Unipolar depression in adults: Investigational and nonstandard treatment

AUTHOR: Michael Gitlin, MD
SECTION EDITOR: Peter P Roy-Byrne, MD
DEPUTY EDITOR: David Solomon, MD

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Oct 2023.**
This topic last updated: **Sep 26, 2023.**

INTRODUCTION

Unipolar depression is highly prevalent and disabling. In addition, treatment of unipolar major depression is often unsuccessful. A prospective, observational study initially treated 2876 outpatients with full doses of citalopram for up to 14 weeks, and found that remission occurred in only 33 percent [1]. With each successive treatment trial, the rate of remission progressively declined [2].

When depression does respond to treatment, it frequently recurs. Following recovery from one major depressive 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 [3].

As a result, many therapies have been investigated for treatment of depression, but have not been widely adopted, due in part to limited evidence of their efficacy, safety, and tolerability, and the absence of regulatory approval. This topic reviews the evidence for these nonstandard treatments, which may be used in patients not responding to standard treatments for resistant depression.

The general principles and prognosis for the initial treatment of depression are discussed separately, as are the choice of therapy for the initial treatment of depression and the evidence of efficacy of standard therapies, and the evidence for standard therapies that are used for

initially treating depression in primary care patients and in patients with general medical illnesses. Continuation and maintenance treatment of major depression, the treatment of resistant depression, and the clinical manifestations and diagnosis of depression are also discussed separately.

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

OVERVIEW

The treatments for unipolar major depression that are discussed in this topic are typically not used due to limited evidence of their efficacy, safety, and tolerability. For some treatments, the evidence of efficacy is inconsistent, such that some studies indicate the treatment is helpful and other studies do not. Several of the therapies have been investigated in small samples or only one trial and the results need to be replicated before they become standard treatments. In some trials, problematic methods include analyses of study completers (per protocol analysis), which can potentially bias the results, rather than analyzing all patients who were randomized (intent to treat analysis). Another limitation is the lack of longer (eg, >8 weeks) trials to evaluate the benefits and risks; maintenance treatment generally consists of the regimen that achieves remission. In some cases, the treatments lack regulatory approval and are available only through a research protocol.

For unipolar major depressive episodes that are highly resistant to many treatments, investigational and nonstandard approaches may be warranted, instead of pursuing further trials with standard treatments that may be futile [4]. As an example, investigational treatments may be of interest to patients who do not respond to or tolerate, or who decline, the following standard treatments:

- Antidepressants – Several trials (eg, three to six) with different drugs and classes, including older drugs such as tricyclics or monoamine oxidase inhibitors

- Adjunctive drugs – Multiple trials (eg, two to four) that combine antidepressants with different adjunctive drugs, such as second-generation antipsychotics, lithium, ketamine/esketamine, triiodothyronine, or a second antidepressant

- Adjunctive psychotherapy – At least one trial administered in conjunction with pharmacotherapy

- Repetitive transcranial magnetic stimulation – At least one course (eg, 20 to 30 treatments)

- Electroconvulsive therapy (ECT) – At least one course (eg, 6 to 12 treatments), which includes bilateral electrode placement if patients do not improve initially with right unilateral ECT

Investigational and nonstandard treatment includes complementary and alternative therapies, such as dietary supplements and herbal medicines, and practices such as acupuncture, massage, meditation, and yoga [5]. These therapies serve as adjuncts or alternatives to standard (conventional) interventions. Among these therapies are nutraceuticals (nutrient-based products) and phytoceuticals (plant-based products). Treatment that combines standard and complementary therapies is called integrative medicine [5,6]. Additional information about complementary and alternative medicine is available through the United States National Center for Complementary and Integrative Health, which is part of the National Institutes of Health.

The use of complementary and alternative medicine to treat depression appears to be common [7]. A nationally representative survey in the United States found that among individuals with self-reported depression, approximately 50 percent used a complementary and alternative therapy in the past year [8]. Among individuals treated by a conventional clinician, two-thirds also used a complementary and alternative therapy.

Prescribed medications and complementary/alternative treatments differ in multiple ways:

- Medications undergo a rigorous process to gain approval by regulatory agencies such as the US Food and Drug Administration and the European Medicines Agency for specific indications. By contrast, nonstandard treatments do not.

- The quality controls for potency of prescribed medications do not exist for nonstandard treatments, which leads to marked variability in potency across manufacturers of the same nutraceuticals and phytoceuticals. This hampers the utility of these agents.

- Complementary/alternative treatments generally have fewer side effect burdens compared with prescribed medications.

TREATMENTS THAT MAY BE BENEFICIAL

Medications that may be beneficial — Investigational and nonstandard medications that may be beneficial are listed below alphabetically.

Botulinum toxin — Randomized trials suggest that adjunctive botulinum toxin may benefit patients with unipolar major depression, but loss of blinding due to the drug's effect upon facial muscles is common [9,10]. A pooled analysis of individual patient data from three randomized trials (total n = 134 patients), each lasting six weeks, compared onabotulinumtoxinA (29 units for females or 40 units for males) with placebo [11]. At baseline, antidepressants were prescribed to 64 percent of the patients; onabotulinumtoxinA and placebo were injected in a single session into the glabellar frown muscles of the forehead. Remission occurred in more patients who received active treatment than placebo (31 versus 7 percent), and adverse events for the two groups were comparable. However, the investigators acknowledged the difficulty of blinding patients and outcome raters.

