Unipolar major depression with psychotic features: Acute treatment

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Literature review current through: **Oct 2023.**
This topic last updated: **Jan 24, 2022.**

INTRODUCTION

Unipolar major depression with psychotic features is a severe subtype of unipolar major depression (major depressive disorder) [1]. The psychotic symptoms are delusions and/or hallucinations that are frequently consistent with depressive themes of guilt and worthlessness [2]. Psychotic depression and nonpsychotic depression differ in their diagnosis, treatment, and prognosis.

This topic reviews the acute treatment of unipolar major depression with psychotic features. Maintenance treatment and prognosis are discussed elsewhere, as are the epidemiology, pathogenesis, clinical features, assessment, and diagnosis of psychotic depression. (See "Unipolar major depression with psychotic features: Maintenance treatment and course of illness" and "Unipolar major depression with psychotic features: Epidemiology, clinical features, assessment, and diagnosis".)

TERMINOLOGY

Unipolar major depression with psychotic features is characterized by an episode of unipolar major depression that includes delusions and/or hallucinations [2].

Unipolar major depression (major depressive disorder) is diagnosed in patients who have suffered at least one major depressive episode (table 1) and have no history of mania (table 2) or hypomania (table 3) [2]. A major depressive episode is a two week or longer period with five or more of the following symptoms: depressed mood, loss of interest or pleasure in most activities, insomnia or hypersomnia, change in appetite or weight, psychomotor retardation or agitation, low energy, poor concentration, guilt, and recurrent thoughts about death or suicide. The clinical presentation and diagnosis of unipolar major depression are discussed further elsewhere. (See "Unipolar depression in adults: Assessment and diagnosis".)

The primary distinction between unipolar major depression with psychotic features and unipolar major depression without psychotic features is that psychotic depression includes [2]:

- Delusions – False, fixed beliefs
- Hallucinations – False sensory perceptions

The clinical features, diagnosis, and differential diagnosis of unipolar major depression with psychotic features are discussed separately. (See "Unipolar major depression with psychotic features: Epidemiology, clinical features, assessment, and diagnosis".)

TREATMENT

General principles — Most episodes of unipolar major depression are treated by internists [3]. However, unipolar psychotic depression is more difficult to treat and most patients are referred to psychiatrists [4].

The goal of treating unipolar psychotic depression is remission, which is defined as resolution of both the psychotic symptoms (delusions or hallucinations) and depressive symptoms. Patients whose psychosis resolves and whose depression improves to the point that only one or two symptoms of mild intensity persist are also regarded as remitted. For patients who do not achieve remission, a reasonable goal is response, which is defined as stabilization of the patient's safety and substantial improvement in the number, intensity, and frequency of psychotic and mood symptoms.

Depressive and psychotic symptoms should be monitored regularly with clinical interviews that pay particular attention to:

- Suicidal ideation
- Suicide plans

- Psychotic symptoms that place the patient at imminent risk of coming to harm (eg, auditory hallucinations commanding the patient to kill themselves)

The frequency of assessment generally ranges from daily to monthly, depending upon the severity of persistent symptoms. Hospitalized patients are monitored daily, and patients with active suicidal ideation, a specific plan, and intent to kill themselves may require constant observation. Outpatients who have not achieved substantial improvement in the number, intensity, and frequency of psychotic and mood symptoms are generally seen weekly; those who have improved substantially may be seen every two to four weeks until they remit.

Patients with psychotic depression can also be monitored with the Psychotic Depression Assessment Scale, but this is not standard clinical practice. The scale is a clinically valid, empirically tested, 11-item, clinician-administered instrument [5-9]. The scale consists of the six-item melancholia subscale of the Hamilton Rating Scale for Depression [10] and five psychosis items from the Brief Psychiatric Rating Scale [11]. The use of scales to monitor symptoms of depression is discussed separately. (See "Using scales to monitor symptoms and treat depression (measurement based care)".)

First line — We suggest treating unipolar major depression with psychotic features with either of the following [12,13]:

- Antidepressant plus an antipsychotic, or
- Electroconvulsive therapy (ECT)

This approach is consistent with treatment guidelines from the American Psychiatric Association [12,13].

Choosing a treatment — A review of low quality studies found that ECT and the combination of an antidepressant plus an antipsychotic each improved symptoms of unipolar psychotic depression to a similar degree [14]; thus, the initial choice for treating unipolar psychotic depression is based upon other factors. Combination pharmacotherapy is generally selected as initial treatment because it is easier to administer, more widely available, and more acceptable to patients compared with ECT [15].

