Unipolar depression in adult primary care patients and general medical illness: Evidence for the efficacy of initial treatments

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Literature review current through: **Oct 2023.**
This topic last updated: **Apr 15, 2023.**

INTRODUCTION

Depression is highly prevalent. Community surveys in 14 countries have estimated that the lifetime prevalence of unipolar depressive disorders is 12 percent [1]. In patients with general medical illnesses such as diabetes or coronary heart disease, the prevalence of major depression is estimated at 10 to 20 percent [2].

In addition, disability due to depression is common. The World Health Organization ranks unipolar major depression as the 11th greatest cause of disability and mortality in the world, among 291 diseases and causes of injury [3]. In the United States, major depression ranks second among all diseases and injuries as a cause of disability, and dysthymia ranks 20th [4].

Major depression is also highly recurrent. Following recovery from one episode, the estimated rate of recurrence over two years is greater than 40 percent; after two episodes, the risk of recurrence within five years is approximately 75 percent [5].

This topic reviews the efficacy of standard therapies for the initial treatment of depression in primary care patients and in patients with general medical illnesses. The choice of therapy for the initial treatment of depression and the general evidence of efficacy of standard therapies are discussed separately, as are the general principles and prognosis for the initial treatment of

depression, and the evidence for therapies that are not typically used. 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 adults and initial treatment: General principles and prognosis".)
- (See "Unipolar depression in adults: Investigational and nonstandard treatment".)
- (See "Unipolar depression in adults: Continuation and maintenance treatment".)
- (See "Unipolar depression in adults: Choosing treatment for resistant depression".)
- (See "Unipolar depression in adults: Assessment and diagnosis".)

DEPRESSED PRIMARY CARE PATIENTS

Many or most depressed outpatients are treated by primary care clinicians rather than psychiatrists [6]. As an example, a representative survey of the United States household population found that among patients with unipolar major depression who received antidepressants (n = 363), primary care clinicians administered the treatment in 67 percent of the cases [7].

Evidence of efficacy

Antidepressants — Several types of antidepressants are available to treat unipolar major depression (table 1 and table 2):

- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin-norepinephrine reuptake inhibitors
- Atypical antidepressants
- Serotonin modulators
- Tricyclic antidepressants
- Monoamine oxidase inhibitors (MAOIs)

The pharmacology, administration, and side effects of these drug classes are discussed separately.

- (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects".)
- (See "Serotonin-norepinephrine reuptake inhibitors: Pharmacology, administration, and side effects".)

- (See "Atypical antidepressants: Pharmacology, administration, and side effects".)
- (See "Serotonin modulators: Pharmacology, administration, and side effects".)
- (See "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects".)
- (See "Monoamine oxidase inhibitors (MAOIs): Pharmacology, administration, safety, and side effects".)

SSRIs, serotonin-norepinephrine reuptake inhibitors, atypical antidepressants, and serotonin modulators are considered second-generation antidepressants, which are more commonly prescribed by primary care clinicians than tricyclics and MAOIs [7].

For primary care patients with unipolar major depression, evidence supporting the use of antidepressants includes meta-analyses of randomized trials in patients who were not necessarily treated in primary care settings. (See "Unipolar major depression in adults: Choosing initial treatment", section on 'Efficacy of antidepressants'.)

In addition, antidepressants have demonstrated efficacy for major depression in primary care clinics:

- A pooled analysis of 28 randomized trials (5940 depressed, primary care patients who were typically treated for six to eight weeks) estimated that response rates (eg, reduction of baseline symptoms ≥50 percent) in patients who received second-generation antidepressants or placebo were 63 and 35 percent [8].

- Meta-analyses of 66 randomized trials (n >15,000 depressed patients) found that the efficacy of SSRIs, other second-generation antidepressants, and tricyclics was superior to placebo [9]. However, the clinical effects compared with placebo were small to moderate (eg, odds ratio for SSRIs 1.7, 95% CI 1.4-2.0; odds ratio for tricyclics 1.8, 95% CI 1.4-2.2).

Several studies have evaluated whether some specific second-generation antidepressants are superior to others, and have found that the comparative efficacy is generally comparable. As an example, a review concluded that all second-generation antidepressants were typically suitable for the initial treatment of depression in primary care patients, based upon systematic reviews, conventional meta-analyses, and network meta-analyses of patients who were not necessarily treated by primary care clinicians [10].