Celecoxib — Multiple meta-analyses of randomized trials indicate that celecoxib, an anti-inflammatory drug, can ameliorate depressive syndromes [12-14]. As an example, a meta-analysis of 10 trials, lasting six weeks or one year, compared celecoxib (200 or 400 mg per day) with placebo in 2750 patients with either major depression or depressive symptoms; study drugs were used as monotherapy or add-on therapy (generally with a selective serotonin reuptake inhibitor [SSRI]) [15]. Improvement was greater with celecoxib and the clinical effect was small to moderate; in addition, adverse gastrointestinal or cardiovascular effects were comparable for celecoxib and placebo. However, heterogeneity of the benefit across studies was high, as was risk of bias.

Some clinicians suggest that anti-inflammatory drugs such as celecoxib should be reserved for patients with signs of increased inflammation, as indicated by elevated inflammatory biomarkers (eg, C-reactive protein) [16]. (See "Unipolar depression: Neurobiology", section on 'Inflammation'.)

Cytokine inhibitors — Cytokine inhibitors are anti-inflammatory drugs that may be useful for depressive syndromes [17]. A meta-analysis of eight randomized trials compared cytokine inhibitors with placebo for 12 or 52 weeks in patients with depressive symptoms (n >3300) [14]. Active treatments included adalimumab, ixekizumab, or methotrexate; nearly all patients had somatic comorbidity, such as psoriasis or rheumatoid arthritis, and received study treatments as monotherapy. Improvement of depression was superior with cytokine inhibitors and the clinical effect was moderate. However, heterogeneity across studies was large, and the analysis

did not clarify whether improvement of depression was independent of improvement in somatic morbidity.

Glucocorticoids — Glucocorticoids are anti-inflammatory drugs that may temporarily help treatment-resistant depression [17]. A meta-analysis of two trials compared corticosteroids (corticotropin-releasing hormone, dexamethasone, or hydrocortisone) as add-on treatment for two or four days in 59 patients with unipolar major depression [14]. Improvement was superior with glucocorticoids and the clinical effect was large. However, long-term use of glucocorticoids is associated with serious potential side effects and toxicities and should generally be avoided.

Minocycline — For patients with treatment-resistant depression, multiple randomized trials indicate that the antibiotic minocycline may be beneficial and well tolerated [17,18]. Two separate meta-analyses of the same three trials compared minocycline (200 mg/day) with placebo, either as add-on therapy or monotherapy, in 151 patients with depressive syndromes [14,19]. Improvement was greater with active drug and the clinical effect was large; in addition, adverse effects were comparable for the two groups. However, heterogeneity of the benefit across studies was moderate to large.

Some clinicians have emphasized that anti-inflammatory drugs such as minocycline should be reserved for patients with signs of increased inflammation, as indicated by elevated inflammatory biomarkers such as C-reactive protein [16]. Limited evidence supporting this approach includes a four-week randomized trial that compared add-on minocycline (200 mg/day) with placebo in 39 patients with treatment-resistant depression plus low-grade inflammation, defined as C-reactive protein serum concentration ≥1 mg/L. Although the benefit of minocycline and placebo was comparable, among patients with C-reactive protein ≥3 mg/L, improvement was greater with minocycline.

Additional information about inflammation in unipolar depression is discussed elsewhere. (See "Unipolar depression: Neurobiology", section on 'Inflammation'.)

Scopolamine — Studies of intravenous scopolamine monotherapy suggest that the drug has antidepressant effects, and that augmentation with scopolamine may also be helpful [20,21]. As an example, a six-week randomized trial compared oral scopolamine (0.5 mg per twice per day) with placebo in 40 patients with major depression who were treated with citalopram (40 mg per day) [22]. Exclusion criteria included cognitive impairment, narrow-angle glaucoma, and prostatic hypertrophy; all patients received an eye examination and all males age >40 years underwent a digital rectal examination prior to enrollment. Remission occurred in more patients treated with scopolamine than placebo (65 versus 20 percent). However, scopolamine caused higher rates of blurred vision, dizziness, and dry mouth.

Statins — Combining statins with antidepressants may be efficacious for treating unipolar major depression [23]. Two separate meta-analyses of the same three randomized trials lasting 6 to 12 weeks compared statins with placebo in 165 patients treated with SSRIs [24,25]. Improvement was greater with statins than placebo, and the clinical effect was moderate to large. In addition, the safety profile of statins and placebo was comparable. Another meta-analysis included seven trials, lasting six weeks to four years, in 1576 patients; improvement of depression was greater with statins than placebo, and the effect was small to moderate [14].

Information about the administration and potential adverse effects of statins is discussed separately. (See "Statins: Actions, side effects, and administration".)