However, because ECT is generally faster than pharmacotherapy, ECT should be used initially for patients with severe psychosis that places the patient at imminent risk of coming to harm (eg, the patient is distracted by hallucinations to the point of unwittingly walking into moving traffic), severe suicidality (eg, active suicidal ideation with a plan and intent), or malnutrition secondary to food refusal. Initial treatment with ECT is also reasonable for patients who prefer it

or responded well to it during prior episodes of unipolar psychotic depression. Another factor to consider is cost [16-18].

Studies showing that the combination of an antidepressant and an antipsychotic is comparable with ECT for unipolar psychotic depression were generally open-label, and often included nonrandom assignment or consisted of retrospective chart reviews [19]. Patients with heterogeneous diagnoses were included, and different types of ECT (bilateral and unilateral) were compared with different combinations of tricyclic antidepressants and first-generation antipsychotics prescribed at varying doses for different lengths of time [20].

Antidepressant plus antipsychotic — Based upon randomized trials [21-25], we prefer the combination of an antidepressant and an antipsychotic rather than antidepressant monotherapy or antipsychotic monotherapy for unipolar psychotic depression. This results in better patient adherence and outcomes [26] and is consistent with multiple practice guidelines [12,13,27,28].

Choosing a combination — We favor treating unipolar psychotic depression with antidepressant/antipsychotic combinations that have demonstrated efficacy in randomized trials. The following combinations have shown beneficial effects compared with antidepressant monotherapy, antipsychotic monotherapy, or placebo in well-designed, sufficiently large trials:

- Sertraline plus olanzapine [21]
- Fluoxetine plus olanzapine [22]
- Venlafaxine plus quetiapine [23]
- Amitriptyline plus haloperidol [24]
- Amitriptyline plus perphenazine [25]

None of the combinations have been compared in head-to-head trials.

However, it is reasonable to initially treat psychotic depression with a combination that has not been studied in randomized trials. Many alternative combinations are available from existing antidepressants (selective serotonin reuptake inhibitors [SSRIs], tricyclics, serotonin-norepinephrine reuptake inhibitors [SNRIs], and antidepressants with a unique mechanism of action) and antipsychotics (first- and second-generation).

We typically use sertraline plus olanzapine as initial pharmacotherapy for unipolar psychotic depression because this combination has been studied in the most patients. Based upon the randomized trial that established the efficacy of this combination, we typically use the following dose schedule [21]:

- Initial dose of sertraline 50 mg/day plus olanzapine 5 mg/day
- Increase sertraline by 50 mg/day and olanzapine by 5 mg/day every three days as tolerated
- Attempt to reach sertraline dose of at least 100 mg/day and olanzapine 10 mg/day within seven days of starting treatment
- Minimum target doses are sertraline 150 mg/day and olanzapine 15 mg/day, usually beginning no later than week two
- Maximum target doses are sertraline 200 mg/day and olanzapine 20 mg/day, usually beginning no later than week three
- Allow slower titration or temporary dose reductions of one or both medications if side effects occur; however, subsequent dose increases should be attempted

Older adult patients can initially receive sertraline 25 mg/day and olanzapine 2.5 mg/day. The dose is then increased by the same amount every three to five days to a minimum target dose of sertraline 150 mg/day and olanzapine 15 mg/day, and a maximum target dose of sertraline 200 mg/day and olanzapine 20 mg/day.

Three percent of patients receiving sertraline plus olanzapine withdrew from the trial because of intolerable side effects [21]. Adverse effects of the combination included:

- Weight gain of at least 2.7 kg (54 percent of patients)
- Sedation (29 percent)
- Orthostasis (16 percent)
- One or more falls (16 percent)
- Significant increases in serum cholesterol, triglyceride, and glucose concentrations from baseline to study termination

Additional information about the side effects of sertraline and olanzapine are discussed separately. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects", section on 'Side effects' and "Second-generation antipsychotic medications: Pharmacology, administration, and side effects", section on 'Adverse effects'.)

The combination of an antidepressant plus a phenothiazine antipsychotic (eg, chlorpromazine, fluphenazine, mesoridazine, perphenazine, thioridazine, and trifluoperazine) may cause adverse drug interactions. In a case control study, the medication history was examined in 1814 cases of sudden cardiac death and 1171 controls who survived an acute myocardial infarction;

the analyses controlled for risk factors such as hypertension, diabetes, and hypercholesterolemia [29]. Compared with controls, cases were significantly more likely to have been treated with phenothiazines plus any antidepressant (odds ratio 9.6, 95% CI 1.2-80.8).