However, some studies suggest that specific antidepressants may differ in their efficacies. A network meta-analysis of 87 randomized trials (nearly 20,000 primary care patients with unipolar major depression) compared remission rates among 10 second-generation antidepressants (citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, paroxetine, reboxetine, sertraline, and venlafaxine), using indirect comparisons of the drugs

(through their relative effect with a common comparator, usually placebo), as well as analyzing direct comparisons between drugs; the study concluded that the probability of remission was greatest with escitalopram [11].

The comparative efficacy of antidepressants is discussed in greater detail separately. (See "Unipolar major depression in adults: Choosing initial treatment".)

Adherence — Antidepressant side effects can diminish adherence to treatment [12]. In a randomized trial that compared fluoxetine, desipramine, and imipramine in 536 depressed primary care patients (doses were determined by the primary care physicians), discontinuation of treatment due to side effects during the first month was less with fluoxetine than desipramine and imipramine (9 versus 27 and 28 percent) [13].

Adherence to antidepressants, which is often poor in depressed primary care patients [12], may be improved with education. However, it appears that both adherence and depressive symptoms improve more when education is combined with other interventions. A qualitative systematic review of 26 randomized trials (n >11,000 patients with unipolar depression; nearly all treated within primary care) found that education alone was often not beneficial [14]. By contrast, education that was part of collaborative care was frequently effective for adherence and depression outcomes. Education about adherence and collaborative care are each discussed separately. (See "Unipolar depression in adults and initial treatment: General principles and prognosis", section on 'Adherence to treatment' and 'Collaborative care' below.)

Collaborative care — Collaborative care integrates psychiatric treatment into primary care practices. Patients are treated by a team that usually includes a primary care clinician, a case manager who provides support and outreach to patients, and a mental health specialist (eg, psychiatrist) who provides consultation and case supervision [15-21]. Other elements include a structured treatment plan that involves pharmacotherapy and/or other interventions (eg, patient education, cognitive-behavioral therapy, or problem solving therapy), scheduled follow-up visits, communication among the members of the treatment team, and measurement based care. (See "Using scales to monitor symptoms and treat depression (measurement based care)".)

Many studies demonstrate that collaborative care improves depression outcomes [22-26]:

- A meta-analysis of 37 randomized trials (n >12,000 depressed patients) found a significant but clinically small effect favoring collaborative care over standard primary care, which persisted for up to five years; heterogeneity across studies was moderate [27].

- A subsequent meta-analysis of 79 randomized trials (n >24,000 depressed patients) that compared collaborative care with usual primary care (eg, pharmacotherapy alone) found that after six months, response (reduction of baseline symptoms ≥50 percent) occurred more often with collaborative care (relative risk 1.3, 95% CI 1.2-1.4); heterogeneity across studies was large [19]. The benefits of collaborative care persisted for up to 24 months.

- A more recent meta-analysis of nine randomized trials (n >2000 depressed patients) compared collaborative care with usual care during follow-up lasting 12 or more months, and found that remission occurred in more patients who received collaborative care [28]. However, the clinical effect was small and heterogeneity across studies was large.

In meta-analyses of randomized trials that compared collaborative care with usual care in primary care patients with depression and chronic conditions (eg, arthritis, asthma, cancer, coronary heart disease, diabetes, and HIV), improvement of depressive symptoms, psychosocial functioning, and mental and physical quality of life was greater with collaborative care than usual care [29,30]. Analyses found that all-cause mortality was comparable for the two treatment groups, as was diabetic control in those studies addressing comorbid diabetes. However, one trial set goals concurrently for both diabetes and depression ("treat-to-target" or goal oriented therapy), and found statistically significant improvements in HbA1c as well as depression [31].

Other randomized trials have shown collaborative care is superior to usual care for treating depression in adolescents [32], military personnel [33], patients attending obstetrics and gynecology clinics [34], socioeconomically disadvantaged pregnant and postpartum women [35], and advanced cancer patients receiving palliative care [36].

Integrating case managers and mental health clinicians into collaborative care programs through telemedicine may be effective for small practices that lack on-site mental health specialists [21]. One 12-month randomized trial compared practice-based collaborative care (on-site primary care clinician and nurse care manager) with telemedicine-based collaborative care (on-site primary care clinician, as well as off-site nurse care manager and pharmacist by telephone and a psychologist and psychiatrist via videoconferencing) in 364 patients who screened positive for major depression [37]. Assessments 18 months postbaseline found that remission occurred in more patients who received telemedicine-based collaborative care than practice-based collaborative care (26 versus 10 percent). However, poor implementation of practice-based collaborative care reduces confidence in these findings.