Zuranolone — Zuranolone can be efficacious for depression and appears to have a relatively rapid onset of action. Two randomized trials, each lasting two weeks, both found that zuranolone was beneficial in patients with unipolar major depression (n = 89 and 534) [26,27]. As an example, the larger trial compared zuranolone (50 mg/day) with placebo as monotherapy or add-on treatment; greater improvement of depression occurred with zuranolone by day 3, and the clinical advantage of zuranolone throughout treatment was small to moderate [27]. Adverse effects that occurred in at least 5 percent of the patients treated with zuranolone and twice as often with zuranolone than placebo included dizziness and somnolence.

Other randomized trials have found that zuranolone can help patients with postpartum depression. (See "Severe postpartum unipolar major depression: Choosing treatment".)

Complementary and alternative treatments that may be beneficial

Bright light therapy — Using bright light therapy, also called phototherapy, to treat nonseasonal unipolar major depression is consistent with multiple practice guidelines [28-32]. In addition, the intervention is a standard, widely used treatment for mild to moderate unipolar major depression with a seasonal pattern.

Based upon randomized trials, the general principles for using bright light therapy in nonseasonal unipolar major depression include the following:

- Patients – Treatment is efficacious for mild to moderate depression (eg, no suicidal behavior), but not severe depression [33].
- Format – Bright light therapy can be administered as monotherapy [33-35], or in combination with pharmacotherapy, such as an SSRI [36-38].
- Dose – Prescribe a dose of 5000 to 10,000 lux for 30 to 60 minutes/day in the morning rather than other times of day [33,34,36,37].

- Duration – The minimum necessary length of treatment appears to be two weeks [34], and some trials have lasted five or eight weeks [33,34,36,37].

Evidence supporting the use of bright light therapy for nonseasonal depression includes several meta-analyses of randomized trials [34-38]. As an example, a meta-analysis of 13 trials compared bright light therapy with control conditions (eg, red or dim light) in 565 patients [33]. Response (reduction of baseline symptoms ≥50 percent) occurred in more patients who received active treatment than controls (59 versus 38 percent).

Additional information about bright light therapy, including administration, safety, and side effects, is discussed separately in the context of seasonal affective disorder. (See "Seasonal affective disorder: Treatment", section on 'Bright light therapy'.)

Carnitine supplements — Carnitine supplements are dietary supplements that are derived from amino acids and may be useful for treatment of unipolar depression. A meta-analysis of nine randomized trials compared carnitine supplements with placebo in 467 patients with depressive syndromes that were the primary indication or a secondary indication in patients with fibromyalgia, migraine, or minimal hepatic encephalopathy [39]. Carnitine supplements (most often 3 g/day) and placebo were prescribed as monotherapy in the large majority of patients, and or as add-on treatment with an antidepressant. The median length of treatment was eight weeks. Improvement of depression was greater with carnitine supplements than placebo and the clinical effect was large. In addition, the risk of adverse effects in the two groups was comparable. However, inconsistency across studies was large and there was evidence of publication bias.

Additional information about carnitine supplements is available from the United States National Institutes of Health: Office of Dietary Supplements.

Chronotherapy — Chronotherapy combines at least two of the following: sleep deprivation, bright light therapy, and sleep phase advance. Sleep deprivation involves depriving patients their normal sleep, either for the entire night or the second half of the night. Sleep phase advance involves going to bed and waking up earlier than usual. Each component of chronotherapy is administered for different lengths of time. It is hypothesized that chronotherapy resets and stabilizes circadian rhythms by synchronizing internal circadian rhythms to the environmental light/dark cycle [40].

Based upon randomized trials, chronotherapy may perhaps be a useful adjunct for short-term treatment of depression. A meta-analysis of four trials compared chronotherapy (sleep deprivation plus bright light therapy) with control conditions (exercise, dim light, or usual care) in 202 patients with depressive syndromes treated with pharmacotherapy [40]. Improvement of

depression on day 5 to 7 was greater with chronotherapy than control conditions, and the clinical effect was moderate to large. However, it's not clear whether sleep deprivation provided any additional benefit to bright light therapy, which appears to be beneficial as monotherapy. (See 'Bright light therapy' above.)

If sleep deprivation is used as a monotherapy for depression, its benefits are transient, such that increased depressive symptoms typically recur after a full night of sleep.

Creatine — Combining creatine with an antidepressant may be useful in the short-term treatment of depression. An eight-week randomized trial compared creatine monohydrate (5 g per day) plus escitalopram (10 to 20 mg per day) with placebo plus escitalopram in 52 women with unipolar major depression [41]. Exclusion criteria included comorbid renal disease and serum creatinine levels that exceeded the normal range (>1.1 mg/dL). Remission occurred in more patients who received creatine than placebo (52 versus 26 percent). Adverse events were comparable for the two groups, and serum creatinine and blood urea nitrogen levels were within normal limits during the trial.

Additional information about creatine is available from the United States National Institutes of Health: Office of Dietary Supplements.

Folate derivatives — Although the evidence suggests that the folate derivatives methylfolate and S-adenosyl methionine (SAMe) may perhaps be beneficial for unipolar depression, multiple randomized trials indicate that folate (folic acid) is not. (See 'Complementary and alternative treatments' below.)

