Unipolar major depression with psychotic features: Maintenance treatment and course of illness

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INTRODUCTION

Unipolar major depression with psychotic features is a severe subtype of unipolar major depression (major depressive disorder) [1,2]. The psychotic symptoms are delusions and/or hallucinations that are frequently consistent with depressive themes of guilt and worthlessness [3]. Psychotic depression and nonpsychotic depression differ in their diagnosis, treatment, and prognosis.

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

DEFINITIONS

Unipolar major depression with psychotic features — Unipolar major depression with psychotic features is characterized by an episode of unipolar major depression that includes delusions and/or hallucinations [3].

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) [3]. 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. (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 [3]:

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

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".)

Remission — Remission is defined as the resolution of psychotic symptoms, and either resolution of depressive symptoms or improvement to the point that only one or two symptoms of mild intensity persist. Remission of unipolar psychotic depression is discussed separately. (See "Unipolar major depression with psychotic features: Acute treatment", section on 'Time to recovery'.)

TREATMENT

Indications — Maintenance treatment is indicated for unipolar psychotic depression because patients who remit are at high risk of suffering another episode of major depression, with or without psychotic features [1,4,5]. As an example, an observational study found that recurrence of major depression occurred in 74 percent of patients who remitted from an episode of unipolar psychotic depression [1]. However, there is relatively little high quality evidence to guide decisions about maintenance treatment.

Choosing treatment — Pharmacotherapy is generally used for maintenance treatment of unipolar psychotic depression. For acutely ill patients who remit with an antidepressant plus an antipsychotic, we usually maintain the same combination at the same dose for at least four to six months, at which point it may be feasible to gradually discontinue the antipsychotic while

maintaining the antidepressant. However, it may be necessary to lower doses or switch the antidepressant and/or the antipsychotic because of side effects (eg, weight gain due to olanzapine). Switching drugs is discussed separately. (See "Unipolar major depression with psychotic features: Acute treatment", section on 'Duration of therapy and switching drugs'.)

Patients with unipolar psychotic depression who remit with electroconvulsive therapy (ECT) are generally started on an antidepressant/antipsychotic combination [6]. The combination is started the day after ECT is completed, unless the patient is suffering cognitive impairment secondary to ECT, in which case maintenance pharmacotherapy is delayed until the impairment has dissipated. Choosing a combination is discussed separately. (See "Unipolar major depression with psychotic features: Acute treatment", section on 'Choosing a combination'.)

However, maintenance ECT should be offered to patients who repeatedly remit with ECT and then relapse during maintenance combination pharmacotherapy. Maintenance ECT is discussed separately. (See "Overview of electroconvulsive therapy (ECT) for adults", section on 'Continuation and maintenance ECT'.)

Duration and discontinuation — During maintenance treatment of unipolar psychotic depression with combination pharmacotherapy, the antidepressant is generally maintained longer than the antipsychotic. Most authorities discontinue the antipsychotic after four to six months of sustained recovery from the episode of unipolar psychotic depression, and continue the antidepressant [7-9]. If the patient has side effects (eg, tardive dyskinesia with a first generation antipsychotic or weight gain with a second generation antipsychotic) and is clinically stable, it is reasonable to taper the antipsychotic sooner than four months. Conversely, for patients who relapsed while discontinuing the antipsychotic during maintenance treatment of prior episodes of psychotic depression, it is reasonable to maintain the antipsychotic for at least 6 to 12 months.

We suggest slowly tapering the antipsychotic over one month to increase the probability of detecting incipient depressive and psychotic symptoms before a full-blown episode of psychotic depression recurs [10]. Each week we taper by approximately 25 percent of the dose used to achieve remission. As an example, olanzapine 20 mg/day is reduced each week by 5 mg/day. If symptoms recur during the taper, the dose is usually titrated back up to the full dose used initially to achieve remission. If a full-blown episode develops despite increasing the dose and does not improve within four to eight weeks, we suggest switching to an alternative antipsychotic. Switching drugs is discussed separately. (See "Unipolar major depression with psychotic features: Acute treatment", section on 'Duration of therapy and switching drugs'.)

For patients with unipolar psychotic depression who successfully taper and discontinue the antipsychotic, but subsequently relapse during maintenance treatment with antidepressant monotherapy, we suggest restarting the antipsychotic that was discontinued. The relapse is treated as a new acute episode; acute treatment is discussed separately. (See "Unipolar major depression with psychotic features: Acute treatment", section on 'Treatment'.)