Specific interactions between antidepressants and antipsychotics may be determined using the Lexicomp drug interactions tool (Lexi-Interact Online) included in UpToDate.

Duration of therapy and switching drugs — Following protocols used in randomized trials, unipolar psychotic depression is treated with an antidepressant plus an antipsychotic at minimum target doses or higher for four to eight weeks before determining whether the combination is effective [22-25]. Intervening adverse effects may necessitate discontinuing one or both drugs sooner than four weeks.

If patients do not respond to or tolerate sertraline plus olanzapine, we suggest using another combination with demonstrated efficacy in a randomized trial, including fluoxetine plus olanzapine, venlafaxine plus quetiapine, amitriptyline plus haloperidol, or amitriptyline plus perphenazine. The new combination is started and titrated up with the goal of reaching minimum target doses within two weeks, while the failed combination is concurrently tapered and discontinued over one to two weeks.

For patients who do not respond to or tolerate sertraline, fluoxetine, venlafaxine, or amitriptyline, it is reasonable to use another SSRI, SNRI, tricyclic, or an antidepressant with a unique mechanism of action. Similarly, if patients do not respond to or tolerate olanzapine, quetiapine, haloperidol, or perphenazine, it is reasonable to use another second- or first-generation antipsychotic, except for clozapine, which can cause agranulocytosis. Most authorities and clinicians switch antidepressant classes when starting a new course of combination pharmacotherapy. Antidepressants and antipsychotics are discussed separately. (See "Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects" and "Serotonin-norepinephrine reuptake inhibitors: Pharmacology, administration, and side effects" and "Tricyclic and tetracyclic drugs: Pharmacology, administration, and side effects" and "Second-generation antipsychotic medications: Pharmacology, administration, and side effects" and "First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects".)

Evidence of efficacy — Data suggest that for individuals with unipolar psychotic depression, the combination of an antidepressant and an antipsychotic may be more effective than antidepressant monotherapy, antipsychotic monotherapy, or placebo [30-32]. However, the efficacy of antidepressant monotherapy and antipsychotic monotherapy appears to be comparable with placebo [32,33].

As examples, in a meta-analysis of randomized trials, the combination of antidepressant and antipsychotic monotherapies led to a greater rate of response (defined as >50 percent reduction in baseline symptoms) than antipsychotic monotherapy (n = 447; relative risk 1.8, 95% CI 1.4-2.4), antidepressant monotherapy (n = 245; relative risk 1.4, 95% CI 1.1-1.8), or placebo (n = 148; relative risk 1.9, 95% CI 1.2-2.8) [32]. Discontinuation for any reason was comparable for the groups. However, in a different meta-analysis, despite similar rates of all-cause discontinuation and reported side effects, sedation was greater with combination therapy than with antidepressant monotherapy (relative risk 2.8, 95% CI 1.1-6.8) [31].

In an analysis of two of the trials in the meta-analysis, treatment with either antipsychotic monotherapy (olanzapine) or antidepressant monotherapy (amitriptyline) led to response rates comparable with those in the placebo groups (n = 201; relative risk 1.13, 95% CI 0.7-1.7 and n = 27; relative risk 8.4, 95% CI 0.5-142.2, respectively) [32].

Evidence from this meta-analysis was deemed low certainty because of risk of bias and heterogeneity across studies.

Electroconvulsive therapy — ECT uses two scalp electrodes to administer an electric current to anesthetized patients and induce a tonic-clonic seizure. Initial treatment for most patients with unipolar psychotic depression consists of an antidepressant plus an antipsychotic. However, because ECT is generally faster than pharmacotherapy, clinicians should use ECT initially for patients with:

- Psychosis that places the patient at imminent risk of coming to harm (eg, psychotic symptoms prevent the patient from attending to basic needs)
- Severe suicidality (eg, active suicidal ideation with a plan and intent)
- Malnutrition secondary to food refusal

Patients who responded well to ECT during prior episodes of unipolar psychotic depression are also good candidates for initial treatment with ECT.