In addition, case management administered by nurses through online messages to patients can improve depressive disorders, based upon a randomized trial (n = 208 patients) that compared

online-based collaborative care with usual primary care [38].

Based upon the evidence, the American College of Physicians recommends that depressed primary care patients be treated within the context of collaborative care [39].

Factors associated with better outcomes — Meta-analyses of randomized trials that compared collaborative care with usual care for primary care patients with depression indicate that the following factors predict better outcomes with collaborative care [23,27]:

- Case management provided by nurses
- Case managers with a mental health background
- Regular, planned supervision of case managers and caseload review by a mental health specialist (typically a psychiatrist)
- Good medication adherence

In addition, a study of registry data found that patients with depression who are treated within a collaborative care model are more likely to improve if they follow up with a clinician within four weeks of initially presenting with depression [40]. Among patients who do not improve after eight weeks of treatment, improvement is more likely to occur if they consult with a psychiatrist within the subsequent four weeks.

One meta-analysis (37 randomized trials, n >12,000 depressed patients) found that among patients who received collaborative care, the benefit of psychotherapy plus pharmacotherapy was comparable to the benefit of pharmacotherapy alone [27]. In addition, depression outcomes did not improve by increasing the number of patient visits with the collaborative care case manager (which ranged from 2 to 14 among the trials). However, in a subsequent randomized trial that compared a single visit with a case manager with usual care in 375 primary care patients with depression, the intervention had no effect upon depression, suggesting that at least two visits may be necessary for an effective collaborative care program [41].

Psychotherapy — Although psychotherapy is generally administered in specialty psychiatric settings, randomized trials indicate that psychotherapy may also be effective in primary care settings [42,43]:

- A meta-analysis of 15 trials (n >1500 primary care patients with depressive disorders) compared psychotherapy (primarily cognitive-behavioral therapy or problem solving

therapy) with a control condition (eg, usual care), and found a significant but clinically small effect favoring psychotherapy; heterogeneity across studies was moderate [44].

- A meta-analysis of 30 randomized trials (n >5100 patients) compared psychotherapy with a control condition (eg, usual care or placebo), and found a significant, clinically small to moderate effect favoring psychotherapies such as cognitive-behavioral therapy (CBT) and interpersonal psychotherapy [45]. In addition, less resource intensive forms of CBT that involved minimal to no contact with patients appeared to provide effects comparable to face to face CBT.

For primary care patients with mild to moderate episodes of unipolar major depression, limited evidence suggests that a relatively brief version of interpersonal psychotherapy (eg, administering 8 sessions rather than 16) may be suitable [46].

Although computerized versions of psychotherapy such as CBT have been developed, it is not clear that these are generally beneficial [47]. As an example, a four-month, open-label trial randomly assigned primary care patients with depression (n = 691) to a commercial computerized CBT program plus usual care, a free computerized CBT program plus usual care, or usual care alone [48,49]. Although patients assigned to computerized CBT received weekly telephone support, uptake and use of CBT was low, and improvement across the three groups was comparable.

Efficacy of antidepressants compared with psychotherapy — In a practice guideline for internists and primary care clinicians who treat unipolar major depression [50], the recommendations were based in part upon a pooled analysis of five randomized trials that compared second-generation antidepressants with CBT in 660 patients [51]. Response with antidepressants or CBT was comparable (46 and 44 percent of patients). Additional information about the efficacy of antidepressants compared with psychotherapy is discussed separately. (See "Unipolar major depression in adults: Choosing initial treatment".)

DEPRESSION IN GENERAL MEDICAL ILLNESS

Patients with general medical illnesses often suffer depressive syndromes, which are associated with increased physical symptoms; functional impairment; poor adherence to diet, exercise, and medications; and increased medical costs [2,52,53]. As an example, depression predicts worse outcomes in stroke, myocardial infarction, and diabetes [54-58]. Additionally, there is evidence that depression may increase the risk of developing general medical diseases [56]. (See "Psychosocial factors in acute coronary syndrome".)

The diagnosis of depressive syndromes in the physically ill can be complicated; symptoms such as a dysphoria and lack of energy may be due to the physical illness and/or depression. Depression associated with specific general medical conditions is discussed separately.