Methylfolate — Adjunctive methylfolate, which is the form of folate that crosses the blood brain barrier, may be effective for treatment-resistant depression [42]. A meta-analysis of two small randomized trials compared methylfolate (15 mg/day) with placebo as add-on treatment in 99 patients with unipolar major depression that had not responded to an antidepressant (eg, SSRI) [43]. Improvement was greater with active drug and the clinical effect was moderate to large. Use of methylfolate for depression is consistent with multiple practice guidelines [5,29,44].

S-adenosyl methionine — SAMe is a metabolite of folate that facilitates the synthesis of neurotransmitters (including dopamine, norepinephrine, and serotonin) and is available over-the-counter as a dietary supplement in the United States [45]. It is not clear whether SAMe is beneficial for unipolar major depression, due to the lack of high-quality evidence supporting its use [45]. Nevertheless, multiple practice guidelines recommended SAMe as adjunctive treatment for unipolar depression [5,29,44].

Evidence supporting the use of SAMe includes a six-week randomized trial that compared add-on SAMe (800 mg twice per day) with placebo in 73 patients with unipolar major depression who failed treatment with an SSRI or serotonin-norepinephrine reuptake inhibitor; remission occurred in more patients who received SAMe (26 versus 12 percent) [46]. In addition, discontinuation of treatment due to adverse effects was numerically less with SAMe than placebo (5 versus 9 percent).

However, other randomized trials that evaluated SAMe for depression have yielded results that are difficult to interpret due to methodologic problems. As an example:

- A 12-week randomized trial in 189 patients found that response to SAMe (1600 to 3200 mg/day), escitalopram (10 to 20 mg/day), or placebo was comparable [47]. These results rendered the study a failed trial, given that escitalopram is a well-established antidepressant based upon its efficacy in multiple trials [48].

- A meta-analysis of four randomized trials (n = 619 depressed patients) found that improvement was comparable with either SAMe or imipramine; however, the trials lacked a placebo arm to calibrate the results [45].

General information about SAMe is available from the United States National Institutes of Health Office of Dietary Supplements and the National Center for Complementary and Integrative Health.

Glycyrrhizic acid — Glycyrrhizic acid is an herbal extract that may accelerate response to initial treatment of depression. A four-week randomized trial compared glycyrrhizic acid (150 mg three times daily) plus escitalopram (5 to 20 mg/day) with placebo plus escitalopram in patients with unipolar major depression (n = 56) [49]. Response occurred in more patients who received adjunctive glycyrrhizic acid than placebo (67 versus 38 percent). In addition, the rate of adverse events in the two groups was comparable.

Meditation — Meditation may be beneficial as add-on treatment for treatment-resistant depression [50]. An eight-week, open-label randomized trial compared adjunctive meditation with a wait list control condition in patients (n = 25) with unipolar major depression that did not respond to at least eight weeks of antidepressant treatment [51]. The meditation intervention was a group program that included breathing exercises, yoga postures, and sitting meditation; the program required 3.5 hours/day for the first week and 2 hours/day for the remaining seven weeks. Adjunctive meditation led to greater improvement of depression and was well tolerated.

Meditation is a component of mindfulness-based cognitive therapy, which is a standard treatment that combines the clinical application of mindfulness meditation with elements of

cognitive-behavioral therapy. (See "Unipolar major depression: Treatment with mindfulness-based cognitive therapy".)

Music therapy — Music therapy includes regular meetings with a therapist who uses music to help patients process and express their experiences and feelings [52]. The intervention can be administered in an individual or group format, and consists of active methods (compositional, improvisational, or recreative) in which patients make music, and receptive methods in which patients listen to music.

The evidence that suggests adjunctive music therapy may be helpful includes a meta-analysis of three open-label randomized trials and one prospective controlled observational study that compared music therapy plus usual care (eg, antidepressants and psychotherapy) with usual care alone in a total of 219 patients with unipolar depression [52]. Music therapy included 12 to 48 sessions administered over six weeks to three months. Improvement was greater in patients who received music therapy, and the clinical benefit was large.

N-acetylcysteine — N-acetylcysteine is derived from the amino acid cysteine, is available over-the-counter, and may possibly be useful for treatment-resistant depression [53]. A 12-week randomized trial compared N-acetylcysteine (1000 mg twice daily) with placebo as add-on treatment in 252 patients with unipolar major depression [54]. Improvement at week 12 was comparable for the two groups, but follow-up assessments at week 16 found that response occurred in more patients who received add-on N-acetylcysteine than placebo (37 versus 25 percent). Adverse gastrointestinal and musculoskeletal complaints were greater with N-acetylcysteine.

Omega-3 fatty acids — Omega-3 fatty acids (n-3 polyunsaturated fatty acids), which are found in high concentrations in some “oily” species of fish, may be helpful as add-on therapy for unipolar major depression [55,56]. For patients treated with omega-3 fatty acids, we suggest prescribing either of the most widely studied formulations [5,30,56]:

- Pure eicosapentaenoic acid 1 to 2 g/day
- Eicosapentaenoic acid 1 to 2 g/day plus docosahexaenoic acid 1 to 2 g/day, in a ratio greater than 2:1

The starting dose of eicosapentaenoic acid is 1 g/day [56]. For patients who tolerate the medication but do not respond satisfactorily for after two to four weeks, the dose is increased to 2 g/day. An adequate acute treatment trial lasts at least eight weeks; randomized trials have lasted up to 16 weeks.