Based upon meta-analyses of randomized trials, the efficacy of ECT for treating unipolar major depression with or without psychotic features is well established [12,13,34-37], and a review found that response to ECT appears to be better in psychotic depression than nonpsychotic depression [34]. As an example, a prospective observational study included patients with unipolar psychotic depression (n = 77) or unipolar nonpsychotic depression (n = 176), who received bilateral ECT three times per week, and found that remission occurred in more psychotic patients than nonpsychotic patients (83 versus 71 percent) [38]. In a retrospective study that included severely depressed patients treated with ECT (n = 627), response occurred in more psychotic patients than nonpsychotic patients (89 versus 82 percent) [39].

ECT is generally safe and there are no absolute contraindications, even in patients whose general medical status is compromised [37]. However, safety concerns regarding ECT necessitate preprocedure medical consultation. Adverse effects include cardiopulmonary events, aspiration pneumonia, fractures, dental and tongue injuries, headache, nausea, and cognitive impairment. Medical consultation prior to ECT is discussed separately. (See "Medical evaluation for electroconvulsive therapy".)

Electrode placement and other aspects of ECT technique for treating unipolar psychotic depression have not been standardized. Thus, ECT is typically administered with the same technique used for other indications and is generally given three times per week on alternating days. Most patients, regardless of indication, remit with 6 to 12 treatments, but some patients may require 20 or more. Additional information about ECT is discussed separately. (See "Overview of electroconvulsive therapy (ECT) for adults" and "Unipolar major depression in adults: Indications for and efficacy of electroconvulsive therapy (ECT)" and "Technique for performing electroconvulsive therapy (ECT) in adults".)

Resistant patients — Initial treatment of unipolar psychotic depression may fail to stabilize the patient's safety and substantially improve the number, intensity, and frequency of psychotic and mood symptoms. Patients resistant to one or two courses of an antidepressant/antipsychotic combination as initial treatment should receive ECT [40]. Conversely, patients who initially receive an unsuccessful course of ECT should receive combination pharmacotherapy. ECT and choosing a pharmacotherapy combination are discussed separately. (See 'Electroconvulsive therapy' above and 'Choosing a combination' above.)

For patients who do not respond to combination pharmacotherapy and who decline or do not have access to ECT, adding both lithium plus a specific type of psychotherapy may possibly improve outcomes; however, there is little evidence to support these adjunctive treatments. Other augmentation strategies have not been studied.

Lithium — Case reports describe patients with unipolar psychotic depression who initially did not respond to an antidepressant plus an antipsychotic, but subsequently improved with lithium augmentation [41-43]. Lithium is added after four to eight weeks of unsuccessful treatment with an antidepressant plus an antipsychotic, at a dose sufficient to achieve a 12-hour serum trough level of 0.5 to 1.0 mEq/L. At least two to four weeks at therapeutic levels is necessary to determine whether lithium augmentation is beneficial.

Adjunctive treatment with lithium for unipolar major depression without psychotic features is discussed separately. (See "Unipolar depression in adults: Treatment with lithium".)

Psychotherapy — Psychotherapies studied for unipolar major depression with psychotic features include acceptance and commitment therapy, which teaches patients to increase their acceptance of unavoidable distress, to simply notice their psychotic symptoms without considering them as either true or false, and to identify and work toward personally valued goals [44,45]. An open-label randomized trial found that in 18 patients with unipolar psychotic depression, symptomatic improvement occurred in significantly more patients who received acceptance and commitment therapy (average three sessions) plus treatment as usual, compared with patients who received treatment as usual alone.

Another therapy studied for psychotic depression is acceptance-based depression and psychosis therapy; this intervention combines elements of acceptance and commitment therapy with behavioral activation (which focuses upon reducing avoidance of activities) [46]. An observational study of 14 patients with psychotic depression who were treated with acceptance-based depression and psychosis therapy for up to six months suggests that the therapy may possibly be beneficial.

Refractory patients — Unipolar psychotic depression that does not respond to one or two courses of an antidepressant plus an antipsychotic, a course of ECT, and adjunctive lithium and acceptance and commitment therapy should be treated with additional trials of an antidepressant plus an antipsychotic. Most authorities and clinicians switch antidepressant classes when starting a new course of combination pharmacotherapy (eg, switch from an SSRI to either an SNRI or a tricyclic). Patients with chronic, unremitting moderate to severe symptoms may require close monitoring and supervision within a structured setting (eg, group home or hospital), depending upon the risk of imminent harm to self or others. Choosing a pharmacotherapy combination and switching drugs are discussed separately. (See 'Choosing a combination' above and 'Duration of therapy and switching drugs' above.)