We suggest maintenance treatment with an antidepressant for a minimum of two years and as long as the patient's lifetime, consistent with practice guidelines from the Canadian Network for Mood and Anxiety Treatments [4]. The duration of maintenance treatment depends upon clinical factors and is generally longer in patients with [11,12]:

- Residual symptoms, particularly suicidal ideation
- Ongoing comorbid psychopathology
- Psychosocial stressors
- A history of suicide attempts
- A greater number of prior major depressive episodes
- A history of longer or more severe (eg, psychotic) depressive episodes
- An early age of onset of unipolar major depression

For patients who decide to discontinue their antidepressant, we suggest tapering it over two months to increase the probability of detecting incipient depressive and psychotic symptoms before a full-blown episode of psychotic depression recurs. Every other week we taper by approximately 25 percent of the dose used to achieve remission. As an example, sertraline 200 mg/day is reduced every other week by 50 mg/day.

If depressive symptoms recur during the antidepressant taper, the antidepressant dose is generally titrated back up to the full dose used initially to achieve remission. If psychotic symptoms also recur during the antidepressant taper, the antidepressant dose is titrated back up to the full dose, and the previously used antipsychotic is restarted and titrated up. If a full-blown psychotic depressive episode develops despite increasing the antidepressant dose and resuming the antipsychotic, and does not improve within four to eight weeks, we suggest switching to an alternative antidepressant/antipsychotic combination. Switching drugs is discussed separately. (See "Unipolar major depression with psychotic features: Acute treatment", section on 'Duration of therapy and switching drugs'.)

For patients with unipolar psychotic depression who successfully taper and discontinue both the antipsychotic and antidepressant, but subsequently relapse, we suggest restarting the same combination that was discontinued. The relapse is treated as a new acute episode; acute

treatment is discussed separately. (See "Unipolar major depression with psychotic features: Acute treatment", section on 'Treatment'.)

Monitoring the patient — Patients with unipolar psychotic depression who remit should be regularly interviewed and monitored for recurrence of depressive and psychotic symptoms. Particular attention is given to suicidal ideation that includes a plan, and to psychotic symptoms that place the patient at imminent risk of coming to harm (eg, auditory hallucinations commanding the patient to kill herself). Patients with psychotic depression can be monitored with the Psychotic Depression Assessment Scale, which is a clinically valid, 11-item, clinician-administered instrument [13,14]. The scale consists of the six-item melancholia subscale of the Hamilton Depression Rating Scale and five psychosis items from the Brief Psychiatric Rating Scale. The use of scales to monitor symptoms of depression is discussed separately. (See "Using scales to monitor symptoms and treat depression (measurement based care)".)

For patients with unipolar psychotic depression who remit and remain stable, monitoring can be tapered, with progressively longer intervals between assessments. As an example, a patient who is seen every two weeks at the time of remission can be seen every two weeks for one or two more visits, then monthly for one to three visits, then every two months for one to three visits, and then every three to six months. More frequent visits should be scheduled for patients who develop depressive or psychotic symptoms; monitoring acutely ill patients is discussed separately. (See "Unipolar major depression with psychotic features: Acute treatment", section on 'General principles'.)

Evidence of efficacy — For patients who recover from an episode of unipolar major depression with psychotic features, the best evidence indicates that maintenance treatment with an antidepressant plus an antipsychotic is superior to an antidepressant alone. In one study, patients acutely ill with unipolar psychotic depression were treated with open-label sertraline (median dose 150 mg/day) plus olanzapine (median dose 15 mg/day) for up to 12 weeks [10,15]. Patients who achieved remission of their psychotic features, and whose depression either remitted or nearly remitted, continued treatment with open-label sertraline plus olanzapine for eight weeks; near remission was defined as reduction of baseline depressive symptoms ≥50 percent, along with a rating of much or very much improved. At the end of the eight weeks, patients (n = 126) who continued to meet criteria for remission or near remission continued to receive open-label sertraline, and were randomly assigned to double-blind olanzapine or placebo for 36 weeks. Patients assigned to placebo were switched (cross-tapered) from olanzapine to placebo over four weeks. The results during the randomized treatment phase included the following:

- The primary outcome was relapse, which was defined as one or more of the following: reoccurrence of major depression and/or psychosis, having a suicide plan, attempting suicide, or admission to an inpatient psychiatric unit. Relapse occurred in fewer patients treated with sertraline plus olanzapine than sertraline plus placebo (20 versus 55 percent, hazard ratio 0.25, 95% CI 0.13-0.48). In addition, the number of patients with a psychotic relapse was three times smaller with olanzapine than placebo (6 and 19 percent [4/64 and 12/62]).

- Weight gain was greater with olanzapine – Olanzapine caused a mean weight gain of 2.6 kg (5.7 lb), whereas placebo caused a mean weight loss of 1.4 kg (3.1 lb). (The weight gain with olanzapine during randomized treatment was in addition to the 5.4 kg [12 lb] weight gain that occurred during open-label treatment with olanzapine.)

