monotherapy or methylphenidate monotherapy. In addition, discontinuation of treatment due to side effects appeared to be comparable for the three groups. It is worth noting that stimulants can lead to adverse cardiac effects, and that the maximum dose of citalopram recommended by the US Food and Drug Administration for patients age >60 years is 20 mg/day. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Citalopram'.)

Aripiprazole — For patients with treatment-resistant late-life depression, multiple randomized trials indicate that adjunctive aripiprazole can be efficacious:

- A 12-week trial compared add-on aripiprazole with placebo in patients (n = 181) who did not initially remit with open label venlafaxine [162]. Aripiprazole was started at 2 mg per day and titrated up as needed and tolerated to a target dose of 10 mg per day (range 2 to 15 mg per day; median final daily dose 7 mg). Remission occurred in more patients who received aripiprazole than placebo (44 versus 29 percent). However, aripiprazole caused more akathisia (26 versus 12 percent of patients) and Parkinsonism (17 versus 2 percent). Weight gain was also greater with active drug than placebo (1.9 versus 0.0 kg).

- A subsequent, 10-week trial enrolled 413 patients who had not responded to adequate treatment with a mean of two antidepressants (eg, duloxetine, escitalopram, or venlafaxine), and randomly assigned them to augmentation with aripiprazole or switching to extended-release bupropion [163]. Aripiprazole was started at 2 mg per day and titrated up as needed and tolerated to a maximum dose of 15 mg per day. Bupropion was started at 150 mg per day and titrated up as needed and tolerated to a maximum dose of 450 mg per day. Improvement was greater with adjunctive aripiprazole than switching to bupropion. However, adverse effects that appeared to be greater with aripiprazole than bupropion included akathisia (11 and 2 percent of patients), fatigue (9 and 1 percent), and weight gain (15 and <1 percent).

Information about adjunctive second-generation antipsychotics for the general population of patients with treatment-resistant depression is discussed separately. (See "Unipolar depression in adults: Treatment with second-generation antipsychotics".)

Other — Other add-on medications that can be used with antidepressants in treatment-resistant late-life depression include lithium and triiodothyronine. (See "Unipolar depression in adults: Treatment with lithium" and "Unipolar depression in adults: Augmentation of antidepressants with thyroid hormone".)

Quetiapine monotherapy — Although monotherapy with the second-generation antipsychotic quetiapine may be effective for major depression, the risk of short- and long-term side effects is

such that quetiapine is not a first- or second-line treatment. Evidence for the efficacy of quetiapine includes a nine-week randomized trial that compared quetiapine extended-release monotherapy (50 to 300 mg per day, median dose 159 mg per day) with placebo in 335 patients with late-life, nonpsychotic, unipolar major depression [164]. Remission occurred in more patients who received quetiapine than placebo (45 versus 17 percent). Discontinuation of treatment following an adverse event occurred in more than twice as many patients who received quetiapine (10 versus 4 percent). Common side effects of quetiapine included sedation, dry mouth, and extrapyramidal symptoms. Although these findings indicate that quetiapine extended release may have some utility for major depression, ongoing concerns remain about safety issues and side effects, especially with long-term treatment. The use of second-generation antipsychotics as adjunctive treatment for unipolar major depression that does not respond to antidepressant monotherapy is discussed separately. (See "Unipolar depression in adults: Treatment with second-generation antipsychotics".)

Neurostimulation — Several brain stimulation procedures for treating major depression are clinically available or under investigation. An overview of these procedures is discussed separately. (See "Unipolar depression in adults: Overview of neuromodulation procedures".)

Electroconvulsive therapy — Electroconvulsive therapy (ECT) remains an important and viable treatment option in older adults. ECT is used for depressed patients who have not responded to adequate antidepressant trials, and patients with severe major depression that is life-threatening or significantly impairs functioning [84,165-168]. Indications for use, description of the procedure, morbidity, and risk assessment for ECT are discussed separately. (See "Overview of electroconvulsive therapy (ECT) for adults" and "Unipolar major depression in adults: Indications for and efficacy of electroconvulsive therapy (ECT)", section on 'Older age' and "Technique for performing electroconvulsive therapy (ECT) in adults" and "Medical evaluation for electroconvulsive therapy".)