While treatment of depression in patients with general medical illnesses improves depression and functional outcomes (see 'Antidepressants' below), it is unclear whether treatment of depression alone improves general medical outcomes because of conflicting results across multiple studies [16,56,59-65]. However, trials which use collaborative care approaches that are aimed at improving both comorbid depression outcomes and medical disease control have been successful. As an example, a 12-month, single-blind, randomized trial enrolled 214 patients with depression and poorly controlled diabetes, coronary heart disease, or both, and compared treatment as usual with collaborative care, in which a medically supervised nurse provided guideline-based care for managing depression and the general medical illness [31]. Improvement of glycated hemoglobin levels, low-density lipoprotein (LDL) cholesterol, and systolic blood pressure levels, as well as depressive symptoms, was greater with collaborative care. By contrast, other studies have found that treating depression alone without including interventions for improving medical disease control after acute coronary syndromes does not improve mortality [66,67]. Improvement in general medical outcomes may depend upon whether interventions are specifically targeted at both depression and improving medical disease control versus depression alone.

Evidence of efficacy

Antidepressants — For patients with unipolar major depression and comorbid general medical illnesses, evidence supporting the use of antidepressants includes meta-analyses of randomized trials in depressed patients who did not necessarily have comorbid illnesses. (See "Unipolar major depression in adults: Choosing initial treatment", section on 'Efficacy of antidepressants'.)

In addition, meta-analyses of randomized trials have demonstrated that antidepressants are effective for depression in patients with general medical conditions:

- A meta-analysis of 25 trials (1674 depressed patients with a variety of physical diseases) found that improvement of depressive symptoms occurred in more patients who received antidepressants than placebo (odds ratio 2.3, 95% CI 1.8-3.0). In addition, discontinuation of treatment for any reason was comparable for the two groups [68].

- A subsequent meta-analysis of 25 trials (2338 patients with unipolar major depression and various comorbid general medical illnesses) found that response (reduction of baseline depression symptoms ≥50 percent) occurred in more patients who received

antidepressants than placebo (risk ratio 1.4, 95% CI 1.3-1.6); heterogeneity across studies was not significant [69].

- A meta-analysis of seven trials compared antidepressants with placebo in 306 patients with depression and diabetes mellitus, and found a significant, clinically moderate to large benefit favoring antidepressants; heterogeneity across studies was moderate [65]. In addition, glycemic control was superior in patients who received antidepressants.

Large trials have also found that antidepressants are effective for major depression in patients with coronary heart disease [70]. In addition, antidepressants can be used to treat depression in patients with chronic pain. (See "Pharmacologic management of chronic non-cancer pain in adults", section on 'Antidepressants'.)

SSRIs — For treatment of depression in patients with comorbid general medical disorders, selective serotonin reuptake inhibitors (SSRIs) have been more widely studied in high-quality trials than other antidepressant classes. As an example:

- A systematic review included a meta-analysis of 24 randomized trials that compared SSRIs with placebo for treating depression in 2133 patients with medical diseases such as asthma, cancer, coronary heart disease, diabetes, infection with the human immunodeficiency virus, Parkinson disease, and stroke [53]. The analysis found a significant, small to moderate clinical effect favoring SSRIs over placebo; however, heterogeneity across studies was moderate and discontinuation of treatment due to adverse effects was greater with SSRIs. The review included a second meta-analysis of eight trials (411 patients) that compared SSRIs with tricyclics; both efficacy and tolerability were comparable for the two groups.

- One randomized trial compared sertraline (50 to 200 mg/day) with cognitive-behavioral therapy (CBT; 10 sessions administered as group therapy) in patients with major depression plus type 1 or 2 diabetes mellitus [71]. After three months, patients who responded (reduction of baseline depression symptoms ≥50 percent) continued treatment for another 12 months; depression outcomes at the end of 15 months were superior with sertraline than CBT, and the clinical effect was moderate.

Other classes — In addition to their efficacy for the general treatment of unipolar major depression, serotonin-norepinephrine reuptake inhibitors appear to be efficacious for treating depression in patients with general medical comorbidity. One eight-week, randomized trial compared duloxetine (60 mg per day) with placebo in 311 patients ≥65 years of age with unipolar major depression; 75 percent had arthritis, diabetes mellitus, and/or vascular disease [72]. Remission of depression occurred in more patients treated with duloxetine than placebo

(27 versus 15 percent), and physical health status and pain relief were also superior with active treatment. In addition, discontinuation of treatment due to adverse effects was similar for duloxetine and placebo (approximately 9 percent of patients).