Omega-3 fatty acids are generally well tolerated and carry little risk of serious adverse effects [30,56]. The most common mild side effects include belching, fishy aftertaste, nausea, pruritus, and skin eruptions. However, patients receiving omega-3 fatty acid-containing products (or substantially increasing the content of omega-3 fatty acids in their diets) in conjunction with an anticoagulant should be monitored for signs and symptoms of bleeding or excessive bruising [5,30]. Specific interactions of omega-3 fatty acids with other medications may be determined using the Lexicomp drug interactions tool (Lexi-Interact Online) included in UpToDate.

Evidence supporting augmentation of antidepressants with omega-3 fatty acids (especially eicosapentaenoic acid) for unipolar depression includes multiple meta-analyses of randomized trials [30,53,56,57]. Across different meta-analyses, the primary findings include the following:

- Improvement is greater with omega-3 fatty acids than placebo, and the clinical benefit is generally moderate [58-61].
- Omega-3 fatty acids are efficacious when combined with antidepressants, but not as monotherapy [58,60,61].
- Formulations of pure or mainly eicosapentaenoic acid are efficacious, whereas formulations of pure or mainly docosahexaenoic acid are not [58,60,61]. In addition, there is a dose-response relationship with eicosapentaenoic acid.
- Baseline severity of depression is not associated with efficacy [61].
- The benefit of omega-3 fatty acids may be limited to patients without general medical comorbidity (eg, coronary heart disease, diabetes, or neurologic disease) [59].

The potential value and relative safety of omega-3 fatty acids for treating depressive syndromes is underscored by their inclusion in multiple practice guidelines [5,28,29,56].

The United States National Center for Complementary and Integrative Health and the National Library of Medicine discuss the use of omega-fatty acids, including its use for depression.

Information about the benefits, adverse effects, and safety of omega-3 fatty acids for cardiovascular health is discussed separately. (See "Fish oil: Physiologic effects and administration".)

Probiotics — Probiotics are live microorganisms such as bacteria and yeast, and multiple small studies suggest that adjunctive probiotics are potentially efficacious for treating depression. A meta-analysis of five, low-quality randomized trials compared add-on probiotics with placebo in

254 depressed patients treated with an antidepressant (usually an SSRI); improvement was greater with probiotics and the clinical benefit was large [62]. In addition, a subsequent eight week trial in 49 patients with treatment-resistant depression found that improvement was greater with an add-on multistrain probiotic than placebo on one outcome measure, but comparable on another [63]. Side effects in the probiotic group were mild.

Additional information about probiotics is available at the United States National Center for Complementary and Integrative Health and National Institutes of Health: Office of Dietary Supplements.

St. John's wort — For patients who present with unipolar major depression, St. John's wort (extracts of the plant *Hypericum perforatum*) appears to be helpful. Nevertheless, we suggest that clinicians **not** prescribe it. Preparations of the drug vary in potency and are not standardized, the proper dose of St. John's wort is not clear, it is not known if the drug is appropriate for patients with severe depression, and the active component is not known [64-67]. St. John's wort preparations are often of poor quality or adulterated with other *Hypericum* species and food dyes. In addition, the maximum duration of treatment in randomized trials is 12 weeks and the persistence of the drug's effects are thus not known. Avoiding St. John's wort for the initial treatment of major depression is consistent with practice guidelines from the American Psychiatric Association, Royal Australian and New Zealand College of Psychiatrists, and the United Kingdom National Institute of Health and Clinical Excellence [28,64-66]. Nevertheless, other treatment guidelines endorse St. John's wort [5,29,68].

Randomized trials indicate that St. John's wort can be efficacious and is relatively well tolerated [42]:

- A systematic review of randomized trials concluded that the efficacy of St. John's wort was superior to placebo and comparable to standard antidepressants, and that tolerability was superior with St. John's wort compared with standard antidepressants; however, interpretation of the results is difficult because country of origin was associated with the benefits of St. John's wort [69].

- A meta-analysis of 27 randomized trials compared St. John's wort with SSRIs in patients diagnosed with depressive syndromes (n = 3126), and found that improvement, response, and remission were each comparable for the two groups, whereas adverse effects were less likely to occur with St. John's wort (relative risk 0.77, 95% CI 0.70-0.84) [70]. A subsequent meta-analysis (27 trials, 3808 patients) found similar results [71].

St. John's wort can potentially cause serious drug-drug interactions [72]. As an example, St. John's wort appears to induce metabolism of other drugs (eg, anticoagulants, anticonvulsants,

antiretrovirals, immunosuppressants, and hormonal contraceptives) via CYP3A4 hepatic enzymes. Also, concurrent use of St. John's wort with SSRIs can cause the serotonin syndrome [28,42]. Specific interactions of St. John's wort with other medications may be determined using the Lexicomp drug interactions tool (Lexi-Interact Online) included in UpToDate.