Other brain stimulation therapies — Other brain stimulation therapies have been evaluated for treatment of medication-resistant depression; these therapies include repetitive transcranial magnetic stimulation, deep brain stimulation, and vagus nerve stimulation. However, there are no randomized trials that have demonstrated any benefit of these modalities in older adults. Neuromodulation is discussed in more detail separately. (See "Unipolar depression in adults: Overview of neuromodulation procedures" and "Unipolar depression in adults: Indications, efficacy, and safety of transcranial magnetic stimulation (TMS)", section on 'Older adult' and "Unipolar depression in adults: Treatment with surgical approaches".)

Exercise — Systematic reviews of controlled trials indicate that physical exercise is beneficial for depressed patients 60 years and older [117,169,170]. As an example, a meta-analysis of seven

randomized trials (n = 519 patients) compared exercise with a nonexercise control condition; exercise typically consisted of three to five sessions (each lasting 30 to 45 minutes) per week, for three to four months [171]. The analysis found a significant, but clinically small effect favoring exercise.

Physical exercise may be a first-line treatment for patients with mild or moderate depression, but it may be difficult for them to engage in exercise. Thus, additional treatment with medications or psychotherapy may be needed.

The two main types of exercise are cardiovascular (aerobic) activities such as walking, running, or swimming, and resistance training (nonaerobic) that involves lifting weights. Both types of exercise can help reduce depressive symptoms, but the results appear to be more consistent for cardiovascular exercise [169]. One review found that late-life depressive symptoms were substantially reduced in more patients who participated in short-term (eg, 12-week), supervised, group-based, cardiovascular exercise programs, compared with patients in control groups (45 to 65 versus 25 to 30 percent) [5].

The benefits of exercise appear to persist in depressed, older patients who continue to exercise for the long term. A study randomly assigned 438 adults with osteoarthritis, 60 years or older, to cardiovascular exercise, resistance exercise, or health education classes (to control for the therapeutic effects of socialization) [172]. The exercise programs were conducted under supervision for three months in a facility, and then for 15 months at home with face-to-face or telephone contact by the exercise leader. Among the 98 patients with major depression, the reduction in depression rating scale scores at month 18 was significantly greater for those assigned to cardiovascular exercise compared with health education (40 versus 20 percent reduction). Resistance exercise did not differ significantly from health education.

Additional information about exercise and treatment of depression as well as exercise in older adults (including assessment of individuals with cardiovascular contraindications to physical activity), is discussed separately. (See "Physical activity and exercise in older adults".)

Bright light — Bright light therapy may be beneficial for depressed patients who do not have seasonal affective disorder. A three-week randomized trial compared bright light treatment (pale blue, approximately 7500 lux) with placebo (dim red, approximately 50 lux) in 89 older patients with nonseasonal major depression. Response (improvement from baseline ≥50 percent) occurred in more patients who received bright light (58 versus 34 percent), which was well-tolerated [173].

Collaborative care — Collaborative care programs emphasize patient education and use nonphysician mental health professionals or depression care managers to integrate psychiatric

and primary care; these programs (also called integrative care and care management) for older adult depressed patients can improve outcomes [174,175]. As an example, the 12-month, multisite Improving Mood-Promoting Access to Collaborative Treatment (IMPACT) program compared collaborative care with usual care in 1801 primary care patients with late life major depression and/or persistent depressive disorder (dysthymia), and found that cost effectiveness and improvement of symptoms (including suicidal ideation), physical functioning, and quality of life were greater with collaborative care [52,109,111]. In addition, the benefits were sustained one year after termination of the collaborative intervention [176]. Other trials have found comparable results [51,177,178].

Collaborative care appears to improve general medical outcomes as well as depression. Patients at one of the IMPACT study sites were followed for eight years, including 168 patients without cardiovascular disease at baseline [179]. Cardiovascular events (fatal or nonfatal myocardial infarction or stroke) occurred in fewer patients who received collaborative care than usual care (28 versus 47 percent).

In addition, collaborative care programs may decrease all-cause mortality in late-life depression. A randomized trial compared collaborative care with usual care in 396 older primary care patients with unipolar major depression as well as 203 patients with minor depression [180]. The study also enrolled 627 patients without depression. Collaborative care involved depression care managers (social workers, nurses, or psychologists) who were supervised by psychiatrists and worked with primary care physicians to provide antidepressants and/or psychotherapy for depression; increase antidepressant doses or switch antidepressants when indicated; and monitor symptoms, side effects, and adherence to treatment. Patients were treated for up to 24 months and followed for a median of 98 months, during which time 405 patients died. The primary findings were as follows:

- Among patients with major depression, the risk of death was 24 percent less with collaborative care than usual care (hazard ratio 0.76, 95% CI 0.57-1.00).
- The risk of death for patients with major depression who received collaborative care and patients who were not depressed was comparable (hazard ratio 1.1, 95% CI 0.8-1.4). By contrast, mortality was greater (nearly twice as high) for patients with major depression in usual care, compared with nondepressed patients (hazard ratio 1.9, 95% CI 1.6-2.3).
- For patients with minor depression, collaborative care did not affect the risk of mortality.