Tricyclic antidepressants are also beneficial for depressed patients with medical comorbidity. A meta-analysis of eight randomized trials compared tricyclics with placebo for treating depression in 324 patients with general medical diseases, and found a significant, moderate to large clinical effect favoring tricyclics over placebo; heterogeneity across studies was small [53]. However, there was a trend for a greater rate of dropout due to adverse effects in patients who received tricyclics.

Collaborative care — Collaborative care integrates psychiatric treatment into primary care practices; general information about collaborative care is discussed elsewhere in this topic. (See 'Collaborative care' above.)

For patients with depressive syndromes and comorbid general medical illnesses, collaborative care can improve depression and comorbid medical illnesses [73]:

- **Depression** – Evidence that collaborative care can improve depression includes meta-analyses based upon 31 randomized trials in depressed patients (n >10,000), which compared collaborative care with usual care; the primary findings included the following [74]:
  - Among patients with chronic physical conditions such as diabetes and/or cardiac disease, improvement of depression was greater with collaborative care than usual care, and the clinical effect was small to moderate. Also, the number and type of chronic conditions did not moderate the treatment effect.
  - The benefit of collaborative care for depression was comparable for patients with comorbid general medical illnesses and patients without comorbidity.
- **General medical illnesses** – Randomized trials indicate that collaborative care can also improve outcomes in general medical illnesses such as diabetes. As an example:
  - A meta-analysis of 7 trials lasting 12 to 52 weeks compared collaborative care with usual care in patients with comorbid depression and diabetes (n = 1895); improvement of depression was greater with collaborative care, as was improvement of diabetes [75]. The benefits were small to moderate for both depression and glycemic outcomes, and improvement of diabetes appeared to be independent of improvement of depression. However, heterogeneity across studies was large.

- A subsequent, open-label trial from India compared collaborative care with usual care in patients (n = 404) with at least moderate depressive symptoms plus type 2 diabetes mellitus and poor control of at least one of the following cardiometabolic indices: hemoglobin A_{1c}, systolic blood pressure, or low-density lipoprotein cholesterol [76]. Patients received study treatment for one year and were assessed two years after study entry. The primary outcome was reduction of baseline depressive symptoms ≥50 percent plus reduction of at least one of the following: hemoglobin A_{1c} by at least 0.5 percentage points, systolic blood pressure by at least 5 mm Hg, or reduction of low-density lipoprotein cholesterol by at least 10 mg/dL. At the two-year assessment, improvement of depression plus at least one cardiometabolic parameter occurred in more patients who received collaborative care than usual care (72 versus 55 percent). However, the usual care in this study may differ from usual care in trials from health care systems in more developed countries.

Psychotherapy — Psychotherapy is effective for patients with general medical problems, based upon meta-analyses of randomized trials in depressed patients who did not necessarily have comorbid illnesses. (See "Unipolar major depression in adults: Choosing initial treatment".)

In addition, psychotherapy has demonstrated efficacy for depressed patients with specific general medical diseases:

- A meta-analysis of four randomized trials (647 patients with depression and diabetes mellitus) compared psychotherapy (primarily cognitive-behavioral therapy) with usual care or a waiting list control; remission was more likely in patients treated with psychotherapy (odds ratio 3, 95% CI 2-5) [65].

- A subsequent four-week randomized trial compared self-help cognitive-behavioral therapy (based upon a workbook, compact disc, and a brief weekly telephone call from a therapist) with a waiting list control in 82 patients with mild to moderate depression and rheumatic disease [77]. Improvement of depressive symptoms was greater with active treatment.

- More recently, a six-month randomized trial compared cognitive-behavioral therapy (weekly individual sessions lasting one hour) plus usual care (eg, antidepressants) with usual care alone in patients with unipolar major depression plus heart failure [78]. Remission of depression was greater with cognitive-behavioral therapy plus usual care than usual care alone (51 versus 20 percent).