Additional information about St. John's Wort is discussed separately. (See "Clinical use of St. John's wort".)

The United States National Center for Complementary and Integrative Health website, which is part of the National Institute of Health, also discusses St. John's Wort, including its use for depression.

Whole body hyperthermia — Multiple randomized trials suggest that whole body heating may possibly ameliorate depression [73]:

- A randomized trial compared a single session of whole body hyperthermia with a sham condition in 29 patients with unipolar major depression who were subsequently followed for up to six weeks [74]. Neither antidepressants nor psychotherapy were allowed during the trial, and all patients were otherwise medically healthy. Whole body hyperthermia was induced with infrared lights and heating coils that raised the core body temperature to 38.5°C (101.3°F); the mean length of time required to do so was 107 minutes. Improvement was greater with whole body hyperthermia than the sham condition within one week and the benefit of active treatment persisted for six weeks. Adverse effects for the two groups were comparable.

- In an open-label, eight-week randomized trial, 36 patients with unipolar depressive syndromes were randomly assigned to hyperthermic baths or a sham control condition two times per week for two weeks [75]. Patients receiving antidepressants at baseline continued pharmacotherapy during the trial. During treatment with hyperthermic baths, patients immersed their entire bodies, except the head, in a 40°C (104°F) pool for 20 to 30 minutes. Patients were then wrapped in warm blankets with hot water bottles filled with boiling water for at least 30 minutes. The control condition consisted of exposure to green light (<400 lux) for less than 40 minutes. At week 2, after four interventions, improvement of depression was greater with active treatment. However, at week 8, improvement was comparable in the two groups.

TREATMENTS THAT DO NOT APPEAR TO BE BENEFICIAL

Medications

- **Buprenorphine plus samidorphan** – Buprenorphine and samidorphan each act upon opioid receptors. A meta-analysis of five trials typically lasting four to six weeks compared add-on buprenorphine plus samidorphan with placebo in patients who did not respond to an antidepressant (n >1200); the combination provided no advantage over placebo [76].

- **D-cycloserine** – A small, six-week randomized trial in 26 patients with unipolar major depression resistant to antidepressants found that improvement was greater with add-on D-cycloserine (1000 mg/day) than placebo [77]. However, a previous trial by the same investigators in 22 treatment-resistant patients found that a smaller dose of adjunctive D-cycloserine (250 mg/day) was not beneficial [78].

- **Memantine** – A meta-analysis of three randomized trials in 92 patients with unipolar or bipolar depression found that the likelihood of response with memantine (generally 20 mg/day) or placebo, either as monotherapy or augmentation, was comparable [79].

- **Metyrapone** – The antiglucocorticoid metyrapone does not appear to help patients with treatment-resistant depression, based upon a five-week randomized trial in 143 patients treated with add-on metyrapone (500 mg twice daily) or placebo [80].

- **Nitrous oxide** – Nitrous oxide is a clinically available N-methyl-D-aspartate (NMDA) receptor antagonist akin to ketamine and is a standard anesthetic drug that has been studied in patients with treatment-resistant depression. A randomized trial compared adjunctive inspiratory nitrous oxide (50 percent nitrous oxide plus 50 percent oxygen) with placebo (50 percent nitrogen plus 50 percent oxygen) in patients with treatment-resistant depression who were receiving a stable treatment regimen (n = 20) [81]. Study drugs were administered in a single session lasting one hour. Improvement of depression was greater with add-on nitrous oxide than placebo at 2 hours, 24 hours, and one-week posttreatment. However, longer term benefits and toxicity of nitrous oxide are unknown. In addition, nitrous oxide may be abused because of its intoxicating properties.

- **Pindolol** – Although the combination of pindolol plus an antidepressant has demonstrated efficacy as initial treatment for major depression, the benefits appear to wane or disappear. Two separate meta-analyses of randomized trials compared pindolol with placebo in patients with unipolar major depression who were treated with selective serotonin reuptake inhibitors (SSRIs; total n = 889 patients) [82,83]. Both meta-analyses found that within two weeks, response (reduction of baseline symptoms ≥50 percent) was substantially more likely with adjunctive pindolol than placebo. However, within six weeks, the advantage of pindolol in one meta-analysis was marginal [82] and in the other study had disappeared [83].

- **Pioglitazone** – A meta-analysis of two randomized trials in 77 patients with unipolar major depression found that the benefit of antidepressants plus add-on treatment with pioglitazone or placebo was comparable [14].

- **Riluzole** – An eight-week randomized trial in 104 patients with treatment-resistant depression found that improvement with antidepressants plus adjunctive riluzole (50 mg twice daily) or placebo was comparable [84].

- **Testosterone**

  - **Males** – For depressed men who do not have hypogonadism, it appears that exogenous testosterone is not beneficial [85]. A meta-analysis of two randomized trials (n = 103 depressed, eugonadal men) compared intramuscular testosterone with placebo and found that active treatment was not beneficial [86].