The elements of collaborative care are also helpful in psychiatric practices. A six-month randomized trial compared care management plus pharmacotherapy with pharmacotherapy alone in 57 older patients, who were treated for depressive disorders in a psychiatric clinic

[181]. Care management consisted of eight telephone calls from a psychologist, who educated patients about depression, treatment options, and adherence; monitored symptoms and adverse events; and reminded patients about their next visit to the clinic. Remission occurred in more patients who received care management plus pharmacotherapy than pharmacotherapy alone (55 versus 29 percent).

Additional information about collaborative care in mixed age populations is discussed separately. (See "Unipolar depression in adult primary care patients and general medical illness: Evidence for the efficacy of initial treatments", section on 'Collaborative care'.)

Home-based care — Home-based interventions for mildly depressed, older patients with limited mobility or access to care may be helpful. However, the availability of home-based interventions is limited.

Evidence supporting the efficacy of home-based care includes the following [182]:

- A four-month randomized trial compared at-home care with a waiting list control condition in 208 older African Americans with depressive symptoms [183]. The active treatment was administered by social workers and included referrals for medical and social services, education about depression and stress reduction, and behavioral activation. Remission of symptoms occurred in more patients in the intervention group than the waiting list group (44 versus 27 percent).

- A one-year randomized trial compared home-based treatment with usual care in 138 patients with either minor depression or persistent depressive disorder (dysthymia) [122]. The home-based program was administered by social workers and included eight sessions of problem solving therapy and behavioral activation, as well as recommendations to patients' physicians about use of antidepressants; usual care included a letter to patients' physicians about the depression diagnosis. Remission was greater in patients who received home-based care than usual care (36 versus 12 percent).

Family support — Family members should be involved in the care of patients with late-life major depression, and be educated about the signs and symptoms, treatment, and prognosis of the illness [174]. The family can provide information about symptoms that the patient may not reveal and can encourage adherence to treatment. Family meetings for assessment and treatment of patients with major depression are discussed separately. (See "Unipolar depression in adults: Family and couples therapy".)

Other — Cognitive impairment in late-life depression raises the question as to whether cholinesterase inhibitors are useful; however, a review of four randomized trials found that

cholinesterase inhibitors as adjunctive treatment with antidepressants provided no clear benefit [184]. In the largest trial, donepezil was compared with placebo as add-on maintenance treatment with an antidepressant in patients age 65 years and older [185]. Cognitive functioning was superior with donepezil at one year but not two years. However, donepezil appeared to increase the risk of recurrence of major depression. In addition, cholinesterase inhibitors may provoke symptoms (eg, dysphoria) that mimic depression. Thus, their use in this population requires close monitoring.

PREVENTION

Efforts to prevent late-life depression have included use of marine omega-3 fatty acids; however, the evidence indicates this treatment is not effective. As an example, a five-year randomized trial compared omega-3 fatty acids with placebo in more than 18,000 patients (mean age 68 years) without depression [186]. Active treatment consisted of eicosapentaenoic acid 465 mg/day and docosahexaenoic acid 375 mg/day. Depressive symptoms were comparable in the two groups.

Omega-3 fatty acids have also been studies for treating acute major depression. (See "Unipolar depression in adults: Investigational and nonstandard treatment", section on 'Omega-3 fatty acids'.)

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: Coping with high drug prices (The Basics)")

- Beyond the Basics topics (see "Patient education: Coping with high prescription drug prices in the United States (Beyond the Basics)")