- Increase in waist circumference was greater with olanzapine – Olanzapine caused a mean increase in waist circumference of 1.5 cm (0.6 in), whereas placebo caused a mean decrease of 2.0 cm (0.8 in).

- Parkinsonism was greater with olanzapine than placebo.

- One or more falls occurred in roughly twice as many patients who received olanzapine than placebo (31 and 18 percent).

COURSE OF ILLNESS

Unipolar major depression with psychotic features is associated with more recurrences of major depression (with or without psychotic features) and a higher mortality rate, compared with unipolar nonpsychotic depression [16].

Most patients with unipolar psychotic depression suffer multiple recurrences of major depression either with or without psychotic features [17]. Observational studies show that the median time to recurrence may be as long 2.6 years after recovery from the first lifetime episode of psychotic depression [18], and as short as 26 weeks in patients who have a history of multiple depressive episodes [19].

In addition, patients who recover from unipolar psychotic depression are more likely to suffer a recurrence of major depression than are patients who recover from unipolar nonpsychotic depression [12,20-24]:

- A one-year, community survey of 114 patients with unipolar psychotic depression and 662 patients with unipolar nonpsychotic depression found that recurrence of major depression

occurred in more patients with psychotic depression than nonpsychotic depression (74 versus 62 percent) [1].

- A two-year, observational study of 87 patients with unipolar psychotic depression found that recurrence of major depression was greater for patients who remitted from psychotic depression compared with patients who remitted from nonpsychotic depression (47 versus 15 percent) [9].

- A six-year observational study of 1053 patients with unipolar psychotic depression and 1315 patients with unipolar nonpsychotic depression examined rehospitalization after first lifetime admission; readmission occurred sooner for patients with psychotic depression (2.6 versus 3.6 years) [18].

The higher rate of recurrence in psychotic depression compared with nonpsychotic depression is probably responsible for the greater disability and use of services in patients with psychotic depression [19,21,25].

Patients who recover from an episode of unipolar psychotic depression are often psychotic during subsequent recurrences of major depression [2,17,23], and the delusional content may be consistent from one episode of psychotic depression to the next [26]. In addition, the risk of psychotic features during a recurrent episode of major depression is higher in patients who recover from psychotic depression compared with patients who recover from nonpsychotic depression [17,27].

Mortality — Unipolar major depression is associated with increased all-cause mortality compared with the general population [28], and mortality also appears to be greater for psychotic depression than nonpsychotic depression [29]. As an example, an 18-year national registry study compared all-cause mortality in patients with first-episode psychotic depression (n >19,000) or severe nonpsychotic depression (n >90,000) [30]. After adjusting for potential confounding factors (eg, age at initial diagnosis and comorbid psychiatric and general medical disorders), the analyses found that the risk of death was 40 percent greater in psychotic depression (hazard ratio 1.4, 95% CI 1.3-1.5). The risk was highest in the first year after the initial diagnosis of psychotic depression, and more than half the deaths occurred within five years of the initial diagnosis. Psychotic depression was associated with elevated mortality due to suicide and death from accidents and cardiovascular diseases.

Suicidal ideation and suicide attempts in patients with unipolar psychotic depression are discussed separately. (See "Unipolar major depression with psychotic features: Epidemiology, clinical features, assessment, and diagnosis", section on 'Suicidality'.)

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 an episode of unipolar major depression that includes delusions and/or hallucinations. 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 (table 1). (See 'Definitions' above and "Unipolar major depression with psychotic features: Epidemiology, clinical features, assessment, and diagnosis", section on 'Diagnosis'.)

- Unipolar major depression with psychotic features is a highly recurrent illness. For patients with unipolar psychotic depression that remits, we suggest initial maintenance treatment with the antidepressant and antipsychotic combination that achieved remission, rather than discontinuing the antipsychotic and using antidepressant monotherapy (**Grade 2B**). For acute and maintenance treatment, we frequently use sertraline as the antidepressant and nearly always use olanzapine as the antipsychotic.

  The antipsychotic is generally tapered and discontinued after sustained recovery for four to six months, and the antidepressant is maintained for at least two years. Maintenance ECT is a reasonable option for patients who fail multiple courses of maintenance pharmacotherapy. (See 'Treatment' above.)

- For patients with unipolar psychotic depression, the median time to recurrence of major depression (with or without psychotic features) may be as long 2.6 years after recovery from the first lifetime episode of psychotic depression, and as short as 26 weeks in patients who recover from psychotic depression and have a history of multiple depressive episodes. (See 'Course of illness' above.)

- All-cause mortality appears to be greater for unipolar psychotic depression than nonpsychotic depression. (See 'Mortality' above.)

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