    In a subsequent meta-analysis of 27 randomized trials that compared testosterone with placebo in 1890 males with depression, improvement was greater with testosterone [87]. Nevertheless, some experts concluded that the results did not support using testosterone to treat unipolar depression, based upon the following methodologic problems [85]:

    - Many of the patients entered the trials without depressive disorders such as unipolar major depression or persistent depressive disorder (dysthymia). In addition, the heterogenous patient population included males with a variety of general medical conditions, including hypogonadism.

    - Risk of bias in the underlying trials was high or not clear.

    - The clinical benefit of testosterone in the meta-analysis was small and may not have been clinically meaningful.

    - The long-term safety of testosterone is unknown.

    In males with hypogonadism, it is not known whether testosterone improves unipolar major depression [85]. (See "Testosterone treatment of male hypogonadism", section on 'Other possible effects'.)

  - **Females** – Testosterone does not appear to be beneficial for females with treatment-resistant depression. An eight-week randomized trial compared add-on, low-dose testosterone cream (mean 12 mg/day) with placebo in female patients with treatment-

resistant unipolar major depression (n = 101); response was nearly the same in both groups (approximately 48 percent) [88].

Complementary and alternative treatments

- **Cannabis** – For treatment-refractory depression, we suggest that patients avoid using plant-based and pharmaceutical cannabinoids due to the lack of any apparent benefit and the potential for adverse effects and harms.

  Evidence indicating that cannabis is not helpful for depression includes a systematic review and meta-analysis of 12 randomized trials that compared adjuvant cannabinoids with placebo in 1656 patients with depressive syndromes [89]. The primary indication in each trial was a general medical disorder, such as chronic noncancer pain or multiple sclerosis, with depression as a secondary indication. Active treatment in nearly all trials consisted of pharmaceutical grade delta-9-tetrahydrocannabinol (THC) in the form of dronabinol, nabilone, or nabiximols. During treatment that generally lasted 4 to 12 weeks, improvement of depression was comparable with cannabinoids and placebo.

  The same review also examined the adverse effects of adjunctive cannabinoids in patients with symptoms of depression, anxiety, attention deficit hyperactivity disorder, or posttraumatic stress disorder [89]. A meta-analysis of 10 trials (n = 1495 patients) found that adverse events were two times more likely to occur with cannabinoids than placebo (odds ratio 2.0, 95% CI 1.2-3.3). In addition, a meta-analysis of 11 trials (n = 1621 patients) showed that discontinuation of treatment due to adverse events was nearly three times more likely with add-on cannabinoids (odds ratio 2.8, 95% CI 1.6-4.9).

  The risk of harm from using cannabis in patients with depression led The National Academies of Sciences, Engineering, and Medicine to issue a report in 2017, which concluded that cannabis use is associated with an increased incidence of suicide attempts and deaths [90]. The following year, the American Psychiatric Association formally opposed the use of cannabis as medicine, due in part to the risks of cannabis in patients with unipolar major depression, including increased rates of suicide attempts [91]. A 2022 practice guideline from the Canadian Network for Mood and Anxiety Treatments recommends not using cannabis to treat depression because it is associated with a worse course of illness and poorer functioning, including increased suicidal ideation [92].

  Additional information about the adverse consequences of cannabis use are discussed in separately. (See "Cannabis use and disorder: Epidemiology, pharmacology, comorbidities, and adverse effects".)

- **Folate** – Two meta-analyses of randomized trials (n = 657 and 671) indicate that add-on folate (folic acid), at a dose of (0.5 to 10 mg per day), is not useful for treatment-resistant depression [43,57]. In addition, other studies of folate have raised safety concerns, including masked B12 deficiency [93].

  Additional information about folate is available from the United States National Institutes of Health: Office of Dietary Supplements and MedlinePlus.

- **Inositol** – A meta-analysis of two randomized trials lasting four weeks in 78 patients receiving SSRIs for unipolar major depression found that the benefits of add-on inositol (12 mg/day) and placebo was comparable [94].

- **Magnesium** – In a meta-analysis of eight randomized trials in 538 patients with depressive syndromes who were treated for 1 to 12 weeks with magnesium (225 to 4000 mg/day) or placebo, improvement was comparable [95].

- **Rhodiola** – Evidence regarding the efficacy of the herb *Rhodiola rosea* in depressed patients is mixed. In a 12-week trial that evaluated adjunctive Rhodiola, 98 patients with mild to moderate unipolar major depression were each treated with sertraline (dose not specified) and randomly assigned to adjunctive Rhodiola 0.3 g/day, Rhodiola 0.6 g/day, or placebo [96]. Improvement of depression was greater with each dose of adjunctive Rhodiola than placebo, and Rhodiola was well tolerated.

  In two monotherapy trials that compared Rhodiola with placebo for depression, the results were inconsistent. A six-week trial in 89 patients found that Rhodiola 340 mg/day and Rhodiola 680 mg/day were each more efficacious than placebo [97]. By contrast, a 12-week trial in 38 patients found that improvement with Rhodiola 340 mg/day and placebo was comparable [98].

  General information about Rhodiola is available from the United States National Center for Complementary and Integrative Health.