SUMMARY

- **Epidemiology and diagnosis**
  - **Impact** – Late-life depression often goes undetected and has a significant adverse impact on quality of life, outcomes of medical disease, health care utilization, and morbidity and mortality. The overwhelming majority of older adults with depression initially present to primary care, often with somatic complaints. (See 'Introduction' above.)
  - **Risk factors** – Depression is not a normal consequence of aging. Healthy independent older adults have a lower prevalence rate of major depression than the general population. Rates increase greatly with medical illness, particularly cancer, myocardial infarction, and neurological disorders such as stroke and Parkinson disease. (See 'Risk factors' above.)
  - **Suicide** – Suicide rates are approximately twice as high in older adults, with the rate highest for white men over 85 years of age. Most older adults who commit suicide had seen a clinician within the previous month. (See 'Suicide risk' above.)
  - **Minor depression** – Minor depression in late life is more prevalent than major depression, has significant health consequences, and responds to treatment. (See 'Minor depression' above.)
  - **Psychotic depression** – Delusional (psychotic) depression is a very severe illness and can be lethal. Cognitive deficits may be pronounced and similar to dementia. However, both depressive symptoms and cognitive impairment respond to treatment with antidepressants, distinguishing these patients from those with Alzheimer disease and secondary depression. (See 'Psychotic depression' above.)
  - **Vascular depression** – Depression associated with cerebrovascular disease is characterized by psychomotor retardation, anhedonia, greater frontal executive dysfunction, and poor insight. (See 'Vascular depression' above.)
  - **Screening** – Depression in older adults can be challenging to diagnose. Screening instruments are available that can help identify patients who need further evaluation for depression. (See 'Screening instruments' above.)

- **Treatment**

  - **Psychotherapy** – Psychotherapy is effective in older adults, although for moderate to severe depression in late life, pharmacotherapy or a combination of pharmacotherapy and psychotherapy is recommended. (See 'Psychotherapy' above.)

  - **General principles of pharmacotherapy** – Medication monotherapy is preferred in older adults in order to minimize drug side effects and drug-drug interactions. Initial medication dosage should be adjusted for the older adult, typically halving the usual starting dose for younger patients but full therapeutic doses are often required to achieve the desired responses. (See 'Medication selection and management' above.)

    All medications typically take four to six weeks to show efficacy; in older patients, a full antidepressant response may not occur until 8 to 12 or even 16 weeks of therapy. Long-term treatment may be necessary to prevent recurrence. (See 'Medication selection and management' above and 'Duration of treatment' above.)

    Patients should be contacted or seen within two weeks of initiating medication to discuss tolerance and adjust dose as indicated, and should have an office visit within two to four weeks of treatment to assess response, monitor for side-effects, and address any complications or deterioration. (See 'Medication selection and management' above.)

  - **Selective serotonin reuptake inhibitors** – Selective serotonin reuptake inhibitors are first-line antidepressants because of safety and tolerability. However, in patients age 60 years and above, the maximum recommended dose of citalopram is 20 mg per day due to concerns about dose-dependent QT interval prolongation that can lead to arrhythmias. (See 'Selective serotonin reuptake inhibitors' above and "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects".)

  - **Serotonin-norepinephrine reuptake inhibitors** – Venlafaxine and duloxetine are frequently used as second-line agents and may be particularly helpful in patients with depression and neuropathic pain. (See 'Serotonin-norepinephrine reuptake inhibitors' above.)

  - **Atypical antidepressants** – Mirtazapine may be useful for patients with insomnia, agitation, restlessness, or anorexia and weight loss. (See 'Atypical antidepressants' above.)

- **Tricyclic antidepressants** – Tricyclic antidepressants are third- or fourth-line therapy in older adults due to significant arrhythmic side effects, as well as anticholinergic effects causing urinary retention, orthostasis, and possible exacerbation of dementia. These drugs, when necessary, are probably best managed by a psychiatrist or physician with special expertise and experience in managing these medications in older adults. (See 'Tricyclic and tetracyclic antidepressants' above.)

- **Monoamine oxidase inhibitors** – Monoamine oxidase inhibitors can be used for depression that is resistant to other agents. This class of drugs has not been well studied in older adults. They should also be prescribed by a psychiatrist or physician with special expertise and experience with these medications, because of their serious side effect profile. (See 'Monoamine oxidase inhibitors' above.)

- **Collaborative care** – There is evidence that for older primary care patients with major depression, improvement of symptoms (including suicidal ideation), physical functioning, and quality of life is greater, and that mortality is lower, with collaborative care than with usual care. (See 'Collaborative care' above.)

- **Electroconvulsive therapy** – Electroconvulsive therapy (ECT) is used more frequently in older patients than in younger patients, and may be effective for the older patient who is intolerant of medications or not responding to adequate medication trials. ECT is generally well tolerated in the older patient, although it causes transient memory loss. (See "Unipolar major depression in adults: Indications for and efficacy of electroconvulsive therapy (ECT)", section on 'Older age'.)

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