Digital interventions — Although psychotherapy is traditionally delivered face-to-face with an individual patient, digital interventions delivered using mobile- or web-based platforms may increase access, and multiple randomized trials suggest this format may perhaps be

efficacious [79]. As an example, two randomized trials each lasting six weeks compared behavioral activation with usual care in primary care patients with clinically significant depressive symptoms (Patient Health Questionnaire-9 ≥10) (table 3), as well as hypertension and/or diabetes [80]. Active treatment was administered by free smartphones with an application consisting of 18 sessions that could each be completed in less than 10 minutes; nurse assistants facilitated treatment through telephone calls. The primary findings were as follows:

- At the three-month follow-up, reduction of baseline symptoms ≥50 percent occurred in more patients who received digital behavioral activation than usual care:
  - Trial one (n = 790) – 41 versus 29 percent
  - Trial two (n = 410) – 53 versus 34 percent

  Both trials also showed that quality of life and functioning were each superior with active treatment.
- However, at the six-month follow-up, both trials found that outcomes were comparable for the two groups.

Exercise — For depressed patients with chronic medical illnesses, exercise can reduce depressive symptoms. However, it is not clear if exercise is beneficial for major depression or other depressive syndromes. In addition, our clinical experience is such that many depressed patients with general medical illnesses will not accept an exercise intervention due to fatigue, lack of motivation, or problems ambulating.

Evidence supporting the use of exercise includes a meta-analysis of 90 randomized trials (n >10,000 patients with depressive symptoms and chronic medical illnesses such as cancer, cardiovascular disease, chronic obstructive pulmonary disease, chronic pain and fibromyalgia, multiple sclerosis, and spinal cord injury) that compared exercise training with nonexercise control conditions [81]. Studies of patients with a clinical diagnosis of depression were excluded. Exercise training consisted of an average of three sessions per week, 42 minutes per session, and lasted for an average of 17 weeks. Compared with control conditions, exercise led to a significant, clinically small to moderate reduction of depressive symptoms; heterogeneity across studies was moderate. In addition, larger antidepressant effects occurred in patients with greater baseline depressive symptoms and patients who achieved recommended levels of physical activity.

SUMMARY

- Unipolar depression is highly prevalent, disabling, and recurrent. (See 'Introduction' above.)

- Evidence supporting the use of antidepressants for primary care patients with unipolar major depression includes randomized trials in patients who were not necessarily treated in primary care clinics. In addition, antidepressants have demonstrated efficacy for major depression in patients treated by primary care clinicians. (See 'Antidepressants' above and "Unipolar major depression in adults: Choosing initial treatment", section on 'Efficacy of antidepressants'.)

- Adherence to antidepressants is often poor in depressed primary care patients, but can be improved with education combined with other interventions, such as collaborative care. (See 'Adherence' above.)

- Collaborative care integrates psychiatric treatment into primary care practices. Patients are treated by a team that usually includes a primary care clinician, a case manager, and a mental health specialist. Other elements include a structured treatment plan, scheduled follow-up visits, communication within the treatment team, and measurement based care. Many randomized trials demonstrate that collaborative care improves depression outcomes in primary care patients, and can improve outcomes for general medical illnesses. (See 'Collaborative care' above and 'Collaborative care' above.)

- Although psychotherapy is generally administered in specialty psychiatric settings, it is also effective in primary care settings. (See 'Psychotherapy' above.)

- Patients with general medical illnesses often suffer depressive syndromes, which are associated with increased physical symptoms; functional impairment; poor adherence to diet, exercise, and medications; and increased medical costs. (See 'Depression in general medical illness' above.)

- Evidence supporting the use of antidepressants for patients with unipolar major depression and comorbid general medical illnesses includes randomized trials in patients who did not necessarily have comorbid illnesses. In addition, antidepressants have demonstrated efficacy for major depression in patients with comorbidity. (See 'Antidepressants' above and "Unipolar major depression in adults: Choosing initial treatment", section on 'Efficacy of antidepressants'.)

- Psychotherapy is effective for depression in patients with comorbid general medical problems, based upon randomized trials in depressed patients who did not necessarily have comorbid illnesses. In addition, psychotherapy has demonstrated efficacy for

depressed patients with specific general medical diseases. (See "Unipolar major depression in adults: Choosing initial treatment" and 'Psychotherapy' above.)

- Exercise can reduce depressive symptoms in patients with chronic medical illnesses. However, it is not clear if exercise is beneficial for major depression or other depressive syndromes. (See 'Exercise' above.)

ACKNOWLEDGMENT

The UpToDate editorial staff acknowledges Wayne Katon, MD, now deceased, who contributed to an earlier version of this topic review.

Topic 90154 Version 33.0

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