Family support — Family members should be involved in the care of patients with unipolar psychotic depression, and be educated about the signs and symptoms, treatment, and prognosis of the illness. 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".)

TIME TO RECOVERY

Observational studies show that about 50 percent of patients with unipolar psychotic depression recover within two to three months, and the large majority of patients recover

within 6 to 12 months:

- A five-year observational study of 61 in- or outpatients with unipolar psychotic depression estimated that the median time to recovery from prospectively observed episodes was 10 weeks [47]
- A two-year, prospective observational study of 53 patients hospitalized for unipolar psychotic depression estimated that 50 percent recovered within nine weeks of admission, 75 percent within six months, and 94 percent within 24 months [48,49]
- A one-year, community survey of 92 patients with unipolar psychotic depression found that during prospective follow-up, recovery occurred in 81 percent [1]

However, a few patients may remain ill for approximately 10 years or longer [50].

The rate of recovery may be less in unipolar psychotic depression than nonpsychotic depression [50,51]. In a community survey of 92 patients with unipolar psychotic depression and 532 patients with unipolar nonpsychotic depression, recovery during one year of prospective follow-up occurred in significantly fewer psychotic patients than nonpsychotic patients (81 versus 89 percent) [1].

Functional recovery — Social and occupational impairment usually occurs in unipolar psychotic depression [47,50]. We suggest that patients gradually resume their normal activities following remission of the mood episode. As an example, patients can return to work on a part-time schedule and incrementally increase the hours to full-time.

Functional recovery often lags recovery from psychotic and depressive symptoms [47,52]. A prospective, two-year observational study of 53 patients with unipolar psychotic depression found that functional recovery (occupational and residential status) occurred in 29 percent, whereas recovery from the mood episode occurred in 94 percent [49]. Based upon clinical experience, a quick and full recovery of psychosocial functioning is more probable in patients aged 30 to 65 years with good pre-morbid functioning, a first lifetime episode of unipolar psychotic depression, or a good response to treatment.

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".)

SUMMARY AND RECOMMENDATIONS

- Unipolar major depression with psychotic features is characterized by delusions and/or hallucinations that accompany a two week or longer period with five or more of the following symptoms: depressed mood, loss of interest or pleasure in most activities, insomnia or hypersomnia, change in appetite or weight, psychomotor retardation or agitation, low energy, poor concentration, guilt, and recurrent thoughts about death or suicide. (See 'Terminology' above and "Unipolar major depression with psychotic features: Epidemiology, clinical features, assessment, and diagnosis", section on 'Diagnosis'.)

- First-line acute treatment for unipolar major depression with psychotic features is either electroconvulsive therapy (ECT) or combination pharmacotherapy with an antidepressant and an antipsychotic. For patients with mild to moderate disease, we suggest initial treatment with combination pharmacotherapy rather than ECT (**Grade 2B**). Combination pharmacotherapy is generally easier to administer, more widely available, and more acceptable to patients compared with ECT. (See 'First line' above.)

- We prefer sertraline plus olanzapine as initial pharmacotherapy for unipolar psychotic depression because this combination has been studied with the most patients in randomized trials. Reasonable alternatives include fluoxetine plus olanzapine, venlafaxine plus quetiapine, amitriptyline plus haloperidol, or amitriptyline plus perphenazine. (See 'Choosing a combination' above.)

- For patients with unipolar psychotic depression that includes severe psychosis or suicidality, or malnutrition secondary to food refusal, we suggest initial treatment with ECT rather than combination pharmacotherapy (**Grade 2B**). In addition, initial treatment with ECT is reasonable for patients who prefer it or responded well to it during prior episodes of unipolar psychotic depression. (See 'First line' above and 'Electroconvulsive therapy' above.)

- Patients with unipolar psychotic depression who do not respond adequately to one or two courses of combination pharmacotherapy should receive ECT. Conversely, patients initially treated with an unsuccessful course of ECT should receive combination pharmacotherapy. (See 'Resistant patients' above.)

- Approximately 50 percent of patients with unipolar psychotic depression recover within two to three months and the large majority of patients recover within 6 to 12 months. (See 'Time to recovery' above.)

- Social and occupational impairment usually occurs in unipolar psychotic depression, and functional recovery often lags recovery from psychotic and depressive symptoms. Patients may find it helpful to gradually resume their normal activities following remission of the mood episode. (See 'Functional recovery' above.)

Topic 16546 Version 25.0

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