- **Sarcosine** – Sarcosine (also known as N-methylglycine) is derived from the amino acid glycine [99]. A six-week randomized trial compared sarcosine (mean dose 900 mg per day) with citalopram (mean dose 27 mg per day) in 40 patients with unipolar major depression [100]. Remission occurred in more patients who received sarcosine than citalopram (65 versus 5 percent), and the most common side effects of sarcosine were nausea and sedation. However, problems with the study include the relatively low dose of citalopram, a high rate of attrition, and a remission rate with citalopram that was substantially lower than is typically observed [101].

- **Vitamins** – Multiple randomized trials indicate that vitamins do not increase the benefits of antidepressants for the initial treatment of unipolar major depression:

  - A 52-week trial compared citalopram (20 to 40 mg/day) plus vitamin B_{12} (0.5 mg/day), folic acid (2 mg/day), and vitamin B_6 (25 mg/day) with citalopram plus placebo in 146 patients [102]. Remission after 12 weeks was nearly identical for vitamins and placebo (78 and 79 percent).

  - A 12-week trial compared thiamine (vitamin B1, 300 mg/day) with placebo in 51 inpatients treated with fluoxetine (20 mg/day) [103]. Although improvement at week 6 was greater with thiamine than placebo, at week 12 improvement was comparable for the two groups.

- **Zinc** – Zinc is an essential trace mineral that has been examined in poorly conducted studies of unipolar depression [53]. A meta-analysis of three small randomized trials, lasting 6 to 12 weeks, compared an antidepressant plus zinc (25 mg/day) with an antidepressant plus placebo in 104 patients with unipolar major depression [59]. Improvement was greater in patients who received zinc than placebo, and the clinical benefit was moderate to large. However, attrition was high in each study, and each trial used a completer (per protocol) analysis rather than an intent to treat analysis.

  Additional information about zinc is discussed separately. (See "Overview of dietary trace elements", section on 'Zinc'.)

  Further information about zinc is reviewed on the United States National Institutes of Health: Office of Dietary Supplements website.

MEDICATIONS THAT CAN HELP IN RELATED CONDITIONS

Although the following medications have failed to demonstrate efficacy for unipolar major depression, they can be efficacious for related conditions and thus may play an adjunctive role for depression.

- **Buspirone** – Two randomized trials (n = 119 and 102) compared buspirone with placebo as augmentation in patients who did not respond to initial treatment of major depression with a selective serotonin reuptake inhibitor; response with adjunctive buspirone and placebo were comparable [104,105]. However, given buspirone's efficacy in generalized anxiety disorder, which is frequently comorbid with depression, it may play an adjunctive role in some patients with major depression.

- **Lamotrigine** – Lamotrigine has yielded negative results for unipolar major depression in randomized trials:

  - Three trials (total n >900 patients) that compared lamotrigine monotherapy (≤200 mg per day) with placebo for up to eight weeks found no benefit for lamotrigine [106].

  - In two trials for treatment-resistant, unipolar major depression (total n = 130), add-on lamotrigine was no more effective than placebo [107,108].

  Despite these negative data, some clinicians observe benefits from lamotrigine in unipolar depressed patients. Whether this reflects a placebo response or the presence of a small subgroup of responsive patients is unknown. Lamotrigine's efficacy in bipolar disorder, especially in preventing and possibly treating acute bipolar depression, may be related to the occasional efficacy of lamotrigine in unipolar depressed patients.

SOCIETY GUIDELINE LINKS

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

INFORMATION FOR PATIENTS

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

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

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

- Beyond the Basics topics (see "Patient education: Depression in adults (Beyond the Basics)" and "Patient education: Depression treatment options for adults (Beyond the Basics)" and "Patient education: Electroconvulsive therapy (ECT) (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Overview** – Many nonstandard therapies that have been investigated for treating unipolar major depression are typically not used due to limited evidence of their efficacy, safety, and tolerability. In some cases, the treatments lack regulatory approval, are available only through a research protocol, or are conceptualized as complementary and alternative therapies. Nevertheless, for depressive episodes that are resistant to many treatments, investigational and nonstandard approaches may be warranted, instead of pursuing further trials with standard treatments that may be futile. (See 'Overview' above.)

- **Treatments that may be beneficial** – Based upon randomized trials, several investigational and nonstandard treatments may be beneficial, including medications such as botulinum toxin, celecoxib, cytokine inhibitors, and zuranolone. In addition, complementary and alternative therapies that may be effective include bright light therapy (for nonseasonal depression), omega-3 fatty acids, and the folate derivatives methylfolate and S-adenosyl methionine. (See 'Treatments that may be beneficial' above.)

- **Treatments that do not appear to be beneficial** – Treatments that do not appear to be beneficial include pharmacotherapies such as buprenorphine plus samidorphan, pindolol, and testosterone, as well as complementary and alternative therapies such as folate, magnesium, and sarcosine. (See 'Treatments that do not appear to be beneficial' above.)

  In addition, for patients with treatment-resistant depression, we recommend **not** prescribing cannabis because of its lack of benefit and potential adverse effects and serious harms (**Grade 1B**). (See 'Complementary and alternative treatments' above.)

ACKNOWLEDGMENTS

The UpToDate editorial staff acknowledges Paul Ciechanowski, MD, who contributed to an earlier version of this topic review.

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

Topic 90155 Version 38.0

→